Child India

September 2021

Monthly e-Newsletter of Indian Academy of Pediatrics

IAP EXECUTIVE COMMITTEE - 2021

PRESIDENT	DR PIYUSH GUPTA
PRESIDENT-ELECT	DR REMESH KUMAR R
IMM. PAST PRESIDENT	DR BAKUL JAYANT PAREKH
VICE-PRESIDENT (CENTRAL ZONE)	DR N RAVI KUMAR
VICE-PRESIDENT (EAST ZONE)	DR ATANU BHADRA
VICE-PRESIDENT (NORTH ZONE)	DR SANGEETA YADAV
VICE-PRESIDENT (SOUTH ZONE)	DR MAJ K NAGARAJU
VICE-PRESIDENT (WEST ZONE)	DR JAYANTKUMAR V UPADHYE
SECRETARY GENERAL	DR G V BASAVARAJA
TREASURER	DR PURNA A KURKURE
EDITOR-IN-CHIEF, IP	DR DEVENDRA MISHRA
EDITOR-IN-CHIEF, IJPP	DR S THANGAVELU
JT. SECRETARY - LIAISON	DR HARISH KUMAR PEMDE
JT. SECRETARY - ADMIN	DR SAMIR HASAN DALWAI

Executive Members

DR BATCHU RAJSEKHAR (AP)
DR P ANIL KUMAR (AP)
DR DEVAJIT KUMAR SARMA (Assam)
DR BIRENDRA KUMAR SINGH (Bihar)
DR SUJIT KUMAR SINHA (Bihar)
DR ARUN BANSAL (Chandigarh)
DR ARVIND PRAKASH SAVANT (Chhattisgarh)
DR ANURAG AGARWAL (Delhi)
DR PEEYUSH KHANNA Delhi)
DR AJAY KUMAR GUPTA Delhi)
DR SHIVANAND Y GAUNS (Goa)
DR CHETAN G TRIVEDI (Gujarat)
DR YOGESH N PARIKH (Gujarat)
DR SANDIP K TRIVEDI (Gujarat)
DR SATISH KUMAR SHARMA (Haryana)
DR NARENDER S YADAV (Haryana)
DR RAVINDER K GUPTA (J & K)
DR JOY BHADURI (Jharkhand)
DR MALLESH GOWDA GS (Karnataka)
DR PREETI M GALAGALI (Karnataka)
DR SUMITHA NAYAK (Karnataka)
DR RAJAKUMAR N MAROL (Karnataka)
DR RIAZ I (Kerala)
DR JEESON C UNNI (Kerala)
DR MK NANDAKUMAR (Kerala)
DR JAYAKUMAR C PANICKER (Kerala)
DR KEWAL KISHORE ARORA (MP)
DR MAHESH MAHESWARI (MP)
DR ANAND S DESHPANDE (Maharashtra)
DR ANIL SHRIRAM RAUT (Maharashtra,)
DR NARENDRA R NANIVADEKAR (Maharashtra)
DR PRASHANT B JADHAV (Maharashtra)
DR PARAMANAD G ANDANKAR (Mumbai)
DR BISHWAJIT MISHRA (Odisha)
DR NARAYAN P MODI (Odisha)
DR HARPREET SINGH (Punjab)
DR MANMEET KAUR SODHI (Punjab)
DR DEVENDRA SAREEN (Rajasthan)
DR RAKESH KUMAR JORA (Rajasthan)
DR SUDIP DUTTA (Sikkim)
DR JANANI SHANKAR (Tamil Nadu)
DR R PALANI RAMAN (Tamil Nadu)
DR R SOMASEKAR (Tamil Nadu)
DR A JALEEL AHAMED (Tamil Nadu)
DR A YASHOWANTH RAO (Telangana)
DR K NARAHARI (Telangana)
DR UPPIN NARAYAN REDDY (Telangana)
DR PARTHASARTHI CHAKRABARTI (Tripura)
DR RAJEEV KRASHAK (UP)
DR SANJAY NIRANJAN (UP)
DR OM SHANKAR CHAURASIYA (UP)
DR UTKARSH SHARMA (Uttarakhand)
DR ASOK KUMAR DATTA (West Bengal)
DR SUBROTO CHAKRABARTTY(West Bengal)
DR SWAPAN KUMAR RAY (West Bengal)
DR SHEILA S MATHAI (Services)
DR RUCHIRA GUPTA (Chief Org. Secretary)

CONTENT

Editor's Note

Dear friends,

Population screening in India is a challenge for a variety of reasons. "The Complex Promise of Newborn Screening" by Dr. Fiona Miller, presented in 2007, documents the reasons why. Today, nearly all the hurdles presented herewith are still relevant, including the following:

- The newborn screening (NBS) programs can make only a minor contribution to reducing the global burden of infant morbidity and mortality;
- Access to healthcare for the poor, particularly in rural areