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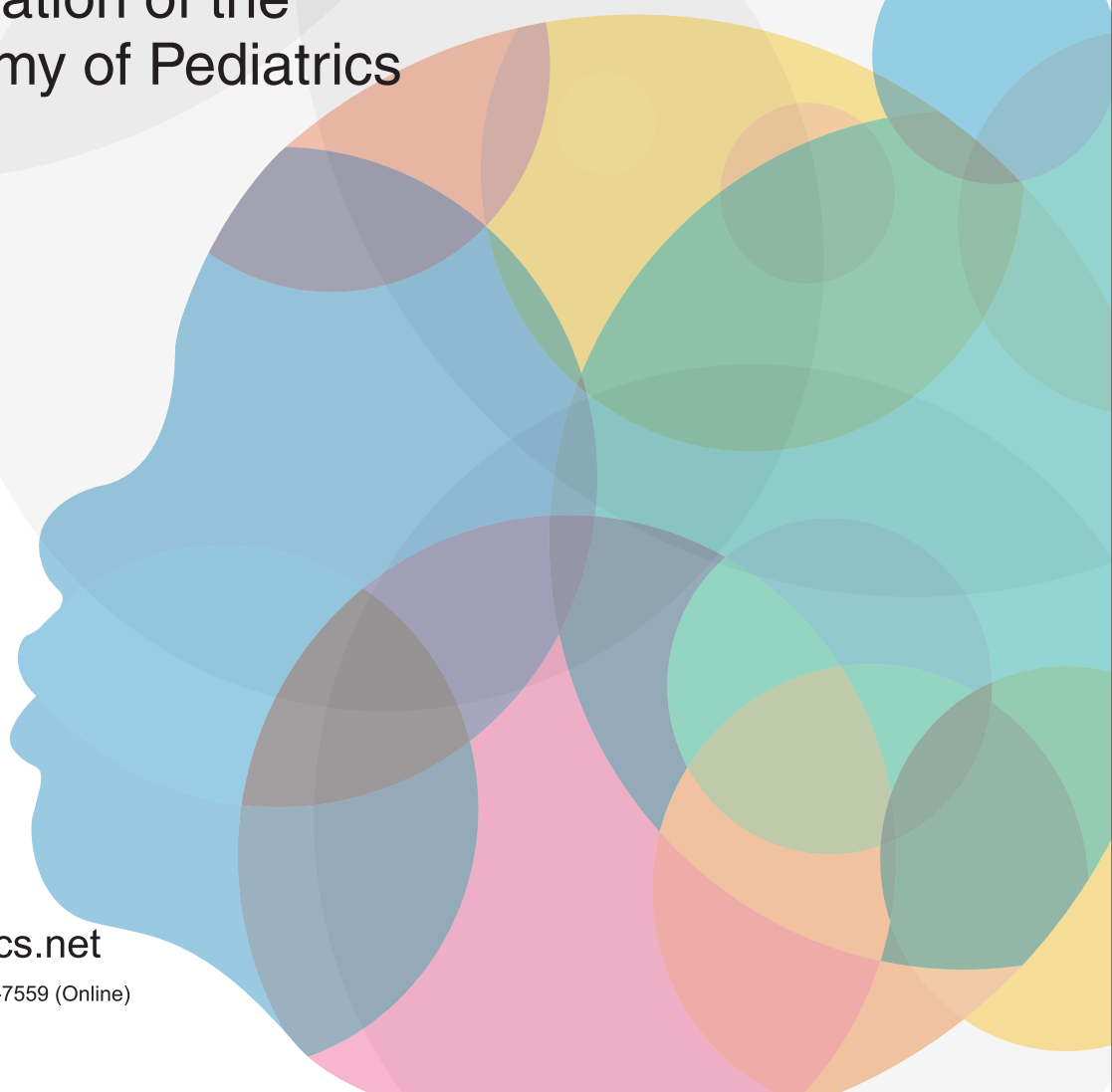

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IAP Guidelines for pediatric skincare state that ideal care of newborn skin comprises of:[1]

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- Protection of barrier function[1]
- Prevention of skin dryness[1]
- Promotion of normal development of the skin[1]

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IAP: Indian Academy of Pediatrics, HMP: Hydrophobically Modified Polymer

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EDITORIAL COMMENTARY

Expanding Dietary Therapy Beyond the Classic Ketogenic Diet: On the Use of the Modified Atkins Diet and Low Glycemic Index Treatment in Pediatric Epilepsy

Robyn Whitney, Rajesh Ramachandran Nair

Comprehensive Epilepsy Program, Division of Neurology, Department of Paediatrics, McMaster University, Hamilton, ON, Canada.

Correspondence to: Rajesh Ramachandran Nair, Comprehensive Epilepsy Program, McMaster Children's Hospital McMaster University, Hamilton, Ontario, Canada. rnair@mcmaster.ca

Approximately one third of children with epilepsy are deemed medically refractory. Non-pharmacological interventions, such as dietary therapies, provide an opportunity to achieve seizure control, in those whose seizures cannot be controlled by anti-seizure medications (ASMs) and are not candidates for epilepsy surgery. A variety of forms of dietary therapy are available, including the classic ketogenic diet (KD), medium-chain triglyceride diet (MCT), the modified Atkins diet (MAD) and the low glycemic index treatment (LGIT) [1]. The KD may be difficult to adhere to for some patients, due to a variety of reasons such as cost, ease of administration, palatability, and side effect profile. Recently, there has been increasing interest in less restrictive forms of dietary therapy, such as the MAD and LGIT with the goal of improving compliance and with the benefit of maintaining seizure control [1-10].

Although the benefits of individual dietary therapies have been documented, studies comparing the effectiveness of more liberal forms of diet therapy (i.e. MAD, LGIT) are lacking [10]. In addition, there is a paucity of studies comparing the effectiveness of the MAD and LGIT to the classic KD [10]. However, recently, an RCT from India compared the efficacy of the MAD, KD and LGIT and demonstrated a similar median reduction in seizure burden between all three diets. Further, neither the MAD or LGIT met noninferiority criteria when compared to the KD [10]. In this issue of *Indian Pediatrics*, Gupta, et al. [11] compare the effectiveness of the MAD and LGIT diet among children with medically refractory epilepsy. The authors assert that although the MAD is more liberal than the classic KD, it may have drawbacks with compliance and that LGIT may be viewed as more palatable with a milder side effect profile, and also provide the benefit of seizure control. The authors compared the effectiveness of the MAD and LGIT with the hypothesis that there would be no difference in seizure control between the two therapies [11].

In this open label RCT, children aged 6 months to14 years with medically refractory epilepsy were randomized to either the MAD or LGIT as add on therapy and were followed for a total of 12 weeks [11]. The primary outcome was the proportion of children achieving seizure freedom at 12 weeks [11]. Secondary outcomes included the proportion of children who achieved >50% and >90% seizure reduction at 12 weeks [11]. Gupta, et al. [11] demonstrate that in the short-term, seizure freedom and 90% seizure reduction rates are similar between the MAD and LGIT. Albeit, few children on either diet obtained seizure freedom, which is not uncommon with dietary therapy [4-8]. Despite this, both therapies provided benefit with a substantial portion of patients achieving 50-90% seizure reduction [11]. At 12 weeks, there was some benefit in achieving 50-90% seizure reduction with LGIT, although this finding should be interpreted with caution given the small case counts and effect size [11]. Larger studies are therefore needed to replicate these findings. When compared to previous studies, the proportion of patients achieving at least a 50% seizure reduction with LGIT was higher at 3 months, while the effectiveness of the MAD was lower [4,6,7-9]. Moreover, the number of patients achieving at least 50% seizure reduction at 1 month with LGIT was lower than previous reports [8]. A drop in efficacy of the MAD between 1 month and 3 months was also reported. The reason for the drop in efficacy of the MAD between 1 and 3 months, is unknown. Compliance was reported to be sustained throughout the study, although could conceivably result in this decrease. The authors claim that the higher response with LGIT at 3 months may be due to the fact that previous studies were conducted in adults and patients with tuberous sclerosis complex. Although, other pediatric cohorts of LGIT have documented lower

rates of patients achieving >50% seizure reduction at 3 months (i.e. 30-50%) [8,9].

The etiologies of epilepsy were not clear in the present study, nor were the spectrum of epilepsy syndromes, which was a drawback of the study (some had Lennox Gastaut syndrome and West syndrome). Neonatal problems were documented, although it is unclear, whether these conditions were responsible for the epilepsy. This information would have been helpful to determine if certain epilepsy syndromes/etiologies respond better to either diet. A shortcoming of the study was the lack of long-term follow up. Longer term studies are needed to determine the comparable efficacy of the diet, and the authors do acknowledge this. Further, the median age of patients in each group was young (i.e. 24-30 months) and the generalizability of the results to older children is unclear. Only five patients across the study were lost to follow-up and no children appeared to withdraw from the study secondary to adverse events, which was a strength of the study. Although longer term studies are needed to determine whether compliance as well as tolerability are sustained, given that these are reported benefits of the diets. The inclusion of children with normal development in future studies would be important. Further, future studies should also address the effects of both diets on cognition and quality of life.

Overall, the authors should be commended for their study. Their work further emphasizes the need to consider the spectrum of dietary therapies when encountering patients with refractory epilepsy. An individualized approach, which considers a myriad of factors when prescribing dietary therapy, is important [10].

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Cerebral Palsy and Rehabilitative Care: The Role of Home-Based Care and Family-Centered Approach

SONIKA AGARWAL,[1] MARK S SCHER,[2] ANN TILTON[3]

[1]Division of Child Neurology, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [2]Rainbow Babies and Children's Hospital/MacDonald Hospital for Women, University Hospitals Cleveland Medical Center, Case Western Reserve University School of Medicine, Cleveland, OH, USA; [3]Section of Child Neurology, Children's Hospital, New Orleans, LA, USA.

Correspondence to: Sonika Agarwal, Assistant Professor of Clinical Neurology and Pediatrics, Division of Child Neurology, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA. agarwals2@chop.edu

Goswami, et al. [1] published an open-label randomized control trial to evaluate the efficacy of adjunctive individualized home-centered activity-based therapy in children with spastic diplegic cerebral palsy (CP) at ages 5-12 years [1]. Children in the intervention arm were prescribed parent-supervised home-centered activity-based therapy in addition to institutional physiotherapy.Main outcome measures compared mean changes in the 6-minute-walk test scores at 6 month from baseline between the two groups. Adjunct home-centered activity-based therapy was found to be safe and feasible. However, no appreciable gains in any of the primary (3.5 m vs 3 m) or secondary outcomes variables were reported.The conceptual design of the trial focused on addition of interventional measures for the care of children with CP, incorporating a family-based model, which would be economically viable and feasible in resource-limited settings. The authors recognized the older ages of children selected for the study as a confounding factor, given more limited adaptive responses later during childhood, to the positive effects of earlier developmental neuroplasticity.

A recent systematic review specifically discussed the feasibility and effectiveness of home-based physiotherapy programs in children with cerebral palsy, and found large variability in the study design, patient selection, intervention characteristics, and outcome measures [2]. Overall compliance to home-based training program implementation was moderate to high, ranging from 56-99% and an improvement in arm-hand performance within group across time was demonstrated [2]. Parent interviews highlight the key role of parent/family coaching and partnership with interdisciplinary care teams for continued motivation and success of home-based rehabilitative care [3].

The concept of 'First 1000 days' stresses the greater potential for positive adaptive effects of developmental neuroplasticity to interventions during critical/sensitive periods of brain development [4]. This concept includes timelier diagnoses for CP-risk children during prenatal trimester-specific, neonatal and early childhood time-periods [5]. Outcome studies of therapeutic interventions for children with CP require examinations of younger children before two years of age. During this time-period, rehabilitative care and therapies in a child's home can leverage the more positive adaptive effects of consistent parental involvement. Establishing high compliance by families to maintain their daily environmental routines, with continued supervision and training with a trained team of health professionals empowers parents to develop a strong partnership for long-standing success.

The COVID-19 pandemic reinforces global social, economic, psychological, educational and healthcare challenges for children with CP and their families. These confounding factors are specific to resource-rich or poor nations, including 'medical deserts' within countries where medical care is potentially more available. Innovative technologies such as improved telemedicine combined with expanded outreach services across all therapy-based developmental domains can potentially improve opportunities for more effective interventions. Ben-Pazi, et al. [6] emphasized more timely and consistent digital healthcare (telemedicine) for children with CP to encourage high levels of participation, with families as stakeholders motivated to the success of therapy programs. Community-based telemedicine kiosks within resource-poor communities would utilize publicly owned computers, smartphones, or software provided by this program for virtual initial and follow-up consultations with multidisciplinary care teams.

Future feasibility studies would assess strategies of video-monitoring of home-based therapies with greater supervision and parental training to achieve more positive results. Feasibility studies require larger sample sizes with younger age groups to assess the beneficial effects of environmental interventions during the first 1000 days. India is the second largest user of mobile phones worldwide, relying on this technology to provide health information and supportive healthcare in rural Indian regions [7]. Future studies that incorporate digital health technology such as telemedicine would expand the interventional tools and access platforms needed to reduce neurologic morbidities.

King, et al. [8] stressed the conceptual framework of family-centered care for service delivery as the best practice for early intervention of pediatric rehabilitative care. Family-centered service recognizes the unique nature of family as the key factor for the continuity of care to address a child's abilities and needs [8]. Strengths and deficiencies of each child-family unit are taken into consideration, to formulate the most effective team, resource, therapy and community support to optimize favorable outcome for a child with CP. This experimental design concept was presented by Goswami, et al. [1] as an important contribution to guide the direction of future research with a family-centered approach.

Outcomes research of rehabilitative care for children with CP is presently limited by the heterogeneity of selected patient populations and study designs, and by paucity of instruments and scales to accurately measure potentially subtle but important functional improvement. Given that the challenges of effective rehabilitative care, community integration, accessibility, resources and outcomes research vary worldwide, countries with large and diverse populations like India could conduct larger trials with greater statistical power analyses. Integration of digital technology platforms, home-based care with a family-centered approach that serve children with CP as well as other neurodevelopmental disorders could be more critically investigated to improve patient-centric and population-based care practices. Global initiatives and partnerships need to support all nations and regions with funding and resources challenges. This will contribute to the worldwide reduction in the burden from brain disorders across the life span [4].

Contributors: SA: reviewed the literature and the paper for the editorial, prepared the manuscript, reviewed edits, and finalized the final version; MS: reviewed the paper and the editorial, edited, and critically reviewed the final version; AT: reviewed the paper and the editorial, edited, and critically reviewed the final version.
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RESEARCH PAPER

Modified Atkins Diet vs Low Glycemic Index Treatment for Drug-Resistant Epilepsy in Children: *An Open Label, Randomized Controlled Trial*

Surbhi Gupta,[1] Surekha Dabla,[2] Jaya Shankar Kaushik[1]

From Departments of [1]Pediatrics and [2]Neurology, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India.

Correspondence to: Dr Surekha Dabla, Senior Professor, Department of Neurology, Pt BD Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana 124 001, India. surekhadabla@yahoo.co.in

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Objective: To compare the efficacy of the modified Atkins diet (mAD) and low glycemic index treatment (LGIT) among children with drug-resistant epilepsy.

Design: Randomized, open labelled, controlled clinical trial. **Setting**: Tertiary care referral center.

Participants: Children aged 6 months to 14 years with drug-resistant epilepsy.

Intervention: mAD (*n*=30) or LGIT (*n*=30) as an add-on to the ongoing antiseizure drugs.

Main outcome measures: Proportion of children who achieved seizure freedom as defined by complete cessation of seizure at 12 weeks as primary outcome measure. Secondary outcome measures were proportion of children who achieved >50% and >90% seizure reduction at 12 weeks, and adverse effects of the two therapies.

Results: Of the 60 recruited children, 3 in the mAD group, and 3 in LGIT group were lost to follow-up. The proportion of children with seizure freedom [16.6% vs 6.6%; relative risk reduction (RRR) (95% CI), 1.5 (-10.9, 0.5); *P*=0.42] and >90% seizure reduction [30% vs 13.3%; RRR, -1.2 (-5.5, 0.2); *P*=0.21] was comparable between the mAD and LGIT group at 12 weeks. The proportion of children with >50% seizure reduction was significantly higher at 12 weeks among those who received LGIT as compared to the mADgroup [73.3% vs 43.3%; RRR (95% CI) 0.4 (0.1-0.6); *P*=0.03] although the effect size was small. The diet was well tolerated with lethargy being the most common adverse effect in children in mAD (53.3%) and LGIT (66.7%) groups.

Conclusion: The present study with limited sample size shows that seizure freedom at 12 weeks was comparable between mAD and LGIT for the treatment of drug-resistant epilepsy.

Keywords: *Dietary therapy, Efficacy, Ketogenic diet.*

Clinical Trial Registration: CTRI/2017/12/010898

Published online: February 25, 2021; ***PII:*** S097475591600297

Ketogenic dietary therapies are useful non-pharmacological therapeutic options in the management of drug resistant epilepsy [1]. Types of dietary therapy for epilepsy include the classical ketogenic diet, modified Atkins diet, low glycemic index treatment, and medium-chain triglyceride diet [2]. The classical ketogenic diet (KD) is high-fat (80%), low protein (15%), and low carbohydrate (5%) diet effective in drug-resistant epilepsy [3-5]. However, KD is a tedious procedure with a need for dietician as it is a stringent diet, requires lot of calculations and weighing of the food items, which makes it challenging to administer in resource-constrained settings. The modified Atkins diet (mAD) is a more liberal, less restrictive, and more palatable type of diet, which yields high compliance and similar effectiveness as compared to classical KD [6-9]. However, compliance, and weighing of food items is a drawback of this diet as well.

The low glycemic index treatment (LGIT) was developed as a liberalized alternative to the KD and mAD for seizure management [10-12]. LGIT diet includes food with a glycemic index less than 50. The LGIT is gaining popularity for treatment for epilepsy due to its effectiveness, mild side effect profile and more palatability. Hence, the present study was designed with a hypothesis that the two groups (LGIT and mAD) would not have a significant difference in seizure control outcome.

Accompanying Commentary: Pages 811-12

METHODS

This open-label, randomized controlled trial was conducted in the Departments of Pediatrics and Neurology of a public sector tertiary-care referral center. The data were collected from February, 2018 to March, 2019. Ethical approval from the institutional ethics

committee was obtained, and a written informed consent was taken from the parents. Children aged six months to 14 years with drug-resistant epilepsy (failure of adequate trials of two tolerated, appropriately chosen anti-seizure drug schedules, whether as monotherapies or in combination to achieve sustained seizure freedom [13]) were enrolled. Children with known or suspected inborn error of metabolism, systemic illness, and severe acute malnutrition were excluded.

Eligible children were randomized to receive either mAD or LGIT along with their ongoing conventional anti-seizure drug. Each child was subjected to clinical history and examination. Seizure type, frequency, age at onset, perinatal details, family history, developmental status and treatment history was recorded. If the child was on any syrup formulation, it was converted to tablets to avoid sugar intake. Adrenocorticotropic hormone (ACTH) and oral steroids (if any) were tapered off two weeks before starting the dietary treatment. A baseline video-electroencephalogram (EEG), whenever possible for a minimum of 1 hour including at least one sleep-wake cycle was performed in all children at the time of enrolment.

Eligible children were randomized using a computer-generated random number list in two groups: mAD and LGIT. Both groups were subjected to baseline one-week observation period, during which parents were asked to maintain a daily seizure log. Anti-seizure medications remained unchanged unless medically indicated, e.g. drug toxicity, or status epilepticus, in which case appropriate changes were made and the same was documented. Children were reviewed as outpatients every two weeks during the trial period. A 24-hour dietary intake chart was reviewed at each visit to compute calorie and carbohydrate intake and to evaluate and reinforce compliance with the prescribed diet. Weight was checked at each visit.

Percentage reduction in seizure frequency as compared to the baseline was assessed as per the parental seizure records. Seizure frequencies were recorded daily by parents. The seizure frequency at 4 weeks and 12 weeks was calculated based on the average of last one week. Based on comparison of these frequencies with baseline one-week frequency, children were classified as seizure freedom, >50% seizure reduction (50-90% reduction) and >90% seizure reduction. Parents were asked to measure urine ketones twice weekly. EEG was repeated at 12 weeks. Tolerability of the diet and any adverse events was evaluated using parental interviews at each visit, specifically asking about vomiting, lethargy, poor appetite, refusal to feed and constipation, in addition to others parental concerns. Liver and renal function tests and fasting lipid profile were performed at baseline and repeated at the end of 4 weeks and 12 weeks.

The sample size was estimated by use of null hypothesis that the two groups would not have a significant difference in seizure control outcome and by defining 30% as the minimum outcome difference of clinical importance. We estimated a sample size of 27 in each group to enable detection of a difference that was significant at 5% with a power of 80%. Assuming 10% drop out, a sample size of 30 was computed in each group.

Statistical analysis: Univariate analysis was done to assess the distribution of data in groups and to choose the appropriate statistical test. The proportion of children with seizure freedom and greater than 50% and 90% seizure reduction were compared between groups using Fisher exact test or Chi-Square test. The effect size was expressed in terms of relative risk reduction (RRR) and 95% confidence interval. For the purpose of RRR calculation, mAD group was considered as intervention and LGIT group was considered as control; achievement of seizure freedom, >90% reduction and >50% reduction were considered as good outcome. An intention to treat analyses was performed. A *P* value of less than 0.05 was considered significant.

RESULTS

Of the 94 eligible participants, finally 30 children

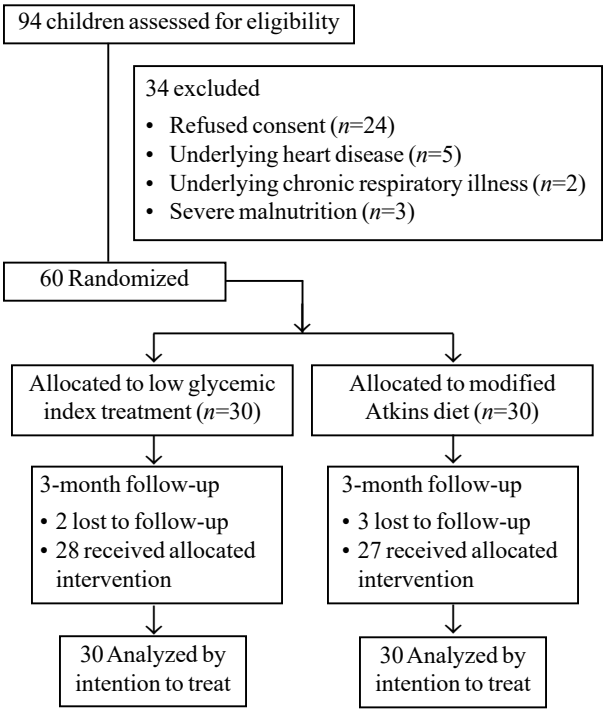

Fig.1 Study flow chart.

received mAD and 30 received LGIT, of which five were lost to follow-up at 12 weeks **(Fig. 1)**. The baseline characteristics were comparable the two groups. (**Table I**), except higher proportion of Microcephaly among children in mAD group (*P*=0.03).

The proportion of children who achieved seizure freedom at 12 weeks was comparable between the two groups (*P*=0.42), and the chance of seizure freedom with mAD was better [RRR (95% CI) = -1.5 (-10.9, 0.5)]. Similarly, the number of children who had more than 90% seizure reduction been also similar between the groups (*P*=0.21), but the proportion of children with 50-90% seizure reduction was significantly higher in LGIT group (*P*=0.03) at 12 weeks (**Table II**). However, the significance of LGIT superiority at 12 weeks needs to be interpreted in context of small effect size [RRR=0.4 (0.1-0.6)].

The diet was well tolerated in both the groups. Lethargy was the most common side effect. Two children in both groups had significant weight loss as compared to baseline and severe respiratory tract infections requiring hospitalization (serious adverse event).

DISCUSSION

The present randomized control study with a limited sample size shows that proportion of children with seizure freedom was comparable between low glycemic index treatment and modified Atkins diet for the treatment of drug-resistant epilepsy. LGIT diet was significantly more effective in achieving >50% reduction in seizure as compared to mAD diet at 12 weeks follow-up; although, with a small effect size (RRR=0.4).

Around 47-56% of patients on LGIT are reported to had achieved more than 50% reduction in seizure frequency [10-12]. In our cohort, 73.3% achieved more than 50% reduction in LGIT group probably because the previous studies were conducted among those with tuberous sclerosis and adults. In a pediatric study from middle east, 78% of children who received LGIT had achieved >50% reduction at the end of 2-month period [14]. The superiority of LGIT at 12 weeks in the present study needs to be interpreted in the context of the small effect size. LGIT in the present study had revealed disappointing results in terms of early seizure control within four weeks, or achievement of seizure freedom or >90% reduction. Most studies have used >50% reduction in seizure frequency as their study outcome instead of seizure cessation [10-12]. The other outcome measure includes percentage change in seizure frequency [15]. Minimal adverse effect profile, good tolerability of diet and efficacy in long term (3 months) are strong points to consider LGIT as an alternative to mAD in achieving seizure reduction [14-15]. However, cessation of seizure in DRE looks unrealistic, and LGIT does not promise to deliver the same.

Table I Baseline Characteristics of Children With Drug Resistant Epilepsy (*N*=60)

	Modified Atkins diet (n=30)	*Low glycemic index treatment (n=30)*
Age (mo)[a]	30 (12,60)	24 (23.5,51)
Male gender	22 (73.3)	25 (83.3)
Age at onset of epilepsy (y)[a]	0 (0, 3)	0.5 (0, 3)
Type of seizure [b]		
Tonic clonic	14 (46.7)	19 (63.3)
Epileptic spasms	13 (43.3)	9 (30)
Myoclonic	0	2 (6.7)
Focal	2 (6.7)	0
Neonatal problems	21 (70)	17 (56.7)
Birth asphyxia	11 (52.4)	15 (88.2)
Meningitis	6 (28.6)	2 (11.8)
Hyperbillirubinemia	1 (4.7)	0
Hypoglycemia	3 (14.2)	0
Microcephaly[c]	16 (53.3)	7 (23.3)
EEG findings		
Multifocal epilepsy	17 (56.7)	24 (80)
Hypsarrhythmia	11 (36.7)	6 (20)
LGS	2 (6.7)	0

EEG: Electroencephalography; LGS: Lennox-Gestaut syndrome; Data in no. (%) except [a]median (IQR); [b]Focal to bilateral tonic clonic one child in modified Atkins diet group; All P>0.05 except [c]P=0.03.

Table II Seizure Freedom and Adverse Effects Among Children With Drug Resistant Epilepsy

Outcome measure	*Modified Atkins diet (n=30)*	*Low glycemic index treatment (n=30)*	*RRR (95% CI)*
Seizure freedom[a]			
12 wk	5 (16.6)	2 (6.6)	-1.5 (-10.9-0.5)
50-90% seizure reduction			
4 wk[b]	19 (63.3)	7 (23.3)	-1.7 (-4.5, -0.3)
12 wk[c]	13 (43.3)	22 (73.3)	0.4 (0.1,0.6)
>90% seizure reduction[a]			
12 wk	9 (30)	4 (13.3)	-1.2 (-5.5, -0.2)
Adverse effects			
Lethargy	16 (53.3)	20 (66.7)	0.2 (-0.2, -0.5)
Constipation	15 (50)	9 (30)	-0.6 (-2.2, -0.1)
Vomiting	5 (16.7)	3 (10)	-0.7 (-5.4, -0.6)
Severe adverse effect	2 (6.7)	2 (6.7)	0 (-5.6, -0.8)

[a]None of participants achieved seizure freedom or >90% seizure reduction at 4 weeks. P<0.01; [c]P=0.03. RRR: Relative risk reduction.

WHAT IS ALREADY KNOWN?

- Modified Atkins diet is an efficacious and less restrictive alternative to ketogenic diet for management of drug-resistant epilepsy.

WHAT THIS STUDY ADDS?

- Proportion of children with seizure freedom was comparable between low glycemic index treatment and modified Atkins diet for the treatment of drug-resistant epilepsy.

Proportion of children with more than 50% reduction dropped from 63.3% at 1-month to 43.3% at 3-month in the present study. In contrast, previous studies have revealed slightly better efficacy (52-68%) [6-9] of mAD at 3-month follow-up. Although reported compliance with diet was satisfactory in the present study, it is difficult to provide an alternative explanation for marginally reduced efficacy of mAD and drop of efficacy from 1-month to 3-month follow-up. Studies have demonstrated efficacy of mAD to a tune of 45.5% at 6-month follow up [16]. We enrolled children with drug-resistant epilepsy and defined the same as failure of two adequate and appropriate anti-seizure medication. There has been lot of variation in the study inclusion in other studies. Many have used terms like medically intractable epilepsy [10], and many have adopted failure of three anti-seizure medication as their inclusion criteria [14]. Most children in present study were in the age group of 30 months in both the study groups. This means that we had included younger children with drug-resistant epilepsy. Many of them are either West syndrome or those progressing to Lennox Gestaut syndrome as evident from the type of seizure and their EEG findings. The adverse effect profile and frequency was similar to previous report [7-9].

A recent Indian study [15] compared mAD, LGIT and KD in a three-armed controlled trial. The study was conducted among 152 participants aged between 1-15 years with intractable epilepsy. They did not find any significant difference in seizure reduction at 24 weeks in the three groups. Nonetheless, patients on LGIT demonstrated >50% seizure reduction with a better safety profile [15]. Authors had considered percent seizure reduction as outcome measure limiting the comparability of findings to present study, but both have demonstrated comparable efficacy of mAD and LGIT.

Standardized definitions of drug-resistant epilepsy, and outcome parameters including seizure freedom, and more than 50% reduction in seizure were adopted to allow comparability of the results. Limitations of the study include small sample size, relatively short follow up period till three months, and lack of formal developmental and cognitive assessment. In addition, serial EEGs were not performed in the study to document improvement in the burden of epileptiform discharges. We did not find a statistically significant difference between mAD and LGIT in seizure freedom among children with drug resistant epilepsy. Numerical superiority of LGIT over mAD at 12 weeks for achieving >50% seizure reduction needs to be interpreted in the context of limited sample size, short follow up period and small effect size. Further multicenter randomized controlled trials may be considered with larger sample size and longer follow-up period.

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Contributors: SD, JSK: conceptualized the idea; SG, JSK: drafted the manuscript; SD, JSK: provided intellectual inputs. All the authors approved the final version of the manuscript.
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NOTES AND NEWS

RESEARCH PAPER

Efficacy of Daily Supplementation of Milk Fortified With Vitamin D2 for Three Months in Healthy School Children: *A Randomized Placebo Controlled Trial*

RAMAN KUMAR MARWAHA,[1] AASHIMA DABAS,[2] SEEMA PURI,[3] MANI KALAIVANI,[5] VINEET DABAS,[4] SANGEETA YADAV,[2] ARJUN DANG,[6] R PULLAKHANDAM,[7] SUSHIL GUPTA,[8] ARCHANA NARANG[9]

From [1]Society for Endocrine Health Care of Elderly, Adolescents and Children, New Delhi; Departments of [2]Pediatrics and [4]Orthopedics, Maulana Azad Medical College and Lok Nayak Hospital, New Delhi; [3]Food and Nutrition, Institute of Home Economics, University of Delhi; [5]Biostatistics, All India Institute of Medical Sciences, New Delhi; [6]Dr Dangs Lab, New Delhi; [7]Biochemistry Division, Indian Council of Medical Research, National Institute of Nutrition, Hyderabad; [8]Endocrinology, Sanjay Gandhi Post Graduate Institute, Lucknow; [9]Homeopathy, BR Sur Homeopathic college, New Delhi.

Correspondence to: Major General RK Marwaha, President, Society for Endocrine Health Care of Elderly, Adolescents and Children (SEHEAC), Flat no. 17, Gautam Apartments, Gautam Nagar, New Delhi 110 049. marwaha_ramank@hotmail.com

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Objective: To evaluate the efficacy of daily supplementation of 200 mL milk fortified with 240 IU of vitamin D2 (ergocalciferol).

Design: Double-blind randomized controlled trial.

Settings: School-based study in Delhi between October and December, 2019.

Participants: 235 healthy children aged 10-14 years.

Intervention: Daily supplementation of 200 mL milk fortified with 240 IU of ergocalciferol in intervention group (*n*=119) and 200 mL of plain milk in control group (*n* =116) for 3 months.

Outcome Measures: Change in serum 25 hydroxy vitamin D (25(OH)D), parathyroid hormone (PTH), bone formation and resorption markers, and urinary calcium creatinine ratio (U-Ca/CrR).

Results: The mean (SD) baseline serum 25(OH) D level in control and fortification groups was 11.9 (3.8) and 11.4 (3.6) ng/mL (*P*=0.23), respectively. The serum 25(OH)D levels did not increase post-intervention with the dose used for fortification, but were significantly higher in intervention group as compared to control group [10.8 (3.4) *vs* 6.7 (3.5) ng/mL; *P*<0.001]. A higher proportion of secondary hyperparathyroidism was observed post-intervention in control (39%) than in intervention group (13.3%); *P*<0.001. Serum carboxy-terminal telopeptide levels were similar in both groups but the serum procollagen type1 N-terminal propeptide levels were higher in the control than intervention group (*P*<0.007), following supplementation.

Conclusion: Supplementation of milk fortified with approximately 240 IU vitamin D2 for three months did not achieve sufficient serum 25(OH)D levels in Indian children with vitamin D deficiency during winter.

Keywords: *Bone health, Deficiency, Food fortification, Secondary hyperparathyroidism.*

Trial Registration: CTRI/2019/09/021073 ***Published online:*** *July 23, 2021;* ***PII****: S097475591600353*

Optimum calcium and vitamin D intake during childhood and adolescence helps achieve peak bone mass which acts as a safeguard against osteoporotic fractures later [1]. Consequences on overall health require a population based approach for prevention of vitamin D deficiency like food fortification [2], as therapeutic supplementation throughout life is not practical. A recent meta-analysis of the effects of vitamin D fortification showed good efficacy of fortified dairy products to increase vitamin D levels [2]. At present, systematic voluntary or mandatory fortification of milk and milk products is being undertaken only in few countries like Finland, Norway, Sweden, Canada and USA [3].

In view of vitamin D deficiency being a serious public health problem, Food Safety and Standards Authority of India (FSSAI) issued instructions for voluntary fortification of milk and oil with vitamin A and D2 to provide approximately one-third (200-300 IU/L) of the recommended daily dietary allowance [4]. However, the adequacy and efficacy of these doses of vitamin D2 need to be assessed in children.

We, therefore, undertook a double-blind randomized controlled trial in healthy school children to evaluate the efficacy of daily supplementation of 200 mL fortified milk (approximately 240 IU of vitamin D2) on the serum vitamin D levels. The secondary objectives included effect of this intervention on serum levels of calcium, parathyroid hormone, alkaline phosphatase and bone markers.

METHODS

This randomized double-blind parallel placebo controlled study was conducted from October 1, 2019 (autumn) to December 30, 2019 (winter). The study protocol was approved by the Institutional Ethics Committee and the trial was registered prospectively at the clinical trial registry of India. Apparently healthy school children, aged 10-14 years, who consented were recruited from two fee- paying schools in Delhi following approval from the school management. Written consent from parents of eligible children and written assent from children was solicited. Children with clinical features of rickets, history of any chronic systemic illness, renal stones, history of milk allergy, intake of vitamin D in last six months in doses exceeding 600 IU/day or if consuming drugs like steroids, anti-tubercular/anti-epileptic drugs were excluded.

Block randomization with varying block size of 2 or 4 was used within each school to allocate the children into fortified and control arm, respectively using the computer-generated randomization list. Allocation concealment was done using opaque envelopes which were prepared by a person other than investigators. Participants were assigned to one of the two groups as per the code by the respective class teachers. The participants and care providers were blinded to the randomization. The teachers knew the codes as group A and B but did not know whether milk in the respective group was fortified or not.

Two sets of strawberry flavored ultra-heat treated toned milk in sterilized and homogenized 200 mL tetra packs were provided in the month of September, 2019 for the study by Mother Dairy Fruit and Vegetable Pvt. Ltd, a licensed and registered firm by FSSAI. First set was provided with 1200 IU of vitamin D2 per litre of milk (approximately 240 IU of vitamin D2 in each tetra pack) whereas other set was without fortification. The tetra packs were similar in appearance, odor and taste with labels known only to the manufacturers. The shelf life of tetra packs containing fortified and unfortified milk was 120 days at normal ambient temperatures, and were required to be kept in cool, dry and pest free ambience. Samples of milk were collected randomly at the time of production and after completion of the study for stability and estimated by LC-MS method (AOAC 2016.05).

Intervention group received fortified milk whereas control group received unfortified milk for 3 months. Daily supplementation for 6 days a week was carried out at schools under the supervision of teachers and investigating staff. Tetra packs were provided to the parents every month for Sundays and planned holidays. Parents were advised to collect the tetra packes from the school for unplanned holidays. A Whatsapp group was created by each teacher with parents and chief co-ordinator for day-to-day communication, monitoring and ensuring compliance during planned and unplanned holidays.

Brief history and clinical examination including anthropometry were performed. Heights were measured to nearest 0.1 centimeter with portable Holtain stadiometer (Holtain Inc.) with the child positioned in the Frankfurt plane. Weights were measured to nearest 0.1 kg with the digital weighing machine. The weighing scale and stadiometer were calibrated using the standard weight and height, respectively. Children were advised against any change in lifestyle during the study period. Two day (one working day and one holiday) 24-hour dietary recall method and food frequency questionnaire were used to gather data on dietary pattern and nutrient intake at baseline. The consumption of calcium and vitamin D rich foods, and amount and type of milk and oil consumed (fortified or not) were also recorded. The household measures used for data collection were standardized in the laboratory to obtain the actual weight of raw foods going into each preparation. Subsequently the data on food consumption in household measures were converted into raw ingredients. The nutrient intakes were then obtained by using the Diet Cal software [5]. No dietary counselling was provided during the study period.

Blood samples were collected in the fasting state between 8-9 AM at baseline and after three months (end-line). They were centrifuged and serum separated into aliquots at the study site and transported in dry ice to the laboratory. Serum calcium, phosphate, alkaline phosphatase (ALP), 25-hydroxy vitamin D [25(OH)D], parathyroid hormone (PTH) and spot urinary calcium creatinine ratio (U-Ca/CrR) were estimated the next day. Two aliquots were frozen -70^{0}C for estimation of bone markers. Serum 25(OH)D was estimated by chemiluminescence (DiaSorin Inc.) and PTH by electro-chemiluminescence method (Roche Diagnostics). Intra and inter-assay coefficient of variation was 3.5% and 5% for serum 25(OH)D and 2.4% and 3.6% for PTH. Serum 25(OH)D level of <20 ng/mL was defined as insufficiency and <12 ng/mL as vitamin D deficiency (VDD) [6]. Secondary hyperparathyroidism was defined as PTH >65 pg/mL. Serum calcium, phosphate and ALP were estimated by auto-analyzer Cobas C-501 (Roche Diagnostics). Serum bone markers viz., C-terminal crosslinked telopeptide of type 1 collagen (CTx-1) and propeptide of N-terminal of type 1 collagen (PINP) were measured by Elecsys 2010 based on principle of electrochemimmunoassay. U-Ca/CrR was estimated using Cobas C-3 (Roche Diagnostics) with a level >0.21 suggestive of hypercalciuria [7].

The sample size was calculated assuming baseline mean (SD) of serum 25(OH)D of 11.7 (5.36) ng/mL in both groups. Expecting no change in control group and an increase of 3 ng/mL in serum 25(OH)D levels after 3 months of supplementation with combined SD of 3 ng/mL [8], the estimated sample size was 68 per group. The assumed alpha error and power were 5% and 90%, respectively. The total number of subjects required for the study with 20% drop out rate was 90 per group.

Statistical analysis: Continuous variables were summarized as mean (SD) (normally distributed) or median (Q1,Q3) (non-normally distributed). Categorical variables were presented as proportions. Baseline characteristics were compared between the groups using unpaired *t*-test or Chi-square test as appropriate. Intention-to-treat (ITT) analysis was done for effect on serum 25(OH)D and serum PTH levels and per protocol (PP) analysis was carried out for other biochemical variables. All the outcomes were compared between the groups using unpaired *t*-test/ Wilcoxon rank sum test and within the group (from baseline to 3-months) using paired *t*-test/Wilcoxon signed rank test. The results were presented as difference and 95% confidence interval. *P* value less than 0.05 was considered statistically significant.

RESULTS

The flow of the study participants is shown in **Fig. 1**. **Table I** shows the baseline demographic characteristics. No child from either of the group reported any discomfort or gastrointestinal side-effects after consuming milk. Samples of milk were collected randomly at the time of production and on completion of the study for stability, which showed serum 25(OH)D levels of 236 IU/200 mL and 221 IU/200 mL, respectively indicating <10% variation.

The baseline serum 25(OH)D levels were similar in the control and fortification groups (**Table I**), with significantly higher end-line levels in the intervention than in the control group as shown in **Table II**. The number of subjects with vitamin D deficiency and insufficiency at baseline were 70 (60%) and 46 (40%) in the control group and 65 (54.6%) and 54 (45.4%) in the intervention group, respectively (*P*=0.37). Vitamin D deficiency, insufficiency and sufficiency after three months were noted in 101 (97%), 3 (3%), 0 in control and 74 (70%), 31 (29%), 1 (1%) in the intervention group, respectively (*P*<0.001). The median (Q1,Q3) percentage rise in serum 25(OH) D was significantly higher among subjects with serum 25 (OH)D levels <12 ng/mL [*n*=58, 10.64 (–48.71, –5.66)] than those with levels >12 ng/mL [*n*=48, -20.41 (–34.36, –7.67)] in the intervention group (*P*<0.001). There was poor

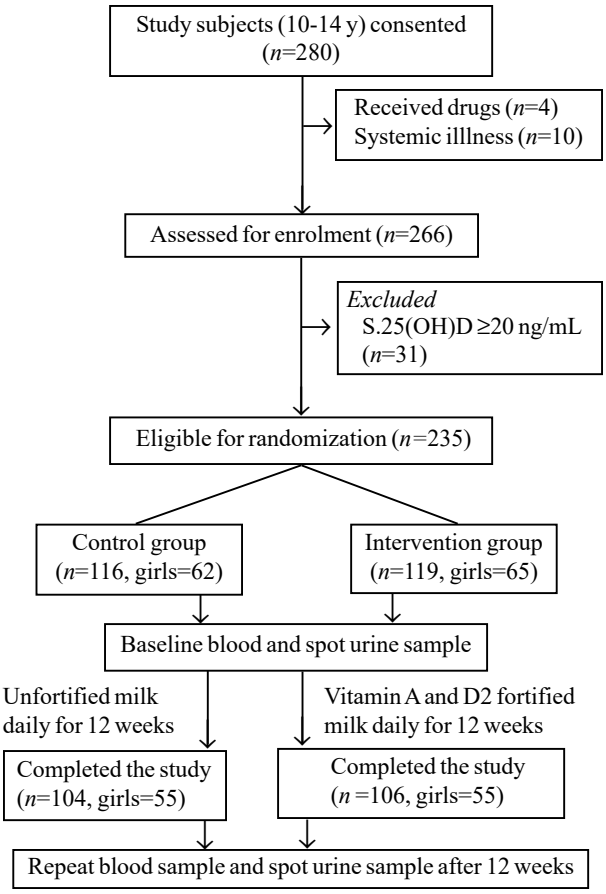

Fig. 1 CONSORT flow diagram for the study.

Table I Baseline Characteristics of the Study Population

Parameter	*Unfortified group (n=119)*	*Fortified group (n=116)*
Age, y	10.4 (0.8)	10.3 (0.5)
Body mass index, kg/m^2	16.8 (3.2)	16.7 (3.3)
Calcium, mg/dL	9.97 (0.3)	10.01 (0.3)
Phosphorus, mg/dL	5.02 (0.49)	5.01 (0.46)
ALP, IU/mL	258.83 (72.3)	253.49 (62.3)
25(OH)D, ng/mL	11.97 (3.79)	11.42 (3.63)
PTH, pg/mL[a]	45.8 (35.5, 60.0)	52.3 (35.3, 61.6)
CTX, pg/mL	1705.7 (483.2)	1685.4 (400.7)
PINP, ug/dL	655.3 (203.4)	679.9 (211.4)
Urine Ca: Cr ratio[a]	0.04 (0.01, 0.1)	0.05 (0.03, 0.09)

Data expressed as mean (SD) or [a]median (IQR); ALP-alkaline phosphatase, 25(OH)D- 25 hydroxy vitamin D, PTH- parathyroid hormone, CTX- C-terminal crosslinked telopeptide of type 1 collagen, PINP- propeptide of N-terminal of type 1 collagen, Ca:Cr- calcium: creatinine P>0.05 for all variables

Table II Biochemical Parameters After Intervention in Unfortified and Fortified Groups

Parameter	*Unfortified group (n=104)*	*Fortified group (n=106)*	*P value*
Calcium, mg/dL	9.88 (0.3)[c]	9.98 (0.3)	0.01
Phosphorus, mg/dL	4.97 (0.45)	4.96 (0.42)	0.80
ALP, IU/mL	273.24 (75.5)[c]	251.32 (57.7)	0.02
25 (OH)D,ng/mL[b]	6.73 (3.5)[a]	10.81 (3.5)	<0.001
PTH, pg/mL[b,a]	52.6 (38.8,75.2)[c]	46.5 (32.2,58.8)[c]	0.007
CTX, pg/mL	1023.22 (317.7)[c]	982.42 (304)[c]	0.35
PINP, ug/dL	736.33 (201.4)[c]	657.32 (216.5)	0.007
Urine Ca:Cr ratio[a]	0.04 (0.02,0.1)	0.04 (0.02,0.08)	0.86

All parameters are serum unless stated. [c]P<0.05 for intragroup comparison from baseline to post-intervention value. Data expressed as mean (SD) or [a]median (Q1, Q3). [b]n=116 and 119 in unfortified and fortified group, respectively (intention to treat analysis). ALP-alkaline phosphatase, 25(OH)D-25 hydroxy vitamin D, PTH-parathyroid hormone, CTX-C-terminal crosslinked telopeptide of type 1 collagen, PINP-propeptide of N-terminal of type 1 collagen, Ca:Cr-calcium: creatinine.

correlation between serum 25(OH)D and gender or BMI (P>0.05).

The prevalence of secondary hyperthyroidism increased from 18.1% to 39% (P<0.001) in the control group and decreased from 22.7% to 13.3% (P<0.001) in the intervention group, with significant inter-group difference (P<0.001). An inverse correlation was observed between serum 25(OH)D and PTH both at baseline in control (r=-0.23, P=0.01) and intervention groups (r=-0.29, P=0.001) and following supplementations in both groups (r= -0.23, P=0.01); (r= -0.29, P=0.001), respectively. No subject in either group developed hypercalciuria following supplementation.

The overall energy intakes were less (70.6%) than the RDA, with adequate protein intakes in the study group. The mean (SD) intake of calcium in intervention and control groups was 655.3 (224.1) and 617 (240.3) mg/day with dairy calcium contributing an intake of 57.4% and 58.4% in both groups. The vitamin D intake through fortified foods ranged from 17-97 IU/day in both the groups.

DISCUSSION

The present study demonstrated higher serum 25(OH)D levels following consumption of vitamin D2 fortified milk (240 IU/200 mL) for a period of 3 months as against consumption of unfortified milk, with significant decrease in secondary hyperparathyroidism.

Several studies in children have similarly observed higher serum 25(OH)D levels after consumption of vitamin D fortified milk than unfortified or no milk at all [2,3, 9]. Higher serum 25(OH)D levels were seen in children who consumed at least 450 mL/day of vitamin D fortified milk than those who drank < 300 mL/day after adjusting for age and sex [9].

The serum 25(OH)D levels did not increase above the baseline in the fortified group with the current levels of fortification; however, the decline was lesser than the unfortified group. This suggested that 240 IU of additional vitamin D2 through fortified milk for 3 months was not adequate during harsh winter months with high atmospheric pollution recorded in Delhi during the study period, when the availability of UVB rays was low [10,11]. Inadequate synthesis of vitamin D3 during winter months in children has been similarly reported earlier [12].

Vitamin D3 has higher efficacy than D2 in raising serum 25(OH)D levels [13-15]. However, whether fortification with D3 instead of D2 would have resulted in higher serum 25(OH)D levels is debatable and outside the purview of the current study. A rise in serum 25(OH)D levels was reported earlier with almost similar dose of 200 IU of D3 supplementation for 12 months [16], unlike no change observed in another study after 11 weeks of supplementation in healthy adolescents with baseline vitamin D sufficiency [17]. These contrasting observations could be because of varying baseline 25(OH)D levels, duration of intervention, vitamin D preparations and modes of supplementation. The rise in serum 25(OH)D was significantly higher in those with lower baseline serum 25(OH)D levels in the present study, as also reported earlier [8,16,18,19].

A significant reduction in serum PTH levels and secondary hyperparathyroidism in the intervention group suggests the role of even a small amount of vitamin D administered with calcium in reducing negative consequences on bone mineral metabolism. Similarly, inverse correlation between serum 25(OH)D and PTH levels have been documented earlier [16,18,20].

Earlier studies have not reported a significant effect on either bone formation or resorption markers [21,22]; however, a decrease in resorption markers like serum CTx and urinary deoxypyridiniline is reported following vitamin D supplementation [23,24]. In the present study, a significant decline in serum CTx levels in both the groups with no appreciable inter group differences, could be due to the additional calcium provided through milk. Similar observation was also reported in healthy premenopausal women following calcium supplementation [25]. No significant change in serum PINP levels following supplementation in the intervention

WHAT IS ALREADY KNOWN?

- Fortification of milk with vitamin D is an effective strategy for preventing vitamin D deficiency.

WHAT THIS STUDY ADDS?

- Consumption of 200 mL of fortified milk (containing 240 IU vitamin D2) for 12 weeks is inadequate in preventing vitamin D deficiency in school children from Delhi during winter season.

group concurs with earlier studies where bone specific ALP, serum osteocalcin and serum PINP remained the same [21,22,24]. These variations in bone markers following vitamin D supplementation may be due to differences in age of subjects, doses of vitamin D, duration of supplementation and baseline serum 25(OH)D etc. Spot U-Ca/CrR measured revealed no significant difference in the median U-Ca/Cr ratios at baseline and follow-up.

The main strength of the study was the evaluation of the efficacy of supplementing vitamin D2 fortified milk in children. The study; however, had limitations like absence of data on environmental pollution and sunlight exposure, lack of comparison with D3 fortified milk, and inability to carry out 24-hour urinary calcium excretion for definite diagnosis of hypercalciuria.

To conclude, supplementation of milk fortified with 240 IU Vitamin D2 for 12 weeks is not adequate to achieve vitamin D sufficiency, though it does reduce the decline in serum 25(OH)D levels during winter in prepubertal Indian children with vitamin D insufficiency.

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Ethics clearance: Institutional Ethics Committee, Maulana Azad Medical College; No. F.1/MAMC/IEC/(68/03/2019)/No 153, dated 09 August, 2019.
Contributors: RKM: conceptualizing and designing the study, clinical evaluation and preparation of the manuscript; AD,VD: clinical evaluation, analysis of data and preparation of manuscript; SY: designing the study and preparation of manuscript; SP: designing of dietary proforma, analysis of dietary data, manuscript preparation; AD: (Arjun Dang) Biochemical and hormonal evaluation, manuscript review; KV: sample size calculation and statistical analysis, manuscript preparation; PR: conceptualization and preparation of manuscript; SG: analysis of bone markers, manuscript review; AN: sample and data collection and data entry, manuscript review. All authors have read and approved the final manuscript.
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RESEARCH PAPER

Add-on Home-Centered Activity-Based Therapy vs Conventional Physiotherapy in Improving Walking Ability at 6-Months in Children With Diplegic Cerebral Palsy: *A Randomized Controlled Trial*

Jyotindra Narayan Goswami, Naveen Sankhyan, Pratibha Singhi

From Pediatric Neurology and Neurodevelopment Unit, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh;

Correspondence to: Prof Pratibha Singhi, Director, Department of Pediatrics Neurology and Neurodevelopment, Medanta, The Medicity, Gurgaon, Haryana. doctorpratibhasinghi@gmail.com

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Background: Institutional physiotherapy as a standard of care for management of cerebral palsy (CP) has certain shortcomings, especially in resource-constrained settings. This is a proof-of-concept trial to evaluate the efficacy of individualized home-centered activity-based therapy in children with spastic diplegic CP.

Design: Randomized controlled trial (open-label).

Settings: Tertiary-care hospital with pediatric neurology services (July, 2014 to July, 2016).

Participants: Consecutive sample of 59 children (5-12 y) with spastic diplegic CP (Gross Motor Function Classification System scores II-III) without fixed lower-limb contractures, illnesses impeding physiotherapy or history of recent botulinum toxin injection/surgery were recruited.

Procedure: Children were randomized to Intervention or Control arms. Their 6-minute-walk Test (6MWT) scoring and clinical examination were performed at baseline, 3 and 6 months. Children in Intervention arm (*n*=30) were prescribed parent-supervised home-centered activity-based therapy (walking, standing, squatting, climbing upstairs/downstairs, kicking a ball, dancing, riding a tricycle/bicycle) in addition to their institutional physiotherapy. Children in Control arm (*n*=29) were prescribed ongoing institutional physiotherapy alone. Logbooks, home videos and telephonic follow-ups were used to ensure compliance.

Main outcome measures: Comparison of the mean change in 6MWT scores at 6 months (from baseline) between the two groups.

Results: Median (IQR) change in 6MWT scores at 6 months (from baseline) in the Intervention and Control arms were 3.5 (-5.3, 9) m and 3 (-7.8, 6.3) m

Conclusions: Adjunct home-centered activity-based therapy was safe and feasible, but did not result in appreciable gains over 6 months.

Keywords: *Neurorehabilitation, Play therapy, Brain injury, Perinatal brain injury.*

Clinical Trial Registration No. **:** NCT02412007 ***Published online:*** May 28, 2021; ***PII***: S097475591600332

Physical therapy is the cornerstone in the management of cerebral palsy (CP). Various targets of physical therapy include spasticity-reduction, functional mobility optimization and prevention of secondary musculoskeletal complications [1]. Numerous schools of physical therapy are based on different principles, and have their own pros and cons [2]. Existence of a multitude of physical therapy techniques indicates that a singularly effective regime for children with CP is yet to be formulated. Apart from physical therapy, holistic rehabilitative practices aim to improve affected individuals' functional capabilities so that they may gainfully participate in day-to-day activities [3].

Activity-based therapy is generating interest as an alternative mode of CP rehabilitation [4]. The philosophy behind this modality is functional improvement through repetitive performance of activity-based training, lifestyle modifications, and mobility-enhancing devices rather than traditional passive physiotherapy protocols. Activity-based rehabilitative regimes that have been scientifically evaluated and found effective include Constraint-Induced Movement Therapy (CIMT) (for hemiparetic CP rehabilitation), treadmill therapy (for gait disorders) and Robotic arm technique. For conventional physical therapy, the deficiency of physiotherapists, equipment and rehabilitation centers are limiting factors in resource-limited settings [6]. A simple home-based regime empowers parents and truncates expenses of institutional care [7]. The role of home-centered, activity-based therapy in children with diplegic CP has not been evaluated till date. Our study was designed as a proof-of-concept trial to look into the efficacy of home-centered

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activity-based therapy in children with spastic diplegic CP in resource-limited settings.

METHODS

This randomized controlled trial (RCT) was conducted in a tertiary-level pediatric teaching hospital and its associated rehabilitation centre from July, 2014 to July, 2016 after obtaining approval from the institutional ethics committee.

Children between 5 and 12 years of age, clinically diagnosed with spastic diplegic CP with Gross Motor Function Classification System (GMFCS) Score II/ III were eligible. Spastic diplegic CP was defined as 'CP with predominant bilateral lower limb involvement with hyperreflexia, spasticity and relative non-involvement of upper limbs'. Enrolled children required a minimum visual acuity of 6/60 and the ability to follow single-step commands. They were enrolled if their parents/primary caregivers were willing and capable of following instructions and maintaining an activity log. Informed consent from the parent(s)/primary caregiver(s) and assent (as and when applicable, from a child) were obtained before enrolment. Children with fixed lower-limb contractures or deformities affecting stance and gait, chronic systemic/acute illnesses interfering with physiotherapy and children who received botulinum toxin injection or underwent corrective orthopedic surgery up to one year prior to the day of screening were excluded.

A detailed general and systemic examination of every child was performed and findings recorded on proforma. Each child was scored for 6-minute-walk-test (6MWT) (in meters), 10-metre-fast-walk-test (10MFWT)(in seconds), modified Ashworth scale (MAS), modified Tardieu scale (MTS), Gross Motor Function Classification System (GMFCS), Gross Motor Function Measure-88 (GMFM-88) (D & E) and Cerebral Palsy Quality of Life (CP-QoL) (Primary-caregiver).

Randomization was done by another person who was otherwise not involved in any other aspect of the trial. Block randomization of varying sizes was prepared with an open access randomization software (*www.randomizer.org*). Allocation concealment was achieved using sealed opaque envelopes. Envelopes were kept in custody of a person not involved in the study.

Scoring for 6MWT: Test arena comprised of a marked, flat, non-slippery, rectangular cemented area with a perimeter of 34 meters. Children were made to walk along the outer boundary of the area after an initial demonstration. If at any point, the child had difficulty walking (due to any reason) or did not want to walk, he or she could stop. In that case, the test would be postponed to a later date. Practice trial immediately preceding test was avoided to reduce fatigue [8]. The parents/primary caregivers were instructed to encourage the child throughout the process. In case a child needed one-hand support, the parent/primary caregiver walked alongside the child holding his/her hand. Distance covered in 6 minutes was recorded in meters (up to nearest centimeter). The test was videographed for future reference.

Scoring for 10MFWT: Test area comprised of a cemented, flat, non-slippery, rectangular floor. Start and finish lines were marked with parallel white lines 10m apart. An explanation and demonstration preceded the test. To start, the child was made to stand with toes touching the start-line. On being told to start, the child had to start walking. The stop command was given after the child had walked 5m past the finish line so that he/she may not decelerate until after reaching the 10 m mark [9]. Time to walk 10m was recorded with a stopwatch with the least count of 0.01 seconds. The test was video graphed for future reference.

Eight activities were recommended in the 'Intervention Arm,' viz., walking on plain surface, standing from squatting position and squatting from standing position on level floor, climbing up and down a flight of stairs, kicking a football while standing, dancing on level floor, riding a tricycle/bicycle (with additional support wheels) depending on child's age and functional capability. Every child was expected to perform at least seven out of eight activities (exception being cycling) to the best of his/her ability. Parents/primary caregivers were given a brief overview of the interventions in the language they understood. They were taught how to keep the activities interesting by incorporating them within play activities. Activities were tailored according to the age and functional capacity of the child and modified periodically to avoid monotony. Strict compliance was emphasized upon. At the outset, videographic demonstrations of the activities were displayed to the parents. Videos were prepared in the same centre previously and approved by all the researchers involved in the study. The parents/primary caregivers were asked to make their children perform the activities under the researcher's supervision. Doubts were clarified and modifications suggested. A logbook was issued to each parent/primary caregiver with simple instructions written in English and Hindi and sketches depicting the activities. The logbook had an earmarked space for every day ,in which the parent/primary caregiver was instructed to record whether the pre-assigned activity was performed as advised or not. There was a 'remarks' column for noting any deviations.The logbook was

designed to serve as the main mechanism to ensure compliance. At the completion of the study, percentage compliance was calculated from the entries in the logbooks. In addition, home videos taken by parents acted as a reinforcement of compliance. The activities were designed to be repeated three times per session, with three sessions per day for five days per week. In case of any acute illness, pain, injury, compelling domestic issues or in the case of a child strongly resenting therapy, a break could be allowed but the parent/primary caregiver was supposed to record it in the logbook. These activities were in addition to activities that were already being performed as a part of an ongoing physiotherapy program. Parents/primary caregivers of children in the Control arm were advised to continue ongoing physiotherapy i.e. certain sets of active and passive exercises that were administered by certified physiotherapists after individualized assessment as per guidelines. Three physiotherapists offered conventional physiotherapy in the study centre. These manoeuvres were tailored to the needs of a child with periodic reassessment and modification as per the disability, tolerability of intervention and clinical response (spasticity, stability of gait, etc). Techniques of conventional physiotherapy are described in **Web Box I**.

Besides filling the logbook, the parents/primary caregivers also made intervention home videos periodically, which were perused by one investigator at follow-up. Telephonic follow-up was done at 2 weeks of enrolment. The telephone number of the primary investigator was shared with parents/primary caregivers for addressing queries. In addition, parents who expressed difficulty in understanding the procedures were contacted telephonically to reinforce the prescribed procedures. Follow-up visits were planned at 3 months (+ 1 week), 6 months and (+ 2 weeks) after enrolment. Doses of drugs (such as baclofen or antiepileptics) were not modified for study purposes. If any child developed seizures during the course of study, he/she was managed as per standard protocol.

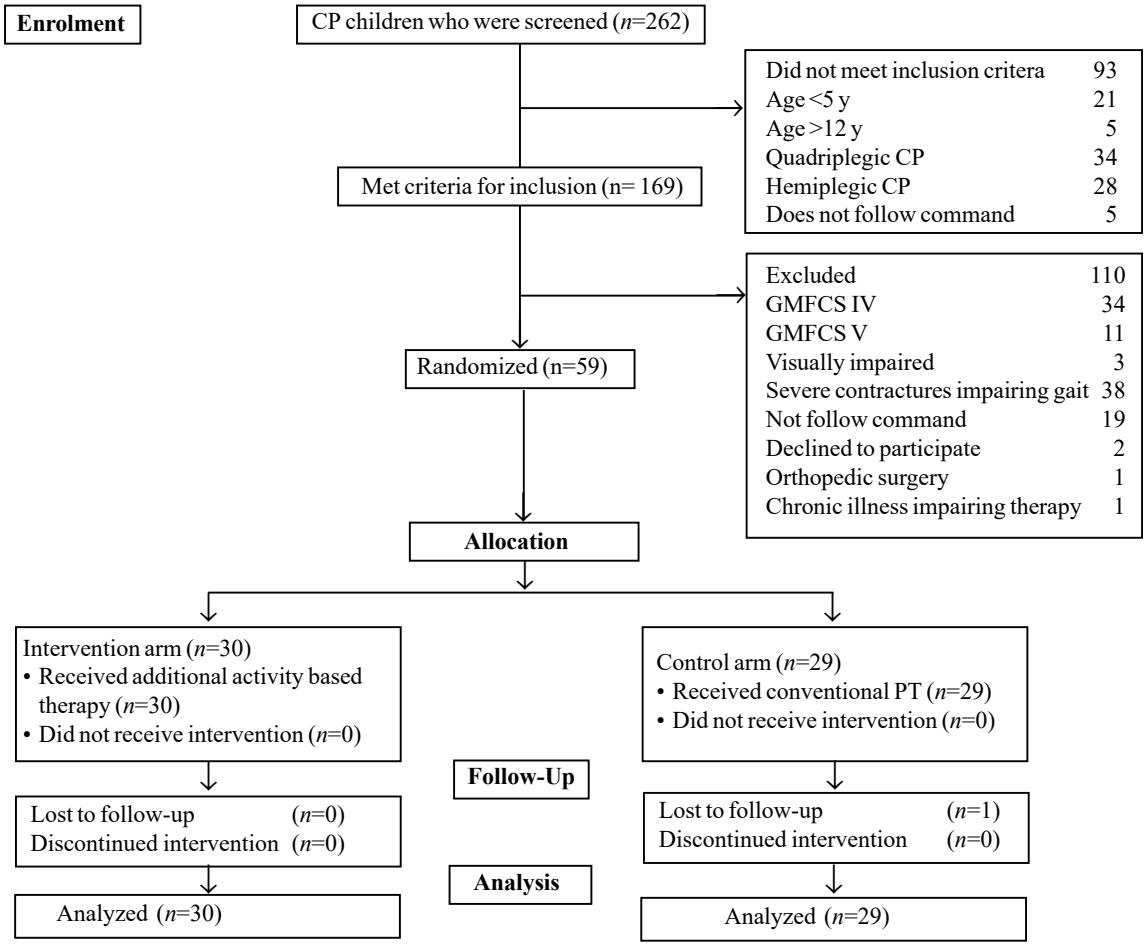

Fig. 1 CONSORT flow diagram for the study.

The primary study outcome was change in 6 MWT score at 6 months. The secondary outcomes included change in 10MFWT score (in seconds), MAS, MTS, GMFM-88 (D & E), CP-QoL (Primary caregiver version) scores at 3 and 6 months, and change in 6MWT score at 3 months. A single investigator assessed all the outcomes.

For sample size calculation, it was assumed that the intervention would result in 60 m change in distance covered in 6MWT. This value of 60 m was an extrapolation from the study by Fitzgerald, et al. [10] in children with CP (GMFCS II) wherein, the standard deviation was 77. Keeping α as 0.05 and power of study as 80%, a sample size of 27 in each group was required . Assuming a 10% loss to follow-up, the targeted sample size was 59 (minimum 30 children per group).

Statistical analysis: Data were recorded on a Microsoft Excel spreadsheet. Statistical analysis was performed using the statistical software SPSS (IBM Corp), Version 20. Student t-test was used to compare the difference in the means between the two groups for parametric variables, while non-parametric variables were expressed as median (IQR) and compared using Mann-Whitney U test

RESULTS

Two hundred and sixty-two children with CP were screened, among whom 169 met inclusion criteria and 59 were enrolled (**Fig. 1**). Thirty children were randomized to the Intervention arm and 29 to the Control arm. One child allocated to the control arm withdrew from the study.

The mean (SD) ages of children in the study was 115 (23.1) months. Anthropometric and clinical characteristics of the two groups were comparable at baseline (**Table I**). Five children (intervention arm: 3, control arm: 2) had fresh onset seizures during the study period in all of which oral sodium valproate was initiated. Good seizure control was achieved in four of them with monotherapy of sodium valproate (dose range 15-40mg/kg/day) while one child (intervention arm) required additional therapy with oral clobazam. Except for a brief interruption of their respective intervention schedules, there was no long-term interruption of the rehabilitation program in any of these children. The majority of children in both groups achieved a compliance rate of 80-100%, There were no differences in the compliance rates between the children in the two groups, as derived from logbooks filled by the primary caregivers, with 93.3% and 93.1% children in intervention and control group, respectively having rates >60%.

The difference in mean 6 MWT between baseline and 6 months was 3.5m and 3m in the Intervention and Control Arm, respectively (**Table II**). There was no significant change in any of the secondary outcome variables (**Web Table I**).

Table I Baseline Characteristics of Children with Diplegic Cerebral Palsy in the Intervention and Control Arms

Characteristic	*Intervention arm (n=30)*	*Control arm (n=29)*
Age, mo[a]	73(65-89)	71(63-79)
Males	19 (32)	24 (41)
Functional status		
GMFCS II	16 (53)	11 (40)
GMFCS III	14 (47)	18 (60)
Assistive devices		
Ankle-foot-orthosis	10 (33)	14 (48)
Knee-ankle-foot-orthosis	2 (7)	2 (7)
Epilepsy	8 (27)	8 (28)
Refractive error	8 (27)	6 (21)
Receiving baclofen	17 (57)	20 (69)

All values in no. (%) or [a]mdian (IQR). GMFCS: Gross motor functional classification scale.

DISCUSSION

The study is a proof of concept trial to evaluate the efficacy of a home-centered activity-based rehabilitation program for children with diplegic CP. Childrn with diplegia constitute a major subset of CP [11]. It is probable that children younger than 5 years would probably have responded better owing to their neuro-plasticity. However, they were excluded from the study due to issues in eliciting cooperation, validity of 6MWT in toddlers, and because activity regime would have required significant modification in younger children.

Common interventions for physiotherapy in CP children include strength and functional training; weight supported treadmill training (WBSTT), and neuro-developmental treatment (NDT) [2]. None of these techniques are universally applicable. Children in this study followed a standardized institutional physiotherapy

Table II Change in 6-Minute Walk Test (6MWT) Scores in Children With Spastic Diplegia in the Two Groups

	Intervention arm (n=30)	*Control arm (n=29)*
Baseline	227.5 (168.8,340)	243.0 (142.5,350)
3 mo	225.5 (165.5,343.3)	230.0 (134.5,336)
6 mo	229.0 (165.3,340.8)	246.0 (141,336)
0-6 mo[a]	3.5 (-5.3, 9.0)]	3.0 (-7.8,6.3)

All values in median (IQR). [a]Difference between scores at baseline and at 6 months. P>0.05 for all comparisons.

regime comprising of passive joint mobility and assisted gait training as outlined in methodology. Activity-based therapy refers to a regime of age-appropriate motor activities such as walking, for example, which involves multiple repetitions of coordinated, reciprocal limb activities [12]. CIMT is a popular and effective example of upper limb activity-based therapy [13-15]. Activity-based therapy for lower limbs may include day-to-day activities like climbing stairs, walking, and sit-to-stand. Intense activity-based training, lifestyle modifications, and mobility-enhancing devices are hypothesized to increase motor activity leading to better physical and mental health cognitive performance in people with motor impairments [12]. The neurophysiological basis of improvement rests on the principles of neuroplasticity [4,16,17]. There is a scientific basis to the assumption that regular activities performed by a child with CP would lead to alteration in the representation of the motor cortex with corresponding motor improvement. Intensive upper limb rehabilitation has been seen to be associated with enhanced motor area activation and size in children with CP [18]. Brains of individuals with CP have been noted to display adaptation in the motor areas subsequent to rehabilitation and activity [19]. Hence, the hypothesis of the index study appears biologically plausible. In order to explore neuroplastic modeling, researchers have attempted integrated neurorehabilitation using combined modalities of physical therapy, magnetic stimulation and nutraceuticals [20].

Simple, interesting, age-appropriate, safe, economically feasible and objectively assessable activities within the ambit of day-to-day functioning were incorporated in the study. Walking was a key component. Maher, et al. [21] studied a walk-based model of rehabilitation in children with CP between 8-17 years of age in the Step Up study. Azizi S, et al. [22] demonstrated that anti-gravity treadmill therapy is effective in improving gait in CP. Squatting and standing are additional tasks included in the activity schedule meant to increase the strength of lower limb musculature and to promote functional mobility. Contemporary systematic review has quoted Level II (b) evidence in support of sit-to-stand training for improvement of balance [23]. Climbing up and down stairs is intended to improve functional mobility. Kicking a football has not been reported as a specific therapeutic modality for rehabilitation in CP. It is anticipated to increase lower limb strength, balance, and coordination while sustaining the child's interest. Cycling was chosen to improve lower limb strength and joint mobility, reduce spasticity and to make the program joyful for the children. However, this was reserved as an optional activity depending on the child's ability, interest and availability of cycle. The cycles used were either tricycles or bicycles with two accessory balancing wheels. The utility of different types of cycling in neurorehabilitation has been previously reported [24,25]. Dancing has been included in order to promote joint mobility and balance while maintaining the child's interest in the program, as previously reported [26,27]. However, in the present study, the dancing activity was an unstructured one. In the present study, activity-based interventions were chosen so that the children could perform them either independently or with minimal assistance. So children with functional levels of GMFCS IV-V were excluded from our study.

The role of task-directed rehabilitation is evident from contemporary upper limb rehabilitation programs [29]. There is a growing body of evidence of molecular plasticity and functional recovery secondary to CIMT [30]. The test-test reliability and validity of 6MWT in children and adolescents with CP has been previously demonstrated [31,32]. A timeline of 6 months for measuring the primary outcome was adopted in our study arbitrarily as it was anticipated that there would be some change in the functional status of the children by that period without suffering significant attrition. Home-based rehabilitation is exalted in view of benefits such as better compliance, involvement and empowerment of parents, economical and feasible [33]. The greatest strength of the study is that it highlights the feasibility of a home-based rehabilitation program in resource-constrained settings. This family-based model simplistic model is appealing because it is economically viable and suits the needs of resource-constrained settings. However, the comparable difference in 6MWT at 6 months (from baseline) in the two groups indicates the fact that adjunctive home-centered activity-based therapy does not improve the outcome associated with regular institutional physiotherapy. The initial 3-month decline and the latter 3-month improvement noted in the study were higher in the Control arm. This phenomenon may be probably due to fewer fluctuations in 6MWT in children receiving both home-based and institutional therapy due to a stable trajectory. It is unlikely that compliance issues could explain the differential trends because compliance was stable across the study in both groups. Satisfactory adherence was maintained throughout the study indicating that, if applied in the community, this model is likely to be well accepted. There was no intervention-related adverse effects eliciting the safe nature of the regime.

The results do not show a significant difference between the two groups probably because of certain limitations in the study design such as brief follow-up period, low intensity of interventions, Parent/primary

WHAT IS ALREADY KNOWN?

- Physiotherapy plays a major role in the management of children with cerebral palsy.

WHAT THIS STUDY ADDS?

- Adjunctive home-centred activity-based therapy does not improve the functional outcomes of children with CP as measured by 6-Minute-Walk-Test scores at 6 months when compared with those receiving institutional physiotherapy alone.

caregiver report-based compliance assessment and varied etiologies of CP. There was no mechanism in the study, which could ensure absolute uniformity in the administration of interventions and live monitoring of the same. A feasible approach to compliance monitoring was adopted at the cost of increasing bias. Despite concealed group allocation, follow-up and evaluation were open-label with the potential risk of bias. The novelty of the study lies in its practical model whereby a simplistic home-centered program, with day-to-day activities, have been analyzed in children with diplegic CP. Hence no analytical comparison to other similar studies could be drawn.

Our study revealed that home-centred activity-based therapy is a feasible and practical modality of CP rehabilitation; however, significant benefits were not appreciable over a 6-month period, therefore, reinforcing need for intense institutional-based therapy. We suggest a larger study size with more intensive intervention strategy, prolonged follow-up interval and more stringent compliance monitoring be conducted in order to effectively evaluate the efficacy of home-centered activity-based programme in children with CP.

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CLIPPINGS

Evaluation of putative CSF biomarkers in paediatric spinal muscular atrophy (SMA) patients before and during treatment with nusinersen (J Cell Mol Med. 2021 Jul 27. Online ahead of print)

Nusinersen, being the longest validated therapy for SMA, requires biomarkers to validate its therapeutic effects. This single-centre pilot study analyzed CSF candidate biomarkers (phosphorylated heavy chain (pNf-H), light-chain neurofilaments (NfL), total tau protein (T-Tau), neurogranin, α secretase BACE-1 and alpha-synuclein) in 193 CSF samples of 44 pediatric SMA types 1, 2 and 3 patients before and under nusinersen treatment and related them to standardized clinical outcome scores. pNf-H and NfL correlated with disease severity and activity, emphasizing their relevance as marker of neuronal loss and clinical outcome. T-Tau was significantly correlated with motor function scores in SMA type 1 making it an interesting marker for treatment response. Additionally, baseline T-Tau levels were elevated in most SMA patients possibly reflecting the extension of neuronal degeneration in pediatric-onset SMA.

KAUSIK MANDAL
kausik@sgpgi.ac.in

Web Table I Secondary Outcome Variables Among the Two Groups

	Intervention arm (n=30)	*Control arm (n=29)*	*P value*
10 Minute Fast Walk Test (10MFWT) Scores (s)			
Baseline	9 [6.6,14.1]	8.4 [6.9,13.1]	0.62
0-3 mo[a]	0.4 [(-) 0.1, 1.2]	0.2 [(-) 0.6, 0.7]	0.55
0-6 mo[b]	(-) 0.2 [(-)1.4, 0.8]	(-) 0.2 [(-)0.9, 0.6]	0.61
Modified Ashworth scale (MAS)			
Baseline	15.5 [13.8,18]	15.5 [12.8,19]	0.90
0-3 mo[a]	0.4 [0,0]	0.2 [0,0]	0.05
0-6 mo[b]	(-) 0.2 [0,0]	(-) 0.2 [0,0]	0.83
Modified Tardieu scale (MTS)			
Baseline	86.5 [65.8,101.3]	88 [56,123.5]	0.74
0-3 mo[a]	(-) 1.0 [(-)10.5 ,3]	(-) 4.0 [(-)14.5,2]	0.64
0-6 mo[b]	2.5 [(-)3.3,18.5]	0 [(-)11.5,16]	0.82
Gross Motor Function Measure -88 (GMFM-88) (D & E)			
Baseline	50.9 [41.2,68.5]	51.5 [42.1,70.2]	0.70
0-3 mo[a]	0 [0,0.7]	0 [0,0.9]	0.99
0-6 mo[b]	0 [0,4.6]	0 [0,8.3]	0.30
Cerebral palsy-quality of life (CP-QoL): Primary caregiver version			
Baseline	303 [285.5,322.5]	297 (254.0,328.5)	0.80
0-3 mo[a]	2.5 [(-)1.3, 8.5]	0 [(-)4.5, 5.5]	0.20
0-6 mo[b]	3.5 [0,8.8]	3 [(-)5.5,2]	0.70
6 Minute walk test (6MWT) Scores (m)			
0-3 mo[a]	3.0 [-6,6]	-6.0 [-12.5,0.25]	0.70

Values in median (IQR). Total scores are depicted for all the scales used. [a]Difference between score at baseline and at 3 mo; [b]Difference between score at baseline and at 6 mo.

Web Box I

Techniques of conventional physiotherapy:

(*a*) Passive manual muscle stretching of involved muscle (commonly thigh adductors, tendo-achilles, and hamstrings). Stretches were performed using gradual manual pressure. Each stretch was initially performed up to five times. In subsequent sessions, the number of repetitions was gradually increased to a maximum of fifteen per circuit, with repetitions up to 3 sets per muscle group per session. Sessions were prescribed five days per week.

(*b*) Gait training was administered as per protocol. Assistance was provided, if required, by an attendant. Sessions were performed once daily and difficulty level increased as per child's response by increasing distance, duration and incline of the walking platform. Climbing steps was the next goal.

RESEARCH PAPER

Clinical Outcome of Guillain-Barré Syndrome in 108 Children

Sandip Sen, Anil Kumar, Banasree Roy
From Dr BC Roy Postgraduate Institute of Pediatric Science, Kolkata, West Bengal.

Correspondence to:
Dr Banasree Roy, 19C/3
Abinash Chandra Banerjee Lane,
Kolkata 700 010, West Bengal.
drbr1978@rediffmail.com
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Objectives: To review the clinical outcome and electrophysiologic characteristics of children with Guillain-Barré syndrome (GBS) from Eastern India. **Methods:** The hospital records of the children aged less than 12 years with a final diagnosis of GBS at our hospital from November, 2015 to December, 2018 were reviewed. Disabilities were assessed at 8-weeks and 6-month follow-up using Hughes scale (0-6). **Results:** Demyelinating variety in 57 patients (52.8%) was more common than the axonal variety (33.3%). 71.1% (32/45) of GBS patients had recovered (scale 0,1) during the follow up period of 6 months. These included 67.7% (21/31) of the axonal variety and 78.6% (11/14) of the demyelinating variety. **Conclusion:** Irrespective of the severity, disability is less with the demyelinating variety as compared with the axonal subtype.

Keywords: *Acute Inflammatory demyelinating polyneuropathy, Disability, Follow-up, Prognosis.*

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Guillain-Barré syndrome (GBS) is presently the most common cause of acute flaccid paralysis in our country. Among children in India and neighboring areas, the axonal variety predominates [1-5]; the demyelinating variety predominates in South America [6], other parts of Asia [7-9] and Europe [10,11]. This difference in subtypes across geographical areas is not clearly understood [12]. Data on the common subtype in Eastern India is lacking, including data on outcome as pertaining to its subtypes, which this study attempts to address.

METHODS

This is a hospital record review conducted in a pediatric tertiary care hospital between November, 2015 to October, 2018. During this period, 144 children with acute flaccid paralysis (AFP) were admitted, among whom, 108 were diagnosed as GBS (Asbury and Cornblath criteria [13]), and included in our study after excluding GBS variants (n=12), hypokalemic periodic paralysis (n=4), transverse myelitis (n=6), traumatic neuritis (n=2) and those who did not give consent (n=12). Ethical clearance was obtained from institutional ethics committee. Informed consent was taken before enrolment. Intravenous immunoglobulin therapy was given to all patients.

Nerve conduction study was done within 48 hours in 99 (91.7%) patients, after initial stabilization. All the patients underwent stool examination for poliovirus detection. Lumbar puncture was done in 102 (94.4%) patients in the second week after disease onset. Hughes GBS disability grade was applied to assess the outcome at eight weeks (n=66) and six months (n=45) after discharge [14].

Statistical analysis: SPSS 24.0 and Graph Pad Prism version 5 were used for analysis. Proportions were compared by Chi-square test or Fischer exact test, as appropriate. P value <0.05 was considered to be statistically significant.

RESULTS

A total of 108 cases (66 boys) of GBS in the age range 1.2 to 10 years, median (IQR) age of 4.2 years (2 year 3 month - 5 year) were enrolled in the present study. Preceding respiratory and gastrointestinal infections were found in 33.3% (n=36) and 25% (n=27) children, respectively. History of antecedent illness was present in 72 (66.7%) patients including diphtheria-tetanus-whole cell pertussis vaccination in one child.

At presentation, there was quadriparesis in 8.3% and paraparesis in 27.8% of children. Ascending paralysis was the most common mode of presentation in 99 (91.7%) children. Maximum number of children (83.3%) reached peak disability within two weeks of onset of symptoms. Areflexia was found in 94.4% children, and 19.4% and 25% showed facial weakness and bulbar palsy, respectively. Dysautonomia presenting as excessive sweating (n=18), hypertension (n=9), sinus tachycardia (n=15), sinus bradycardia (n=6), sinus arrhythmia (n=9)

fluctuating blood pressure (*n*=6) and postural hypotension (*n*=3) were seen in 47.2% (*n*=51) of the patients. Sensory symptom was the first symptom in 66 (61.1%) patients as compared to motor symptoms in 42 (38.9%) patients. The most common initial sensory symptom was paresthesia (33.3%) in the form of pin and needle sensations, burning sensation and itching. Among other initial sensory presentations generalized muscles aches were found in 8.3% of cases, numbness of legs in 5.5%, pain in the back and neck in 8.3%, and pain in legs in 5.5% cases. Pain at some time during the illness was present in 86% of patients. In this study, demyelinating pattern (AIDP) was seen in 52.8% (*n*=57), axonal pattern in 33.3% (*n*=36); whereas, 5.6% (*n*=6) had normal NCV pattern. In the axonal variety, there were 34 cases of acute motor axonal neuropathy (AMAN) and two cases of acute motor sensory axonal neuropathy (AMSAN). Albuminocytological dissociation was found in 54 (50%) patients.

Pediatric intensive care unit (PICU) care for the management of dysautonomia and respiratory paralysis was required in 54 patients. Mechanical ventilation for respiratory failure was required in 24 (22.2%) patients, out of which nine (8.3%) died during the acute phase of the illness. Dysautonomia, bulbar involvement and diarrhea were associated with all of the nine patients who died. The causes of death were cardiac arrest in the context of dysautonomic syndrome in four patients, ventilator-associated pneumonia (VAP) in three patients, adult respiratory distress syndrome (ARDS) in one, and sepsis in one patient. The duration of ventilation was 2-64 days with a mean of 20.12 days and the range of hospital stay was 2-74 days with a mean of 16.5 days. During ventilation, one patient developed pneumothorax, nine developed VAP and 19 patients (17.9%) required tracheostomy.

Out of 108 patients, 99 were discharged but only 66 (66.7%) patients were available for follow up at 8 weeks after the onset of illness, and 45 patients after 6 months (**Table I**). The reasons for not following up were amelioration of weakness, minor sensory symptoms, distance from the hospital and follow up at their nearby clinics. In the present study, three patients developed chronic inflammatory demyelinating polyneuropathy (CIDP) during the follow up period and were treated with IVIG and steroids.

Table I Outcome at 8 Weeks and 6 Months Follow-up in Children With Guillain-Barré Syndrome

Disability scale	Grade 0	Grade 1	Grade 2	Grade 3
At 8 wk (n=66)	24 (36.4)	16 (24.2)	11 (16.7)	15 (22.7)
Axonal (*n*=46)	15	12	8	11
Demyelinating (*n*=20)	9	4	3	4
At 6 mo (n=45)	21 (46.7)	11 (24.4)	10 (22.2)	3 (6.7)
Axonal (*n*=31)	13	8	7	3
Demyelinating (*n*=14)	8	3	3	0

DISCUSSION

This is a single center study done in eastern India which included 108 children with GBS and compared their outcome at eight weeks and six months follow up. Of the 99 patients available for electrophysiological studies 52.8% had the demyelinating subtype and 33.3% had the axonal variety.

In the present study, those having the axonal variety had higher Hughes disability score at presentation, at the peak of disease, on discharge and on follow up at eight weeks and six months respectively. Axonal variety had a higher incidence of GI symptoms in our study as well as other studies [7,15] while antecedent upper respiratory illness was more common in the demyelinating variety as also noted in few previous studies [3,7,15]. The reasons why some infections are more common in certain subtypes of GBS are not very clear.

In a study by Korinthenberg, et al. [10] on 95 children there was an improvement of 96% (91/95) (75% Grade 0 and 21% Grade 1) at the end of an observation period of 288 days. They had 74% of the demyelination subtype, which probably explains their excellent outcome. Kalra, et al. [2] in their studies in 52 children conducted in northern India revealed a recovery rate of 87.5% at 1 year follow up and 95% thereafter. In a study from southern India, Kannan, et al. [15] all 43 children recovered (Grade1,2) at 6 month follow up. They reported a mix of axonal (44.2%) and demyelinating (48.8%) subtypes. Recently Yadav, et al. [1] studied 36 children and reported a recovery rate of 84.4% (27/32) (Grade 1,2) at 3 month follow up. Their predominant subtype was the axonal variety (69.4%). We had a higher number of axonal variety in follow up as compared to the demyelinating subtype (31 vs 14). This was probably due to persistence of weakness in axonal type which also explains the poorer outcome of our study. Data has been difficult to analyze as a few studies [1,15] have used a Hughes disability score of 1 and 2 to discuss outcome while others [2,10], including the present study, have used a score of 0 and 1. More meaningful comparisons could have been done if the same disability scores were used. The overall prognosis in most studies was excellent and it has been observed by most of the studies that a longer duration of follow-up showed improved disability ratings and scores [1,6,10].

The limitations of this study is being a single center study, absence of a longer period of follow up and insufficient numbers to draw strong conclusions

correlating the GBS subtype with the outcome. Demyelinating variety was more common than the axonal subtype in this cohort. Presence of gastrointestinal symptoms, bulbar palsy and respiratory failure were suggestive of axonal subtype. At both 8 weeks and 6 months follow-up, the demyelinating variety had a better outcome as compared to the axonal variety.

Ethical approval: Institutional Ethics Committee, Dr. BC Roy Post Graduate Institute of Paediatric Sciences; No. BCH/ME/PR/2660B, dated September 25, 2017.
Contribution: SS,AK: concept and design of study; AK,BR: acquisition of data; SS,AK: data analysis and interpretation; SS,AK,BR: drafting of manuscript; SS,AK,BR: critical revision of manuscript. All authors approved the final version of manuscript.
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CLIPPINGS

Expert recommendations and clinical considerations in the use of onasemnogene abeparvovec gene therapy for spinal muscular atrophy (Muscle Nerve. 2021 Jun 30.Online ahead of print).

Onasemnogene abeparvovec is an adeno-associated virus-based gene replacement therapy. It delivers functional human SMN through a one-time intravenous infusion. In addition to substantially improving survival, onasemnogeneabeparvovec was found to increase motor milestone attainment and reduce the need for respiratory or nutritional support. This expert opinion provides recommendations and practical considerations on the patient-centered decisions like the need for patient-centered multidisciplinary care, patient selection to identify those with underlying medical conditions or active infections, importance of retesting patients with elevated anti-adeno-associated virus serotype 9 antibodies, guidelines for prednisolone tapering and monitoring for potential adverse events, including hepatotoxicity and thrombotic microangiopathy.

Risdiplam-treated infants with type 1 spinal muscular atrophy versus historical controls (N Engl J Med. 2021;385:427-35)

Type 1 SMA is characterized by onset before 6 months of age and such children are unable to sit. This study was an open-label study of risdiplam on 41 infants with type 1 SMA who were 1 to 7 months of age at enrolment. After 12 months of treatment, 12 infants (29%) met the primary end point and were able to sit without support for at least 5 seconds, a milestone not attained in this disorder in natural course. Other secondary end points measured by CHOP-INTEND, HINE-2 and survival without permanent ventilation were also significantly different in the study group as compared to historical controls.

KAUSIK MANDAL
kausik@sgpgi.ac.in

RESEARCH PAPER

Vitamin D, Bone Mineral Density and Serum IGF-1 Level in Non-ambulatory Children With Cerebral Palsy

NAMITA GWASIKOTI,[1] KAPIL BHALLA,[1] JAYA SHANKAR KAUSHIK,[1] VEENA SINGH GHALAUT,[2] ZILE SINGH KUNDU[3]
From Departments of [1]Pediatrics, [2]Biochemistry and [3]Orthopedics, Pt. BD Sharma PGIMS, Rohtak, Haryana.

Correspondence to: Dr Kapil Bhalla, Department of Pediatrics, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak 124 001, Haryana. kapil_bhalla@yahoo.com
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Objective: To compare serum 25-hydroxy vitamin D (25-OHD) status, bone mineral density and Insulin-like growth factor (IGF-1) level among children with cerebral palsy (CP) aged 1 to 8 years with age- and gender-matched controls. **Methods:** A cross-sectional study enrolled 30 children in each group: CP with epilepsy, CP without epilepsy, and healthy controls. Bone mineral density (BMD), serum 25-OHD levels, and serum insulin like growth factor (IGF)-1 levels were measured. **Results:** *z*-scores of BMD [-1.80 (1.03), -2.12 (0.85) vs -1.40 (0.90); *P*<0.01], 25-OHD levels [19.26 (8.28), 20.59 (8.92) Vs 26.79 (12.76) ng/mL; *P*<0.01] and IGF-1 levels [20.90 (6.42), 23.37 (8.11) vs 31.77 (11.21) ng/mL; *P*<0.01] were significantly low among children with CP with epilepsy, CP without epilepsy when compared to controls . **Conclusion:** Children with CP with or without comorbid epilepsy were prone to vitamin D deficiency, low bone mineral density and growth hormone axis suppression with low IGF-1 levels.

Keywords: *Antiepileptic drugs, BMD, Dyskinetic cerebral palsy, Epilepsy, Osteoporosis.*

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Cerebral palsy (CP) is a group of non-progressive disorders of movement and posture that result in activity limitation [1]. The motor disorder of cerebral palsy is often accompanied by disturbance of sensation, cognition, behavior, and epilepsy [2]. The risk factors that predispose children with CP to low bone mineral density include physical inactivity, lack of adequate sunlight exposure, poor nutrition, and intake of antiepileptic drugs [3-6]. Low bone mineral density predisposes to osteoporotic fractures leading to further inactivity and functional loss [7]. Non-ambulatory children with CP are also prone to vitamin D deficiency, low intake of calcium and low sunlight exposure [3,8].

Insulin like growth factor-1 (IGF-1) stimulates the synthesis of bone-specific proteins and osteoblasts in cell and organ cultures [9,10]. Both bone mineral density (BMD) and IGF-1 levels were found significantly low in children with spastic CP with higher gross motor functional classification system GMFCS [11]. Few antiepileptic drugs (AEDs) can cause decrease in BMD attributed to the increased enzyme induction and expression of CYP21 leading to increased inactivation of vitamin D [12]. The spectrum of CP in India is shifting from quadriplegic CP to more of diplegic CP over last 10 years [13]. Indian children with cerebral palsy are also at high risk of malnutrition [14]. There is limited literature on BMD among Indian children with CP. Hence, the present study was conducted to evaluate the vitamin D levels, IGF-1 levels, and BMD in non-ambulatory patients with CP.

METHODS

This was a cross-sectional study conducted in a tertiary care hospital from January, 2018 to April, 2019. Patients were recruited from pediatric and pediatric neurology outpatient units. Clearance was obtained from the institutional ethics committee and a written informed consent was obtained from the caregiver.

Thirty children aged 1-8 years were recruited in each of the following three groups: Group I – CP with GMFCS III-V with epilepsy (on AEDs for at least two years), Group II - CP without epilepsy, and Group III – age- and gender-matched healthy controls who belonged to same community. Children on vitamin D or calcium supplementation in last six months, and those with ambiguity in clinical diagnosis were excluded from the study.

After taking a thorough history, each participant underwent detailed clinical evaluation including anthropometric and functional ability assessment GMFCS. Bone mineral density (BMD) of lumbar vertebrae (L2-L4) was determined by dual energy *X*-ray absorptiometry (DXA). Serum 25-hydroxy vitamin D (25-OHD) levels were measured by radioimmunoassay (RIA). Serum IGF-1 levels

were measured by ELISA method using DRG IGF-1 600 ELISA (EIA-4140) kit.

Considering the proportion of vitamin D deficiency to be 66% in children with CP and 36.7% in healthy controls based on previous published data [3], a sample size of 28 (rounded to 30 in each group) was computed assuming an alpha error of 0.05 and power of 90%.

Statistical analysis: Outcome variables were compared between the three groups by using analysis of Variance (ANOVA) for multi-group comparisons followed by Tukey test. Logistic regression analysis was performed to determine the predictors of low BMD. A *P* value <0.05 was considered as significant.

RESULTS

A total of 90 children (30 in each of three groups) were enrolled in the study. Baseline characteristics were mostly comparable between the groups **(Table I)**. Of the 30 children with comorbid epilepsy, 21 (70%) were on valproate, 2 (2.1%) were on levetiracetam, 10 (33.3%) children were on clonazepam, 3 (10%) on vigabatrin and one child was on phenytoin.

Table I Baseline Characteristics of Children With Cerebral Palsy and Controls

Baseline characteristics	*Cerebral palsy with epilepsy (n=30)*	*Cerebral palsy without epilepsy (n=30)*	*Controls (n=30)*
Age in years[a]	3 (1.75-5.25)	3.5 (2-7)	4 (2-6.25)
Male gender	22 (73.3)	21 (70)	19 (63.3)
BMI[b,c]	14.89 (2.58)	14.07 (2.29)	16.21 (2.6)
WFA <-3 SD[d]	4 (13.3)	8 (26.7)	1 (3.3)
WFH <-3 SD	5 (16.7)	7 (23.3)	2 (6.7)
HFA <-3 SD[e]	4(13.3)	11(36.7)	12 (40.0)
Type of cerebral palsy			
Diplegia	6 (20)	7 (23.3)	-
Hemiplegia	6 (20)	2 (6.7)	
Quadriplegia	13 (43.3)	18 (60)	
Dyskinetic	1 (3.3)	2 (6.7)	
Mixed	4 (13.3)	1 (3.3)	
Etiology			
HIE	21 (70)	18 (60)	-
Prematurity	5 (16.7)	5 (16.7)	
Kernicterus	0	2 (6.7%)	
Meningitis	1 (3.3)	5 (16.7%)	
GMFCS			
Grade III	12 (40)	8 (26.7)	-
Grade IV	16 (53.3)	20 (66.7)	
Grade V	2 (6.7)	2 (6.7)	

Data expressed as no. (%), [a]median (IQR) or [b]mean (SD). GMFCS:Gross motor functional classification system. [c]P<0.001, [d]P<0.05, [e]P=0.05, BMI: body mass index; WFA: weight for age; WFH: weight for height; HFA: height for age; HIE: hypoxic ischemic encephalopathy.

The serum 25-OHD levels, IGF-1 levels and BMD *z*-score in the three groups are shown in **Table II**. Post hoc analysis revealed that BMD *Z*-scores (*P*=0.37), serum IGF-1 levels (*P*=0.53) and 25-OHD levels (*P*=0.87) were comparable between CP with epilepsy and CP without epilepsy. There was a significant correlation between serum IGF-1 levels and serum 25-OHD levels (r=0.88; *P*<0.001). Regression analysis model revealed that low BMD was predicted by lower age [OR (95% CI): 1.05 (1.02-1.08); *P*=0.005] and GMFCS level [OR (95% CI): 0.86 (0.71-1.01); *P*=0.038].

DISCUSSION

The present study revealed that comorbid epilepsy in children with CP did not affect BMD and serum 25-OHD levels. However, children with CP without epilepsy had significantly lower BMD when compared to age-matched controls. 25-OHD levels and IGF-1 levels were significantly low in children with CP with or without epilepsy when compared to controls.

The present study findings are in concurrence with another study which found that severity of functional ability (GMFCS level 4,5) correlated negatively with BMD [15]. However, majority of patients in the present study belonged to GMFCS IV and III.

Children with CP are prone to vitamin D deficiency owing to lower sunlight exposure, non-ambulatory status and poor nutritional intake. Findings of low vitamin D level among children with CP in this study were consistent with previous studies [8,12,15]. Similar serum vitamin D levels in those with or without epilepsy could be with use of non-enzyme inducing drugs in the epilepsy group in this study.

Table II Bone Mineral Density and Other Markers in Children With Cerebral Palsy (CP) and Healthy Controls

Variable	*CP with epilepsy (n=30)*	*CP without epilepsy (n=30)*	*Control (n=30)*
BMD (*z*- score)[a]	-1.80 (1.03)	-2.12 (0.85)	-1.40 (0.90)
25-OHD, ng/mL[b]	19.26 (8.28)	20.59 (8.92)	26.79 (12.76)
IGF-1, ng/mL[b]	20.90 (6.42)	23.37 (8.11)	31.77 (11.21)

Data expressed as mean (SD). [a]P<0.01 for CP without epilepsy and control and P=0.23 for CP with epilepsy and control; [b]P <0.01 for both CP with epilepsy and controls and CP without epilepsy and control. BMD – Bone mineral density; 25-OHD -25 hydroxy vitamin D; IGF-1-Insulin like growth factor.

WHAT THIS STUDY ADDS?

- Non-ambulatory children with cerebral palsy with or without epilepsy have low bone mineral density, low serum vitamin D levels, and low IGF-1 levels as compared to healthy controls.

GH and IGF-1 are principal regulators of bone-cell function. IGF-1 has stimulatory effects on the synthesis of bone specific proteins and osteoblastic proliferation in cell and organ cultures. Patients with CP have significantly low levels of IGF-1 and low BMD which makes them prone for osteoporotic fractures [4,11,15]. Low levels of IGF-1 in children with CP could also be attributed to malnutrition and liver disorders. In this context, GH level estimation would have been more useful than IGF-1 level. However, GH levels were not estimated as the procedure is tedious and there is need for hospital admission.

Selection of age- and gender-matched controls in the present study served as comparator for the observations of BMD, IGF-1 and vitamin D levels in children with CP. This study analyzed bone mineral metabolism in terms of suppression of growth hormone axis (IGF-1), bone mineralization (BMD) and nutritional status (vitamin D). Limitations of the study include cross-sectional descriptive study design with limited sample size and absence of liver function tests. Most of the enrolled children were non-ambulatory where factors like sunlight exposure, presence of feeding difficulties and history of use of dairy products would have been useful; however, these were not recorded in the study.

The study concludes that spinal BMD, serum vitamin D levels and serum IGF-1 levels were decreased in children with CP with and without epilepsy when compared to healthy controls. Future longitudinal studies are suggested with larger sample size looking for efficacy of interventions like structured exercise program, vitamin D, calcium, and GH supplementation among children with CP.

Ethics clearance: Institutional ethics committee, PLBD Sharma, PGIMS; No. BREC/Th/19/Ped 15; dated March 06, 2020.
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Contributors: KB, JSK: conceptualized the idea; NG, KB, JSK, VSG, ZSK: involved in data collection and patient management; NG, KB, JSK: drafted the manuscript; VSG, ZSK: provided intellectual inputs; all the authors the final version of the manuscript.
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RESEARCH PAPER

Vitamin D Levels in Neonates With and Without Seizures: A Single Center Cross-Sectional Study

JONNALA CHAITANYA REDDY, APURV BARCHE, SNEHA JAGANATHAN ANDRADE, ADITYA VERMA, LESLIE EDWARD LEWIS, JAYASHREE PURKAYASTHA

From Department of Pediatrics, Kasturba Medical College, Manipal Academy of Higher Education (MAHE), Manipal, Karnataka

Correspondence to: Dr Jayashree Purkayastha, Professor, Department of Pediatrics, Kasturba Medical College, Manipal, Manipal Academy of Higher Education (MAHE), Karnataka.
jayashreepurkayastha@yahoo.com
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Objective: To study the serum vitamin D levels in neonatal seizures and vitamin D status of the mothers whose babies had vitamin D deficiency. **Methods**: For this cross-sectional study, vitamin D levels were studied in term and late preterm neonates admitted to NICU with seizures at our tertiary care center. Controls were term and late preterm healthy neonates admitted in the postnatal ward with the mothers in the same center. **Results**: 30 cases and 30 controls were enrolled. The mean (SD) serum vitamin D was 19.33 (7.76) ng/mL among cases and 16.83 (6.74) ng/mL among controls (*P*=0.18). We tested maternal vitamin D levels in babies with seizures and low vitamin D levels. The mean (SD) serum vitamin D level among these mothers (*n*=11) was 13.25 (6.17) ng/mL. ***Conclusions***: There was no statistically significant association between serum vitamin D levels and seizures among neonates in our study.

Keywords: *Hypocalcemia, Neonates, Seizures, Vitamin D.*

Trial registration: CTR1/2018/12/023028

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The incidence of neonatal seizures is 2-4 per 1000 live births. Seizures may be due to electrolyte abnormalities, underlying brain injury, or initial presentation of an underlying inborn error of metabolism [1,2]. Early recognition and management of biochemical disturbances in neonatal seizures are important to prevent further brain damage. Neonates with hypocalcemia may present with seizures secondary to increased excitability of the cell membrane, thus resulting in exaggerated startles, jitteriness, myoclonic jerks, and seizures [2]. Hypocalcemia due to vitamin D deficiency constitutes a major cause of neonatal seizures in developing countries [3]. Maternal vitamin D deficiency results in a poor trans-placental transfer of vitamin D during pregnancy and reduced stores in the newborns [4,5]. Neonates born to vitamin-deficient mothers are at a significantly higher risk to develop hypocalcemic seizures [6]. In addition to hypocalcemic seizures, some neonates with idiopathic seizures also have low vitamin D levels [5].

During early infancy, vitamin D stores depend on intrauterine accretion and breastmilk, in addition to sunlight exposure in the mother. Breastfed neonates born to and nursed by vitamin D deficient mothers have low serum vitamin D levels [7]. We compared vitamin D levels in neonates with seizures with those without seizures, and also studied vitamin D levels among mothers whose babies had seizures and low vitamin D levels.

METHODS

This was a cross-sectional study done from November, 2018 to August, 2020 in a tertiary care center in southern India, after institutional ethics committee clearance.

Term and late preterm (35-40 weeks) neonates admitted to the neonatal intensive care unit (NICU) of our institute with seizures were enrolled as cases. Controls were healthy term and late preterm neonates admitted in the postnatal ward along with their mothers. Exclusion criteria were: neonates with congenital anomalies, meningitis, hypoglycemia, birth asphyxia, or inborn errors of metabolism; neonates with mothers having hepatic, renal, or bone disorders, mothers on enzyme-inducing drugs and COVID-positive neonates; and neonates with vitamin D supplementation or neonates who were administered antiepileptic drugs before admission.

Blood was drawn for 25-hydroxy vitamin D levels (25(OH)D) from enrolled neonates admitted with seizures. The mothers' vitamin D levels were also evaluated in those neonates with seizures who had vitamin D deficiency. Controls were evaluated for vitamin D levels during day 3-7 investigations like serum bilirubin levels.

Informed consent was obtained from both parents. A detailed antenatal, intranatal and postnatal history was taken in a pre-designed proforma. Whether mothers had received antenatal calcium and vitamin D supple-

mentation and compliance history was also taken. Baseline anthropometry was carried out for all neonates at admission. All babies with seizures who satisfied the inclusion criteria were examined at admission with a detailed examination of the central nervous system. Clinical details of the witnessed seizure episode were noted and details at the time of first seizure and the type of seizure were noted. The neonatal seizures were classified as per Volpe classification into subtle, multifocal tonic, focal clonic, focal tonic, and myoclonic.

Blood samples of all neonates with seizures included in the study were sent for vitamin D levels, calcium, and magnesium along with other investigations like sepsis screen (to rule out septicemia), ammonia, lactate, pyruvate, ABG, TMS/GCMS (to rule out IEM), blood glucose, ionized calcium and total calcium, and serum albumin. Blood samples were taken immediately after seizures and before administration of any specific treatment. Second-line investigations were done in cases, as and when indicated. These included electro-encephalography (EEG), cerebrospinal fluid analysis, and neurosonogram/magnetic resonance imaging. Serum vitamin D estimation was done by electro-chemiluminescence immunoassay.

Serum vitamin D concentrations >20 ng/mL was considered as sufficient, between 12-20 ng/mL as insufficient and <12 ng/mL as deficient [7]. Neonatal hypocalcemia was defined as a total serum calcium concentration of <7 mg/dL or an ionized calcium concentration of <4 mg/dL (1 mmol/L) [8].

Statistical analysis: Statistical analysis was done by using the statistical package for social sciences (SPSS) version 20. Mann-Whitney *U* test was used to compare median vitamin D levels among cases and controls. Comparison of mean values was done by paired and unpaired Student *t*-test and chi-square test. *P* value <0.05 was considered significant.

RESULTS

A total of 91 babies with seizures were admitted to the NICU during the study period, of which 61 were excluded. Thirty neonates were enrolled as controls. Baseline characteristics of cases and controls were not significantly different (**Table I**).

Based on the semiology, the most common seizures were multifocal clonic type (*n*=9), followed by focal clonic (*n*=7). Mixed type and subtle seizures were seen in six neonates each, and tonic and myoclonic types in one each. Based on the etiology, idiopathic seizures were the most common (*n*=21) followed by hypocalcemic seizures (*n*=6).

The serum vitamin D levels were higher in cases than the controls (*P*=0.18); although, both groups had levels in the insufficient range (15-20 ng/mL) (**Table I**). There were 16 neonates with seizures with low vitamin D levels (<20 ng/mL). Out of which, five mothers' samples could not be done as they were not willing and/or were not admitted to the same Institute as the babies were outborn. The mean (SD) serum vitamin D levels of remaining mothers (*n*=11) was 13.25 (6.17) ng/mL and the mean serum vitamin D levels of their babies (*n*=11) was 13.04 (4.55) ng/mL. There was no significant association (*P*=0.84) between maternal and neonatal vitamin D levels.

There was no significant association (*P*=0.18) between onset of seizures (within and beyond 72 hours) and vitamin D levels. Levels of vitamin D were low among neonates with hypocalcemic seizures but it was not statistically significant [16.17 (8.79) vs 20.91 (6.88); P=0.11]. Among the cases, EEG was done in 19 babies. Out of the 19 EEGs, only three were abnormal.

DISCUSSION

We found that majority of mother-neonate pairs in this study had low vitamin D levels. Vitamin D levels were low in both cases and controls, with no significant association of low vitamin D level in neonates and occurrence of seizures.

Vitamin D levels were low in controls probably because low birthweight and late preterm babies were more among controls than cases, and mean birth weight was less among controls than cases. Mean vitamin D levels among the mothers whose babies had low vitamin D levels were also low. Possibly mothers in this part of the country have low vitamin D levels as previously also reported [10], which did not improve even after antenatal vitamin D

Table I Baseline Characteristics and Serum Vitamin D Levels in Neonates With Seizures and Controls

Characteristics	*Cases (n=30)*	*Controls (n=30)*
Birthweight, g[a]	3083 (567)	2896 (488)
Low birthweight	5 (17)	7 (23)
Gestational age, wk[a]	38.13 (1.3)	37.5 (1.1)
Male gender	19 (63)	15 (50)
Late preterm	4 (13)	6 (20)
Maternal age, y[a]	29.9 (5.1)	28.9 (4.3)
Cesarean section	18 (60)	21 (70)
Vitamin D levels, ng/mL[b]	19.17 (14.3-21.9)	15.38 (12.3-19.9)

All values in no. (%) except [a]mean (SD) or [b]median (IQR). P>0.05 for all comparisons. All mothers received vitamin D and calcium supplementation during pregnancy.

WHAT THIS STUDY ADDS?

- There was no association of neonatal seizures and vitamin D deficiency.

supplementation. Aparna, et al. [11] also reported that vitamin D deficiency was highly prevalent among pregnant women, lactating mothers, neonates, and/or exclusively breastfed infants. Increasing the dose of antenatal vitamin D supplementation may be considered, if similar findings are seen in larger community-based studies.

Previously, one-third of infants have been reported to have vitamin D levels <10 ng/mL [10]. Fetal and newborn concentrations of 25 (OH) D depend on and correlate with maternal serum levels. Thus, newborns of vitamin D-insufficient mothers are at a greater risk of developing vitamin D deficiency [12]. Although there was no significant difference in vitamin D levels among the two groups in this study, it suggests that vitamin D levels are low among the normal neonate population in India and the mothers. In a similar study conducted by Singh, et al. [13], it was found that 85.7% of the neonates were vitamin D-deficient. Other studies [11,14] also show that majority of the neonates have vitamin D deficiency even in tropical climates.

The study population was small and selective because we did not include extreme, early, and moderate preterm babies as seizures are less common in these babies and we would not get matched controls. This study needs to be done in a larger sample to find the status of vitamin D levels among mothers and babies in the Indian population.

We conclude that hypovitaminosis D in mothers is also associated with hypovitaminosis D in neonates. There is a need to assess the vitamin D status of pregnant and lactating women and to consider routine vitamin D supplementation or to increase the dose of vitamin D supplementation among pregnant and lactating women in this region. Routine vitamin D supplementation among healthy newborns also need to strengthened.

Ethics clearance: Institutional ethics committee of KMC; No. 779/2018 dated November 13, 2018.
Contributors: JP, SJA, AB: conceptualization, methodology; JCR: data collection, analysis; JP: original draft preparation. AB, SJA, AV: correction of draft and final preparation. All authors approved the final manuscript.
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RESEARCH PAPER

Sensory Processing Dysfunction and Mealtime Behavior Problems in Children With Autism

Prahbhjot Malhi, Surya Saini, Bhavneet Bharti, Savita Attri, Naveen Sankhyan
From Department of Pediatrics, Post Graduate Institute of Medical Education and Research, Chandigarh.

Correspondence to:
Dr Prahbhjot Malhi, Professor, Department of Pediatrics, Post Graduate Institute of Medical Education and Research, Chandigarh 160 012. pmalhi18@hotmail.com
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Objectives: To compare sensory processing and mealtime problem behaviors among children with autism spectrum disorder (ASD) and typically developing controls, and to examine the relationship between atypical sensory processing and eating problems in children with ASD. **Methods**: 50 children (4-10 years) with a diagnosis of ASD as per DSM-5 were recruited from the pediatric psychology clinic of a tertiary care center in India. The Brief Assessment of Mealtime Behavior in Children (BAMBIC) and the Short Sensory Profile (SSP) were administered to measure feeding and sensory processing problems, respectively. Parents were interviewed about their child's dietary intake using a 3-day dietary recall. **Results**: The ASD group showed greater mealtime behavior problems than the control group and had significantly higher total scores on the BAMBIC (P<0.001), and on two of the three subscales including food refusal (P<0.001) and disruptive behavior (P<0.001). The ASD group, relative to the neurotypical children, showed atypical response on majority of the subscales of the short sensory profile including tactile sensitivity (P<0.001), taste sensitivity (P<0.001), movement sensitivity (P<0.001), under responsiveness (P<0.001), auditory filtering (P<0.001), low weak/energy (P=0.02), and visual/auditory sensitivity (P<0.001). **Conclusions**: The study underscores the need for detailed evaluation of sensory processing and feeding problems of children with ASD so that the interventions can be tailored to address their unique sensory characteristics.

Keywords: *Feeding problems, Nutritional inadequacies, Sensory dysfunction*.

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Children with autism spectrum disorder (ASD) have many aberrant behaviors including limited food preferences, avoidance of certain foods, non-functional mealtime rituals, pica, hypersensitivity to food textures or temperatures, eating only specific brands of foods, and smelling food items before consuming [1-3]. In a recent study, Mayes, et al. [4] assessed the aberrant eating behaviors of 1462 children with ASD. They found that 70% of children with ASD had feeding difficulties compared to only 5% of the typically developing children. The authors argued that early unusual feeding patterns of behavior in children might help distinguish autism from other disorders and should be considered a red flag for autism by clinicians [4]. Indeed, research indicates that atypical food preferences may be prevalent as early as 15 months of age, and this may increase the risk for nutritional deficiencies and malnutrition among children with ASD [5-7]. Mealtimes are especially challenging for parents, and studies show greater parental stress associated with the feeding of their autistic children and increased caregiver burden [7-9].

Research suggests an association between sensory processing problems, food refusal, and nutritional adequacy in children with ASD [7,10,11]. For instance, Nadon, et al. [10] examined the relationship between sensory processing problems and the number of eating difficulties reported by parents in 95 children aged 3-10 years with ASD. They found that children with tactile, visual or auditory sensitivities were more likely to have a more restricted food repertoire than children with typical sensory processing profile [10]. Thus, there is a need to understand the complexity of sensory sensitivity issues leading to a narrower range of diets, and design specific strategies to decrease challenging mealtime behaviors. Despite a growing body of literature on feeding selectivity in children with ASD, limited research has been done regarding sensory processing dysfunction and food selectivity issues in children with ASD, particularly in developing countries. There is a need to address some of the factors associated with challenging mealtime behaviors among children with ASD to address the nutritional inadequacies found in these children. This study aims to compare sensory dysfunction and the

number of mealtime behavior problems among ASD and typically developing controls, and to examine the relationship between atypical sensory processing and atypical eating in children with ASD.

METHODS

Fifty children with ASD (DSM-5 criteria), aged 4 to 10 years, were consecutively enrolled from the pediatric psychology clinic and neurodevelopment clinic of a pediatrics department in an advanced pediatric center. All children with any chronic medical condition, on any exclusion diet, and any medications that could alter feeding were excluded. A total of 28 age-matched (within four months) typically developing children were recruited as controls. The study was approved by the Institute review board, and informed signed consent was obtained from the caregivers.

Tools: Brief assessment of mealtime behavior in children (BAMBIC) consists of 10 items and these assess three domains of mealtime behaviors including food refusal, limited variety of food intake, and disruptive mealtime behaviors [12]. The parent has to respond to each item of the scale using a 5-point scale ranging from always to never. The responses to each item were summed to yield a total score. Higher scores indicated more problem feeding behaviors. Short sensory profile (SSP) is a 38-item questionnaire that assesses seven sensory domains: tactile, taste/smell, movement, under-responsive/seeks sensation, auditory filtering, low energy/weak, and visual/auditory [13]. Each item is answered on a 5-point scale with responses ranging from always to never, with higher scores indicating more typical performance while low scores indicate heightened sensitivity in that area.

Parents were interviewed about their child's dietary intake using a 3-day dietary recall. Parents were asked to list the food items and the quantity which their child consumed during breakfast, lunch, snack, and dinner time. The three-day recall of macro- and micro-nutrient consumption was calculated and compared with the recommended dietary allowances (RDA) as per age requirements provided by the ICMR 2017 using the Diet Software. For food selectivity, parents were asked to report whether their children would eat commonly consumed foods present in an Indian diet (vegetables, proteins, fruits, dairy products, starches) and the responses were recorded as: almost never/rarely, sometimes and frequently/always. Based on the caregivers' responses, the two groups were compared on food selectivity as defined by the percentage of children who almost never or rarely consumed various foods. The height and weight of all participants was taken, and body mass index (BMI) was calculated.

Statistical analysis: The two groups were compared using the *t* test for continuous variables and chi-square test for categorical variables. Multivariate stepwise regression analysis was performed to identify the predictors of the total score on the BAMBIC scale among the ASD children. The predictors used in the analysis were the seven subscale scores of the SSP.

RESULTS

We enrolled 50 children with ASD and 28 typically developing children. There were no significant differences among the groups for baseline characteristics (**Table I**). Severe autism, as assessed by the Childhood Autism Rating Scale (CARS), was seen in 38 (76.7%) children.

The ASD group showed greater mealtime behavior problems than the typically developing group and had significantly higher total scores on the BAMBIC (P<0.001), and on two of the three subscales of BAMBIC including food refusal (P<0.001) and disruptive behavior (P<0.001). **Web Table I** presents comparative group responses on each of the BAMBIC items. Children with ASD were more likely to scream or cry at mealtimes (P=0.04), turn their face or body away from food (P=0.03), close the mouth tightly when food was presented (P=0.04), and show aggressive behavior (P=0.04) and disruptive behavior (P=0.006) than typically developing children.

Comparison of the groups on food preferences revealed that a significantly higher proportion of children with ASD refused to eat commonly consumed fruits like apple (P=0.004), pomegranate (P<0.001), and guava (P=0.04); and vegetables like bitter gourd (P=0.004), ladyfinger (P=0.009), potato (P=0.06), and cauliflower (P=0.002), and proteins like red kidney beans (*rajma*) (P=0.004), chick peas (*chana*) (P=0.02), and snacks like cold drinks (P=0.02) and chips (P=0.003). Despite

Table I Comparison of Groups on Socioeconomic and Demographic Variables

Characteristics	*ASD (n=50)*	*TD (n=28)*
Age (y), mean (SD)	5.3 (1.38)	5.96 (1.38)
Boys, *n* (%)	72.0	67.9
Urban residence, *n* (%)	70.0	51.1
Socioeconomic status, n (%)		
Lower	12.0	25.0
Middle	64.0	57.1
Upper	24.0	17.9
Nuclear family, *n* (%)	56.0	53.6

ASD: autism spectrum disorder; TD: typically developing children. All P values >0.05.

limited food diversity, no significant group differences on the mean daily intake of calories (P=0.9) and fats were found. However, children with ASD had lower consumption of proteins (P=0.04), vitamin D (P=0.04) and folic acid (P<0.001) when compared to typically developing children. Among the micronutrients, the mean intake of sodium was also significantly low (P=0.002). The intake of vitamin C, copper, zinc, and calcium were comparable.

Significantly higher proportion of children with ASD showed atypical response on all the subscales on the short sensory profile as compared to typically developing children (**Table II**). The mean total score on the SSP score (P<0.001) and all the subscales of the SSP profile were significantly lower as compared to control group suggesting atypical sensory processing in children with autism. Specifically, ASD children had lower scores than the control group on the subscales of tactile sensitivity (P<0.001), taste sensitivity (P<0.001), movement sensitivity (P<0.001), under responsiveness (P<0.001), auditory filtering (P<0.001), low weak/energy (P=0.02), and visual/auditory sensitivity (P<0.001). Anthropometric parameters were comparable in terms of weight (P=0.0.2) and BMI (P=0.55); however, ASD children had significantly lower height as compared to the typically developing group (P=0.04).

Multivariate stepwise regression analysis revealed that 31% of the total score variance on the BAMBIC scale was explained by two of the SSP subscales, namely the taste sensitivity and the auditory-visual sensitivity. Parents of ASD children with more atypical scores on the taste/smell and auditory/visual subdomains of the SSP were significantly more likely to report mealtime behavior difficulties (P=0.01).

Table II Performance on Short Sensory Profile (SSP) for Children With Autism Spectrum Disorder and Typically Developing Children

Subscales of SSP	*Autism spectrum disorder, n=50*	*Typically developing children, n=28*
Tactile sensitivity	23.63.55)	30.1 (2.99)
Taste sensitivity	11.7 (3.57)	15.9 (2.78)
Movement sensitivity	9.9 (2.73)	12.9 (1.72)
Under responsive	21.4 (4.28)	28.8 (3.92)
Auditory filtering	16.7 (3.93)	24.4 (4.68)
Low/weak energy[a]	22.4 (4.75)	25.0 (4.13)
Visual/auditory sensitivity	17.3 (3.75)	21.3 (2.47)
Total score	123.06 (13.83)	158.32 (15.49)

All values in mean (SD). P<0.001 for all comparisons except [a]P=0.02.

DISCUSSION

We examined sensory sensitivities, mealtime behaviors, and nutritional insufficiencies of children with ASD and compared it to a group of typically developing children matched on age. Parents of children with ASD reported significantly greater number of problem behaviors during feeding, food refusal, higher sensory sensitivities, and nutritional deficiencies as compared to controls. Indeed, the prevalence of a restricted variety of foods consumed by children with autism is 30-84% and these rates are significantly higher than those reported in typically developing children [2,4,14-15]. Moreover, atypical eating behaviors among ASD children are also related to increased problem behaviors in children including heightened irritability, anxiety, emotional lability, and oppositional behavior [3,7].

Previous studies have found a significant association between oral, visual and auditory sensitivities and a number of feeding problems [9-11,16-18]. Evidence indicates that the ASD children with atypical oral sensory processing refuse more foods and eat fewer vegetables and it has been suggested that addressing the oral sensory processing problems may help in mitigating selective and picky eating [7,18,19]. Current findings extend previous research by documenting that the auditory and visual sensitivities may also be associated with limited food repertoire in children with ASD. Possibly, the noise during mealtimes, ongoing conversations, sound of the spoon against utensils and the like may cause the hypersensitive ASD children to overreact, and this may reflect in lower quality of diet, rejection of nutritious foods, and disruptive behaviors at mealtimes. Children with visual sensory dysfunction may also be overly sensitive to the presentation of meals as this may be associated with food aversions, unpleasant food textures, picky eating, and behavioral disturbances.

Previous studies have reported that feeding problems may not translate into non-optimal growth in the short run, and caution should be exercised on anthropometric measures' reliability as measures of dietary adequacy in children with ASD [2,14,20]. Our results further extend these findings that consumption of a limited food variety may put young children with autism at higher risk for nutritional insufficiencies and compromised growth. However, these findings need further corroboration as they are based on a small size of ASD children.

The study has a few limitations including the small sample size, which may have resulted in decreased power for analyzing differences between groups. Moreover, obtaining a reliable three-day dietary record of the child was often challenging as parents had difficulty in

WHAT THE STUDY ADDS?

- Feeding problems in children with autism spectrum disorder are associated with sensory processing sensitivities.

recalling and estimating quantities of various foods consumed by the child. Perhaps maintaining a detailed behavioral mealtime log may help get more valid information on the child's food intake. Future extension of the work needs to incorporate more objective measures along with parent reported questionnaires.

Children with ASD have marked feeding problems along with sensory processing sensitivities, nutritional inadequacies, and compromised growth. The study underscores the need for a detailed evaluation of mealtime behaviors and sensory processing dysfunction of children with ASD, so that interventions can be initiated at the earliest to increase food intake variety and encourage healthy eating habits. Intervention strategies need to be personalized to address each child's unique sensory characteristics, and a sensory integration approach may be used to alleviate mealtime challenging behaviors and caregiver burden.

Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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Contributors: PM, BB, SA, NS: designed the study; PM,BB: supervised the data collection, and analyzed and interpreted the data; SS: collected the data, did the literature search, helped in analysis and interpretation of the data, and drafting of the manuscript; PM: wrote the manuscript with critical inputs from other authors. All the authors read and approved the final manuscript.

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Web Table I Comparison of Children With Autism Spectrum Disorder and Typically Developing Children on Brief Assessment of Mealtime Behavior in Children

Subscale/items of BAMBIC	*Group*	*Never/seldom*	*Occasionally*	*Often/always*	*P value*
Food refusal subscale					
Screams during mealtimes	ASD TD	52.0 75.0	24.0 21.4	24.0 3.6	0.047
Turns face away from food	ASD TD	36.0 67.9	28.0 14.3	36.0 17.9	0.03
Closes mouth when food presented	ASD TD	40.0 67.9	16.0 14.3	44.0 17.9	0.04
Limited variety subscale					
Tries new foods	ASD TD	36.0 42.9	30.0 14.3	34.0 42.9	0.29
Dislikes certain foods	ASD TD	40.0 57.1	26.0 21.4	34.0 21.4	0.32
.Prefers same food	ASD TD	38.0 71.4	34.0 10.7	28.0 17.9	0.01
Accepts variety of foods	ASD TD	30.0 39.3	24.0 7.1	46.0 35.9	0.17
Disruptive behavior subscale					
Aggressive during mealtimes	ASD TD	50.0 78.6	22.0 10.7	28.0 10.7	0.04
Self-injurious at mealtimes	ASD TD	72.0 92.9	18.0 7.1	10.0 0.0	0.07
Disruptive during mealtimes	ASD TD	46.0 82.1	32.0 14.3	22.0 3.6	0.006

Values in percentages. BAMBIC-Brief assessment of mealtime behavior in children; TD- typically developing children; ASD-autism spectrum disorder.

RESEARCH PAPER

Long-Term Morbidity and Functional Outcome of Japanese Encephalitis in Children: *A Prospective Cohort Study*

Abhijit Dutta,[1] Shankha Subhra Nag,[1] Manjula Dutta,[2] Sagar Basu[3]

From [1]Department of Pediatric Medicine, North Bengal Medical College and Hospital, Sushruta Nagar, Siliguri; [2]Department of Microbiology, School of Tropical Medicine, Kolkata; and [3]Department of Neurology, KPC Medical College and Hospital, Kolkata; West Bengal.

Correspondence to:
Dr Shankha Subhra Nag,
Embee Fortune, Flat No. D3H,
Near BSF Camp, Asian Highway 2,
Kadamtala, Siliguri 734 011,
West Bengal.
dr.ssnag@gmail.com
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Objective: To describe the long term morbidity and functional outcome of Japanese encephalitis in children. **Methods:** Laboratory-confirmed Japanese encephalitis cases were enrolled in the study from January, 2016 to September, 2017 and surviving cases were prospectively followed up for 2.5 years to document various morbidities. Outcome was functionally graded at discharge and during follow-up using Liverpool outcome score. **Results:** Out of 56 children enrolled, 10 (17.9%) died during hospital stay; severe sequelae was observed in 17 (30.4%) at discharge. At the end of study, among 37 children under follow-up, 23 (62.2%) recovered fully, 2 (5.4%) showed minor sequelae, 3 (8.1%) had moderate sequelae, and 9 (24.3%) were left with severe sequelae. Common long term morbidities were abnormal behavior (*n*=10, 27%), post encephalitic epilepsy (*n*=8, 21.6%), poor scholastic performance (*n*=8, 21.6%) and residual motor deficit (*n*=7, 18.9%). Improvement of morbidities was noted mostly within initial 1 year of follow-up. **Conclusions**: More than half of the Japanese encephalitis survivors recovered fully, most within the first year after discharge.

Keywords: *Dystonia, Epilepsy, Movement disorder, Quadriplegia.*

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Japanese encephalitis is considered a major public health problem due to its epidemic potential, high case fatality rate up to 30%, and residual neuropsychiatric morbidities in 30-50% [1]. It continues to occur in endemic areas of India, despite the introduction of the vaccine in Universal immunization program in 2011 [2-4]. Quantification of long term outcome and its classification in terms of extent of disability is essential, so that the impact of the disease on independent livelihood can be understood. There is paucity of data regarding long term outcome of JE in children [5-7]. Therefore, this study was conducted to find out the magnitude of morbidity and its evolution over time.

METHODS

This prospective cohort study was conducted from January, 2016 to March, 2020 at a tertiary care teaching hospital of eastern India, after obtaining clearance from the institutional ethics committee. Children aged up to 12 years admitted with acute encephalitis syndrome (AES) were subjected to laboratory tests for detection of JE. Anti-JE IgM antibody capture (MAC) ELISA was performed on cerebrospinal fluid and serum samples using ELISA kit (NIV JE IgM Capture ELISA Kit, version 1.5). Diagnosis of JE was confirmed by detection of anti-JE IgM antibody in cerebrospinal fluid (CSF), or both in CSF and serum samples. Patients with positive results were consecutively enrolled till September, 2017, after taking informed consent from parents. They were managed as per standard guideline including empirical broad spectrum antibiotics and acyclovir, maintenances of fluid, electrolyte, acid-base balance and euglycemia, management of raised intracranial pressure, control of seizures, management of nosocomial infection and other complications, and rehabilitation therapy [8]. Background demographic and relevant clinical data and results of various laboratory investigations including magnetic resonance imaging (MRI) of brain were noted. Discharged patients were followed up for two-and-a-half years at out-patient department and detailed clinical examination was done to document clinical status. They were provided with symptomatic and supportive management during these visits. EEG was performed in children with history of seizures either during hospital stay or during follow-up. After documentation of full recovery, patients were kept under telephonic follow-up till the end of the study.

Table I Morbidity Profile in Children With Japanese Encephalitis at Various Stages of Follow-up

Morbidity	*At discharge (n=46)*	*6 mo (n=38)*	*1 y (n=37)*	*2 y 6 mo (n=37)*
Motor deficit	21 (45.6)	10 (26.3)	7 (18.9)	7 (18.9)
Abnormal behavior[a]	-	18 (47.4)	16 (43.2)	10 (27.0)
Epilepsy	18 (39.1)	12 (31.6)	12 (32.4)	8 (21.6)
Poor scholastic performance[b]	-	12 (31.6)	8 (21.6)	8 (21.6)
Incoordination	13 (28.3)	2 (5.3)	2 (5.4)	2 (5.4)
Feeding problems	13 (28.3)	3 (7.9)	3 (8.1)	3 (8.1)
Dystonia	12 (26.1)	6 (15.8)	2 (5.4)	2 (5.4)
Dysarthria	7 (15.2)	2 (5.3)	2 (5.4)	2 (5.4)
Language difficulty	9 (19.6)	2 (5.3)	2 (5.4)	2 (5.4)
Urinary incontinence	5 (10.9)	2 (5.3)	2 (5.4)	2 (5.4)

All values in no. (%). Evaluation started at [a]1 mo or [b]3 mo of discharge.

The Liverpool Outcome Score (LOS) [9,10], previously validated in Indian children [11], was used in the present study for functional grading of disability at discharge and during follow-up. It assesses motor, cognition, self-care and behavior using ten questions to parents or caregivers, and observation of response to five simple motor tasks given to the child. Outcome grading was assigned based on minimum score obtained in any of the domains. Based on score obtained, LOS classifies outcome as full recovery, minor sequelae, moderate sequelae, severe sequelae, and death.

Statistical analysis: Descriptive statistics were used. Data were analyzed using IBM Statistical Package for Social Sciences version 20.0 (SPSS, IBM Corp).

RESULTS

A total of 194 children with features of AES were screened, and 56 (28.8%) children (57.1% boys) were diagnosed with laboratory confirmed JE during the study period. Anti-JE IgM was detected in both CSF and serum in 44 children, and in only CSF in another 12 children. Two children were below 1 year of age, 17 between 1-5 years and the rest between 5-12 years age group; median (IQR) age of study population was 6 year 3 month (5 year 10 month, 9 year 1 month). Most common clinical features were fever (*n*=56, 100%), altered sensorium (*n*=51, 91.1%), seizures (*n*=36, 64.3%), signs of meningeal irritation (*n*=27, 48.2%) and headache (*n*=21, 37.5%). Glasgow Coma Scale of 8 or less was observed among 12 children (21.4%) at admission. Median (IQR) duration of symptoms before admission and duration of hospitalization was 3.5 (2,5) days and 15.7 (11, 24.2) days, respectively. MRI of brain could be performed in 38 children, of which 26 (68.4%) were abnormal. Common sites of involvement were thalamus (*n*=22, 84.6%), basal ganglia (*n*=16, 61.5%), cortex (*n*=12, 46.2%), brainstem (*n*=9, 34.6%), medial temporal lobe (*n*=6, 23.1%) and cerebellum (*n*=2, 7.7%). Hemorrhagic lesion was found in 3 children (11.5%) in addition to involvement of other parts of brain; 2 had cerebral hemorrhage and 1 had subdural hemorrhage. Ten cases (17.9%) died during the hospital stay. At the time of discharge, 17 children (30.4%) had severe sequelae, 5 (8.9%) had moderate sequelae, 6 (10.7%) developed minor sequelae, and 18 children (32.1%) showed full recovery as per LOS.

At the end of 2 year 6 month of follow-up, we observed full recovery among all children with minor sequelae. Two out of 5 children categorized as moderate sequelae at the time of discharge showed full recovery; 1 child improved and had only minor sequelae. Two children with severe sequelae died within 2 weeks of discharge. Of the 15 surviving patients with severe sequelae, one improved considerably and had only minor sequelae, three improved and were categorized as moderate sequelae, and nine children remained as severe sequelae. Three fully recovered children, and two children each from moderate and severe sequelae group were lost to follow-up. At the completion of the study, it was observed that among 37 children remaining under follow-up, 23 (62.2%) had recovered fully and 14 (37.8%) were left with variable degrees of sequelae (**Fig. 1**).

Motor deficit was noted in 21 children (45.6%) at discharge; quadriparesis in 14, hemiparesis in 6, and monoparesis in one child. With rehabilitation therapy, satisfactory motor improvement was noted in majority of children (66.7%) within the first year of follow-up. Behavioral abnormalities evolved fully at 1 month of discharge and were noted among 24 children; predominant features were excessive anger (*n*=12), irritability (*n*=8), aggressiveness (*n*=5), sudden bouts of

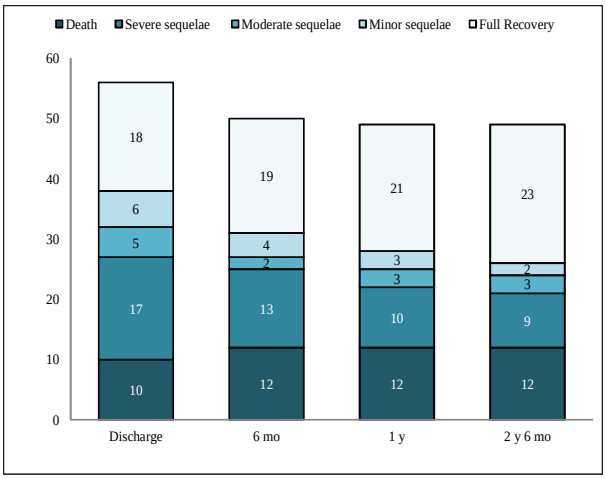

Fig. 1 Sequelae at different stages of follow-up in Japanese encephalitis affected children.

unexplained cry or laughter (n=3), and irrelevant talking (n=1). Four children were unable to recognize family members initially, and the problem persisted in one of them. At the end of follow-up, abnormal behavior persisted in 10 (27%) children.

In the acute phase of the disease, 36 children presented with seizures, mostly of generalized tonic-clonic type; 17 of them needed two or more anti-epileptic drugs (AEDs). EEG was performed in 26 children, 18 (69.2%) were abnormal. These children were having recurrent seizures and AED was continued during follow-up. Among 12 children receiving AEDs at 2 years, therapy was stopped in six as they were seizure free with normal EEG, but two children had relapse of seizures after stoppage of drugs, and therapy was restarted. Till the end of the study, 8 children (21.6%) were on AED.

Among cases under follow-up, 23 children were school-going. Poor scholastic performance was observed in 8 (21.6%) children in the long term; another 7 of them became drop-outs due to motor deficits, behavioral problems and apprehension of seizures. Dystonia was noted in 12 children (26.1%) at the time of discharge, which improved substantially within first 6-9 months. Two children showed persistence of language problem, one with motor aphasia and another with global aphasia. Feeding problems were seen predominantly in first 6 months of follow-up; mostly due to motor deficit, in-coordination and abnormal behavior.

DISCUSSION

In the present study, 56 children diagnosed with Japanese encephalitis were evaluated by Liverpool Outcome Score which showed mortality of 17.9% and 30.4% with severe sequelae at discharge. At the end of 2.5 year follow-up, 62.2% children recovered fully and 37.8% children were left with variable degree of sequelae.

Previous studies have reported a wide range of mortality (8-25%) and severe sequelae (11-25%) with Japanese encephalitis [5,6,12-15]. Subjective nature, and therefore lack of uniformity of classification, and varying duration of follow-up may be responsible for wide range of sequelae noted in different studies. The various morbidities observed in our cohort are in agreement with previous studies [5-7,13,14]. The extent of improvement among different morbidities varied in our study population. Few patients with poor clinical and radiological features showed unexpected remarkable improvement during follow-up. Whereas some survivors with severe sequelae showed improvement of different morbidities; nevertheless they could not be placed at better functional grading as some other domains did not improve. In addition, residual neuro-psychiatric problems prevented a significant proportion of children from returning to normal life.

Only few studies have described long term outcome of Japanese encephalitis affected children beyond 1 year, most probably due to remote residence of patients causing difficulty in follow-up [5-7]. Improvement of morbidities was noted mostly within initial 9-12 months of follow up, and there was no noteworthy additional improvement afterwards. Previous studies also shown majority of improvements within initial 6-12 months for most of the Japanese encephalitis survivors and neurological status at initial months of discharge was predictive of long term outcome [5,6]. Some authors noted neurological deterioration (microcephaly and hyperactive behavior) several years after discharge in some survivors and suggested the need for long term follow up [6]. However, we did not observe worsening of neuro-psychiatric status in any child till the end of follow up.

Relatively smaller sample size is a limitation of the present study. Similarly, we were unable to predict which category of children might improve and to what extent. We suggest future studies to look into these aspects. Considering high mortality and long term morbidities, preventive aspects of the disease need to be prioritized.

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Contributors: AD: conception of the study, acquisition of data and revising the manuscript for important intellectual content. SSN: design of the study, acquisition of data and drafting the manuscript; MD: acquisition of data revising the manuscript for

WHAT THIS STUDY ADDS?

- Nearly two-thirds of survivors of Japanese encephalitis recover without any sequelae.
- Common long term morbidities observed are residual motor deficits and abnormal behavior.

important intellectual content; SB: interpretation of data and revising the manuscript for important intellectual content. All the authors approved the version to be published and agreed to be accountable for all aspects of the work ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CLIPPINGS

Early Cost-Effectiveness of Onasemnogene Abeparvovec-xioi (Zolgensma) and Nusinersen (Spinraza) Treatment for Spinal Muscular Atrophy I in The Netherlands With Relapse Scenarios (Value Health. 2021;24:759-69**)**

The goal of this study was to perform a cost-effectiveness analysis of treatment of SMA I patients with Onasemnogene Abeparvovec-xioi (AVXS-101) in The Netherlands including relapse scenarios. An individual-based state-transition model was used to model treatment effect and survival of SMA I patients treated with AVXS-101, nusinersen and best supportive care (BSC). The model included five health states: three health states according to SMA types, one for permanent ventilation and one for death. Based on this model, treatment with AVXS-101 was found unlikely to be cost-effective under Dutch willingness-to-pay reference values.

KAUSIK MANDAL
kausik@sgpgi.ac.in

RESEARCH PAPER

Antiseizure Drug Levels in Children Aged 2-12 Years Presenting With Breakthrough Seizures: A Single Center Cross-sectional Study

RAJAN GARG,[1] ANJU AGGARWAL,[1] SANGEETA SHARMA,[2] MANISH NARANG,[1] RAJEEV MALHOTRA[3]

From [1]Department of Pediatrics, UCMS and GTB Hospital, Delhi; [2]Department of Neuropsychopharmacology, Institute of Human Behaviour and Allied Sciences, Delhi; and [3]Department of Statistics, Delhi Cancer Registry, Dr. BRAIRCH, AIIMS, New Delhi.

Correspondence to: Dr. Rajan Garg, Department of Pediatrics, University College of Medical Science and GTB Hospital, Delhi110095. drrajang1990@gmail.com
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Objective: To study the antiseizure drug levels and associated factors in children with breakthrough seizures. **Methods:** This cross-sectional study conducted at a public hospital from November, 2017 to April, 2019, included 145 children with epilepsy aged 2 to 12 years presenting with breakthrough seizure. Antiseizure drug levels were measured, and the levels were categorized as within, below, and above the reference range. **Results:** Children with epilepsy receiving sodium valproate, phenytoin and carbamazepine were 111 (73%), 31 (20.4%) and 10 (6.6%), respectively, of which 7 were receiving multiple antiseizure drugs. Drug levels below the reference range were found in 64 (44.1%), within the reference range in 70 (48.3%), and the above reference range in 11 (7.6%) children. **Conclusion:** Nearly half the children with breakthrough seizures had sub-therapeutic levels, especially those on phenytoin therapy. Drug levels in below therapeutic range were not associated with occurrence of breakthrough seizures.

Keywords: *Precipitating factors, Reference range, Therapeutic drug monitoring*.

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In children with well-controlled epilepsy, a breakthrough seizure may occur in up to 40% [1]. International League Against Epilepsy (ILAE) recommends that plasma levels of antiseizure drugs should be interpreted as within, below, and above the reference range [2]. Therapeutic drug monitoring (TDM) helps in dosage individualization based on clinical response [3]. Therefore, a therapeutic range is introduced, which defines drug concentration associated with the best achievable response in a given person. The benefits of TDM are in case of status epilepticus, polypharmacy, change in drug dose/formulation, and clinical toxicity. It also helps to assess compliance, and guide dosage adjustment in children with associated liver and kidney diseases [2,4,5]. Well-delineated precipitating factors precede epileptic attack and commonly include fever, sleep deprivation, and stress [1,6,7]. Non-compliance to the treatment is another common cause [6,7].

There is a relative lack of literature on an antiseizure drug levels in children with a breakthrough seizure. Therefore, this study was planned to describe the association between the occurrence of a breakthrough seizure and anti-seizure drug levels.

METHODS

A cross-sectional study was conducted at the pediatrics department of a public tertiary care hospital from November, 2017 to April, 2019, after obtaining clearance from the institutional ethics committee. A written informed consent was obtained from the parents/ guardians/caregivers.

Children aged 2 to 12 years either having an active breakthrough seizure or those who had a breakthrough seizure within the last 24 hours and receiving either one or two anti-seizure drug (phenytoin, carbamazepine, sodium valproate) were enrolled from the emergency room or the outpatient department. Patient's demographic, clinical, and investigation details (serum sodium and potassium, blood glucose, and total leukocyte count) were recorded in a pre-designed case record form. Compliance with the drugs was ensured after taking a detailed history. For this study, a breakthrough seizure was defined as seizures in a child with epilepsy on one or two anti-seizure drugs, who did not have any seizure activity in the last one month. Generic form of anti-seizure drugs were available free of cost to the patients from the hospital formulary. The dose of antiseizure drug and treatment for epilepsy was given as per the guidelines followed in the hospital. Children who had received a loading dose of any antiseizure drug before presentation, those with deranged blood glucose/serum electrolyte levels, history of myoclonic or absence seizure, and known patients of chronic liver disease/chronic renal disease, meningitis, syndromic epilepsies, and known

non-compliance (missed >3 doses of anti-seizure drug) were excluded.

A venous blood sample (3 mL) was collected aseptically in serum vial before the loading dose of the antiseizure drug. Serum was separated within 30 min and stored at 0-8 ºC. Drug level estimation was done using CEDIA II kits (Thermofisher Scientific/2018) based on recombinant DNA technology to create a homogenous immunoassay system. The minimum detectable concentration of CEDIA Phenytoin II, Carbamazepine II, and Valproic acid II assays was 0.6 mg/L, 0.5 mg/L and 3.0 mg/L. The reference range for serum levels of phenytoin, carbamazepine, and sodium valproate was considered between 10-20 mg/L, 4-12 mg/L, and 50 to 100 mg/L, respectively, as per laboratory and kit specifications.

According to a previous study [8], serum levels of first-line antiseizure drug were in the below reference range in 40% of cases with breakthrough seizures. Using the formula for hospital-based population proportion with confidence interval 95%, estimated prevalence of 40%, power of 80%, a error of 5%, and acceptable absolute precision of ±8% (acceptable relative precision of 20%), the sample size was calculated as 144. Thus, 145 children were planned to be enrolled.

Statistical analysis: Analysis was performed using SPSS version 20 software. Pearson Chi-square / Fisher exact test was used to assess the association between demographic and clinical variables with below and normal reference range of antiseizure drug; the above range subjects were not included in the comparison. The 95% confidence level of below reference range proportion was determined using the binomial Wald method. *P* value of <0.05 was taken as significant.

RESULTS

A total of 145 children (97 males) were enrolled with a mean (SD) age of 6.9 (3.0) years. Generalized seizures were seen in 93 (64.1%) children, and normal development was seen in 90 (62.1%) children. Microcephaly was found in 26 (17.9%) children. All children had baseline laboratory parameters within the normal range. A single drug was being used by 138 children (sodium valproate-104, phenytoin-26, and carbamazepine-8). Two drugs were prescribed in 7 children (5-phenytoin/sodium valproate and 2-carbamazepine/sodium valproate).

Drug levels in the below reference range were found in 64 (44.1%), within the reference range in 70 (48.3%), and above reference range in 11 (7.6%) children. Children with polytherapy had drug levels in below reference range in five children on phenytoin, one on carbamazepine and three on sodium valproate therapy. The proportion of children and the serum level of different drugs is shown in **Table I**. The associated clinical and demographic variables were comparable across the various drug levels of different anti-seizure drugs (**Table II**). Children with focal seizures had twice the number of children in the reference range group as compared with the below reference range group ($P<0.05$). Precipitating factors were fever in 19 (13.1%) and sleep deprivation in 4 (2.8%) children. Precipitating factors were not significantly associated with anti-seizure drug levels (**Table II**).

Table I Antiseizure Drug levels in Children With Breakthrough Seizures

Anti-seizure drug[a]	*Below reference range, n=64*	*Within reference range, n=70*	*Above reference range, n=11*
Valproate	38 (34.2)	62 (55.9)	11 (09.9)
Phenytoin	29 (93.6)	1 (3.2)	1 (3.2)
Carbamazepine	3 (30.0)	7 (70.0)	0

Data in no. (% of row total).[a]*Single drug was received by 138 children, and two drugs were prescribed in 7 children.*

DISCUSSION

The antiseizure drug levels were comparable among the children on monotherapy or polytherapy with sodium valproate, phenytoin and carbamazepine who presented

Table II Demographic and Clinical Characteristics and Serum Drug Levels in Children With Breakthrough Seizures

Characteristics	*Below reference range n=64*	*In the reference range n=70*	*Above reference range n=11*
Mother's education			
Iliterate	22 (15.2)	21 (14.5)	3 (2.1)
Primary	35 (24.1)	31 (21.4)	7 (4.8)
Secondary	5 (3.4)	8 (5.5)	1 (0.7)
Graduate and beyond	2 (1.4)	10 (6.9)	0
Socioeconomic status			
Upper lower	39 (26.9)	39 (26.9)	4 (2.8)
Lower middle	23 (15.9)	25 (17.2)	7 (4.8)
Upper middle	2 (1.4)	6 (4.1)	0
Normal development	41 (28.3)	43 (29.7)	6 (4.1)
Seizure type[a]			
Generalized	48 (33.1)	39 (26.9)	6 (4.1)
Focal	16 (11.0)	31 (21.4)	5 (3.4)
Precipitating factor present	10 (6.9)	12 (8.3)	1 (0.7)

Data in no. (%). For comparison between below reference vs reference range groups, all P>0.05 except [a]*P=0.02.*

WHAT THIS STUDY ADDS?

- No association was found between serum antiseizure drug levels and breakthrough seizures in children compliant to antiseizure drugs.

with breakthrough seizures. Of the total children receiving sodium valproate and carbamazepine, 34.2% and 30% of children had levels below the reference range. However, on phenytoin therapy, 93.6% of children had serum levels below the reference range.

The results of the valproate and carbamazepine group were comparable with two previous Indian studies [8,9]. While in case of phenytoin, previous Indian studies [8,10] reported 43% and 68% patients had drug levels below the reference range, which was quite high as compared to the other antiseizure drugs. The difference in the phenytoin group could be due to narrow therapeutic index, suspension form of syrup, and variable pharmacokinetics in different individuals and age groups [9]. Kumar, et al. [1] reported precipitating factors in 37% of children; though many factors reported by them were not elicited in our study.

Limitations of our study include a cross-sectional study design with no longitudinal follow-up. It is a hospital-based study with only single-center results and a mixed population of children with varied diagnosis. Comparison with a group of children with a well-controlled epilepsy would have increased the validity of the study. The strength of this study includes a large sample size, with breakthrough seizure as the sole indication for TDM, which was done in an accredited lab.

Drug levels within reference range are more important in controlling generalized seizures than focal seizures where other factors may have a greater role. A greater number of children compliant on phenytoin drug had levels below reference range in both groups of with and without precipitating factors. Antiseizure drug levels should not be blindly followed for seizure control in children with breakthrough seizures, and specific indication should be kept in mind before obtaining the drug levels. The concept of therapeutic range should be considered [2]. There is a need for study in a larger sample and a homogenous population to determine critical levels at which breakthrough seizures are likely to occur.

Ethics clearance: Institutional ethics committee of University College of Medical Sciences; No. IEC-HR/2017/32/93, dated October 17, 2017.
Contributors: AA: conception and design; RG: collection and assembly of data; RG,AA,SS,MN: manuscript writing, review of literature, intellectual inputs: RM,RG,AA: data analysis and interpretation. All authors approved the final version of the manuscript, and are accountable for all aspects of the study.
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RESEARCH PAPER

Outcome of Neonates Born to COVID-Positive Women at 6 Months of Age

Dinesh Munian,[1] Rituparna Das,[1] Avijit Hazra,[2] Somosri Ray[1]

From Department of [1]Neonatology, Medical College and Hospital, Kolkata, West Bengal; [2]Department of Pharmacology, Institute of Postgraduate Medical Education & Research (IPGME&R) and SSKM Hospital, Kolkata, West Bengal.

Correspondence to: Dr Somosri Ray, Department of Neonatology, Medical College and Hospital, Kolkata 700 073, West Bengal. dr.somosri@gmail.com
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Objective: To compare clinical and neurodevelopmental outcome at the age of 6 months for neonates born to SARS-CoV-2-positive mothers. **Methods**: Neonates of SARS-CoV-2 positive mothers, admitted in our hospital were assessed for growth, neurodevelopment by Amiel-Tison method, and Developmental Profile (DP3) at discharge as part of another study (July 2020). This data were retrieved and babies followed-up at the age of 6 months. Composite adverse outcome was death within 6 months post discharge or DP3 score <70 and hearing/visual deficit. **Results**: Out of 131 enrolled at discharge, 127 (97%) were followed up. SARS-CoV-2 positive neonates (Group I; 19, 15%) had more symptoms (P=0.012), sepsis (P=0.014), pneumonia (P=0.029), longer hospital stay (P<0.001) following birth compared to group II (SARS-CoV-2 negative neonates;108, 85%). No baby in group I met definition of composite adverse outcome, while in group II it was 0.9% (1 child with DP3 <70 with hearing deficit) (P=1.0) without any difference in hospital readmission, growth, DP3 scores, or tone abnormalities. **Conclusions**: There is no difference in growth, neurodevelopment, and hospital readmission in early infancy among infected and non-infected babies born to SARS-CoV-2 positive mothers.

Keywords: *Corona virus,* SARS-CoV-2*, Neonate, Neurodevelopment*.

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Adverse pregnancy outcomes have been documented with two earlier pathogenic coronavirus infections – severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [1]. However, most severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) -positive neonates (50%) were symptomatic with predominant respiratory symptoms attributed to coronavirus disease (COVID) [2,3] and required intensive care. Among symptomatic SARS-CoV-2 positive neonates, morbidities also relate to prematurity and perinatal events [4].

Information on long term outcome of neonates following COVID-19 is lacking so far. Only a handful of studies are available following SARS [5,6]. Hence, we planned to assess clinical and neurodevelopmental outcome in early infancy for neonates born to SARS-CoV-2 positive mothers.

METHODS

After institutional ethics committee approval, information was retrieved from hospital records for the present study. Demographic details, clinical features, hospital course, and SARS-CoV-2 positively status were collected for all neonates born to SARS-CoV-2 positive mothers during May to July, 2020, as part of a previous study [unpublished data].

Nasopharyngeal and oropharyngeal swabs for COVID-19 real time-polymerase chain reaction (RT-PCR) were sent at 24-48 hours of life [7]. For outborns, if admitted beyond 48 hours, RT-PCR test was done at admission. The test was repeated immediately, if new symptoms appeared, even if the first test was negative; otherwise test was repeated after 5 days. For SARS-CoV-2 positive neonates, repeat test was done after 10 days and they were discharged, if negative.

After parental consent, the children were assessed in the neonatal follow-up clinic at 14 days following discharge, then at 6 weeks, 3 months and 6 months of corrected age. Weight, length and head circumference were measured using electronic weighing scale, infantometer, non-stretchable fiberglass tape, respectively and plotted on WHO growth chart [8]. The advanced or delayed development across five domain scores – physical, adaptive behavior, social-emotional, cognitive and communication – and the general development score were plotted at 6 months of corrected age as per Developmental Profile 3 (DP3) manual by a single investigator [9]. Children were classified as per following scheme: Score <70 – delayed, 70-84 – below average, 85-114 – average, 115-130 – above average, and >130 – well above average.

Neurological examination was done by a single

investigator as per Amiel-Tison method [10]. Retinopathy of prematurity (ROP) screen, if indicated, and brainstem evoked response audiometry (BERA) with age-appropriate behavioral audiometry were done at follow-up. During follow-up, parents were interviewed with pre-tested and pre-validated questionnaire containing questions on details of their baby's readmission (if any till date). The details of readmission were confirmed by checking the discharge certificates or verified from medical records if readmitted in our hospital. All babies readmitted in our hospital underwent RT-PCR for SARS-CoV-2.

Primary outcome was adverse composite outcome defined as death within 6 months post discharge or developmental delay (defined as DP3 score <70) with hearing/visual deficit. Secondary outcomes were DP3 scores, hearing, visual deficit, abnormal tone, growth *z*-scores at follow-up, hospital readmission rate, noninvasive/invasive respiratory support days during readmission.

Statistical analysis: Numerical variables were compared between groups by Student independent samples *t* test, if normally distributed or by Mann-Whitney *U* test, if otherwise. Fisher exact test or Pearson chi-square was employed for intergroup comparison of categorical variables. All analyses were two-tailed and statistical significance was set at $P < 0.05$ for all comparisons.

RESULT

Out of 131 enrolled neonates, results of 127 (97%) babies were analyzed (**Fig. 1**). All mothers were RT-PCR positive at median (IQR) of 5 [2,8] days before delivery. All symptomatic SARS-CoV-2 positive neonates (n=10) had sepsis like manifestations (**Table I**). None had meconium aspiration syndrome, hyaline membrane disease or moderate to severe perinatal asphyxia. SARS-CoV-2 positive neonates (group I) were more symptomatic (P=0.012), more commonly had sepsis (P=0.014) or pneumonia (P=0.029), and had longer duration of hospital stay (P<0.001) compared to group II.

There was no death post-discharge. During follow-up, no infant in group I met definition of composite adverse outcome, while in group II one child (0.9%) had DP3 score <70 with hearing deficit (P=1.0). There were no differences in DP3 scores and anthropometry among the two groups (**Table II**). BERA was done in 2 out of 19 babies in group I, which was normal in all, while in group II, it was done in 10 babies and was normal in 9 babies (P=1.0). No baby had abnormal ROP (done for only 9 babies). No babies other than one with delayed development in group II had abnormal tone.

Seven babies from group II (pneumonia 3, bronchiolitis 1, viral upper respiratory infection and diarrhea 1, sepsis with poor feeding and lethargy 2) and two from group I (bronchiolitis 1, diarrhea 1) were readmitted. SARS-CoV-2 RT-PCR were negative in all 9 readmitted babies. None required noninvasive or invasive mode of ventilation following readmission. There was no difference in course on readmission (**Table II**).

DISCUSSION

In our study, no SARS-CoV-2 positive neonate in infancy met definition of Composite adverse outcome, at 6 months while it was 0.9% in the other group.

Neonates are said to be exposed to SARS-CoV-2 if they are born to the mothers with a history of SARS-CoV-2 infection diagnosed 14 days before or 28 days after

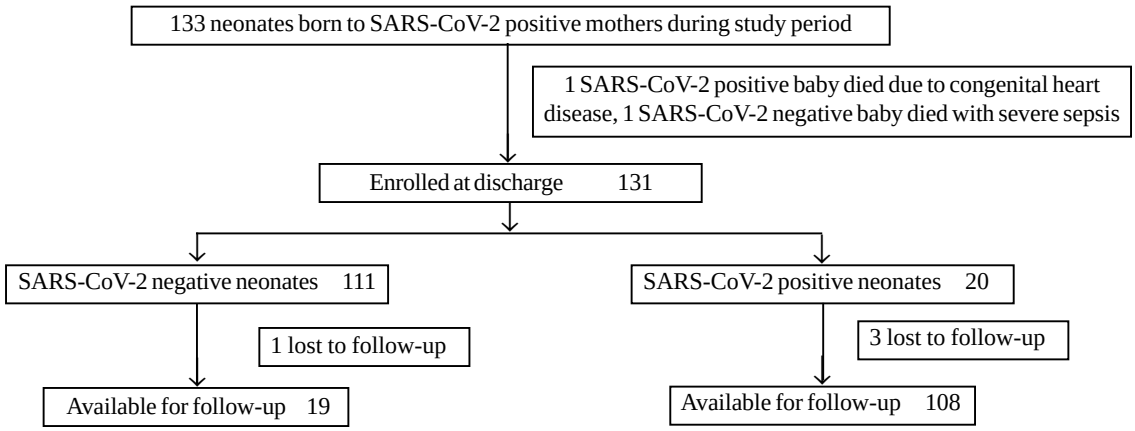

Fig. 1 Study flow chart.

Table I Demographic and Clinical Details of Neonates Born to SARS-CoV-2 Positive Mothers (*N*=127)

Parameters	*SARS-CoV-2 positive (n = 19)*	*SARS-CoV-2 negative (n = 108)*
Gestational age (wk)[a]	37 (36, 38)	37 (36, 38)
Birthweight (g)[a]	2765 (2300, 3135)	2700 (2231, 3000)
Male sex	12 (63.1)	62 (57.4)
Small for gestational age	4 (21)	28 (25.9)
Vaginal delivery	14 (73.7)	66 (61.1)
Age at RT-PCR sampling (h)[a]	48 (38, 96)	48 (40, 79)
Hospital stay after birth (d)[a,b]	10 (8, 16)	6 (3, 7)
Symptomatic babies[c]	10 (52.6)	23 (21.3)
Respiratory distress	7 (36.8)	21 (19.4)
Transient tachypnea of newborn	1 (5.2)	6 (5.5)
Pneumonia[d]	4 (21)	5 (4.6)
Poor feeding/lethargy	3 (15.7)	7 (6.5)
Vomiting	2 (10.5)	7 (6.5)
Diarrhea	2 (10.5)	3 (2.7)
Hypothermia	1 (5.3)	2 (1.8)
Shock	1 (5.2)	1 (0.9)
Seizure	2 (10.5)	2 (1.8)
Probable sepsis[c,e]	9 (47.4)	19 (17.6)
Culture positive sepsis	1 (5.3)	3 (2.7)
Meningitis	1 (5.3)	2 (1.8)
Duration of antibiotics (d)[a]	6 (5, 14)	7 (5, 8.5)
Duration of oxygen (h)[a]	48 (39, 84)	42 (24, 48)

Data in no. (%) or [a]Median (IQR). RT-PCR: Real time polymerase chain reaction, TTNB: Transient tachypnea of newborn. [b]P<0.001, [c]P=0.001. [d]P=0.03. [e]Sepsis screen positive culture negative sepsis accounted for probable sepsis. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2. Positive/negative as per real time polymerase chain reaction (RT-PCR).

Table II Follow-up Data at 6 Months for Neonates Born to SARS-CoV-2 Positive Mothers

Parameters	*SARS-CoV-2 positive (n = 19)*	*SARS-CoV-2 negative (n = 108)*
Weight (g)[a]	6850 (893)	6820 (754)
< -3 *z*-score	2	10
-3 to -2 z score	3	9
-2 to 0 z score	10	75
0 to +2 z score	3	12
+2 to +3 z score	1	2
Length (cm)[a]	64.8 (3.1)	64.9 (2.6)
< -3z score	2	10
-3to -2 z score	4	9
-2 to 0 z score	9	75
0 to +2 z score	3	11
+2 to +3 score	1	3
Head circumference (cm)[a]	41.6 (1.6)	41.5 (1.4)
< -3z score	1	4
-3 to -2 z score	3	11
-2 to -1 z score	3	52
-1 to 0 z score	8	27
0 to +1 z score	4	14
Development assessment		
General developmental score[c]	87.4 (12.3)	90.6 (10.1)
Developmental category[c]		
Below average	8 (42.1)	28 (25.9)
Delay	1 (5.2)	1 (0.9)
Readmission related		
Babies readmitted[c]	2 (10)	7 (6.5)
Age at readmission (d)[a]	105 (21)	68 (45)
Duration of antibiotic (d)[a]	3 (0)	5.3 (1.5)
Duration of oxygen (d) (*n*=7)[b]	3 (0, 0)	4 (3, 4)

DP3:Developmental profile 3, BERA: Brainstem evoked response audiometry, ROP: Retinopathy of prematurity. [a] Mean (SD), [b] Median (IQR), [c] n (%). All P>0.05.

delivery, or if the neonate is directly exposed to close contacts with SARS-CoV-2 infection [11]. In our study, all mothers were positive in the third trimester, within 14 days of delivery. In the absence of testing amniotic fluid or cord blood [12], it was not possible to pinpoint the timing of acquisition and mode of transmission of SARS-CoV-2 in our neonates. In our study, all the symptomatic SARS-CoV-2 positive neonates had sepsis like clinical presentation; it is difficult to interpret whether the clinical course was more influenced by sepsis or SARS-CoV-2.

Till date, no published data on long term outcome of SARS-CoV-2 recovered neonates are available with which our findings may be compared. A multicenter cohort study from 11 hospitals in Massachusetts described short term follow up of 151 newborns born to SARS-CoV-2 positive mothers, till 30 days of hospital discharge although growth, neurodevelopment were not incorporated [13]. In this study, four babies were re-hospitalised, due to laryngomalacia, hyperbilirubi-nemia, ventricular arrhythmia and blood culture positive sepsis, respectively, none directly associated with SARS-CoV-2 infection [13]. Another follow up study from New York showed follow up till day 25 in 23 out of 101 babies born to SARS-CoV-2 positive mothers [14], 4 having readmissions, 3 for fever and 2 for hyperbilirubinemia,

WHAT THIS STUDY ADD?

- There is no difference in growth and neurodevelopment, and rate of hospital readmission in early infancy among SARS-CoV-2 positive and negative neonates born to mothers with perinatal SARS-CoV-2 infection.

none having evidence of SARS-CoV-2 reinfection. Several follow-up studies since the previously known pathogenic corona viral infection outbreak - SARS (2002-2003) are there. The outcomes in children up to 6 months after SARS disease onset, in terms of exercise tolerance, pulmonary function and psychologic status, have been favorable [5,6]. All children post-SARS were found to remain clinically asymptomatic till next 6 month; although, with mild obstructive or restrictive defect on pulmonary function study in 10% of them [15]. Pulmonary function test could be done in our cohort later in life.

The limitations of this study was that only illness severe enough to require hospital admission was considered, which may have left out morbidities like fever, cough and cold controlled with over the counter medicines. Moreover, the person assessing the neurodevelopment was not blinded to the group-assignment. Despite these shortcomings, we may reasonably conclude that there are no differences in growth, neurodevelopment, and hospital readmission in early infancy between SARS-CoV-2 positive and negative neonates born to SARS-CoV-2 positive mothers.

Ethics clearance: Institutional Ethics Committee of Medical College Kolkata; No. MC/KOL/IEC/NON-SPON/1046/02/2021, dated February 20, 2021.
Contributors: SR: substantial contribution in acquisition, analysis of data, drafting the work; DM: substantial contribution in design of the work, interpreting the data, revising it critically for important intellectual content; RD: substantial contribution in acquisition of data, interpretation of results and critical revision of the work; AH: substantial contribution in conception, analysis of data, critical revision of the work. All authors approved the final version to be published.
Funding: None; *Competing interest*: None stated.

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SYSTEMATIC REVIEW

Zinc Supplementation for Prevention of Febrile Seizures Recurrences in Children: *A Systematic Review and Meta-Analysis*

MANISH KUMAR,[1] SWARNIM SWARNIM[2], SAMREEN KHANAM[3]

From Department of Pediatrics, [1]All India Institute of Medical Sciences, Gorakhpur, Uttar Pradesh; [2]Department of Pediatrics, Maulana Azad Medical College, New Delhi; [3]Guru Nanak Eye Center, Maulana Azad Medical College, New Delhi. Correspondence to: Dr Manish Kumar, Department of Pediatrics, All India Institute of Medical Sciences, Kunraghat, Gorakhpur, Uttar Pradesh 273 008. singh.manish.15@gmail.com

Background: Multiple studies have documented lower serum zinc levels in patients with febrile seizures in comparison to febrile patients without seizure. However, there is limited evidence comparing the effects of zinc supplementation with placebo on recurrence of febrile seizures in children. **Objectives:** To study the effects of zinc supplementation on recurrence rate of febrile seizures in children less than 60 months of age. **Design:** Systematic review and meta-analysis of randomized and quasi-randomized controlled trials. **Data Source and selection criteria:** We searched PubMed, EMBASE and CENTRAL databases for articles reporting randomized or quasi-randomized controlled trials comparing the effects of zinc supplementation with placebo on recurrence of febrile seizures in children aged less than 60 months. We performed a fixed effect meta-analysis to provide pooled odds ratio of febrile seizure recurrence. Quality of evidence was assessed using GRADE approach. **Participants:** Children aged less than 60 months. **Intervention:** Zinc supplementation **Outcome measures**: Odds of febrile seizure recurrence. **Results:** Four clinical trials with a total of 350 children were included in the review. There was no statistically significant difference between odds of febrile seizure recurrence during one year follow up, in children on zinc supplementation compared to those on placebo (OR 0.70; 95% CI 0.41 – 1.18, I^2 = 0%). **Conclusion:** Available evidence is very low quality and thus inadequate to make practice recommendations.

Keywords: *Epilepsy, Management, Outcome, Prevention, Recurrence.*

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Febrile seizures are the most common pediatric seizure disorder, primarily affecting children in the age group of 6 months to 5 years, with a global prevalence of 2-5% [1]. The pathophysiology of febrile seizures is not well understood and studies have identified various risk factors, including family history, genetic factors, metabolic changes and micronutrient deficiencies [2-5]. Putative role of zinc in the pathogenesis of febrile seizures has been hypothesized [6-8] with studies showing association of low zinc levels with higher neuronal excitability through its interactions with multiple ion channels and receptors [9-11]. A recent metanalysis found lower serum zinc levels in patients with febrile seizure compared to febrile cases without seizure [12]. However, there is limited available evidence about the role of zinc supplementation in prevention of febrile seizures recurrence, which this review attempts to identify, appraise and synthesize.

METHODS

This systematic review has been conducted in accordance to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13] The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database.

Search strategy and search eligibility: All authors independently searched the databases including PubMed, Embase, Cochrane Central Register of Controlled Trials, from inception to 28 September, 2020. Details of the electronic search strategy and the results are given as **Web Table I.** Cross references of all articles whose full text was screened, was also checked to find additional articles.

Inclusion criteria were original articles, in any language, having randomized or quasi-randomized controlled trial design; population included children less than 60 months of age; intervention studied was zinc supplementation; comparator being placebo; and outcome being febrile seizure recurrences during 1year follow-up.

Data extraction and quality assessment: Data were extracted by all authors independently using a pre-designed form. Any disagreements were resolved with consensus. The recorded details included lead author, year of publication, country, sample size, inclusion and exclusion criteria, gender distribution, mean age, type of zinc salt, dose of zinc, number of recurrences of febrile seizure in intervention and control group, and duration of follow-up.

Quality of each study was assessed using the criteria outlined in the Risk of bias tool in Cochrane handbook for

systematic reviews of interventions [14]. Quality of evidence was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [15], and summary of findings table was generated on GRADEpro GDT software [16].

Statistical analysis: We performed a fixed effect meta-analysis to provide pooled odds ratio of febrile seizure recurrence. Pooled odds ratio (OR) with 95% confidence interval (CI) was calculated for primary outcome. Heterogeneity was assessed using the I^2 statistics. Statistical analysis was performed using Review Manager version 5.4 [17]. .

RESULTS

Our search strategy yielded 132 articles and one additional article was included after manual search. Finally four articles with a total of 350 children were included in qualitative synthesis [18-21] (**Fig. 1**). **Table I** summarizes the characteristics of the included studies. Three of the included studies are from Iran [18-20], while one study was conducted in India [21]. One article was in Persian with English abstract [18]. Age of the children included varied across the studies. Studies by Fallah, et al. [19] and Kulkarni, et al. [21] included children with normal anthropometric measurements. Though zinc sulfate was used as intervention in all the four studies, the doses differed across the studies. All the studies had a follow-up of one year. While in the study by Ahmedabadi, et al. [18] and Fallah, et al. [19], follow up was conducted every three months, children enrolled in study by Kulkarni, et al. [21] were followed up on a monthly basis.

Three studies (18,20,21) had high risk of selection bias, performance bias and detection bias. **Web Fig. 1** summarizes risk of bias for each included study and **Web Fig. 2** depicts risk of bias graph as percentages across all studies. Publication bias was assessed with funnel plot (**Web Fig. 3**); however, this analysis was limited by small number of included studies. The pooled odds of recurrence of febrile seizure during one year follow up was less in intervention group, though it was not statistically

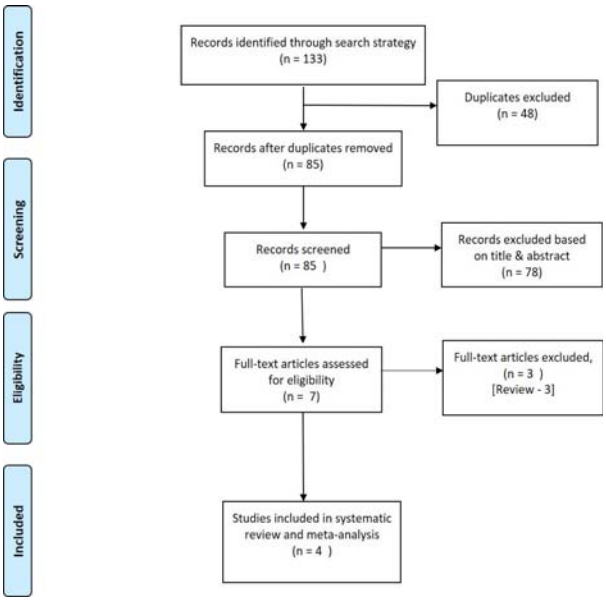

Fig.1 PRISMA flow diagram showing the study selection process.

significant (OR 0.70; 95% CI 0.41 – 1.18, I^2 = 0%). **Fig. 2** depicts the Forest plot for this outcome.

The quality of evidence pooled from included studies was assessed using GRADE approach and a summary of findings table (**Web Table II**) was generated on GRADEpro GDT software [16]. Due to inherent risk of bias of included studies along with inconsistent and imprecise results from these studies, the quality of evidence ranged from low to very low.

DISCUSSION

Available evidence from four randomized/quasi-randomized trials, including a total of 350 children, did not find any significant difference between recurrence rate of febrile seizure in children on zinc supplementation compared to children on placebo.

However, there were differences across the studies. While, Fallah, et al. [19] did not explain the reasons for their

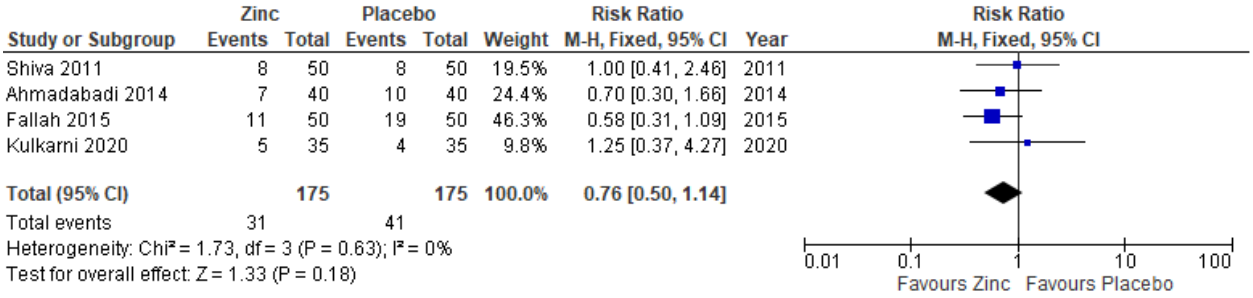

Fig. 2 Forest plot of effect of zinc supplementation on rate of febrile seizure recurrence in children less than 60 months of age.

Table I Characteristics of the Included Studies

Author; year; location	*Sample size (male: female)*	*Inclusion criteria*	*Exclusion criteria*	*Mean age*	*Serum zinc level before inter -vention (μg/dL)*	*Zinc salt; dose*	*Follow-up: duration; frequency*
Shiva; 2009; Iran	100 (60:40)	• Age 1-4 y		Intervention group: 2.1 (0.83) y Control group: 2.2 (1.04) y	Intervention group: 69.9 (10.8) Control group: 70.4 (8.77)	Zinc sulphate; 1mg/kg/d	1 y Not reported
Ahmeda-badi; 2011; Iran	80 (51:29)	• Age 1-5 y • Seizure duration < 15 min • Generalized tonic-clonic seizure • Only one seizure episode in 24 h • Normal neuro-logical develop-ment • No copper, calcium, iron supplementation • No special medication	• Copper, calcium, iron supplemen tation • Any special medication • Seizures associated with meningitis, abscess, Shigellosis • • •	Intervention group: 28.9 (16.19) mo Control group: 27.6 (13.5) mo		Zinc sulphate; 20 mg/d	1 y; Every three mo
Fallah; 2015; Iran	100 (59:41)	• Age: 18 to 60 mo • First simple febrile seizure • Weight and height above the third percentile (NHANES III) • Normal serum zinc level	• Received a zinc combination or supplementation within the past 2 mo • Central nervous system infections • History of previousfebrile or afebrile seizure, neuro developmental delay • Presence of any chronic systemic diseases • Iron deficiency, iron deficiency anemia	Intervention group: 2.37 (0.93) y Control group: 2.58 (1.07) y	Intervention group: 81.7 (13.3) Control group: 84.7 in (12.3)	Zinc Sulfate; 2 mg/kg/d (max 50 mg)	1 y; Every three mo
Kulkarni; 2020; India	70 (39:31)	• Age: 6-60 mo • Simple febrile seizures • Normal anthro-pometric measure-ments	• Taking zinc supplement • Apparent neuro-logical disturbance other than febrile seizure • Failure to thrive	Intervention group: 1.9 (1.01) y Control group: 1.8 (1.14) y	Intervention group: 65.4 (12.21) Control group: 67.3 (9.85)	Zinc Sulfate; 1mg/kg/d	1 year; Every mo

assumption of such a large difference, while calculating the sample size, the other three studies did not mention their strategy for calculation of sample size. Further, the study populations were not similar with respect to inclusion and exclusion criteria. Age groups of children enrolled in included studies had significant variation. Given the fact that febrile seizures are an age-dependent phenomenon with reported peak incidence between 12–18 months [22], such variations may have important ramifications in rate of febrile seizure recurrences across studies. Also, evolving evidence suggests that serum zinc level is lower in patients with febrile seizure [12]. In this light, variation in dose of zinc supplementation in intervention groups of the included studies can affect febrile seizure recurrences. Three of the included studies are on Iranian population, which may affect the generalizability of results for other population group.

Though we searched large and representative databases for this review, we recognize the limitation of not having searched other databases. Available evidence pertaining to zinc supplementation for prevention of febrile seizures is of low to very low quality and thus inappropriate to make a practice recommendation. Included trials were inadequately powered with high risk of bias. Further research, in the form of methodologically robust, multicentric randomized controlled trials, is needed.

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Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

Contributors: MK: conceptualized the review, literature search, data analysis and manuscript writing; SS: literature search, data analysis and manuscript writing; SK: literature search, data analysis and manuscript writing. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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Web Table I Search Strategy

Database	*Search query*	*Results*
PubMed	(((((("febrile seizure"[Title/Abstract]) OR ("febrile seizures"[Title/Abstract])) OR ("febrile fits"[Title/Abstract])) OR ("Febrile Convulsions"[Title/Abstract])) OR ("febrile convulsion"[Title/Abstract])) AND ((Zinc[Title/Abstract]) OR ("zinc"[MeSH Terms]))	35
EMBASE	('zinc'/exp OR 'zinc') AND 'febrile convulsion'	92
CENTRAL	("zinc"): ti,ab,kw AND ("febrile seizure"): ti,ab,kw	5

Web Table II Summary of findings

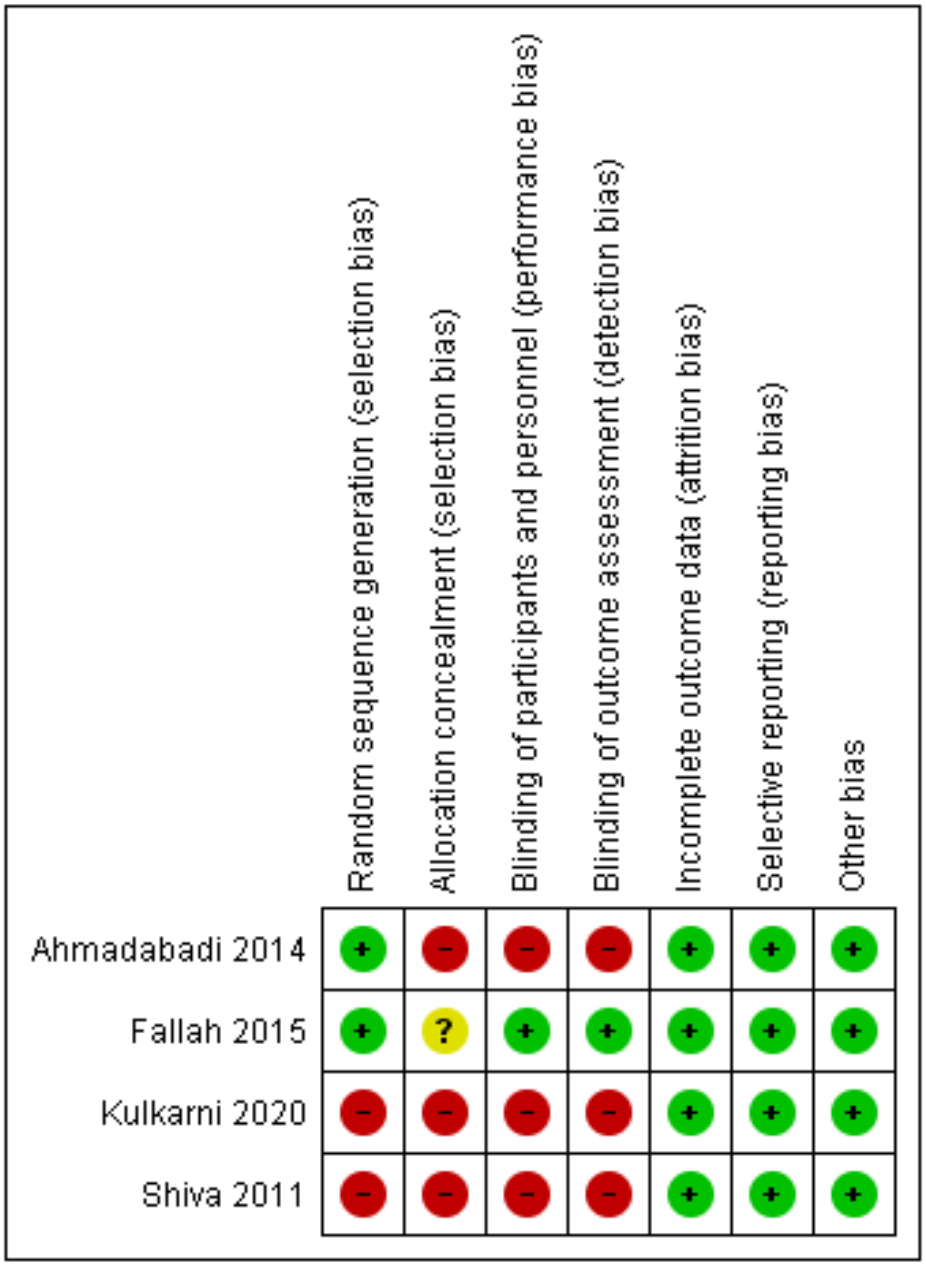
Certainty assessment							**Summary of findings**				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With Zinc**		**Risk with placebo**	**Risk difference with Zinc**
Febrile Seizure Recurrence											
350 (4 RCTs)	very serious [a]	serious [b]	not serious	serious [c]	all plausible residual confounding would reduce the demonstrated effect	⨁◯◯◯ VERY LOW	41/175 (23.4 %)	31/175 (17.7 %)	**OR 0.70** (0.41 to 1.18)	234 per 1,000	**58 fewer per 1,000** (from 123 fewer to 31 more)

Explanations

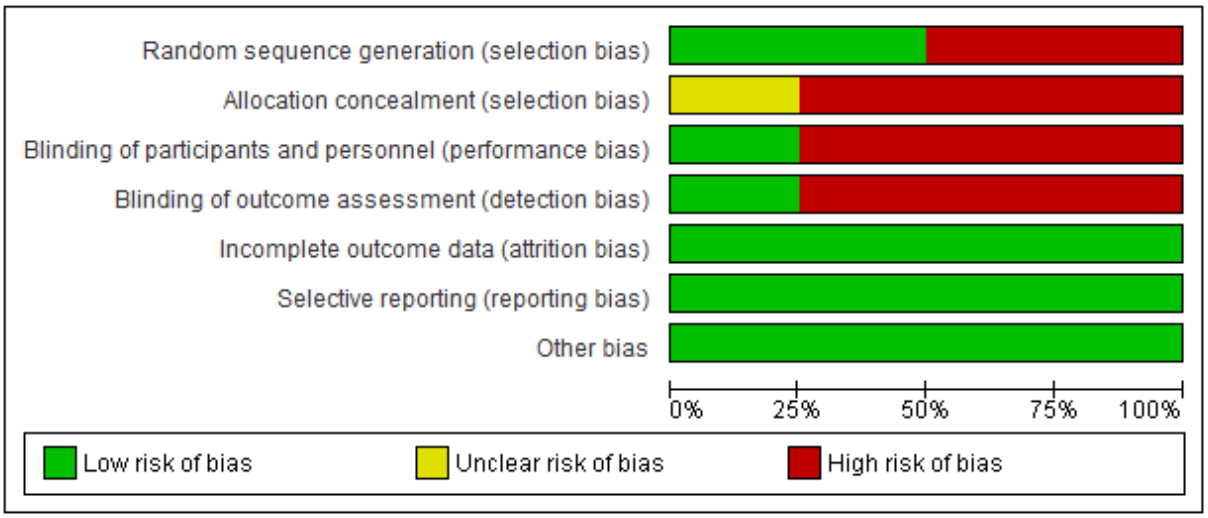
[a] *Shiva 2011, Ahmadabadi 2014 and Kulkarni 2020 had significant risk of bias*

[b] *Odds of recurrence of febrile seizure in intervention group was more in study by Kulkarni 2020 unlike other 3 studies*

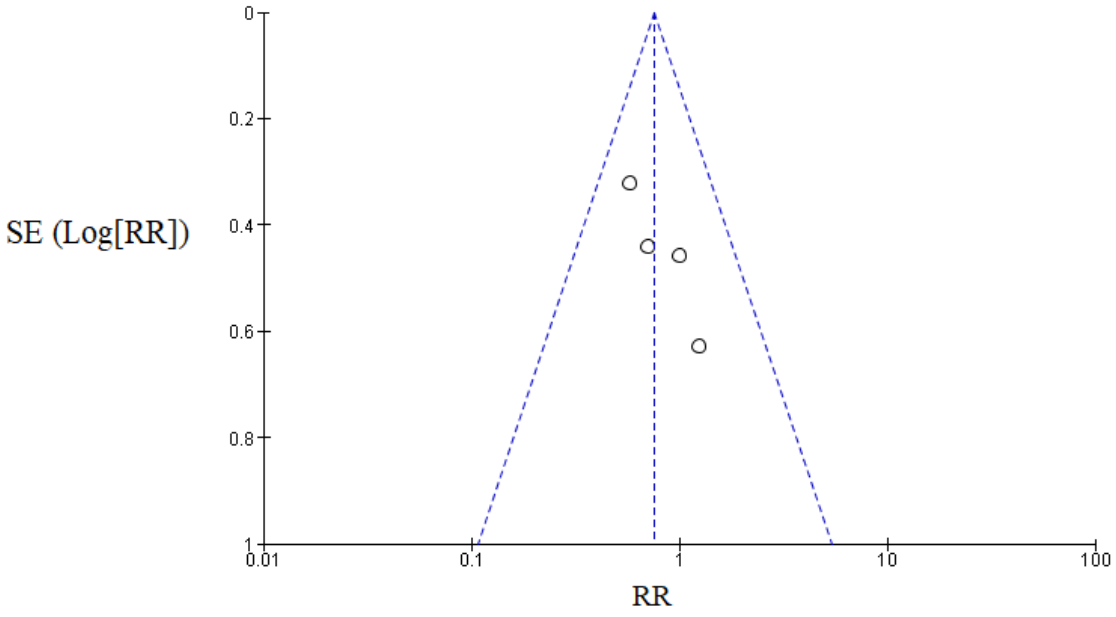
[c] *Pooled 95% CI for odds ratio is wide*



Web Fig. 1 Risk of bias summary depicting authors' judgement regarding risk of bias for each included study.



Web Fig. 2 Risk of bias graph depicting authors' judgement regarding individual risk of bias item as percentages across all studies.



Web Fig. 3 Funnel plot depicting publication bias related to effect of zinc supplementation on rate of febrile seizure recurrence in children less than 60 months of age.

REVIEW ARTICLE

Movement Disorders in Children

RAHUL JAIN,[1] SANJAY PANDEY,[2] SANJAY RAGHAV[3]

From [1]Department of Pediatrics, Lok Nayak Hospital, and [2]Department of Neurology, Govind Ballabh Pant Institute of Postgraduate Medical Education and Research, Maulana Azad Medical College, New Delhi, India; and [3]Department of Neuroscience, Monash University, Clayton, Australia.

Correspondence to: Dr Rahul Jain, 7 Nixon Street, Kepnock, Queensland, Australia-4670. drrahuljain1980@gmail.com

Context: Movement disorders represent a common presentation in pediatrics and are often a source of clinical and diagnostic dilemmas. In this review, we provide an overview of common causes along with simplified clinical approach and management options for major movement disorders. **Sources:** This narrative review is based on contemporary evidence and personal experience. Medline was searched for recent advances, current understanding and consensus on classification, clinical features, diagnosis and treatment. **Results:** Movement disorders are classified as hyperkinetic and hypokinetic disorders, the latter being rare in childhood. The hyperkinetic disorders include dystonia, chorea, athetosis, tics and tremor, stereotypies, myoclonus, startle syndromes and functional disorders. Some movement disorders can be benign and developmental. A large proportion of conditions are genetic in origin with a guarded prognosis. Some of the conditions may be post-infectious, immune-mediated or drug induced. Multiple types of movement disorders are present in many conditions. The age at onset, type and distribution of abnormal movements and presence of associated neurological and systemic features help in narrowing the differential diagnosis. The pharmacotherapy of movement disorders is complex and evolving. **Conclusion**: A synopsis of movement disorders presenting in pediatric age has been provided, incorporating the latest evidence. A simplified approach for clinical diagnosis has been developed for dystonia and chorea.

Keywords: *Approach, Chorea, Dystonia, Myoclonus.*

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Movement disorders are conditions characterized by involuntary postures and/or movements. It represents a common presentation in pediatrics and is often a source of clinical and diagnostic dilemmas [1]. Classically, movement disorders are classified into hyperkinetic and hypokinetic disorders. Hyperkinetic disorders are characterized by abnormal involuntary movements and include dystonia, chorea, athetosis, stereotypies, myoclonus, tics and tremor. Hypokinetic disorders have in common a paucity of movements and include rare conditions like parkinsonism [2]. Dystonia and chorea are the most common forms of movement disorders. In many conditions, multiple types of movement disorders co-exist and it may be difficult to identify the type of movements.

There are no estimates on the prevalence of movement disorders in children or their proportion amongst pediatric presentations. The exact pathophysiology of movement disorders is not well understood; however, evidence suggests the involvement of either basal ganglia or cerebellar circuits in most of the conditions, which includes parts of thalamus and cortex [3]. We, herein, cover common movement disorders with emphasis on treatable conditions.

DYSTONIA

Dystonia is characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements, postures, or both. Dystonic movements are typically patterned (repeatedly involve the same group of muscles), twisting, and may be tremulous [4]. The postures are exaggerated on voluntary actions and during stress and subside during sleep. It may be painful, if severe and continuous. In the affected body parts, muscle tone is typically variable, fluctuating from low to high. Children also demonstrate a splaying approach (spreading of fingers while approaching an object) and striatal toe sign (intermittent/persistent extension of the great toe). Sometimes, patients may show the oscillatory movement of limbs due to intermittent muscle contractions, known as dystonic tremors [5]. Often dystonia co-exists with spasticity in children with a severe brain injury like those with cerebral palsy.

According to a recent consensus [4], each patient with dystonia should be classified on a set of clinical (axis I) and etiological (axis II) descriptors (**Fig. 1**), as it aids in diagnosis and treatment. Historically, dystonia has been classified as primary and secondary. Primary refers to conditions that manifest with pure dystonia, without any associated other neurological features and without evidence of pathological abnormalities. All non-primary dystonia are labelled as secondary. In this review, disorders are grouped based on the presence of associated features, with an added category of acute-onset dystonia and paroxysmal dystonia.

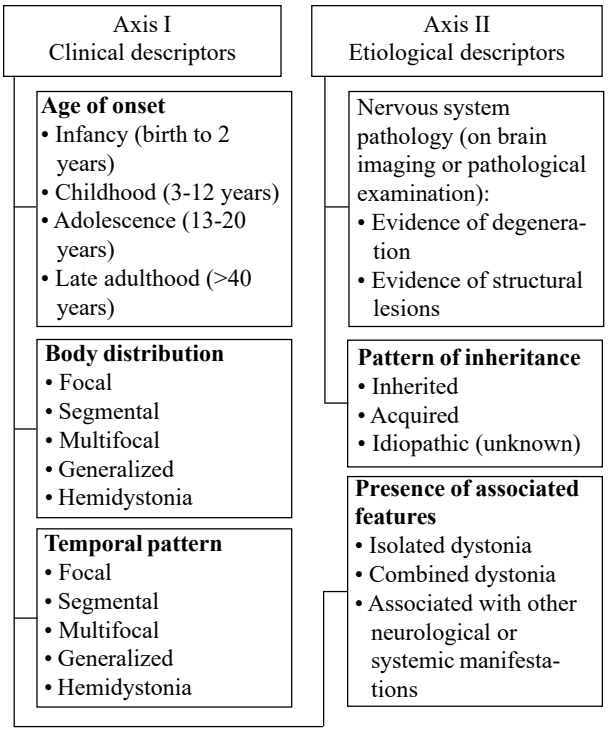

Fig. 1 Classification of dystonia [4].

Isolated Dystonia

Isolated dystonia refers to conditions in which dystonia is the only motor feature, with an exception of tremors [4]. Almost all these conditions are genetic in origin and most children have a period of normal motor development before the onset of dystonia. Most often there is a focal onset of dystonia with gradual progression. As most dystonia are associated with other movement disorders/ neurological comorbidities; with the increasing number of cases described in literature, entities with isolated dystonia are shrinking.

DYT-TOR1 dystonia is the most common entity within this group. It an autosomal dominant disorder with onset in late childhood or adolescence. It starts with focal limb dystonia, later progressing to generalized dystonia. DYT-HCPA dystonia starts within first decade with upper limb and cervical dystonia. Other forms of isolated dystonia can start with cranial or cervical dystonia (DYT-THAP and DYT-ANO3) [5,6].

Combined Dystonia

This group includes conditions in which dystonia is accompanied by features of parkinsonism or myoclonus, in absence of other neurological abnormalities. Dopa-responsive dystonia or Segawa disease (DYT-GCH1) is an important condition in this group. It is an autosomal dominant disorder that presents between 5-10 years of age with limb dystonia, with more severe involvement of lower limbs. The most characteristic feature is diurnal variation with children typically performing motor activities better in the morning or after a nap. Few children have some associated features of parkinsonism. Some cases may mimic spastic cerebral palsy. Dopa-responsive dystonia is a treatable condition and small to moderate doses of levodopa bring about a complete response. This also forms the basis of a trial of levodopa in any child with dystonia [5,7].

Other entities in this group include myoclonus-dystonia (DYT-SGCE, DYT-ANO3, DYT-TOR1A or DYT-CACNA1B) and rapid-onset dystonia-parkin-sonism (DYT-ATP1A3). Myoclonus-dystonia is genetically heterogeneous and can present any time after infancy with upper body myoclonus and limb dystonia. In patients with rapid onset dystonia-parkinsonism, symptoms are triggered with emotional or physical stress and there is often a stuttering course [5,8].

Associated With Other Manifestations

Children with cerebral palsy, and neurodegenerative and metabolic disorders form a major part of this group. Dystonia is often a feature in children with bilirubin induced neurological damage (BIND) and severe hypoxic-ischemic brain injury at birth.

Monoamine neurotransmitter disorders are a heterogeneous group of conditions that result from deficiency of cerebral dopamine, serotonin, or both. Most patients become symptomatic in infancy or early childhood with varying combination of developmental delay, encephalopathy, epilepsy, spasticity, dystonia, chorea and autonomic dysfunction. Some children may show diurnal variation. Analysis of CSF neurotransmitter levels aid in diagnosis. Dopa-responsive dystonia is also a monoamine neurotransmitter disorders but has fewer manifestations [9]

Progressive dystonia and spasticity in early childhood may be a manifestation of hypomyelinating leukoencephalopathies like Pelizaeus Merzbacher syndrome, which typically presents with pendular nystagmus, developmental delay and hypotonia in early infancy. Dystonia and ence-phalopathy can be seen in organic academia and mitochondrial encephalopathies [5]. Pantothenate kinase–associated neurodegeneration (PKAN) presents around 3 years of age with clumsiness and gait abnormality due to lower limb dystonia and spasticity, along with pigmentary retinopathy [10].

In children with onset of dystonia in late childhood or adolescence, Wilson disease is an important differential. Besides dystonia, tremors, dysphagia, dysarthria, drooling and walking difficulty may be present. Almost all patients have Kayser-Fleischer rings on eye examination [11].

Acute-Onset Dystonia and Paroxysmal Dystonia

Acute-onset dystonia can be a manifestation of adverse effects of drugs, stroke, encephalitis, and functional disorder. Anti-emetics (like metoclopramide) and antipsychotic drugs (like haloperidol and risperidone) are most commonly implicated in drug induced dystonia [12]. Dystonia is a common manifestation of neurotuberculosis and Japanese encephalitis.

Some genetic conditions manifest with episodic involuntary movements lasting from seconds to hours, most often with well-defined triggers. In between the episodes, the child is usually normal. This group includes conditions like Paroxysmal kinesigenic dystonia (triggered by sudden movement), Paroxysmal non-kinesigenic dystonia (triggered by stress, alcohol, etc.) and Paroxysmal exertional dystonia (triggered by exercise) [5,13].

Glut-1 deficiency is a rare condition that occurs due to a deficiency of glucose transporter type 1 in the brain. It manifests as absence epilepsy, ataxia, developmental delay and paroxysmal exertional dystonia in early childhood. Low CSF glucose is the biochemical hallmark and symptoms show a dramatic response to ketogenic diet [14].

Status Dystonicus

Status dystonicus, or dystonic storm is a life-threatening condition characterized by frequent or continuous severe episodes of generalized dystonic spasms. Although it can occur in any condition causing dystonia, it is most often seen in children with cerebral palsy and neurodegenerative disorders. Infections (febrile illnesses) and other stressors act as triggers. Severe spasm may result in pain, dehydration, respiratory compromise, rhabdomyolysis and acute renal failure [15,16].

Clinical Approach

While evaluating a child with dystonia, ascertain the age of onset, distribution (focal or generalized), temporal pattern (i.e. diurnal, static, or progressive) and associated neurological and systemic abnormalities. An important clue to etiology is that primary dystonia begins as action dystonia and can persist in kinetic form while secondary or symptomatic dystonia often begins as sustained postures or tonic form. **Fig. 2** provides an algorithm for clinical diagnosis.

Eye examination and brain MRI help in narrowing the differential diagnosis. Eye evaluation should be focused on KF ring, optic atrophy and retinitis pigmentosa. MRI is essentially normal in primary dystonia (DYT dystonia). MRI has diagnostic significance in Wilson disease (T2 hyperintensity in basal ganglia), PKAN ('Eye of the Tiger' sign in globus pallidus), hypomyelinating disorders (white matter changes) and Japanese encephalitis (bilateral thalamic involvement) [5].

Metabolic screening is warranted in a child with encephalopathy. In a child with fluctuating weakness, CSF analysis will help in ruling out neurotransmitter defect and Glut-1 deficiency. A therapeutic trial of levodopa is recommended for all children; although, very few dystonias are levodopa responsive, and there is a lot of variability in dose range for children who do respond [17]. In patients with suspected genetic etiology, dystonia gene panel testing may provide the definitive diagnosis. With the increasing availability of whole exome sequencing (WES), the diagnostic process can be significantly shortened [18].

Management

The drugs used in management of dystonia are detailed in **Table I**. In most patients with severe dystonia, outcomes are unsatisfactory. Neurosurgical procedures like deep brain stimulation (DBS) and intra-thecal baclofen pump (ITB) can be used in refractory dystonia. DBS has shown substantial benefits in children with primary dystonia, whereas in children with dyskinetic cerebral palsy, mild to moderate improvement occurs [22].

The management of status dystonicus is multi-pronged. Patients should be monitored for renal functions, creatine kinase, blood gas, and urine and/or blood myoglobin levels. Addressing the precipitant and providing supportive care (hydration, respiratory support, hemodialysis etc.) is important. The mainstay of therapy is careful use of sedatives. Chloral hydrate is recommended as initial therapy (30-100 mg/kg orally every 3-4 hours). Most patients need the addition of clonidine (initial dose 3μg/kg 8 hourly, can be increased up to 3-5 μg/kg/hour given as 3-hourly dose. In unresponsive patients, continuous midazolam infusion may be effective. Besides sedatives, dystonia specific drugs like trihexyphenidyl, pimozide and tetrabenazine are also required. In patients with poor response to drugs, DBS should be offered. The role of ITB is less clear but may be more effective in patients with concomitant spasticity [15-16].

TREMORS

Tremors refer to rhythmic, regular back-and-forth or oscillatory movement of part of the body about a joint axis [23]. Tremors are classified as resting tremors and action tremors.

Resting tremors are quite rare in childhood; however, can be seen in juvenile parkinsonism, Wilson disease, PKAN, Huntington disease and midbrain lesions [24]. Psychogenic and dystonic tremors can also be present at

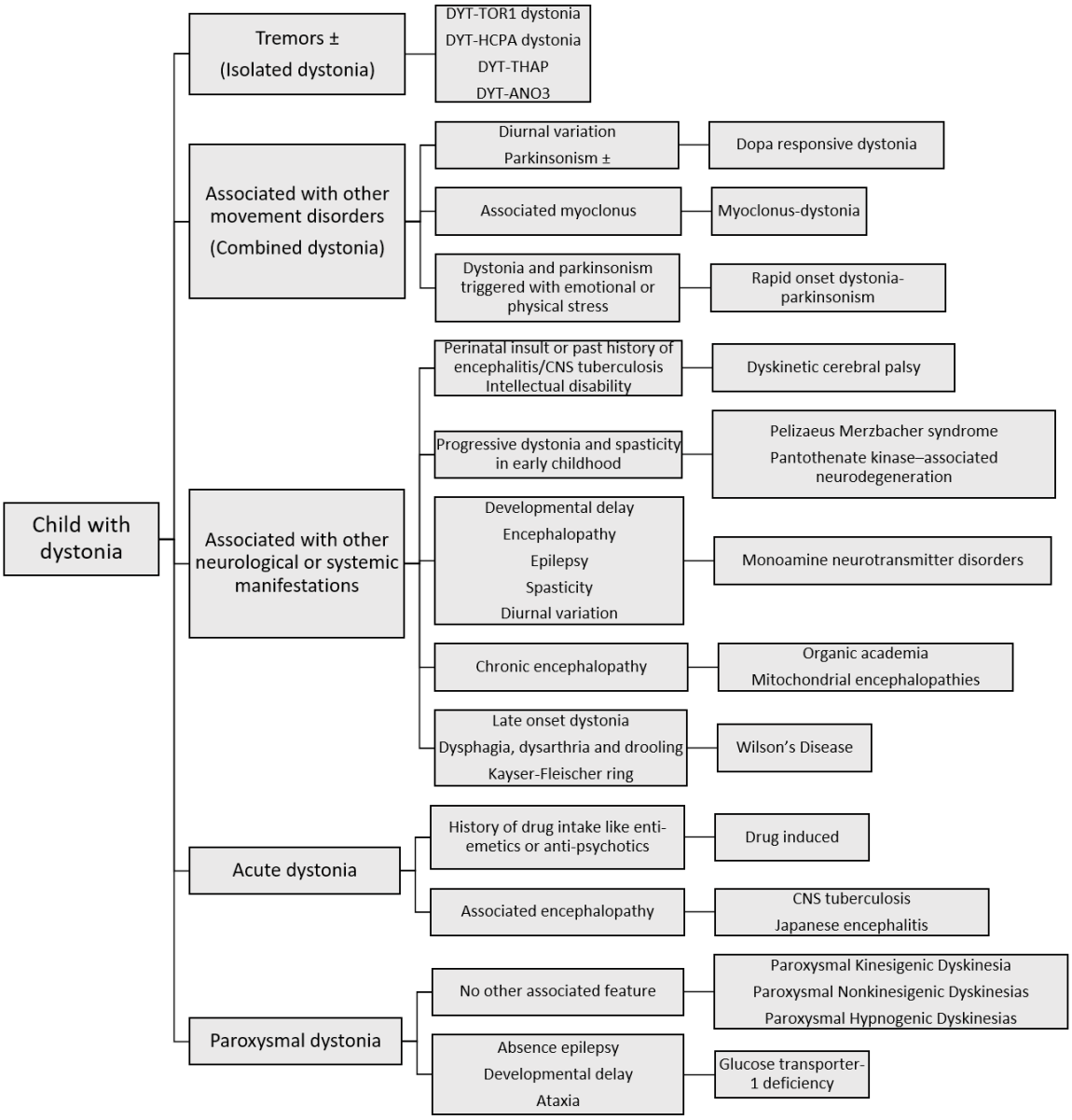

Fig. 2 Clinical approach to diagnosis of dystonia in children.

rest. In context to developing countries, infantile tremor syndrome (ITS) is an important cause. ITS typically manifest in exclusively breastfed infants of vegetarian mothers, with developmental delay/regression, anemia, skin hyperpigmentation, and tremors. Tremors usually start with upper limbs and subside during sleep. Almost all patients have vitamin B12 deficiency and respond to supplementation [25].

Action tremors are further classified as simple kinetic, intention, isometric, task-specific and postural. Simple kinetic tremor is present during simple limb movements. It is typically a feature of essential tremor. Essential tremor affects only the upper limbs and family history is present in many patients. Usually, the onset is in adulthood or later, but can sometimes occur in children. A duration of 3 years is required for diagnosis [24]. Functional and drug-induced tremors can also be simple kinetic. In intention tremor, the amplitude of tremor increases as the body part is reaching a visual target. It is characteristically seen in cerebellar disorders but can also be present in midbrain lesions [24,26].

Postural tremor is seen when a body part is held in a position against gravity. Each individual has some physiological postural tremor, best appreciated in an

Table I Drugs Used for Dystonia [19-21]

Drug name	*Mechanism*	*Dose*	*Side effect*	*Comments*
Levodopa (used in combination with carbidopa)	Dopa agonist	Start at 1 mg/kg/d divided TID. Increase weekly by 1 mg/kg/d to a target dose of 5-10 mg/kg/d	Nausea, diarrhea	3-4 wk trial (at target dose) recommended in all children with dystonia. Effective only in Monoamine neuro-transmitter disorders.
Trihexyphenidyl	Anti-cholinergic	Start at 0.2 mg/kg/d divided TID. Increase weekly by the same dose till a maximum dose of 2 mg/kg is reached or side effects appear	Constipation and dry mouth	Effective in most forms of dystonia
Baclofen	GABAergic	Start at 0.3mg/kg/d divided TID. Titrate weekly by 0.1-0.3 mg/kg/day. Maximum dose 40 mg/d in <2 y and 60 mg/d in ≥2y	Sedation, axial hypotonia	Also effective in spasticity
Clonazepam	GABAergic	Start with 0.25 mg BD. Increase by 0.25-0.5 mg/day every 3-4 d to maximum dose of 0.1-0.2 mg/kg/d	Sedation, confusion	
Tetrabenazine	Block vesicular monoamine trans-porter type 2	Start with 6.25-12.5 mg once/twice daily. Increase by same dose weekly to maximum of 50 mg/d divided BD	Nausea, parkinsonism	Effective in a variety of movement disorders
Botulinum toxin injection	Neuromuscular blockage	Depends on muscles injected		Used for focal dystonia like cervical or upper limb dystonia
Diphenhydramine	H1-antagonist	Initial: 1-2 mg/kg/dose (max 50 mg) IV/IM; may repeat if necessary Subsequent: 5 mg/kg/d in 3-4 divided doses Oral/IV (max 50 mg/dose) for 1-2 d	Sedation	Used for drug induced dystonia

outstretched hand. This can be exaggerated by stress, fasting, illness, strenuous exercise, thyrotoxicosis and drugs like salbutamol and valproate. Isometric dystonia occurs during sustained muscle contraction against stationary objects like while holding a book. Exaggerated physiological tremor and essential tremor can be isometric. Task-specific dystonia is related to specific tasks like writing or playing an instrument [24,26].

Clinical Approach and Management

While evaluating a child with tremors, note the onset, aggravating and relieving factors, drug history and family history. Examine for tremors along with muscle tone and gait pattern. Presence of associated dystonia points towards conditions like PKAN and Wilson disease. Sudden onset and offset and marked variation in the semiology favours psychogenic tremor. Some patients with only dystonia may show tremulous limb movements, referred as dystonic tremors. Other conditions that mimic tremors include jitteriness, seizures, myoclonus, shuddering attacks, and stereotypic movements.

Investigations will depend on the suspected etiology. Thyroid function should be done for enhanced physiological tremors. Neuroimaging and other relevant workup should be done for suspected cerebellar disorder or a neurodegenerative condition. For ITS, vitamin B12 levels should be obtained.

Propanolol is recommended in severe cases of essential tremors and patients with physiological tremors who have functional or social limitations. Other drugs that are effective in essential tremors include primidone and benzodiazepines [24,26].

CHOREA

Chorea refers to involuntary, irregular, non-repetitive dance-like movements of the body parts that appear to flow from one muscle group to another without following any pattern. Children with chorea appear hyperactive or fidgety. The ability to perform voluntary movements remains unimpaired. Many grown-up children with chorea transform the choreiform movement into a voluntary act in order to mask it, referred to as parakinesia [27]. Patients with chorea have motor impersistence, which refers to the inability to maintain sustained postures like keeping tongue protruded or arms outstretched [28]. Like all movement disorders, chorea also disappears during sleep.

Chorea with large amplitude, rapid flinging movements, usually affecting the proximal joints is referred as ballism [23]. Some patients have slower continuous, involuntary writhing movements affecting the distal upper extremities, referred to as athetosis. Athetosis is a distinct movement disorder; however, it co-exists with chorea and ballism, and represents a clinical spectrum [23].

Chorea due to a known or presumed genetic cause is referred as primary chorea. Chorea resulting from infections, injuries, infiltrative conditions or immune mediated disorders affecting the brain is called as secondary chorea.

Primary Chorea

Huntington disease: It is an autosomal dominant disorder that manifest in late adulthood with chorea, dystonia, psychiatric disturbances, and dementia. Juvenile Huntington disease is rare and more commonly present with dystonia, parkinsonism, behavior problems, and cognitive deterio-ration, rather than chorea [29].

Ataxia-telangiectasia: Choreoathetosis involving the upper extremities is an early feature of Ataxia-Telangiectasia, however; it is often mild. Ataxia that develops by 3-6 years of age is the prominent manifestation and brings the child to medical attention [30].

Benign hereditary chorea: It is an autosomal dominant condition with median age of onset of 2.5-3 yrs. The intelligence is normal and the condition tends to become static after the first decade with improvement in adulthood. Some patients have accompanying hypothyroidism and pulmonary disease [31].

Others: In some conditions like spinocerebellar ataxia type 17, ataxia with oculomotor apraxia and Friedreich ataxia, chorea may be an early feature, though ataxia predomi-nantes as the disease progresses. Paroxysmal movement disorders present with intermittent episodes of chorea and dystonia [13]. There is a growing list of genetic etiologies of chorea, with mutation in *ADCY5* and *PDE10A* being important cause of childhood onset movement disorders [32].

Secondary Chorea

Sydenham chorea: This is the most common cause of acute-onset chorea in children. It is a late manifestation of acute rheumatic fever and affects children aged 5-15 years. The chorea mainly involves the upper extremities and at times there may be wide flinging movements (ballism) [27]. The other manifestations include hypotonia, personality changes, emotional lability, obsessive-compulsive symptoms and attention-deficit [33]. Diagnosis is mostly clinical as the laboratory evidence of recent streptococcal infection is often lacking.

Other immune-mediated conditions: Chorea may be the presenting or associated feature in children with systemic lupus erythematosus associated with anti-cardiolipin antibodies. Chorea may be a feature of autoimmune encephalitis, the other manifestations being seizures, encephalopathy and neuropsychiatric disturbances [34].

Chorea associated with brain injury: Children with dyskinetic cerebral palsy may have chorea, besides dystonia. Chorea may be a part of neurological sequelae after viral encephalitis or stroke.

Drug-induced chorea: Certain drugs like trihexyphenidyl, levodopa, phenytoin and carbamazepine can precipitate chorea in a child with other types of movement disorders or brain injury [27].

Clinical Approach and Management

The history should include perinatal events, previous infections and associated symptoms. The child should be examined in a distraction-free environment to note the presence of chorea and any other movement disorder. Video recording of movements by parents at home help in characterization of movements. Child should be examined for motor impersistence, including inability to keep tongue protruded (darting tongue), maintain sustained arm grip on examiners fingers (milkmaid's grip) and keep upper limbs extended above the head with palms facing inwards [28]. A clinical approach to diagnosis is discussed in **Fig. 3**. Diagnostic work-up depends on the suspected etiology.

Atypical antipsychotics like olanzapine or risperidone are effective in the management of acute onset chorea or

acute exacerbation. Tetrabenazine and anti-epileptics like valproic acid and carbamazepine are alternatives. Valproic acid can be tried in patients who fail to respond to anti-psychotics. Patients with severe forms of Sydenham chorea or those unresponsive to antipsychotics may respond to intravenous immunoglobulin or corticosteroids [35,36]. In patients with Huntington disease, the preferred drugs are tetrabenazine, olanzapine, risperidone, and recently, deutetranenazine [37].

TIC DISORDER

Tics refer to repeated, individually recognizable, intermittent movements, movement fragments, or sounds that are almost always briefly suppressible and are usually associated with awareness of an urge to perform the movement [23]. The premonitory urge to carry out the movement is often distressing to older patients. Tics can manifest after 5-6 years of age; however, adolescents are most severely affected. Tics may affect the social functioning of an individual and cause embarrassment. Tics are presumed to be genetic because of the high concordance rate between twins (53%); however, the genetic loci are not known. Mostly, tic is a primary problem, rarely it may be part of other neurological disorders [38,39].

Tics are classified based on type (motor or vocal) and duration. A tic can be simple (like eye blinking, head jerking, facial grimacing, brief vocalization, throat clearing, and sniffing) or complex (like obscene gestures or copropraxia, posturing, echolalia, and coprolalia). A tic disorder that has been there for less than a year or subsides within a year is labelled as transient tic disorder. Those lasting more than a year are called chronic and include Tourette syndrome and persistent motor or vocal tic disorder [38,39].

Tourette syndrome is defined by presence of multiple motor tics (at least two distinct ones) and one or more vocal tics which wax and wane, but have persisted for more than one year [39]. It is commonly associated with behavioral disorders like attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety, mood disorders and disruptive behavior disorders. About two-third of individuals meet the criteria of ADHD or OCD at some time during the course of disease [40]. Persistent motor or vocal tic disorder is defined as having a single or multiple motor or vocal tics which may wax and wane but have persisted for more than one year. Tics may sometimes be part of autism spectrum disorder and neurodegenerative disorders.

Management

Comprehensive behavioral intervention for tics (CBIT) is efficacious in reducing tics and is recommended as the initial treatment. CBIT program consists of habit reversal therapy, relaxation training, and functional interventions to address situations that sustain or worsen tics. If CBIT is ineffective or unavailable, pharmacotherapy can be used. A variety of drugs are effective including alpha-agonists like clonidine and guanfacine, anti-psychotics like haloperidol, pimozide and risperidone and anti-epileptics like topiramate. Alpha-agonists have lower efficacy than anti-psychotics but are preferred due to favorable side effect profile. Alpha-agonists also improve the behavioral comorbidities [41,42].

MYOCLONUS AND STARTLE SYNDROMES

Myoclonus is a sudden, brief, shock-like involuntary movement of the body. It can involve a single body part, one half of body or whole body. Myoclonus is mostly spontaneous, but in some conditions it can be induced by an action or sensory stimuli like light, sound or touch [1]

Hiccups and sleep starts are considered as physiological forms of myoclonus. Sleep starts occur during sleep initiation, manifesting with a sense of falling [1]. Benign neonatal sleep myoclonus and benign myoclonus of early infancy are viewed as developmental conditions (detailed later) [47]. Many young children manifest myoclonus during febrile episodes. Myoclonus can be epileptic as in some epileptic syndromes (like West syndrome and juvenile myoclonic epilepsy) and neurodegenerative disorders [1].

Opsoclonus-myoclonus syndrome (OMS) is a rare immune-mediated condition that manifests acutely or sub-acutely in toddlers with chaotic multi-directional conjugate eyes movements (opsoclonus), myoclonus, ataxia, irritability and sleep disturbance. Approximately half of the patients have associated neural crest tumors (mostly a neuroblastoma). A combination of pulse corticosteroids or ACTH and intravenous immunoglobulins are recommended as the initial treatment. Surgical tumor resection has no effect on the symptoms in the majority [43,44].

Startle syndromes are conditions characterized by exaggerated startle in response to a sound, movement and touch. Hereditary hyperekplexia is an autosomal dominant disorder that manifest in infants and young child with exaggerated startle associated with tonic stiffness of the body, with repeated falls. A bedside test involves demonstration of non-habituating head retraction in response to repeated tapping of the tip of the nose. With increasing age, the severity improves; however, it can be precipitated by stress or fatigue. Most children respond to clonazepam in the dose range of 0.01 - 0.1 mg/kg/day [45,46].

Other conditions associated with exaggerated startle

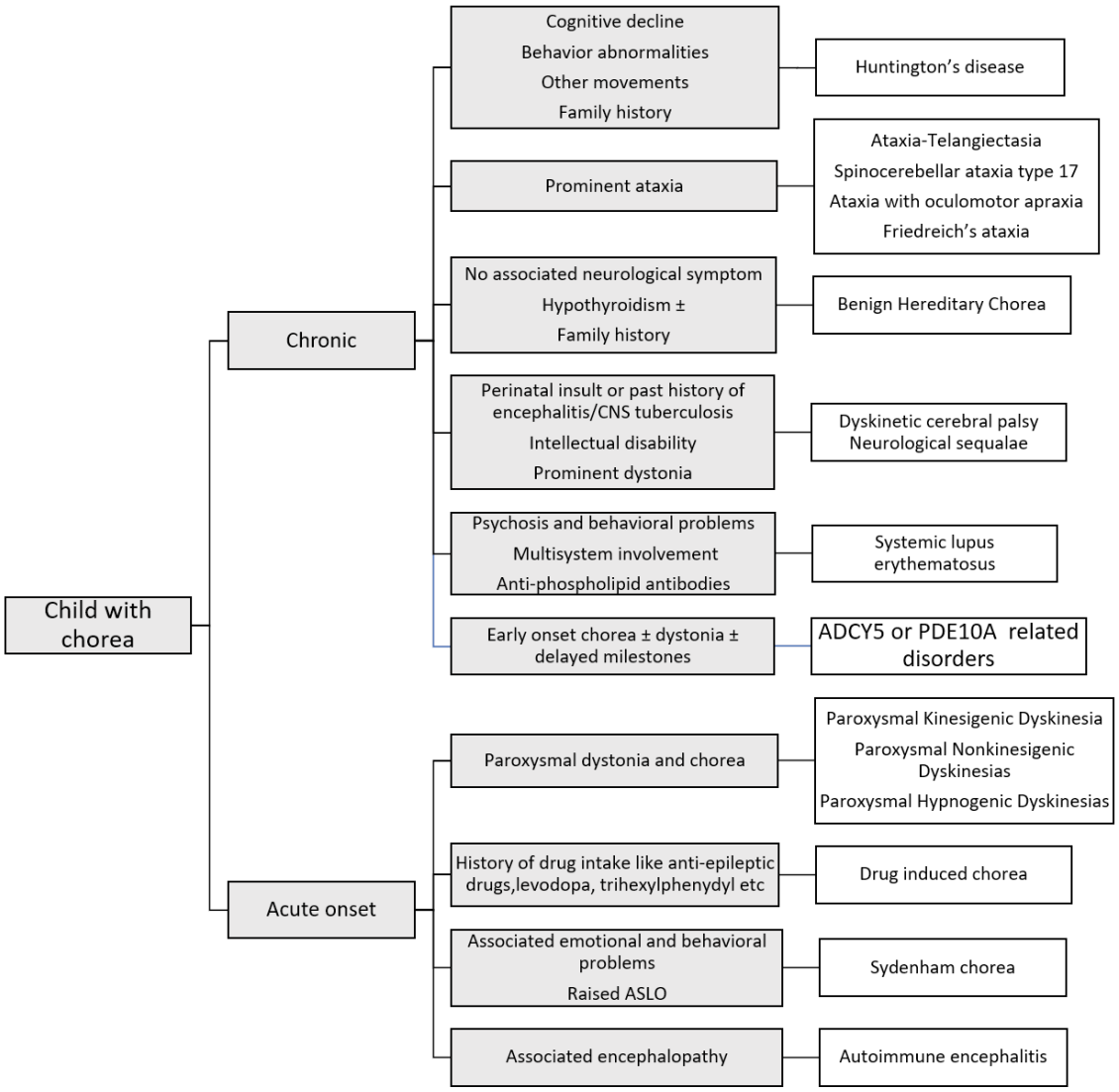

Fig. 3 Clinical approach to diagnosis of chorea in children.

are other forms of hyperekplexia, post-hypoxic and post-traumatic encephalopathy, encephalitis, brainstem dysfunc-tion and neurodegenerative disorders like GM1 ganglio-sidosis and Tay-Sach disease [46].

STEREOTYPIC MOVEMENT DISORDERS

Stereotypies refer to repetitive, non-functional, patterned movements and/or vocalizations that can be suppressed by distraction. Simple stereotypies like leg shaking, hair twirling, body rocking, head banging, and humming are considered as part of normal behavior. Complex stereotypies like hand flapping, oro-facial movement and eye-poking, which interfere with functions or are self-injurious are considered as abnormal [47]. Complex stereotypies are sometimes seen in typically developing children, but tend to remain stable or regress with age. More commonly, they are associated with conditions like autism spectrum disorders, intellectual disability, Rett syndrome, Down syndrome, phenylketonuria, visual or auditory impairment, and acquired brain injury [47,48]. In children with blindness, stereotypies are seen in more than two-third of patients, the common ones are body rocking, repetitive handling of objects, hand and finger movements, eye pressing and eye poking [49]. Behavior therapy (habit reversal therapy) is the mainstay of treatment for stereotypies. Drugs like risperidone and fluoxetine have role in patients with autism [47,48].

PARKINSONISM

Parkinsonism is a hypokinetic movement disorder,

characterized by presence of resting tremors, bradykinesia (paucity or slowness of movements), rigidity (lead pipe type) and postural instability. It can occur in conditions like Huntington disease and Wilson disease, or can be an adverse effect of tetrabenzine. Juvenile Parkinson disease is a rare genetic disorder that manifest with parkinsonism and leg dystonia [50].

FUNCTIONAL MOVEMENT DISORDERS

It refers to involuntary movements that result from abnormal mental state or condition, and are incompatible with recognized neurological and medical conditions. The common presentations in children are tremors, dystonia and myoclonus; others being gait disturbances, tics, chorea and tetany. Many children have identifiable precipitating factors like school examination, bullying, injury, illness, sexual abuse of the child or family member, parental discord or domestic violence, and death of a close relative [51-53]. It is mostly seen in children above 6-7 years and is more common in girls.

The diagnosis is suggested by a history of sudden onset, marked variability of symptoms, and sustained spon-taneous remissions. Examination often shows symptom variation, incongruous movements, distraction during spontaneous speech and behavior, the appearance of symptoms, or worsening during attention and production or suppression of symptoms on examiner's suggestion [51]. In psychogenic tremor, entrainment or alteration with rhythmic tapping of another body part is seen. For management, behavior therapy and relaxation techniques are usually employed. Parental education and counseling are important [53].

DEVELOPMENTAL AND BENIGN MOVEMENT DISORDERS

These are a group of conditions that manifest during specific developmental phases of childhood in absence of associated neurological features. They are considered as manifestation of subtle modification in the developing brain and have a favorable outcome [54]. The common disorders are detailed in **Table II**.

CONCLUSION

Movement disorders in children comprise of a heterogeneous group of conditions with diverse etiologies. The predominant conditions are dystonia, chorea, tics and tremors. Multiple movement disorders coexist in many conditions and often create diagnostic confusion. Presence of other neurological and systemic manifestations helps in narrowing the differential diagnosis. Neuroimaging and genetic studies enables accurate diagnosis. The management of these conditions is often challenging. One should always look for easily treatable conditions like dopa-responsive dystonia and infantile tremor syndrome.

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Table II Common Developmental and Benign Movement Disorders [45]

Disorders	*Age at onset*	*Age at resolution*	*Clinical features*
Jitteriness	<2 wk	< 1 mo	Paroxysmal, bilateral, high frequency tremor involving the extremities and chin, often exaggerated by startle or cry. Sometimes, can be a manifestation of drug withdrawal, hypocalcemia, hypoglycemia or encephalopathy.
Benign neonatal sleep myoclonus	<2 wk	< 6 mo	Myoclonic jerks in sleep, which disappear completely on waking up.
Benign myoclonus childhood	< 1 y	< 3 y	Upper body myoclonus occurs in absence of other neurological of features.
Spasmus nutans	4-18 mo	3- 4 y	Triad of paroxysmal head nodding (usually of no-no type), nystagmus (asymmetric, dysconjugate and horizontal) and torticollis (head tilting).
Benign paroxysmal torticollis	<3 mo	< 4 y	Recurrent episodes of painless rotation and inclination of head, often alternating from side to side. Sometimes associated with lateral incurvation of spine.
Shuddering attacks	< 1y	< 4 y	Brief, paroxysmal episodes characterized by shivering of head, shoulders and sometimes the trunk. Each episode last for few seconds and a child may have up to 100 episodes per day.

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Management of Neurocysticercosis in Children: Association of Child Neurology Consensus Guidelines

NAVEEN SANKHYAN,[1] RAZIA ADAM KADWA,[2] MAHESH KAMATE,[3] LAKSHMINARAYANAN KANNAN,[4] ATIN KUMAR,[5] GOURI RAO PASSI,[6] INDAR KUMAR SHARAWAT,[7] PRATIBHA SINGHI,[8] FOR ASSOCIATION OF CHILD NEUROLOGY DELPHI GROUP FOR NEUROCYSTICEROSIS IN CHILDHOOD*

From [1]Pediatric Neurology Unit, Department of Pediatrics, Post Graduate Institute of Medical Education and Research, Chandigarh; [2]Department of Pediatrics, Ankura Hospital for Women and Children, Hyderabad, Telangana; [3]Division of Pediatric Neurology, Department of Pediatrics, KAHER's Jawaharlal Nehru Medical College, Belagavi, Belgaum, Karnataka; [4]Gleneagles Global Hospital, Chennai, Tamil Nadu; [5]Department of Radiodiagnosis and Imaging, All India Institute of Medical Sciences, New Delhi; [6]Pediatric Neurology Division, Department of Pediatrics, Choithram Hospital and Research Centre, Indore, Madhya Pradesh; [7]Pediatric Neurology Division, Department of Pediatrics, All India Institute of Medical Sciences, Rishikesh, Uttarakhand; [8]Pediatric Neurology and Neurodevelopment, Medanta the Medicity, Gurugram, Haryana.

**List of group members provided as Annexure.*

Correspondence to: Prof Pratibha Singhi, Professor and Chief, Pediatric Neurology and Neurodevelopment, Medanta the Medicity, Gurugram, India. doctorpratibhasinghi@gmail.com

Justification: Neurocysticercosis (NCC) is a significant problem in India and other developing countries; however, several aspects of this disease have no clear, practical guidelines. There is a need for pragmatic guidelines, summarizing the available evidence, and filling in the gaps in evidence with expert advice to manage children with neurocysticercosis. **Process:** An expert group (16 members) and a writing group (8 members) was constituted, consisting of members with varied expertise. It included pediatric neurologists (18), neurologist (1), Neuroradiologists (4), and a parasitologist (1). The writing group divided the six topics and reviewed the literature on the topics individually to determine the clinical questions for which no clear guidance was available from the literature. The experts were then contacted and opinions were obtained online. The Delphi consensus method was adopted to arrive at a general consensus regarding various questions, with both the experts and the writing group members contributing. The final guidelines were then drafted by the writing group. **Recommendations:** Diagnosis of NCC should be based on clinical history and neuroimaging. Contrast-enhanced magnetic resonance imaging of the brain is the modality of choice. For single enhancing lesion, albendazole therapy for 10-14 days is recommended, and it should be combined with praziquantel for 10–14 days for more than one ring-enhancing lesions. For persistent lesion, the same dose and duration of albendazole or concurrent administration of albendazole and praziquantel should be given. Pulse intravenous steroids should be used to reduce the acute symptomatic edema in children with cysticercal encephalitis. Carbamazepine or oxcarbazepine are best suited for seizure prophylaxis for those who present with seizures; phenytoin and levetiracetam are the other alternatives. In the case of NCC presenting with symptoms other than seizures, there appears to be no role for routine anti-seizure medication prophylaxis. For a single ring-enhancing lesion, six months of anti-seizure medication is sufficient if the lesion resolves on follow-up. Those with persistent lesions, calcification, or multiple lesions, require a longer treatment duration of at least 24 months.

Keywords: *Cyst, Epilepsy, Parasitic infestation, Praziquantel, Seizures.*

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The World Health Organization (WHO) considers neurocysticercosis (NCC) as the most common preventable cause of epilepsy in the developing world. Neurocysticercosis accounts for an estimated 2 million people having epilepsy [1-4]. A study among people with active epilepsy found 34% to have NCC based on computed tomography and serology [5]. Around 17.3% of individuals had anticysticercus antibodies in a seroprevalence study conducted in Chandigarh [6]. A study conducted by the World Health Organisation on pig farmers of Uttar Pradesh showed a prevalence of teniasis in 18.6% of individuals, and around half of them had NCC [7]. A recent study showed a 4.5% prevalence of NCC in children attending tertiary care hospitals with acute focal neurological deficit or first episode of seizure [8]. In the Indian subcontinent; however, the spectrum of the disease seems to involve mostly young individuals with a single intraparenchymal cyst. The reason for this difference in clinical expression is unknown, although it could be related to less contact with tapeworm carriers, as similar patterns of disease are seen in people infected in regions where the disease is not endemic and in travelers [9].

Several aspects of this disease have no clear, practical guidelines. Infectious Diseases Society of America

(IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH) published a guideline intended to be applicable and feasible for developed nations (North America) [10]. These recommendations may not be applicable or feasible for developing countries like India, due to limited resources. Thus, there is a need for clear, pragmatic guidelines, summarizing the available evidence, and filling in the gaps in evidence with collated expert advice to manage children with NCC. To this end, the Association of Child Neurology took the initiative to get together experts to look at the evidence and bring forward a practice guideline to aid the management of children with neurocysticercosis.

OBJECTIVES

The guideline aims to provide directions for daily practice for the diagnosis and treatment of neurocysticercosis in children. The guideline not only looks at the up-to-date scientific evidence but also tempers it with expert advice to adapt to the Indian setting.

PROCESS

The writing group formulated six focus areas and several sub-questions, which aimed to cover all clinically relevant areas in diagnosing and managing neurocysticercosis in children. Within the major topics, several questions were shortlisted by the writing group to have further opinions and consensus among a broader range of experts. These included epidemiology, clinical features; Diagnosis: radiological tests, immunological tests, and other methods; antihelminthics: dose, duration, based on lesion load; management of NCC at atypical sites; steroids and anti-seizure drug use; and, statement on follow up, outcomes, and prevention **(Web Box I). Web Fig. 1** shows the constitution of the DELPHI group and the process followed.

The expert group and the writing group consisted of twenty-four members with varied expertise. It included 18 pediatric neurologists, four neuroradiologists, and one neurologist and parasitologist each. The 5-step Delphi process is outlined in **Web Fig. 1.** The writing group members then prepared the manuscript based on the relevant review of the literature and the results of the DELPHI consensus.

Quality of evidence scoring: The literature was selected by the committee members and was graded for quality based on the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) quality-of-evidence system [11]. The quality of articles to substantiate the conclusions by the group is provided with the concluding answer to each question.

Strength of recommendation assessment: On the basis of the selected literature and the online consensus development process, the group reached a consensus on a recommendation. The strength of the recommendation is expressed using the ESCMID strength of recommendation system [11], and many times does not always correlate with the quality of evidence. Hence, high quality of evidence may result in a marginal recommendation for use, while low-quality evidence may result in a strong recommendation for use.

RECOMMENDATIONS

Screening of Contacts

In view of the long incubation period between infection with NCC and the onset of symptoms, many of the tapeworm carriers who originally transmitted the infection may have cleared the intestinal infection or may no longer live near the patient [1,10,12]. Hence, stool examination for ova (which is the only available diagnostic test for tapeworms) is often negative in tapeworm carriers [13]. Even multiple examinations may not detect the tapeworm carrier. Even when ova are found, the morphology of the ova cannot distinguish *T. solium* from other taenia species. Thus, the yield of microscopy for the identification of tapeworm carriers is generally low, even in cases with apparent transmission outside of endemic areas [10]. Nevertheless, among patients who apparently acquired infection in the United States, tapeworms were documented in close contacts of 22% of NCC cases. Thus, most authorities would recommend screening for cases acquired outside endemic areas. Newer methods such as antigen detection in stool or detection of tapeworm-stage specific antibodies by immunoblot might improve the usefulness of screening, but these are presently only research techniques and not commercially available [10].

Recommendation

Routine screening of family members of children with NCC is not recommended. If at all screening is performed, fecal testing of the family for ova/cyst can be done.

Quality of evidence: 3; *Strength of recommendation*: D

Serological and Molecular Studies

The serologic antibody test of choice is the enzyme-linked immunoelectrotransfer blot (EITB) using parasite glycoproteins performed on serum. Enzyme-linked immunosorbent assay (ELISA) using crude antigens to detect antibodies are associated with frequent false-positive and false-negative results and should generally be avoided. Although EITB has 100% specificity and a sensitivity of 98% in patients with two or more cerebral

lesions, up to 50% of patients with a single brain lesion or with only calcified parasites may test negative [10]. The main problem related to ELISA on serum is the poor specificity, which is reported around 70% or less [14], compared with 86% for EITB [15]. The sensitivity of EITB varies with the form of NCC and specimen. In patients with multiple parenchymal, ventricular or subarachnoid NCC, the sensitivity of serum EITB is close to 100%. However, the sensitivity is poor in patients with a single parenchymal lesion or with only calcifications. Testing of serum is generally more sensitive than CSF using the EITB assay [16].

Antigen-based tests: They are also reported to be less sensitive than EITB. However, positive results correlate with the number of viable cysticerci. Parasite antigens are commonly detected in both serum and CSF in cases with multiple cysticerci such as subarachnoid NCC, and serial measurements may be helpful in the follow-up of complex cases [4].

Molecular tests: *T. solium* DNA has been detected by PCR or deep genomic sequencing using CSF of patients with subarachnoid NCC. However, there are no reports of its use in parenchymal NCC cases and its use may be even lesser in patients with a single brain lesion where most diagnostic problems arise. Cell-free *T. solium* DNA has been demonstrated in the urine and serum of patients with NCC, and recent data suggest that monocyte gene expression and serum mass spectrometry profiles could be used to identify NCC cases. To date; however, molecular biology assays are neither practical nor economical for routine case assessments. Techniques promoting amplification of DNA in a simple heating block or water bath may facilitate their application in resource-poor settings and include the loop-mediated isothermal amplification (LAMP) PCR [4].

Recommendation

The use of serological tests for diagnosis and clinical decision-making in children with NCC is not recommended.

Quality of evidence: 2; *Strength of recommendation*: D

Neuroimaging

Neuroimaging is established as a modality that can be used as an absolute diagnostic criterion for NCC [17]. The conclusive demonstration of a scolex within a cystic lesion on either computed tomography (CT) or magnetic resonance imaging (MRI) confirms the diagnosis of NCC **(Table I)**. The scolex is seen as a hyperdense dot within a cystic lesion on CT. It appears as hyperintense on T1-weighted images and hypointense on T2-weighted images on MRI. Sometimes other sequences of MRI are required to identify the scolex such as fluid attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), susceptibility-weighted imaging (SWI), or high-resolution heavily T2-weighted thin images including fast imaging employing steady-state acquisition (FIESTA), constructive interference in steady-state (CISS), or driven equilibrium (DRIVE). The typical appearance of the cyst is a less than 2 cm sized lesion with well-defined thin rounded walls located near the grey-white matter junction or basal ganglia. Other uncommon locations include the posterior fossa, subarachnoid spaces, intraventricular space, and spinal cord.

MRI plays a role in better characterization of the lesion by the demonstration of the scolex and internal characteristics. This further helps in differentiating NCC from its other close differentials, tuberculomas, and metastasis. The solid caseating tuberculomas characteristically have a T2 hypointense core which is not seen in any stage of NCC unless it is significantly calcified. It is one of the most helpful features in differentiating the two. Other features, though not specific, favouring a tuberculoma are a larger size (>2 cm), thicker and irregular walls, marked perilesional edema with mass effect, and associated basal meningitis. The presence of two-three conglomerate lesions may be seen in both entities and is not helpful in differentiation. On the other hand, some features suggest NCC over tuberculoma, such as intraventricular or subarachnoid location and multiple stages present simultaneously and pathognomonic features of individual lesions in case of multiple lesions [18].

MR spectroscopy of tuberculomas show elevated lipids and elevated choline/creatinine and choline/NAA ratios whereas these are not seen in NCC. On the other hand, NCC may show elevated acetate/succinate. Magnetisation transfer (MT) imaging has also been shown to be helpful in differentiating the two. The tuberculomas show a bright cellular component on T1-weighted MT images. The tuberculoma shows a hypointense centre with a hyperintense rim on T1-weighted MT images. The MT ratio of this hyperintense rim is significantly lower for tuberculomas compared to NCC and is due to the high lipid content in them [19,20].

MR also scores over CT for detection of lesions in atypical locations including intraventricular, subarachnoid, and intraspinal space. The high resolution heavily T2-weighted sequences are very useful in this. Even the lesions in the posterior fossa and those close to the skull are better delineated on MRI. Conglomerate lesions, subarachnoid or intraventricular lesions, and

Table I Clinical Features and Neuroimaging Appearance of Neurocysticercosis Based on Cyst Stage and Location

Cyst stage/location	*Clinical features*	*Neuroimaging characteristics*
Parenchymal		
Vesicular[a]	Usually asymptomatic	A thin-walled small CSF-like cyst with an eccentrically located scolex, no contrast enhancement of the cyst's wall, no surrounding tissue edema. The scolex can be iso-intensity or hyper-intensity on both T1-weighted and T2-weighted MR images and may show contrast enhancement.
Colloidal vesicular[a]	Seizures, focal neurological deficit, headache, vomiting, raised intracranial pressure, stroke, and rarely encephalitis	The cyst wall becomes thicker and irregular (late-stage) with contrast enhancement. The fluid within the cyst becomes slightly hyperintense on T1-weighted images and markedly hyperintense on T2-weighted or FLAIR sequences. Scolex decreases in size and eventually disappears. The surrounding tissue edema is striking.
Granular nodular[a]	Similar presentation as colloid vesicular	The cyst may be seen as a nodular or a thick, small, ring-like enhancement. Surrounding edema is not as extensive as the late colloidal vesicular stage and decreases gradually.
Nodular calcified	Focal or generalised seizures, headache, and vomiting.	Nodular calcifications <20 mm in diameter without surrounding edema or contrast enhancement.
Extra parenchymal		
Intraventricular	Commonly presents with acute obstructive hydrocephalus and raised intracranial pressure.	CSF-like cyst with or without scolex in the ventricular system, identified by the high signal intensity mural nodule, cyst wall outlined by cerebrospinal fluid in the ventricle on T1-weighted and FLAIR sequences. Commonly seen in the fourth ventricle, followed by the third, lateral ventricle, and aqueduct of Sylvius.
Subarachnoid	Communicating hydrocephalus, focal neurological deficit, nerve entrapments, thrombotic stroke, hemorrhage, lacunar infarctions, and raised ICP.	CSF-like cysts. Small in sulci, large in fissure or cistern, with a tendency to agglomerate, may cause mass effect and arachnoiditis.
Spinal	Myelopathy and radiculopathy are caused by spinal cord or root compression.	Cysts within the spinal subarachnoid space with or without evidence of inflammation/diffuse spinal arachnoiditis. Intramedullary cysts within the spinal cord.

[a]*Designated viable parenchymal cysts for the purpose of treatment.*

peripheral T2 hypointense ring with increased perfusion are the atypical neuroimaging of NCC [19].

Recommendation

MRI need not be done following CT in the following situations:

i) The CT conclusively demonstrates the presence of a scolex within the cyst; or

ii) In the absence of demonstration of scolex:

  a) If a solitary cystic/ring-enhancing lesion has all other typical sizes, shape, and location characteristics of NCC.

  b) Multiple lesions in different stages are present, including some cystic or ring enhancing or calcified.

Quality of evidence: 3; *Strength of recommendation*: D

MRI should be considered after CT in the following situations:

i) Atypical imaging features (conglomerate lesions, subarachnoid or intraventricular lesions) along with the absence of scolex;

ii) CT features create suspicion of intraventricular, subarachnoid, or intraspinal NCC; or

iii) Atypical clinical features including features of meningitis, encephalopathy, vision loss, fleeting headaches, stroke like features and behavioral changes.

Quality of evidence: 3; *Strength of recommendation*: B

Recommendation

If conventional MRI sequences have not been able to conclusively differentiate NCC from its differentials,

including tuberculoma, by failing to demonstrate scolex, then additional MR sequences may be acquired like MR spectroscopy and magnetization transfer imaging. However, the results of these may be used as supportive evidence rather than in isolation to differentiate the two.

Quality of evidence: 2; *Strength of recommendation*: B

Recommendation

Demonstration of scolex either on CT or MRI is the most conclusive evidence to differentiate between the two. In the absence of that, the features favoring NCC include a solitary well defined, thin-walled cystic or ring-enhancing lesion usually <2 cm in size with mild perilesional edema in a typical location of grey-white matter junction or basal ganglia. The presence of a T2 hypointense central core on MRI is strongly suggestive of tuberculoma over NCC in the absence of calcification as evidenced on CT or SWI sequences on MRI. The multicentricity of lesions with lesions showing different stages/features strongly favors NCC. Findings of MRS and MT imaging may be used as supportive evidence.

Quality of evidence: 2; *Strength of recommendation*: B

Recommendation

If the initial imaging (CT and/or MRI with recommended sequences when indicated) is not conclusive to differentiate NCC from tuberculoma, then a repeat contrast-enhanced MRI may be performed at an interval of 6-8 weeks to look for interval change. The imaging may be performed earlier if indicated by worsening or new clinical symptoms/signs.

Quality of evidence: 3; *Strength of recommendation*: C

Recommendation

The repeat imaging after treatment of NCC should be done at the interval of 6 months unless guided earlier by any worsening/new clinical symptoms/signs. This applies to both single and multiple NCC. MRI may be the preferred modality keeping into account the risk of radiation exposure with CT. The decision of administration of contrast may be left at the discretion of the radiologist, based on findings on plain MRI. A plain CT scan may sometimes be required after MRI if the presence of calcification is not conclusive on the MRI, and is required for clinical management.

Quality of evidence: 2; *Strength of recommendation*: B

Management of Intraparenchymal NCC

Albendazole therapy in solitary cysticercus granuloma (viable cyst, non-calcified): Cysticidal drugs hasten the resolution of NCC and improve the natural course of the disease. Cysticidal drugs have no role in treatment of calcified cysticercal granulomas. Both praziquantel and albendazole have cysticidal activity; however, a few studies have observed that treatment with praziquantel was less effective than albendazole in the complete cyst resolution and seizure control [21,22]. Praziquantel has more complex drug interactions with steroids, which are co-administered in NCC [23].

Albendazole with steroids should be considered for children with neurocysticercosis, to decrease the number of active lesions as well as to reduce seizure frequency. A short-course of albendazole treatment is as efficacious as four weeks treatment course in solitary cysticercus granuloma [24-27]. Monotherapy with albendazole is comparable to combination therapy of albendazole and praziquantel in the single solitary enhancing lesion in CT (SSECTL) [28].

Recommendation

The use of 10-14 days of albendazole therapy for all patients with single viable cyst is recommended.

Quality of evidence: 1; *Strength of recommendation*: B

Albendazole 15 mg/kg/day (maximum 1200 mg/day) in twice-daily doses should be given with meals. The quality of evidence is strong for use of albendazole but not for the duration of use.

Antihelminthic drugs for multiple viable cysts: Albendazole (ABZ) and praziquantel (PZQ) have different mechanisms of action, which may be beneficial when combined together in treating multiple NCC. Praziquantel is a pyrazinoisoquinoline derivative, of which the main pharmacological effects include muscle contractions, paralysis, and tegumentary damage, whereas albendazole is a benzimidazole, whose main mechanism of action is through selective degeneration of cytoplasmic microtubules resulting in energy depletion, disrupted cell division, and altered glucose intake.

Combination therapy with albendazole and praziquantel has been found to be safe and effective without any increase in adverse events. Increased serum albendazole concentrations were observed in patients receiving combination treatment compared with those receiving albendazole alone. Albendazole serum levels increased by 48% when given in combination with praziquantel [29]. Garcia, et al. [29] reported that combination of albendazole and praziquantel was associated with increased albendazole sulfoxide plasma concentrations. This along with a possible synergistic effect of two drugs may be beneficial for patients. A randomized trial of 32 pateints showed that the

combination therapy was more effective in destroying viable brain cysticercosis cysts than ABZ alone [30].

Combined treatment with albendazole and praziquantel was found to be superior in a three-arm randomized double-blinded study. One twenty-four patients (aged 16 to 65 years with 1 to 20 viable cysts) were randomly assigned to three arms (43 received standard dose albendazole; 40 received high dose (22.5 mg/kg/day) albendazole and 41 patients received combination therapy with standard dose albendazole and praziquantel). Complete cyst resolution in MRI brain performed 6 months after initial therapy was seen in 63% of patients who received combination therapy vs 73% and 83% resolution in the standard dose and high dose albendazole, respectively (P=0.141) in patients with one to two viable cysts. However, in patients with three or more then three cysts, complete cyst resolution was seen in 94% of patients who received combination therapy vs 21% and 48% resolution in the standard dose and high dose albendazole, respectively (P<0.001) [31]. Anti-helminthic drugs are not recommended in patients with cysticercal encephalitis or 'starry sky NCC' for fear of worsening the intracranial edema.

Recommendation

Albendazole (15 mg/kg/day) combined with praziquantel (50 mg/kg/day) for 10-14 days is recommended for more than two viable cyst.

Quality of evidence: 1; *Strength of recommendation*: B

Praziquantel dose at 50 mg/kg/day (upto 3600 mg/day), quality of evidence extrapolated from studies done in adult patients.

Treatment of persistent viable cysts: Response to a single course of cysticidal therapy is variable. A persistent cyst is seen in 30-40% of patients with a single viable lesion on follow-up. The persistence of the lesion is associated with seizure recurrence [32,33]. Rajashekar, et al. [32] treated 11 patients with persistent lesions with a repeat course of albendazole for two weeks. A significant reduction in cyst size was observed in two patients and complete resolution in two patients in follow-up CT scans. There are no randomized controlled trials or convincing data to suggest retreatment is better than symptomatic treatment; however, experts recommend retreatment [31]. Options for retreatment include a second course of albendazole or using the combination of albendazole and praziquantel.

Recommendation

There are two options to treat the persistent lesion. One is retreatment with the same dose and duration of albendazole and the second option is the concurrent administration of albendazole and praziquantel as for multiple lesion NCC.

Quality of evidence: 3; *Strength of recommendation*: C

Management of NCC at Atypical Sites

Cysticercal encephalitis: NCC can occur in atypical forms and at atypical sites in rare scenarios. The atypicality may be due to lesion load or due to the site. Rarely the NCC lesions can be in hundreds (miliary NCC) and can present with raised intracranial pressure due to edema associated with degeneration of numerous lesions simultaneously or sequentially [34]. In an even rarer situation, the intracranial lesions may be associated with disseminated lesions in other tissues of the body, primarily the muscles and subcutaneous tissue [35]. The literature on the management of cysticercal encephalitis is restricted to case reports. Due to the rarity of the presentation, there are no trials of drugs or other methods to manage these patients. There is; however, a consensus on avoiding the use of anti-helminthic drugs in these patients for fear of worsening the intracranial edema. Most experts and case reports suggest a beneficial effect of intravenous steroids in relieving the edema caused due to degeneration of cysticerci in cysticercal encephalitis.

The long-term management of cysticercal encephalitis is challenging, and the clinical course is often punctuated by recurrent episodes of symptomatic raised intracranial pressure and/or seizures.

Recommendation

Pulse intravenous steroids should be used to reduce the acute symptomatic edema in children with cysticercal encephalitis. The steroids suggested are methylprednisolone (10-30 mg/kg for 3-5 days; maximum 1000 mg/day) or dexamethasone (3-6 mg/kg/day for 3-5 days; maximum 16 mg/day).

Quality of evidence: 3; *Strength of recommendation*: A

Recommendation

Steroids can be used for long-term management of cysticercal encephalitis to prevent episodes of acute symptomatic cerebral edema in children with cysticercal encephalitis. Steroids in minimal doses and for the shortest possible period are suggested. Rapid tapering to the lowest effective dose and use of intermittent dose (e.g., alternate day) and monitoring for steroid side effects is suggested.The group does not support or recommend against the use of steroid-sparing drugs due to lack of evidence.

Quality of evidence: 3; *Strength of recommendation*: C

Subarachnoid, ventricular and spinal NCC: These varieties of NCC are exceedingly rare in children in the Indian sub-continent. Most of the reports on subarachnoid and ventricular cysticerci are from South-America [36,37]. Due to the rarity of the condition in India, and the availability of recent evidence-based guidelines published by IDSA and ASTMH [10], the group recommended that these guidelines may be adopted for these rarer kinds of NCC.

Steroids and Anti-Seizure Drug Use

Local inflammatory reaction surrounding NCC is widely prevalent as evidenced by worsening of clinical symptoms (e.g., headache), presence of perilesional edema and contrast enhancement on neuroimaging [38], and increased pleocytosis and elevated protein on serial CSF studies [39]. Host immune reaction to the degenerating cysts underly the pathophysiology of neuroinflammation in NCC. The resulting perilesional white-matter edema might occasionally produce focal neurological deficits and other devastating consequences due to mass effect and raised intracranial pressure. This is especially true when the cysts are located in the subarachnoid space, within the ventricles, orbit, brain stem, or the spinal cord. Thus, treatment with anti-inflammatory medications, particularly cortico-steroids is routinely considered in children with NCC.

In most observational and randomized controlled trials of NCC, patients were routinely treated with oral corticosteroids with or without the combination of anti-cysticercal treatment. Oral prednisolone has been used in doses ranging from 1-2 mg/kg/day for 3-10 days in most studies [40,41]. One meta-analysis, which included 13 studies with low-quality evidence, suggested that corticosteroids reduced seizure recurrence rate and hastened lesion resolution in the medium term (6-12 months) [42]. A recent meta-analysis found that the combination of albendazole with oral steroids provided superior seizure prevention and lesion resolution outcomes in cases of solitary cysticercus granulomas. But another meta-analysis concluded that corticosteroid treatment did not impact any outcomes significantly [43]. Thus, the available evidence is still conflicting about the effectiveness of a particular corticosteroid drug, dose, or duration of treatment in different stages of NCC.

Neuroimaging showing new-onset localized inflammation with perilesional edema and contrast enhancement in calcified NCC, years after the initial presentation, are well documented [44-46]. These cases present with seizures recurrences, headaches, or maybe asymptomatic [45]. The role of treatment with steroids in addition to anti-seizure prophylaxis in such cases is unclear. We do not recommend the routine use of steroids in such cases. Steroids might be considered in cases of large perilesional edema causing mass effect, midline shift, or other manifestations of raised ICT.

Recommendation

There is no role for routine use of steroids in cases of contrast-enhancing calcified NCC presenting with recurrence of seizures. Steroid use should be reserved for symptomatic cerebral edema.

Quality of evidence: 3; *Strength of recommendation*: D

Anti-Seizure Prophylaxis

As seizures are the most common presenting symptom, most patients with NCC receive anti-seizure medication (ASM) prophylaxis for varying durations depending on lesion resolution or calcification. Patients with calcified NCC receive long-duration ASM because of seizure recurrences after varying periods of seizure freedom, either on or off ASM. Though there is no high-quality evidence available to indicate the choice, dose, or duration of ASM in different NCC types, monotherapy with phenytoin and carbamazepine has been most commonly used [40], given the focal nature of epilepsy in this population. One pilot study demonstrated the safety, tolerability, and effectiveness of clobazam in NCC, but clobazam treatment was more expensive than phenytoin [47].

Recommendation

In the case of NCC presenting with other symptoms without seizures, there appears to be no role for routine anti-seizure medication prophylaxis.

Quality of evidence: 3; *Strength of recommendation*: D

Recommendation

Carbamazepine or oxcarbazepine are best suited for seizure prophylaxis in children with NCC in India. Phenytoin and Levetiracetam are other alternatives.

Quality of evidence: 3; *Strength of recommendation*: B

Epilepsy Surgery

Residual perilesional gliosis surrounding calcified NCC is thought to be responsible for long-term epilepsy [48]. Though most cases of epilepsy due to calcified NCC are controlled with ASM, a minority end up being drug-resistant. Surgical resection is one of the most effective curative treatment options available in cases of drug-resistant epilepsy due to calcified NCC. The pre-requisites for the surgical resection are that epilepsy

should be truly drug-resistant, seizures are frequent and disabling enough, clinical and video-EEG analysis proves that the calcified NCC is responsible for epilepsy and its removal is likely to cause seizure freedom. In endemic countries, calcified NCC's co-existence with hippocampal sclerosis (dual pathology) is well documented [49-53]. These patients are amenable to surgery, but the surgical strategy should be individualized. Patients with drug-resistant epilepsy should be referred early for consideration of epilepsy surgery.

Recommendation

Epilepsy surgery workup should be considered in children with NCC who failed two appropriately chosen ASM tried in optimal doses.

Quality of evidence: 3; *Strength of recommendation*: B

Optimal Duration of Anti-Seizure Medications

A review published in October, 2019 in the Cochrane Database of Systematic Reviews found four studies (466 patients) which addressed the question of duration of ASMs in patients with neurocysticercosis [54]. There was no difference in seizure recurrence in patients receiving anti-seizure drugs for 6, 12, or 24 months. The odds of seizure recurrence in six months treatment compared with 12 to 24 months treatment was not statistically significant [OR(95% CI) 1.34 (0.73 to 2.47); three studies, 360 participants, low certainty evidence]. When six to 12 months of therapy was compared with 24 months treatment, this too was not statistically significant [OR (95% CI) 1.36 (0.72 to 2.57); three studies, 385 participants; low certainty evidence].

Can the results of this analysis be extrapolated to children? Of the studies included in the analysis, one analyzed children between 3-14 years, one had only adults, one had both children and adults (age range 4-52 years), and the previous study did not clearly mention the age range [55-58]. All studies were single-center studies conducted in India. Notably, these studies excluded patients with persistent lesions, multiple NCC, and those needing albendazole therapy. The presence of calcified lesions was suggested to correlate with seizure recurrence and the need for prolonged therapy.

Two of these studies have suggested that the presence of calcification and persistence of the lesion on neuroimaging increases the risk of seizures and may require longer ASMs. A large prospective study of 185 patients (38.4% children <14 years) evaluated factors that predict seizure recurrence in patients with solitary cerebral cysticercosis granuloma when ASMs were withdrawn 3-12 weeks after cyst resolution on neuroimaging. Calcific residue on CT scan, breakthrough seizures, and a history of more than two seizures were found to be risk factors for recurrence on multivariate analysis [59].

Recommendation

For a single ring-enhancing lesion, six months of therapy anti-seizure medications is recommended if the lesion resolves on follow-up. Those with persistent lesions, calcification, or multiple lesions require a longer treatment duration of at least 24 months.

Quality of evidence: 2; *Strength of recommendation*: B

Recommendation

Anti-seizure medication may be withdrawn after 6 months if there is no calcific residue, there is resolution of cyst on neuroimaging, and the child has had less than three seizures in the past.

Children with evidence of calcification, persistent cyst, or a history of more than two seizures in the past may require a longer duration of therapy.

Quality of evidence: 2; *Strength of recommendation*: B

CONCLUSIONS

These guidelines are intended for pediatricians, neurologists, and family physicians, and reflect our approach to the management of the children with NCC based on the best available evidence in the literature and expert opinions.

Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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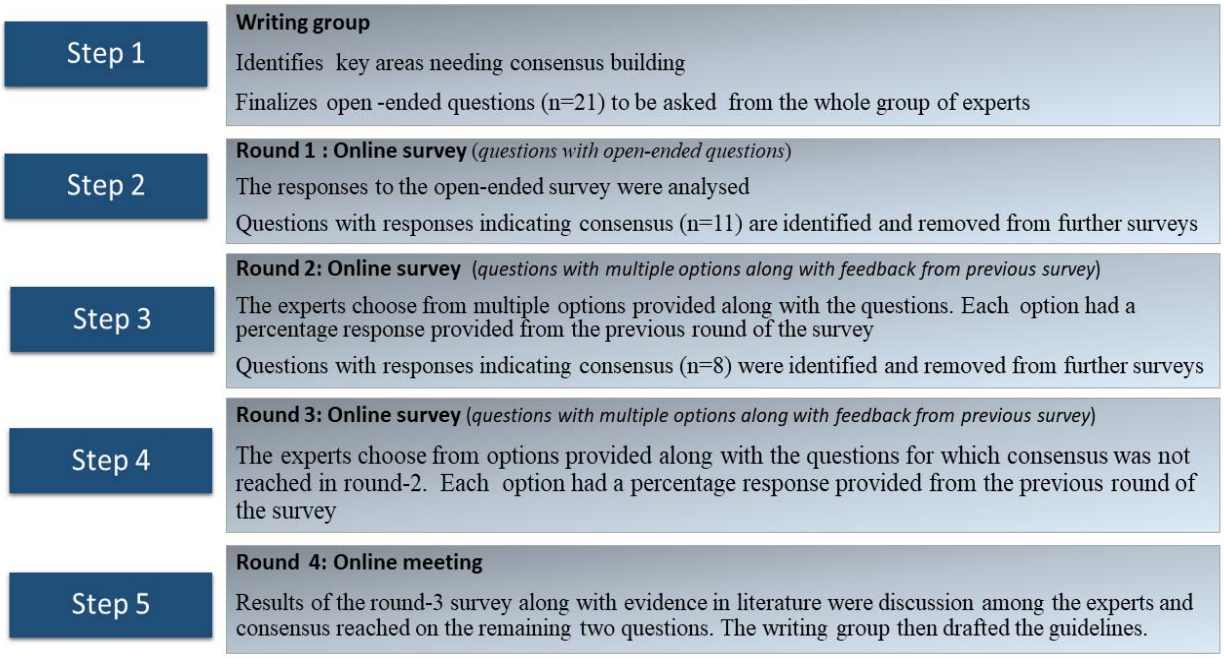
ANNEXURE

Participating Delphi Group Experts*

Rajni Farmania, *New Delhi*; Jatinder Singh Goraya, *Ludhiana, Punjab*; Vineet Bhushan Gupta, *New Delhi*; Rakesh Gupta, *Gurugram, Haryana;* Rakesh Jain, *Gurugram, Haryana*; Prashant Jauhari, *New Delhi;* Gurpreet Singh Kochar, *Ludhiana, Punjab*; Rashmi Kumar, *Lucknow, Uttar Pradesh*; Priyanka Madaan, *Chandigarh*; Abhishek Mewara, *Chandigarh;* Anita Sharma, *Gurugram, Haryana*; Lokesh Saini, *Jodhpur, Rajasthan*; Jitender Saini, *Bangalore, Karnataka*; Gangandeep Singh, *Ludhiana, Punjab*; Nitish Vora, *Ahmedabad, Gujarat*; Sameer Vyas, *Chandigarh*.

**Listed in alphabetical order.*



Web Fig. 1 Step followed in the DELPHI Process

Web Box I Step 1: Open-ended questions for experts

1. In your opinion/ experience, what are the common presenting symptoms of neurocysticercosis apart from seizures, in children?
2. What are the unusual or rare presentations of neurocysticercoses in children seen by you?
3. How in your opinion do symptoms of neurocysticercoses differ in children as compared to adults?
4. In your opinion, should we screen family members of a child presenting with neurocysticercosis? If so how?
5. Do you use serological tests for the diagnosis of neurocysticercosis? If yes in what situation and what test?
6. In your opinion, when will you order an MRI in a child suspected of NCC, who has already had a CT done?
7. What are the special techniques in MRI to help detect NCC and to differentiate from other close differentials? (*Question specifically for experts in radiodiagnosis*)
8. In your opinion, which findings do you rely on to reliably differentiate NCC from tuberculoma radiologically? (*Question specifically for experts in radiodiagnosis*)
9. What in your opinion should be the ideal time to repeat the imaging after treatment of NCC, does it differ in those with one versus those with multiple lesions? Secondly do you order a CT or MRI? Plain or contrast?
10. In case initial imaging is not conclusive to differentiate NCC from tuberculoma, what in your opinion is the role of repeat imaging and to be done at what interval?
11. What is your preferred way to treat ring enhancing lesions that persist after one course of antihelmenthics? Concurrent administration of albendazole and praziquantel OR a longer duration of albendazole OR repeat course of albendazole in same dose OR any other option?
12. In children who do not have seizures but have NCC detected on neuroimaging (e.g., imaged for evaluation of headache). Will you use the following?
    a. Antihelmenthic drugs
    b. Antiseizure medications
13. In your opinion what is the optimal duration of Albendazole in Solitary cysticercus granuloma –one week, two weeks or 4 weeks regimen?
14. What is your preferred way to use antihelminthic drugs for more than two ring enhancing lesions (Not encephalitis) ? Concurrent administration of albendazole and praziquantel OR a longer duration of albendazole OR any other option?
15. What, in your opinion, is the best drug to manage NCC encephalitis with **acute symptomatic** cerebral edema in children (headache, vomiting, behaviour change, papilledema, reduced sensorial level)? Notably, the role of steroid pulses/oral. (which steroid and for how long?
16. What, in your opinion, is the best drug for **long term management of NCC encephalitis** with symptomatic cerebral edema (intermittent headache, vomiting, behaviour change, persistent papilledema)? Notably, the role of steroids and steroid sparing agents
17. Subarachnoid and ventricular cysts are rare in children and in the Indian sub-continent. They are more common in series from the South-America. Evidence based guidelines published by IDSA and ASTMH may be adopted for India for these rarer kinds of NCC.[1] Are you in agreement with this?
18. What anti-seizure drug, dose and duration of therapy would be best suited, as per your practice, in the following situations?
    a. Single ring enhancing lesion
    b. Multiple ring enhancing lesions
    c. Calcified NCC
19. When do you consider epilepsy surgery for calcified NCC?
20. In your opinion what is the treatment of calcified lesions that show edema along with seizures? –would you use antihelminthic drugs and/or anti-inflammatory drugs> which drug do you prefer and the dose/duration you follow.?
21. What is the optimal duration for treatment with antiepileptic drugs in children with NCC and on what criteria must we base our decision to withdraw anti-seizure drug?

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Simulated Patients for Competency-Based Undergraduate Medical Education Post COVID-19: A New Normal in India

ANIL KAPOOR,[1] ANJU KAPOOR,[2] DINESH K BADYAL[3]

From Departments of [1]Medicine and [2]Pediatrics, People's College of Medical Sciences and Research Centre, Bhopal, Madhya Pradesh; and [3]Department of Pharmacology, Christian Medical College, Ludhiana, Punjab.

Correspondence to: Dr. Anil Kapoor, Professor of Medicine, HIG, C/10, PCMS Campus, Bhanpur, Bhopal 462037, Madhya Pradesh. anil.faimer@gmail.com

The conventional medical curriculum in India needed more focus on explicit teaching and assessment of interpersonal and communication skills, professionalism, team-work and reflection for prevention and better management of increasing incidences of violence against doctors by building good doctor-patient relationships. Increasing number of seats in Indian medical colleges, decreasing hospital stay of patients, and decrease in faculty requirements will hamper adequate supervised authentic clinical experiences of undergraduates for developing clinical skills. The recent COVID-19 pandemic has led to a significant decrease in student-patient encounters. Simulated patients are being used in many countries to address many of these issues. To make the Indian medical graduates competent to function as primary physician of first contact, competency-based medical education along with guidelines for use of skill-lab and simulation has been introduced from 2019. The current review is focused on the need and use of simulated patients; their advantages, limitations and role in students' teaching and assessment. It also gives a brief outline of their training process. Simulated patients should be used to supplement day-to-day learning, help in transition to attending real patients and also save enormous faculty time in the post-COVID-19 new normal. However, simulated patients are unlikely to completely replace real patients' experiences.

Keywords: *Clinical skill assessment, Competency-based assessment, Medical education, Simulation, Standardized patient*.

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There has been an increase in incidences of violence against doctors in last few years in India, which had been partly attributed to lack of explicit teaching and assessment of interpersonal and communication skills, ethics, professionalism, team-work and reflection during the undergraduate (UG) training program [1,2]. UG students often miss to develop competence in soft-skills. There is a need to improve doctor-patient relationship with more trust and respect for each other. In order to address these issues and to make the Indian Medical Graduates (IMG) competent to function as a primary physician of first contact, Graduate Medical Education Regulations (GMER) amendment, 2019 has implemented major reforms by introducing competency-based medical education (CBME) [3]. It has emphasized more on knowledge application than knowledge acquisition and recommended use of simulations and simulated patients (SPs) for teaching clinical skills to achieve competencies in a safer environment; simulation labs have been made mandatory in all medical colleges [4].

Since there have been sufficient number of patients available, use of SPs is not a routine practice for teaching UG students in India. However, the times are changing and coronavirus disease 2019 (COVID-19) pandemic has led to significant decrease in student-patient interactions and it seems that SPs are the need of the hour. The current review is focused on the need and use of simulated patients, and their advantages, limitations and role in student's training and assessment. It also gives a brief outline of their training process.

HISTORICAL PERSPECTIVE

The concept of 'simulated patient' (SP) was introduced by Barrows and Abrahamson in 1964 for teaching clinical skills to medical students [5], which was later also expanded to their assessment [6]. During a board examination in psychiatry and neurology, Barrows observed that one patient with syringomyelia became uncomfortable with the way of examination by a resident and tried to fix him by providing wrong information and changing his sensory findings! He also noticed lack of direct observation of students during their encounters with patients; and students committing many mistakes during examinations. This led him to an idea of introducing trained persons, who can be used instead of real patients on whom medical students can do repeated practice and receive corrective feedback to learn the desired skills [7].

The American Board of Pediatrics (1978) has defined five clinical skills (attitude, factual knowledge, interpersonal skill, technical skill and clinical judgment) in which pediatric residents should be competent [8]. Factual knowledge can be assessed by various valid and reliable assessment tools, while assessment of other skills relies more on using standardized patients [7,9,10]. American Board of Internal Medicine, Medical Council of Canada and Educational Commission for Foreign Medical Graduates have also supported the use of standardized patients for assessment of clinical skills [10,11,12].

WHAT ARE SIMULATED PATIENTS?

Barrows initially introduced the term 'the programmed patient' [5] for a normal person who had been trained to act and react like a real patient with an illness and later revised it as 'simulated patient'; while Norman coined the term 'standardized patient' [7,13]. The concept of SP is based on the philosophy of learning by doing and receiving immediate constructive feedback to have authentic experiential learning. Though the terms simulated patient and standardized patient have been used interchangeably, different educationists have described them differently. With simulated patients, the emphasis is on simulation (presenting the symptoms and signs of real patients) while "*standardized patients are those simulated patients who present the patients problem in standardized unvarying way to different students; therefore, they can also be termed as standardized simulated patients"* [14].

Later, standardized patients was used as an umbrella term, covering both the SPs as well as real patients, who have been coached carefully to present their problems consistently in a standardized way, to prevent students from knowing whether they are facing a real patient or a SP [7].

'REAL' PATIENTS IN MEDICAL EDUCATION IN INDIA

Till date, medical students are being trained and assessed on real patients. The greatest advantage of real patients is their availability with real symptoms and abnormal findings e.g., koilonychia, pallor, jaundice, hypertension, cardiac murmurs, irregular pulse, goiter, exophthalmos, pregnancy, edema, ascites, hepatomegaly, splenomegaly, crepitations over lungs etc. They are authentic and well accepted by teachers and students. They do not require any training or added cost for teaching-learning purpose.

However, using real patients can lead to opportunistic teaching; students are taught only those diseases whose patients are available. They are difficult to use in emergency or emotionally charged situations (e.g. HIV positive patients, recently diagnosed cancer patients, dying patients, rape victims, acute exacerbation of psychiatric disorders etc.). Some patients are reluctant to be examined by trainee students; some feel uncomfortable by repeated interrogation and physical examination and become non-cooperative. They may pose different problems to different students; thus making the assessment less reliable [15]. It is difficult to standardize them as they see the situation from their own perspective. Students can not be allowed to examine very sick patients. With increasing number of UG seats in Indian medical colleges, decreasing hospital stay owing to rapid diagnosis with better management, day care facilities and apprehension after COVID-19, we are going to face a shortage of variety of patients in proportion to number of students for providing adequate clinical experiences.

NEED FOR SPs IN CBME

Similar to Barrows' observations, students in India also are mostly not observed while eliciting the history and clinical examination of patients and their mistakes and deficiencies often go unnoticed till they perform poorly in examinations as well as in real life situations. Regular supervision and feedback culture is sub-optimal at most of the medical colleges. Due to decrease in the official requirements of faculty in various departments, it will be difficult to supervise, provide feedback and certify all the students for acquiring all the competencies prescribed in the CBME curriculum, without using SPs. COVID-19 pandemic leading to a significant decrease in student-patient interactions is now a major reason for us to introduce SPs for clinical teaching and it might continue to be a supplement method in the 'new normal.' A scoping review of 33 studies related to use of the SP methodology found 24 studies to be effective in developing clinical skills of students in many countries [16]. Advantages of using SPs are enlisted in **Box I** [7,14,15,17,18].

SPs AS A TEACHING TOOL

SPs are trained to follow a script to reproduce a particular problem or symptoms, and are given a set of guidelines to follow for certain responses and provide specific patient-centered feedback. They are helpful in developing all three domains of learning; technical, communication and cognitive skills.

Technical skills: SPs are effective in improving students' examination skills as students can actually perform various maneuvers on cooperative real human beings. Many physical findings have been simulated with proper training (**Box II)** [7,19]. Make-up or moulage is being used to make realistic portraying of wounds. Some specially trained SPs, known as 'intimate examination

Box I Advantages of Using Simulated Patients

- SPs provide high fidelity learning environment that realistically replicates a patient encounter in a predetermined clinical scenario.
- They can be trained to be mentally prepared to co-operate and examined by numerous students and respond uniformly in every student encounter.
- They provide a safe and non-threatening learning environment that allows mistakes and interruptions to be made.
- Medical students can practice history-taking, clinical examination and counselling skills repeatedly with SPs till they feel ready to face the complex and unpredictable encounters in real world.
- Once trained on SPs, students feel more competent and confident while encountering real patients and patients too feel that an expert is examining them rather than a novice.
- SPs can be used in teaching and assessing critical illnesses and emotionally charged situations, which is practically not feasible with real patients; e.g. confronting with a dying patient, sexually abused patient, psychiatric patient etc.
- They can be manipulated as per educational needs. Complications can be added or deleted in the 'case scripts' based on students' level of training.
- They can be trained to change their presentation quickly so as to demonstrate the response to treatment and course of chronic illnesses in the same setting.
- They can be trained to provide assessment scores and specific patient-centered feedback that students require in order to further enhance their learning in cognitive, psychomotor and affective domains, thus saving enormous faculty time.
- As they are standardized, a criteria referenced assessment of students can be formulated.
- By using SPs in place of real patients, real patients' safety and privacy are maintained; thus avoiding risk of legal issues.
- They can be enrolled in a 'SP bank' and are available for use any time, as and when required.

Box II Some Physical Findings That Can Be Simulated

Central Nervous System

- coma/altered sensorium/confusion
- gait abnormalities/hearing loss/vision loss
- hyperactive tendon reflexes
- neck rigidity/Kernig sign/Babinski sign
- muscle spasm/muscle weakness
- sensory losses
- incoordination/abnormal movements etc.

Abdominal examination

- abdominal tenderness/rebound tenderness
- acute abdomen

Respiratory system

- cough/abnormal breathing pattern

Joint examination

- movement restriction
- tenderness/warmth/redness

Psychological

- depression/agitation

associates' (IEA) or 'teaching associates' allow for female (gynecological teaching associate) and male (urological teaching associate) intimate examinations (breast, pelvic, rectal, testicular), thus avoiding risk of mistreatment to real patients; and these IEAs are reasonably paid for that [20]. Trained SPs provide corrective feedback which allows students to reflect on their performance and improve on weaker areas in a non-stressful and non-threatening environment [21]. Thus, SPs promote self-directed and collaborative learning.

Communication and teamwork skills: Interpersonal and communication skills and professionalism are core competencies as per Accreditation Council of Graduate Medical Education (ACGME) and are must for successful interaction between doctors and patients. However, standard norms were not set for teaching and assessment of these skills in traditional curriculum [17,22,23]. Poor communication with patients and caretakers may lead to dissatisfaction and risk of violence against doctors [24]. SPs provide a unique opportunity to students to learn and practice these soft skills; and also receive constructive feedback from them [17,18,25].

Cognitive skills: SPs are helpful in developing students' clinical reasoning and decision making skills and can address higher levels in cognitive domain. 'Time in - time out' and 'stimulated recall' are two powerful tools to develop competence in clinical reasoning and decision-making [7]. In 'time in - time out' technique, once a group of students had interacted with a SP, teacher calls 'time out' and the SP goes into suspended animation (as if he/she is not there). Meanwhile, teacher discusses with the students what they think is happening with the patient and future course of action then and there only. Once discussion is over, teacher calls 'time in' for the SP to join back and participate in the discussion. This method gives the opportunity to discuss freely regarding differential diagnosis, management, prognosis and sensitive issues

that can not be discussed in front of real patients. In 'stimulated recall', interaction between student and SP is video-recorded and discussed later with the teacher.

Hybrid model: Integrating SPs with mannequins provide opportunities to practice procedural skills on the mannequin while communicating with SPs simultaneously; thus enhancing their technical and interpersonal skills in same sitting [26, 27]. Few examples are wound suturing, giving injections, catheter insertion and conducting delivery, which can be performed side by side on inanimate models attached to SPs.

SPs AS AN ASSESSMENT TOOL

Written examination and viva-voce do not assess clinical competence. Interpersonal skills and clinical performance is rarely observed during students' assessment [10]. Real patients used for clinical assessment of students are usually not standardized, which may affect the reliability of result. In a study, no significant difference was found between undergraduate students' performance on real and simulated patients; students favored use of SPs over real patients for assessment of communication skills [28].

Objective Structured Clinical Examination (OSCE) and Clinical Skill Assessment (CSA) both use SPs as assessment tool. While OSCE assesses discrete skills or small set of skills at one station, CSA assesses a group of clinical skills (history taking, physical examination and patient education) in one encounter [29]. Good reliability and validity of CSA is ensured by using three different types of encounters, as described here [10,30]:

i) *History cases*: are used to assess history taking and interviewing skills of the students.

ii) *History and focused physical examination cases*: are used to assess physical examination skill in addition to history taking and interviewing skills.

iii) *Patient education-counselling cases*: are used to assess the ability to educate patients on common topics (breast/complementary feeding, vaccination, oral rehydration therapy, diabetes education, use of metered-dose inhaler etc.) or counselling in critical or emotionally charged situations.

SPs assess students objectively by filling the case specific content checklists which are pre-designed to determine 'What relevant history questions were asked? Based on that, what physical examination maneuvers were selected to perform? Whether performance was done correctly?'

Before entering into the examination room, each student is given an opening-scenario (basic information of the patient) and examinee's-task (which student has to perform in that station). Time allotted for each station is 10-15 minutes. After every encounter, 5 minutes are given to the student to write a summary of information gathered from the SP, make differential diagnosis and complete other post-encounter exercises. Simultaneously, SP fills two forms: a case specific content checklist (up to 30-35 items) and an interview rating scale. Arizona Clinical Interview Rating scale (ACIR) or Kalamazoo Essential Elements Communication Checklist - Adapted (KEECC-A) are commonly used for assessing the interviewing skill [31,32]. SPs are trained about the criteria on which they have to judge and assess the student's performance and they are found to be precise and consistent in filling the checklists [33].

USE OF CHILDREN AS SPs

Children have been used as SPs since 1980s [34]. A focus group discussion with child SPs (6-18 years) reported that play-acting (simulation) was found to be fun; they learned how to differentiate between a 'bad' and a 'good' doctor. Children and their parents unanimously told that simulation had overall positive effect on them [34]. A pediatric clinical skill assessment (PCSA) of the residents using children (7-11 years) reported child SPs' experience to be quite positive; they could memorize the checklists and rate the residents' performance fairly well and consistently [35]. Another study on the feasibility of using school children (8-10 years) for OSCE showed that these children can score/mark the examinees reasonably well with a reasonable correlation between their scores and examiners' predictions of their scores [36]. Use of child SPs can be very effective in developing 'soft skills' and humanistic values to acknowledge and address children's special needs as patients [37]. The benefits of being a SP (including a child SP) have been reported apparently to outweigh the known risks [38]. A systematic review suggested involvement of adolescent and younger children as SPs to be feasible and valuable; however, it doubted about their reliability to portray the SPs' role and provide feedback [39].

TRAINING OF SPs

It has been stated that *"simulated patients, if appropriately trained, should not be distinguishable from a real patient even by experienced clinicians*" [40]. Medical colleges in many countries have developed dedicated simulated patients training programs. The Association of Standardized Patient Educators (ASPE) has also published standards of best practice (SOBP) [41].

Steps for training SPs are summarized in **Web Box I** [15]. Case scenarios prepared can be totally fictional or

drafted from the case histories of real patients. Patients' own laboratory results and clinical course can be used for discussion [7]. Script of the case scenario, objectives of the case encounter, instructions for the students, time for interaction, scoring system (marks or rating scale), relevant laboratory reports, ECGs, *X*-rays, CT/MRI reports etc. with their interpretation and abnormalities are given and explained to the SPs. Depending on the need, SPs are either required to follow strictly as per the script or given some freedom to tell some of their personal information during the interaction with students. They are trained to act and react in a specific and predictable way, according to the goals of the program (teaching, assessment or both). For doing so, they should be able to observe and memorize the student's verbal and non-verbal actions apart from role-playing [13].

After going through the script, SPs prepare themselves for their role by watching relevant videos, observing previously trained SPs and/or meeting real patients suffering with the same problem [42]. Two to four training sessions, each of 2-3 hours may be needed depending on the scenario and time required for the SP to develop the desired level of competence in performing the role and use of checklists. They are monitored for 'accuracy' (how accurately they portray a given patient) and 'replicability' (how consistent they are in portraying the same patient to different students); and provided further training if needed.

EXPERIENCE WITH SPs IN INDIA

Till date, there is limited documentation of use of SPs for teaching and assessment of students in India. A study on teaching patient interviewing, communication and counseling skills to UGs using Calgary–Cambridge guide format recommended to conduct regular courses on effective communication in the MBBS curriculum [25]. Another study reported use of simulated interviews and role play for training PGs in psychiatry; trainees who performed as SPs reported the need of more clarity on their roles as SPs [43]. A study from dentistry assessed the effect of introducing a 'communication skills course' using interns to role play as SPs, reported improvement in communication skills of dental undergraduates [44]. The standardized patient methodology has also been used to assess standard for quality of care in healthcare settings [45].

SET-UP REQUIRED FOR TRAINING SPs

CBME curricular reforms have recommended every medical college to develop 'Skills laboratory' with dedicated rooms, equipped with facility of video recordings and debriefing [4].These labs can be used by trained faculty of the institute to develop and implement SP training program. People willing to work as SPs can be recruited by advertising in local newspaper, internet or through word of mouth; local actors can also be hired. Persons who are willing to become SPs should be able to act, memorize roles and checklists, good in communication skill, valid and reliable (accuracy and replicability), available at any time and setting (portability), able to adapt to many/different patients' roles and motivated to help educate students [4,11].

To reduce the cost, departmental staff, post-graduates, interns, senior medical students, or even mothers of admitted babies can be trained to participate in the SP program [43,46]. Additionally, nursing and other non-teaching staff, undergraduates, patients with genetic disorders or chronic stable illness like thalassemia, sickle

Box III Limitations of Using Simulated Patients (Adults and Children)

- Difficulty in finding people to work as SPs, especially for intimate examinations.
- Only a limited range of physical findings can be simulated using SPs; we can not teach and assess for organomegaly, heart murmurs etc. in healthy SPs.
- Training of SPs is costly in terms of money and time required, more so with child SPs; SPs have to be paid for every clinical encounter with students.
- Ethical issues in using children as SPs - In accordance with the Constitution of India (The Child Labour (prohibition and regulation) Amendment Act 2012), the minimum age for employment is 14 years; and violation of this rule can result in fine or even imprisonment. Written consent of parents and assent of children from 14-18 years has to be taken before recruiting them.
- Training children as SPs can be more challenging; younger children may have difficulty in understanding what is expected out of them and how to provide feedback. Their behavior may be inconsistent and difficult to control.
- Working long hours for child SPs can be taxing and may have negative psychological effects. They may get bored with repeated encounters leading to non-cooperation, inconsistency in their responses with poor feedback.
- Difficulty in getting child SPs because children are more likely to have acute illnesses, so their clinical findings will change or resolve over a short period of time.
- Parents may be too much concerned about their children's feelings during the SP encounters, and may not allow their child to miss school even for a day.

Box IV Overcoming Problems in Using Child Simulated Patients

- Create scenarios where the adult SPs can be used to portray role of parent of a sick child, to assess history-taking skills of students.
- Take care of child SP's emotional and physical well-being; consider participation of the child SP's family/chaperones during encounters.
- Use adult SPs along with their healthy or sick children (6-14 years) as parents and pediatric SPs and ask students to elicit a complete history of child from parent including parent's concerns. Subsequently, ask students to do physical examination of child OR it is either presumed to be done and normal OR abnormal findings (as per the need of the case) are given on a piece of paper.
- After eliciting the history and a brief clinical examination, include interpretation of relevant laboratory reports, pulmonary function tests, ECGs, *X*-rays, CT scans etc.
- Select children for SPs roles who are cooperative and preferably have interest in acting/drama.
- Use Child SPs for situations/issues that cannot be adequately assessed using other methods.
- Assign the roles to child SPs which match with their personalities, developmental age, and actual complaints/physical problems they might have/had e.g. headache, abdominal pain.
- Older children (≥14 y) can be coached to simulate complicated behaviors or emotional problem they themselves have not encountered.
- Organize SPs-led sessions outside school hours/on holidays with regular breaks for rest and snacks.
- Limit SP encounters up to 10 or less at a time or till the child is comfortable.
- Consider use of patient substitutes such as photos (skin disorders), videos (abnormal movements, gait disorders), mannequins, and computer simulation (audio-visual cardiac/respiratory system findings) for training and assessment of students.

cell disease, cerebral palsy, down syndrome, bronchial asthma, diabetes mellitus, chronic obstructive pulmonary disease, irritable bowel syndrome etc. can also be utilized if they are willing to participate. Limitations of using SPs (adult and children) with Indian perspectives are summarized in **Box III** [15,47-49]. Suggestions to overcome challenges in using child SPs have been presented in **Box IV** [37,49].

Trained SPs are a valuable resource, and retaining them in the SP program requires adequate remuneration, respect and recognition of their efforts, appropriate freedom to teach and give feedback to students [15].

CONCLUSION

SPs are being used for clinical skills' teaching, observing, assessing and giving feedback to medical students in many countries for more than 50 years. They act out scenarios (history, physical examination, inter-personal communication skills, counseling and patient education), can simulate abnormal physical findings, use checklists to assess trainees objectively and give corrective feedback. Encounters with SPs have been found to be beneficial in developing cognitive, technical and communication skills and self-confidence in medical students. SPs are not going to replace real patients but help in transition to real patients. With the implementation of CBME curriculum in India, introducing SPs for training medical students, especially undergraduates, will be an effective approach for developing the desired competencies under supervision and also saving faculty time. If ethical and practical issues are addressed properly, use of child SPs also can be feasible and rewarding. It is recommended to introduce simulated patients in regular practice as a supplement method for teaching and assessment of clinical skills in the post-COVID-19 new normal.

Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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Web Box I Steps of Simulated Patient Training

- Scripts for 'case scenarios', case specific content 'check list' to capture students' behavior and performance, feedback forms, rating scales and post-encounter exercises for the students are developed, reviewed and revised by experts.
- SP is selected based on case to be portrayed (age preferably within two years of required role, gender, built, weight etc) and skills to be taught or assessed.
- Recruited SP is given a case scenario, checklist and instructions beforehand to practice the role.
- First training session – SP reviews the script, patient's attributes and do repetitive rehearsals; trainer demonstrates how to listen and analyze the questions asked by students. They are instructed and trained how to –
  - respond, both verbally and non-verbally.
  - provide relevant information about symptoms of their illness only in response to questions asked by student without adding unnecessary explanations.
  - observe whether students have performed physical examination correctly or not, how to react, identify the gaps and give corrective feedback.
  - reflect on the overall experience with the student's interaction after the encounter is over.
- Second training session – SP does repeated rehearsal with mock students, fills case specific content checklists, scores and feedback. These encounters are video recorded and SP's filled checklists are collected and stored.
- These video recorded 'encounters' between SP and mock students are reviewed by another scorer (SP trainer or faculty member) who gives scores / rating and provides feedback to the SP on how to improvise the act.
- The 'Act' is finalized only after agreement between the ratings of SP and second scorer is reached; till then SP continues to practice with mock students.

Determinants of Vitamin D Deficiency Among Under-five Children in Urban Slums of Mumbai, India

A community-based study was undertaken in an urban slum in Mumbai, between October, 2015 and September, 2017 among 426 healthy children (aged 1–5 years) to assess prevalence of vitamin D deficiency (VDD) and its determinants. VDD was classified as 25(OH)D <20 ng/mL. The prevalence of VDD was 76.8% (*n*=327), and sun-exposure, male sex, and calcium and vitamin D supplementations during infancy were important determinants. Routine supplementation with vitamin D in infancy is likely to reduce the occurrence of VDD in children.

Keywords: *Infant, Rickets, Sun-exposure, Supplementation.*

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Maintaining optimum vitamin D levels among under-five children is a growing concern given its important role in bone mineralization, remodelling, and immunological functions [1]. Nearly 90% of vitamin D requirement is met through exposure of bare arms, and face to midday sun (between 10 AM and 3 PM) for 10-30 minutes, and 10% through diet [2]. Vitamin D deficiency (VDD) therefore is more likely to be prevalent in overcrowded slums compromising adequate sunlight exposure. Studies have reported VDD prevalence ranging from 34 - 80% among children [3,4]. Very few investigated the determinants of VDD such as sun-exposure among under five children [3]. Hence, a community based study was undertaken to assess prevalence and determinants of VDD among children in the age group of 1-5 years.

A total of 426 apparently healthy children aged 1-5 years were enrolled from a selected urban slum of Mumbai after ethics approval and parental consent over a period of 2 years (1 October, 2015 to 30 September, 2017). There were approximately 20000 households in the study area. Initially the list of 759 children (aged 1-5 years) was obtained from anganwadi workers. A trained social worker visited these households to screen the eligible children. Apparently healthy children aged 1-5 years were included and children with chronic illness, skeletal diseases, and those receiving vitamin D supplementation were excluded. In case the house was locked, it was revisited in next three consecutive days. In case of more than one child in the household, krish grid method of sampling was used to select eligible children. Out of 759 children, 195 children were not eligible, parents of 21 children refused, 8 households were locked, 12 children were in households with more than one child, and parents of 97 children did not consent for phlebotomy.

Details about sociodemographic status, diet (24-hour dietary recall) [5], physical activity and clinical profile were recorded, followed by biochemical investigations. The nutrient composition including calcium and phytate was interpreted as per dietary guidelines for Indian children [5]. Direct sun-exposure was calculated considering average duration and percentage of the exposed body surface area between 10 AM to 3 PM over last 6 months [6]

Serum calcium, phosphorus, alkaline phosphatase, 25-Di-hydroxy vitamin D (25(OH)D) and parathyroid hormone (PTH) were estimated in fasting state using automated blood analyzer and commercially available ELISA based diagnostic kits. VDD was classified as 25(OH)D <20 ng/mL [7].

Association of VDD was assessed with variables such as age, sex, socioeconomic status, physical activity; nutrition intake; growth and clinical parameters and biochemical markers. Chi-square test, Pearson correlation and logistic regression were conducted using SPSS Version 19 (IBM Corp) and $P<0.05$ was considered as statistically significant.

The mean (SD) age of the children was 34.8 (13) months with 53.8% boys; 76% children belonged to middle socioeconomic group; 84% were in preschools and 7.5% were involved in outdoor activities at school.

The prevalence of VDD among children was 76.8% (95% CI 73.1-80.5). There was no association of VDD status with age and socioeconomic status; though, it was significantly associated with duration of sun-exposure of less than 10 minutes between 10 AM to 3 PM ($P=0.01$). Despite sun exposure of 10 to 45 minutes in a day, 68.8% children had VDD.

The levels of PTH, alkaline phosphatase and calcium were within normal limits among 83.9%, 92.2% and 87.5% of children, respectively in spite of 25(OH)D <20 ng/mL, with a significant negative correlation (r=-0.12; $P=0.02$) between PTH and 25(OH)D. Clinical signs of VDD i.e., either genu varum, genu valgum, metaphyseal widening or frontal bossing were evident among 42.7% of children with significant association with frontal bossing ($P<0.001$), genu varum ($P<0.001$) and metaphyseal widening ($P=0.02$). It was more common among children having recurrent upper respiratory tract infections (URTI) ($P<0.001$).

VDD had no significant association with consumption of adequate calcium intake (≥600 mg/day) or with consumption of vitamin D rich food. However, it was significantly less among children with adequate dietary calcium intake and supplemented with calcium and vitamin D during infancy ($P=0.02$).

Logistic regression analysis was carried out to look for predictors of VDD (**Table I**). It was found that male children were 43% less likely to have VDD. Children having frontal bossing or ≥6 episodes of URTI in the last one year were approximately 3-times more likely to have VDD than their counterparts. Children who had spent less than 10 minutes in outdoor activities between 10 AM to 3 PM were 75% more likely to have VDD than those who spent more than 10 minutes.

The study specifically elucidates the community-based

Table I Vitamin D Deficiency Among Children by Selected Background Characteristics and Odds of Vitamin D Deficiency (VDD) Among Children (*N*=426)

Characteristics	*VDD, n=327*	*Adjusted OR(95% CI)*
Male sex, *n*=229	168 (73.4)	0.57 (0.35,0.95)
Time spent outdoor[a]		
5-10 min, *n*=211	174 (82.5)	1.75 (1.06, 2.88)
>10 min, *n*=215	153 (71.2)	1.00
Dentition initiation <1 y, *n*=315	239 (75.9)	0.95 (0.53,1.70)
Supplementation during infancy,[b] *n*=160	113 (70.6)	0.56 (0.34,0.92)
Frontal bossing, *n*=192	168 (87.5)	3.07 (1.78,5.30)
Recurrent URTI,[c] *n*=249	209 (83.9)	3.19 (1.93,5.27)

Values in no. (%). Vitamin D deficiency (VDD) was classified as 25(OH)D <20 ng/mL as per Institute of Medicine (IOM) classification. [a]between 10 AM and 3 PM; [b]calcium and vitamin D supplementation; ≥6 upper respiratory tract infections in the last one year.

prevalence of 76.8% and determinants of VDD among a large cohort of under-five children. VDD was significantly associated with duration of sun-exposure reemphasizing the importance sun-exposure for optimal vitamin D status [3,4]. However, prevalence of VDD despite adequate sun exposure among more than 50% children necessitates need of exploring other determining factors among under-fives. Intriguingly, majority had normal PTH despite low 25(OH)D indicating PTH response variation among children [8]. This highlights that physiological difference in PTH response can be a confounder in interpretation of VDD among under-five children.

Our study highlighted significant association of URTI with VDD, unlike with lower respiratory tract infections reported earlier [9]. Significantly lower proportion of VDD with calcium and vitamin D supplementation during infancy endorses the importance of routine supplementation during first year [10]. Certain limitations of the study were inability to correlate seasonal variations, and evaluate bone mineral density among deficient children.

To summarize, sun-exposure, male sex, and calcium and vitamin D supplementations during infancy can be considered as protective against VDD among under-five children.

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Contributors: SS,SB,SC,MIK,BJ: conceptualized and designed the study; SS,BJ: conducted clinical examination, data Collection; MIK,SS: interpreted the biochemical parameters; SB: conducted statistical analysis and interpretation; SS,BJ: drafted the initial manuscript; SB,MIK,SC: reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work

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SUCHITRA SURVE,[1] SHAHINA BEGUM,[2] SANJAY CHAUHAN,[3] MI KHATKHATAY,[4] BEENA JOSHI[5]*

Departments of [1]Clinical Research, [2] Biostatistics, [3] Clinical and Operational Research, [4]Molecular Immunodiagnostics, and [5]Operational Research, Indian Council of Medical Research-National Institute of Research in Reproductive Health, Parel, Mumbai, Maharashtra.

[*]bjoshithane@gmail.com

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Autism Spectrum Disorder in the COVID 19 Era: New Challenges - New Solutions

This survey explored the support available and the effect of lockdown on children with autism spectrum disorder and their families in India and the United Kingdom. Our findings showed significant problems for children and families due to lockdown. App-based information delivered to parents with support showed encouraging feedback.

Keywords: *Anxiety behavior, App-based support, Lockdown, Telehealth*.

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During the coronavirus disease 2019 (COVID-19) lockdown, all face-to-face support and planned activities of children with ASD were interrupted. This brought a significant change of routine for them [1]. They reported higher levels of anxiety, reduced dispositional hope, and psychological well-being [2]. Information technologies have been an essential tool during these challenging times [3]. Studies have reported positive effects of parental empowerment with training and support using technological platforms [4]. We investigate the impact of lockdown on children with ASD and their families in India and the UK.

Parents of 45 children with a confirmed diagnosis of ASD - 15 from Conwall, United Kingdom [mean (range) age, 11.06 (7.02-17.05) years] and 30 from Lucknow, India [mean (range) age, 5.2 (2.11- 8.07) years] participated in the survey. Children with confirmed ASD were identified from clinical records of the child development center in Lucknow and Cornwall. Consent was obtained and General Data Protection Regulation guidelines were followed during data collection and analysis.

A semi-structured survey was constructed. It included four variables: change in behavior (CIB), change in the routine (CIR), regression in skills (RIS), and parental stress (PS) **(Web Fig. 1)**. The final survey was reviewed by an expert panel, and their suggestions were included before conducting the telephonic survey. Speech and language therapists in the UK and trained child psychologists in India conducted telephonic surveys in mid of April over two weeks. Each interview took approximately 45 minutes. All questions on CIB, CIR and RIS were rated on an 8-point scale ranging from 0 to 7 and for PS on a 5-point scale ranging from 0 to 4.

Nonparametric *t*-test, Pearson correlation and multivariate regression analysis were calculated to measure the difference, bivariate associations, and the impact of lockdown on the study variables.

The mean rank for CIR, PS and CIS were higher in the UK as compared to India, whereas there was no significant difference in CIB. CIR and CIB were reported for all children. All parents reported increased PS (**Table I**). There was a significant correlation of change in behavior score with change in routine score (r=0.446, $P<0.01$), regression in skills score ($r=0.750$, $P<0.01$) and parental stress score ($r=0.370$, $P<0.05$). Parental stress score also significantly correlated with change in routine ($r=0.535$, $P<0.01$) and with regression in skills ($r=0.375$, $P<0.05$). Regression in skill and change in routine scores were also significantly correlated ($r=0.410$, $P<0.01$).

Parents and families reported extra difficulties in managing adults with ASD [5,6]. In the UK, children with ASD are provided diagnosis based on NICE guidelines. Necessary support is provided through schools, along with parental courses offered by the local council. Additional help is available through pediatricians, speech and language, child and adolescent mental health services, occupational therapy, and support groups. In Lucknow, children were assessed by a multi-professional team. The diagnosis was confirmed using ADI-R. The families who enroll in the early intervention program were provided with a home program support app.

Disruption in routine due to lockdown affected the behavior of children with ASD [1]. Change in routine was positively and significantly correlated with change in behavior, regression in skills, and parental stress, similar to previous reports [5].

In Cornwall, the parents' interview explained a lack of support or contact because of the long waiting list of appointments with professionals before the pandemic, which worsened with the lockdown. Studies reported a lack of support for both autistic individuals and their family's post-diagnosis prior to lockdown [8,9].

The mainstay of autism treatment is parental training and environmental modification around the child [10]. This study identified a gap in empowering parents with resources post-diagnosis that they can access when required. The app model support has shown promise, but parents needed support,

Table I Impact of Lockdown on Children With Autism Spectrum Disorder and Their Families in India and United Kingdom

Group	*Mean rank* (SD)	*P value*
Change in behavior		
India	24.0 (10.49)	0.45
UK	20.9 (10.49)	
Change in the routine		
India	18.22 (4.44)	0.01
UK	32.57 (4.44)	
Regression in skills		
India	22.28 (2.84)	0.61
UK[a]	24.43 (2.84)	
Parental stress		
India	17.18 (6.30)	0.01
UK	34.63 (6.30)	

Number of families enrolled UK-15, India-30. Proportion of parents who reported changes in the variable during lockdown was 100% for all variables except [a]78.6% for regression in skills from UK.

despite using the app. Due to the lack of appropriate measures, we were unable to measure the psychometric of the survey. However, the finding of this study is based on the direct parent's experiences, which is a strength of the study. The result helped in re-establishing the important role of routine and structure in children with ASD **(Web Table I)**.

In conclusion, COVID-19 lockdown brought an opportunity to reassess our services for children with ASD. Technology-mediated support showed encouraging feedback of being used in combination with clinical practice.

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RAHUL BHARAT,[1*] UZAINA,[2] SANJAY NIRANJAN,[3] TRIBHUVANESH YADAV,[4] SUE NEWMAN,[5] JONATHAN MARRIOTT,[6] GEMMA SMITH,[7] GARIMA SAWLANI[2]
[1] Department of Pediatrics, Royal Cornwall Hospitals Truro, Truro, United Kingdom;
[2] Geniuslane Child Development Centre, Lucknow, India;
[3] Neo Child Clinic, Lucknow, India;
[4] Global Child Clinic, Lucknow India;
[5] Children's Services, Cornwall Partnership
[6]NHS Foundation Trust, Truro, United Kingdom;
[7] ASD Assessment Team, Children's Care Management Centre, Cornwall Partnership NHS Foundation Trust, Truro, United Kingdom.
**r.bharat@gmail.com*

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CLIPPINGS

Treatment of infantile-onset spinal muscular atrophy with nusinersen: final report of a phase 2, open-label, multicentre, dose-escalation study (Lancet Child Adolesc Health. 2021;5:491-500)

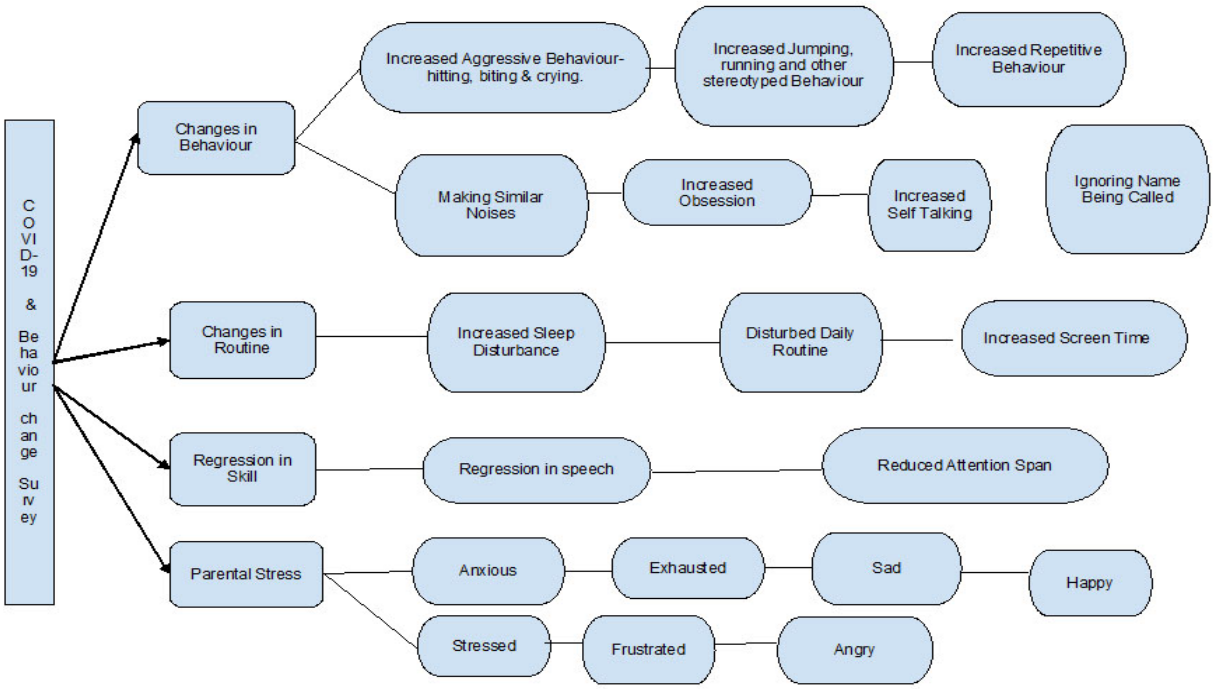
Spinal muscular atrophy (SMA) is a fairly common autosomal recessive, neurodegenerative disease caused by biallelic mutations in the survival motor neuron 1 (SMN1) gene. SMA is characterized by motor neuron degeneration, resulting in progressive muscle weakness, immobility and appreciable morbidities and mortality. Currently, three disease modifying therapeutic options are approved for treatment: Nusinersen (Spinraza), the antisense oligonucleotide given through intrathecal route; Risdiplam, an orally administered splicing modifier of motor neuron 2 (SMN2) and Onasemnogeneabeparvovec (Zolgensma), an adeno-associated virus-based gene replacement therapy.

Nusinersen is the oldest and the most well studied medication among them. It had showed a favourable benefit-risk profile in participants with infantile-onset spinal muscular atrophy at the interim analysis of a phase 2 clinical study. In the above study, authors present the final analysis, assessing the efficacy and safety of nusinersen over 3 years. It recruited 20 symptomatic infants aged between 3 weeks and 6 months with two or three *SMN2* gene copies, between May 3, 2013, and July 9, 2014. Participants received multiple intrathecal loading doses of 6 mg equivalent nusinersen (cohort 1) or 12 mg dose equivalent (cohort 2), followed by maintenance doses of 12 mg equivalent nusinersen. Median time on study was 36·2 months. In the 13 participants with two SMN2 copies treated with 12 mg nusinersen, the HINE-2 motor milestone total score increased steadily from a baseline mean (SD) of 1·46 (0·52) to 11·86 (6·18) at day 1135, representing significant clinical improvement. At study closure (Aug 21, 2017), 15 (75%) of 20 participants were alive. All five deaths (one in cohort 1 and four in cohort 2) were likely to be related to spinal muscular atrophy disease progression.

KAUSIK MANDAL
kausik@sgpgi.ac.in

Web Table I Learning Points From Parental Feedback to Improve Support for Children With Autism and Their Families

Feedback from parents in the U.K.	*Recommendations*
• Lack of contact/support post-diagnosis • Alternative methods of giving post-diagnosis information/recommendations as felt generic/overwhelming at the time • No contact during the waiting time and not able to access other services when on ASDAT pathway • Not knowing who to contact during the waitlist and after diagnosis. • Lack of peer support/families connected.	• Amendment in a diagnostic letter to emphasize the family feedback meeting as an opportunity to support families along with discussing diagnosis. • Possible liaison with National Autism Society to discuss targeted opportunities for parents to connect each other/peer support • Rank information on diagnosis letter/prioritize and make clearer who families can contact and when, e.g. passionate about autism
Feedback from parents in India	*Recommendations*
• Clear and easy to understand information pre-and post-diagnosis • The app is very helpful; it helps parents to manage the child's problem at home • Provides training when the child is not cooperative • The app helped a lot during the lockdown and provided clarity • I was able to access information in my own time	• More support on the application of information provided on the app. • Communication system with the organization to be in-build and recorded on the app



Web Fig. 1 Showing the variables and sub-dimensions studied in the survey.

Cardiac Channelopathies Masquerading as Seizures

Cardiac channelopathies are a group of inherited arrhythmias caused by mutations in the cardiac ion channels. Long QT syndrome (LQTS), the commonest of these disorders, is estimated to affect 1 in 2000 people [1]. The other disorders include Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT) and the short QT syndrome (SQTS). They share a predilection for malignant ventricular arrhythmias, syncope and sudden death. Seizure is a frequent presentation in these disorders and is attributed to arrhythmia related decrease in cardiac output [2]. It is not uncommon for children with these disorders to be inaccurately diagnosed to have epilepsy. We report four children with cardiac channelopathies referred from neurology in whom appropriate therapy resulted in a significant decrease in paroxysmal 'seizure-like' events.

Case 1: A 5-year-old boy was referred to us with multiple seizures after electrocardiographic (ECG) abnormalities were noted during an extended electroencephalogram recording. A younger sibling had multiple episodes of seizures and died at 1 year. There was a history of sudden unexpected death in the family with one drowning. A standard ECG in the present case showed a prolonged QTc (520 ms). Holter evaluation documented multiple self-terminating episodes of Torsades de Pointes (TdP). A provisional diagnosis of LQTS was made. He was started on beta-blockers. The family were unwilling for family screening as well as genetic testing. On follow-up, 6 months later, there were no further symptoms.

Case 2: A 6-year-old girl, the first child of non-consanguineous parents, had a maternal aunt with epilepsy, high pitched sounds being one of the triggers. The child had been diagnosed prenatally to have complete heart block and a pacemaker had been implanted postnatally. She also had multiple episodes of seizures. Three EEGs were reported to be normal. A review of her neonatal ECG showed one episode of TdP (arrow in **Fig. 1a**). On family screening, the mother's ECG showed a prolonged QTc of 480 ms. Anti-epileptic drugs were discontinued, and she was started on beta blockers. Genetic testing revealed a pathogenic mutation in *KCNH2* gene (c.1882G>A), which causes LQTS type 2. Cascade screening confirmed the mutation in both the mother and maternal aunt, and both were started on beta blockers. At follow up of one year, there were no further seizures in the child.

Case 3: A 17-year-old girl, the first child of third-degree consanguineous parents, had recurrent seizures during exertion. Her ECG was normal. There was bidirectional ventricular ectopy on exercise stress testing (arrow in **Fig. 1b**). A clinical diagnosis of CPVT was made and she was started on beta blockers. Genetic testing revealed a pathogenic heterozygous mutation in the *Ryanodine receptor* gene (RyR) associated with CPVT (c.184 C>T). The family refused cascade screening. No further seizures were reported during a follow up period of 6 months.

Case 4: A 9-year-old girl, the first child of non-consanguineous parents, with two younger siblings who had died suddenly and unexpectedly in infancy and multiple sudden unexpected deaths in the father's family was referred for evaluation. She had been treated for seizures from the age of five. A prolonged video-EEG recording was performed. She had one episode of tonic posturing during the recording with normal EEG and TdP on ECG. Baseline ECG showed sinus rhythm with a normal QTc. A presumptive diagnosis of LQTS was made, she was started on beta blocker and genetic testing was organized. There have been no further episodes of seizures for the last 9 months.

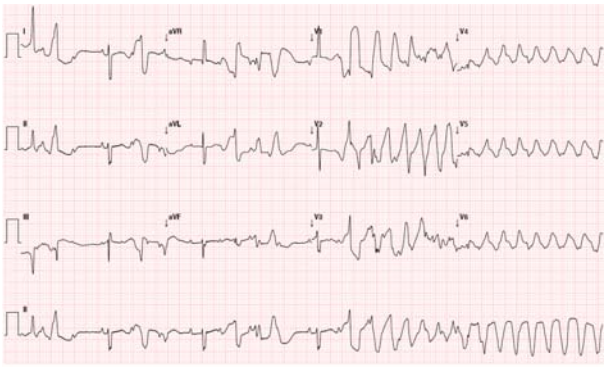


Fig. 1 (*a*) ECG of patient 2 in the newborn period demonstrating polymorphic ventricular ectopy as well as an episode of Torsades de Pointes (TdP).

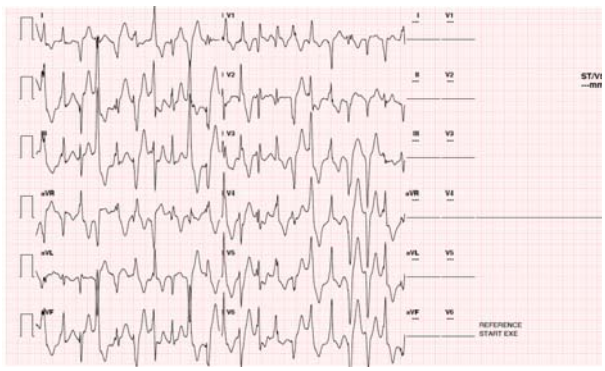


Fig. 1(*b*) ECG tracing from an exercise stress test of patient 3 demonstrating evidence of bidirectional ventricular ectopy.

Cardiac channelopathies are caused by mutations in proteins related to the intra-cellular transport of sodium, potassium and calcium ions. These ion channel abnormalities predispose the patient to episodes of lethal ventricular arrhythmias such as TdP and ventricular tachycardia (VT) or fibrillation (VF). While some may die during such arrhythmias, these lethal arrhythmias can be non-sustained with spontaneous termination. Cardiac output is significantly decreased during these non-sustained episodes and the resultant cerebral hypoperfusion may result in seizures and/or syncope [3]. The term 'torsadogenic seizures' has been used to describe this kind of paroxysmal activity in the past [4]. Misdiagnosis as epilepsy has been shown to be the most important reason for delay in diagnosis and could potentially result in sudden death [5].

A careful history can provide clues to the diagnosis in most patients. A family history of SUD, seizures or syncope in multiple members should raise the suspicion of a cardiac channelopathy [6], as was seen in three of our cases. Recurrent seizures despite appropriate therapy and especially in the absence of pathogenic EEG changes should raise the suspicion of a cardiac channelopathy [6].

Genetic testing by a targeted panel of genes implicated in cardiac channelopathies or an exome wide screening is performed through next generation sequencing. A positive genetic test allows genotype specific therapy [7]. Genetic testing also permits cascade testing in other (even asymptomatic) family members [8] and helps identify individuals at risk and provide appropriate treatment even before clinical manifestations occur. This is especially important in channelopathies as a normal ECG does not rule out the presence of the phenotype. The QTc interval may be normal on a baseline ECG in affected individuals and an exercise stress test or provocative testing with adrenaline may be necessary to identify QTc prolongation. In our series, cascade screening permitted diagnosis in an asymptomatic mother as well as an aunt in whom the symptoms had wrongly been attributed to seizures.

In conclusion, seizures may be the clinical presentation in children with cardiac channelopathy. Red flags such as a family history of sudden death, seizures associated with auditory triggers and recurrent seizures with a normal EEG should raise suspicion and prompt referral to a pediatric cardiologist.The institution of appropriate lifestyle modifications and pharmacological therapy could result in control of symptoms.

DUONG KHANH TOAN,[1] MOHAMMED FAROOQ KUNDE,[1] SESHADRI BALAJI[2] AND MANI RAM KRISHNA[1]*

Department of [1]Pediatric Cardiology, Amrita Institute of Medical Sciences, Kochi and [2]Department of Pediatrics (Cardiology), Oregon Health and Sciences University, Portland, OR, USA.

**mann_comp@hotmail.com*

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Ivermectin Poisoning – Report of Successful Management

Ivermectin is an endectoparasiticide and is the drug of choice in filariasis, scabies (crusted or if topical treatment has failed), and several other infestations [1]. It has a low rate of adverse reactions with toxicity occurring only with overdosing, resulting in adverse prognosis, as no specific antidotes are available [1,2]. Although rare in children, over 150 cases of serious neurological toxicities have been reported in adults [1]. We report a case of ivermectin toxicity with encephalopathy, shock and aspiration pneumonia in a young child and its successful management.

A 6-year-old previously healthy girl (weighing 20.5 kg) presented with a history of accidental consumption of 60 mL of 1% w/v (600 mg) ivermectin lotion (30 mg/kg). She was undergoing treatment for scabies. After four hours of consumption, she had two episodes of vomiting followed by generalized tonic-clonic movements and loss of consciousness. On arrival, she was unresponsive, with Glasgow Coma Scale (GCS) 6/15, with tachycardia, tachypnea, hypotension and oxygen saturation of 79% at room air. Pupils were equal bilaterally (3 mm) with sluggish reaction. There were no signs of meningeal irritation. There was generalized hypotonia with absent deep tendon reflexes and fundoscopic examination was normal. Excessive salivation and bilateral crepitations were present. The child was admitted to the pediatric intensive care unit. Given the poor GCS and respiratory failure, the child was intubated, ventilated, and started on parenteral antibiotics ceftriaxone and clindamycin, along with supportive measures. In view of continuing seizures, intravenous midazolam and

phenytoin were given. In addition to saline bolus, noradrenaline infusion for hypotension was started and carefully titrated. Blood gas analysis showed respiratory and metabolic acidosis. The hemogram on admission showed hemoglobin 9.5 g/dL, platelet count 173×10^9/L; and total leucocyte counts 7.2×10^9/L (neutrophils, 76.7%). Liver function tests and renal function tests, coagulation profile and blood glucose were normal. C-reactive protein (CRP) was elevated 36.4 mg/L. Chest *X*-ray showed left upper lobe collapse and bilateral opacities. The National poison information centre was consulted and supportive management was advised as there was no specific antidote. Her urine output remained normal.

Patient started having high grade fever after 24 hours. Repeat investigations showed leucocytosis of 13.5×10^9/L (neutrophils 83%) and CRP of 67.8 mg/L. Blood culture and endotracheal secretions for culture showed no growth. In view of shock and hypotension, echocardiography was done, which showed normal left ventricular ejection fraction of 65%. Gradually, sensorium improved in the form of intermittent awakening after 48 hours, and GCS became 13/15 by day five. Patient became afebrile after four days. Hemodynamic improvement started only after day three, and vasopressors were slowly tapered off. Ventilatory requirements which were high initially, also decreased from day three and in view of neurological and hemodynamic stability, child was weaned off from ventilator on day five and extubated. Repeat hemogram, CRP and Chest *X*-ray became normal by eighth day. Neuroimaging could not be done initially as the child was critical, and was refused later by parents in view of clinical improvement. She was discharged after nine days of hospitalization in a stable condition on oral clindamycin (total duration of 14 days).

Ivermectin, in standard therapeutic doses, has both excellent parasiticidal efficacy and high tolerability [1]. Ivermectin does not readily cross the blood-brain barrier (BBB) in humans as it is effluxed by ATP-binding cassette subfamily B member 1 (ABCB1) transporter also called P-glycoprotein drug pump or mdr-1 located in the blood/brain barrier [1,3]. Hence, neurological adverse reactions are rare unless there is overdosage [1]. Our patient ingested 30 mg/kg of ivermectin, which was almost 100 times the recommended dose. Usually, a single oral dose of 150 to 300 mcg/kg is recommended, and 200 mcg/kg in scabies [4,5]. We suspected ivermectin poisoning due to the history, since encephalopathy and coma are well-documented side effects of ivermectin treatment in animals, and after ruling out other usual causes of coma. Severe neurological toxicities have been reported in public health programs in Africa, possibly due to concomitant infestations with high densities of loa loa, genetic predisposition, and co-infestations [1,6]. Additional intake of drugs that inhibit CYP3A4 and polymorphisms in the *mdr*-1 gene could also result in toxicity [1]. A recent case report of ivermectin taken in recommended dose, by a 13-year-old child, attributed the resulting neuro-toxicity, to human *ABCB1* nonsense mutations, which had led to loss of the neurological protective ABCB1 activity [3].

In our patient, despite there being no specific antidote, vigorous monitoring, and supportive critical care treatment proved to be lifesaving.

Neetu Talwar,* Niti Tripathi, Krishan Chugh
Division of Pediatric Pulmonology, Fortis Memorial Research Institute, Sector 44, Gurugram, Haryana.
**neetu.talwar1306@gmail.com*

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Multisystem Inflammatory Syndrome in Children Related to COVID-19 With Urticarial Vasculitis – A Double Whammy!

There is still a dearth of data of the involvement of skin in the coronavirus disease 2019 (COVID-19), especially in pediatric patients. Herein, we describe the report of a child with COVID-19 related multisystem inflammatory syndrome in children (MIS-C), who developed hypocomplementemic urticarial vasculitis syndrome (HUVS) after recovery.

A previously healthy 18-month-old boy with a five day history of fever and abdominal tenderness was admitted to the pediatric in-patient department. His mother was suffering from COVID-19. On mucocutaneous examination, the child had multiple annular polycyclic erythematous plaques on trunk with conjuctival erythema (**Fig. 1**). The lesions had been rapidly progressive and persistent for the last three days. The child was febrile (39.4°C) and hypoxemic. The child was also experiencing diarrhea for three days along with hypotension (blood pressure 90/60 mmHg). Laboratory investigations revealed a positive RT-PCR for SARS-CoV-2 on two tests done three days apart, along with metabolic acidosis, leukocytosis, neutrophilia, lymphopenia, anemia and hypoalbuminemia with albuminuria.

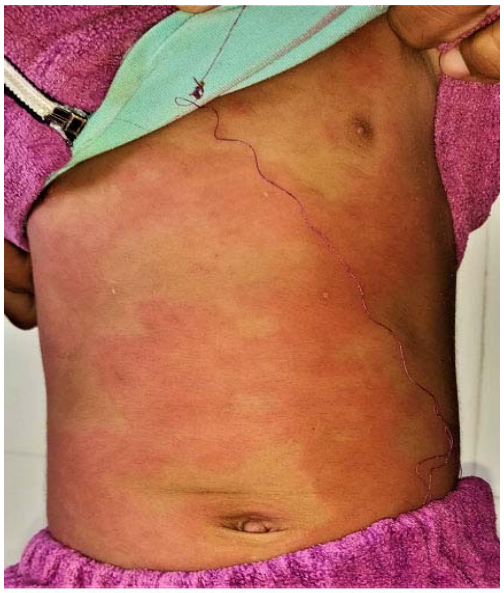

Fig. 1 Multiple annular polycyclic erythematous urticarial plaques on trunk.

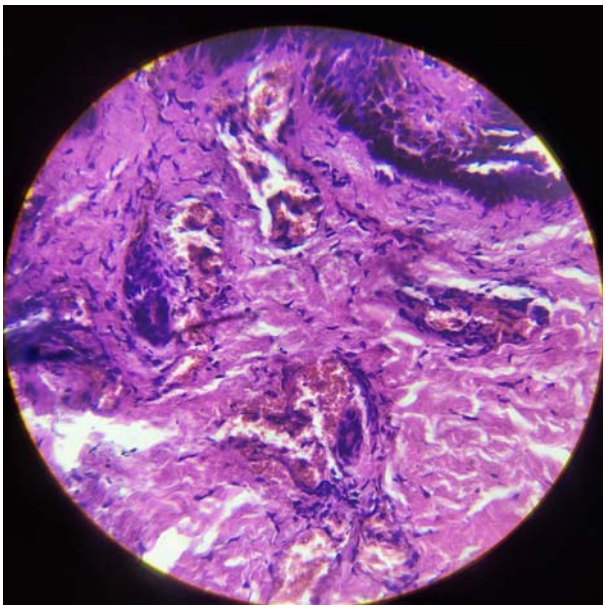

Fig. 2 On histopathological analysis presence of superficial and deep perivascular and interstitial infiltrates, small blood vessel wall degeneration and a leukocytoclasis (H and E, 400x).

Erythrocyte sedimentation rate (21 mm first hour reading) and C-reactive protein (19 mg/dL) were raised.

High resolution computed tomography (HRCT) showed ground glass opacities in <20% of both lungs. A diagnosis of MIS-C was made. Intravenous steroids and blood transfusion were given and ceftriaxone was administered, along with oxygen. Fever and other manifestations subsided in 14 days. However, the urticarial rash kept recurring even after 6 weeks on-and-off treatment with antihistaminics, raising the suspicion of chronic urticaria. Investigations to rule out possible causes of chronic urticaria revealed low complement levels, viz., C3 (30 mg/dL), C4 (6 mg/dL), CH50 (13 U/mL) and C1q (4.1 mg/dL), and persistent hypoalbuminemia. Histopathological analysis demonstrated superficial and deep perivascular and interstitial infiltrates, small blood vessel wall degeneration and a leukocytoclasis (**Fig. 2**).

Significant family history compatible with autoimmune diseases included a maternal grandmother with vitiligo and bullous pemphigoid, as well as hypothyroidism in mother. The child was diagnosed with hypocomplementemic urticarial vasculitis syndrome (HUVS). The child has been prescribed oral hydroxyzine hydrochloride and 4 mg monteleukast daily. Although, the child still develops flares, they are relieved on a temporary basis by a short course of oral steroids.

It has been established that COVID-19 infection can cause delayed hypersensitivity reaction, which can trigger MIS-C and vasculitis in recovering patients [1-3]. We hypothesize that the viral infection can potentially trigger complement deficiency and urticarial vasculitis, as seen in our case. Although our patient is currently not exhibiting any signs of an extracutaneous involvement, his presentation requires close monitoring. Clinicians need to be aware of COVID-19 as a potential cause for such presentation in children.

ALPANA MOHTA,* RAJESH DUTT MEHTA, BHIKAM CHAND GHIYA
Department of Dermatology, Venereology and Leprosy, Sardar Patel Medical College, Bikaner, Rajasthan.
**dralpanamohta10@gmail.com*

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Pediatric Head and Neck Infections at a Tertiary Care Center

Recent reports have advocated the success of conservative treatment over surgery in pediatric head and neck infections [1-4]. A retrospective review of all children less than 18 years admitted with head and neck infections was conducted in our tertiary care center from 2015-2020. Demographic data, sites of infection, microbiological results, and treatment outcomes were recorded. Postoperative infections were excluded from the study. All patients underwent a thorough clinical assessment for 'severe symptoms', which included stridor, inability to swallow, visual and intracranial symptoms, and empirical antibiotics was started. In those without severe symptoms, antibiotics were continued for 48 hours and child reassessed. Computed tomography (CT) was done to assess the extent of involvement. Well-formed abscesses in patients with 'severe symptoms' or failed medical therapy were surgically drained. Intraoperative samples were sent for culture, and antibiotics were changed depending on the sensitivity. Tissue was sent for *Mycobacterium tuberculosis* culture, whenever indicated.

Out of 38 patients admitted, deep neck space infection (21, 55.2%) were most commonly seen, followed by facial (13, 34.2%) and orbital (4, 10.5%), which is similar to previous reports [3,4]. History of recurrent upper respiratory tract infection was seen in majority of cases. Six of the facial abscesses were secondary to pre-auricular sinus and otitis externa, four had septal abscess and three had facial cellulitis. All orbital infections were secondary to sinusitis. One child was anemic, none were immunocompromised.

More than half the children (n=21) had 'severe' symptoms and majority (68%) required surgical drainage. Only size of the abscess (>25 mm vs <25 mm) was significantly (P<0.001) associated with requirement of surgical drainage (**Table I**). The other factors such as age, gender, duration of symptoms or site of abscess were not found to be statistically significant. The predominant organism isolated was *Staphylococcus aureus,* followed by *Streptococcus* spp. [5] and gram-negative bacilli [4]. In 11 patients, *M. tuberculosis* culture was done, but it was not positive.

One child needed a repeat drainage and one child had persistent laryngeal edema necessitating an elective tracheostomy, adding to their morbidity. CT was found to be a useful modality (with a positive predictive value of 86.6%) in evaluating abscesses, as also reported previously [5].

To conclude, deep neck space infections formed the bulk of pediatric head and neck infections and accounted for high morbidity. Majority of our cases required surgical drainage, probably as most of our children presented with severe symptom, which is against the recent trend towards conservative management [1-4]. Size of the abscess was the sole significant predictor for surgical drainage; although, it did not increase the duration of hospital stay.

Table I Factors Associated With Surgical Intervention in Children With Head and Neck Infection

Factors	*Medical management (n=12)*	*Surgical management (n=26)*
Age (y)[a]	5.2 (3.28)	5.1 (4.49)
Female gender	7	11
Duration of symptoms (d)[a]	4.2 (2.3)	5.4 (3.1)
Duration of hospital stay (d) [a,b,c]	5.5 (2.9)	6.1 (5.3)
Site of abscess		
Deep neck infection	8	13
Facial infection	3	10
Orbital infection	1	3
Size of abscess		
<25 mm	12	11
>25 mm[c]	0	15

Data presented as no. (%) or [a]mean (SD). [b]Child who underwent tracheostomy was an outlier with a hospital stay of 29 days. [c]P<0.001.

Ethics clearance: Institutional review board, CMC, Vellore; No. IRB No. 13020/20 dated June 24, 2020.

P Naina,* Snigdha Elaprolu
Department of ENT,
Christian Medical College, Vellore, Tamil Nadu
**drp.naina@hotmail.com*

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Risdiplam - Another ray of hope for SMA patients

Spinal muscular atrophy is an autosomal recessive degenerative disease of motor neurons. Caused by homozygous deletion of *survival motor neuron 1* (*SMN1*) gene on chromosome 5q, characterized by the progressive denervation of muscles leading progressive loss of motor function. SMA is divided into different subtypes based on age of onset and maximum function achieved.

At present the focus of research is on strategies to increase the body's production of the SMN protein. In 2019, FDA approved first gene replacement therapy to be used in SMA (Zolgensma), which acts by replacing the mutated non-working *SMN* gene with a working copy of the gene. The cost of one time intravenous dose for treatment of patients with SMA costs approximately 16 crore rupees.

A team of researchers studied the safety and efficacy of Risdiplam, which is an orally administered molecule that increases the level of functional SMN protein by modifying *SMN2* pre–messenger RNA splicing. Use of risdiplam resulted in higher percentages of SMA affected infants showing improvement of motor functions and attainment of motor milestones compared to the control group, after 12 months of therapy.

Hopefully this will act as a game changer for infants affected with SMA and their families, as this will bring down the cost of treatment and increase the accessibility.
(*New England Journal of Medicine 29 July, 2021*)

Vaccination strategy for the COVID-19 exposed

Since the detection of the first case in China in December, 2019, COVID-19 has spread around the world and infected approximately 200 million people and caused 4.2 million deaths globally. Apart from all this, it had affected the lives of much more people by affecting their livelihood and access to the adequate nutrition. Now, with development of vaccine against the COVID-19, a hope has started to rise that situation will improve. But the cost of vaccine and the availability are the two factors affecting the coverage.

A team from Rush University, Chicago studied the levels of SARS-CoV-2 spike immunoglobin (Ig) G antibody levels after 1 and 2 BNT162b2 doses in previously infected individuals compared with those without previous infection. Their observations showed that higher levels SARS-CoV-2 spike IgG antibody levels in previously infected individuals after 1 dose of BNT162b2 vaccine compared with infection-naive individuals after two doses. In previously infected individuals, after the second dose, the rise in SARS-CoV-2 spike IgG levels was not significant compared with the first dose, suggesting that one dose may be acceptable in this group. But they also cautioned that a positive PCR diagnosis alone was not sufficient to take off the requirement of second dose of the vaccine.

These findings might redefine the current vaccination strategy, especially for previously infected individuals, and could free up of millions of additional doses thus decreasing the burden on the economies and increase the availability for larger masses.
(*JAMA Network Open 6 August, 2021*)

Spectral power of EEG: Classify HIE in real time

Birth asphyxia is a major cause of neonatal mortality worldwide, contributing to upto 24% of all neonatal deaths and 11% of under-5 deaths globally. A significant proportion of these babies survive with life-long morbidities. Picking up the moderate and severe forms of the hypoxic ischemic encephalopathy (HIE) is relatively easier compared to the milder form due to lack of definition and evolution of the clinical signs over a period.

Researchers from the Dallas, Texas studied the electroencephalographic (EEG) power as an objective biomarker of the evolution of clinical signs of encephalopathy in newborns with various forms of HIE. Their findings revealed that the delta power and total power are sensitive real time markers for tracking the evolution of HIE from one form to another and can help in picking up the mild forms also. This can help in monitoring and timely beginning of the interventions in order to improve the overall outcome of such babies.
(*Pediatric Neurology 12 June, 2021*)

Adolescent mental wellbeing: Time to act

Mental health is one of the important aspects of health, which is started getting attention over last few decades. But with the easy availability of internet and round the clock access to it, more and more youngsters are getting addicted to the screens and spending most of their time indoors with limited physical activity. This is not only affecting their physical health but also causing a decline in their mental wellbeing.

Recently, in an international multi-centric observational study, involving 577 475 adolescents, researchers studied the gender-stratified relationships between screen time, mental wellbeing and physical activity. Results showed that increased screen time, exceeding 1 hour per day is detrimental for the mental wellbeing of adolescents, on the contrary, increased physical activity levels are beneficial for the mental wellbeing.Duration of the screen time and physical activity are the two main factors which have a dose dependent association with life satisfaction and mental wellbeing in the adolescents.

Thus, it is high time to plan and implement some public health strategies in order to save our younger generations from the ill effects of the technology.
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RAJESH KUMAR MEENA
raj.mamc@gmail.com

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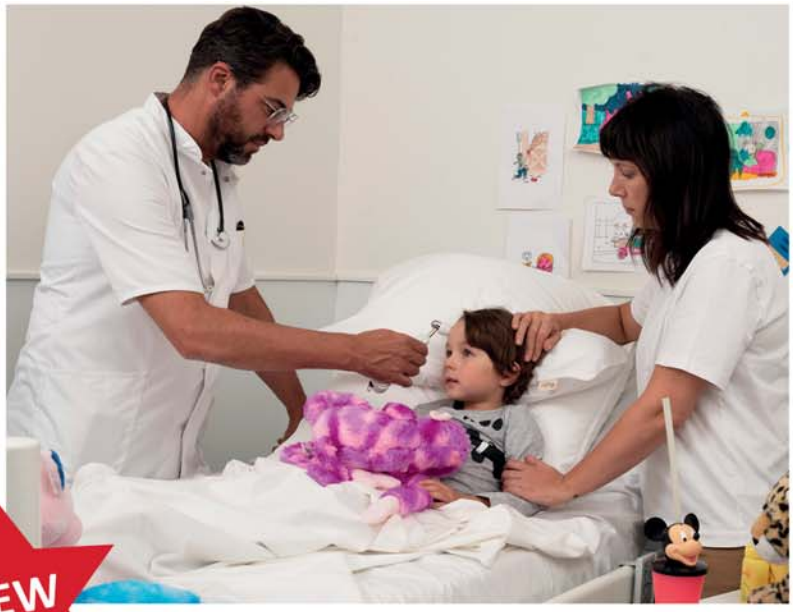

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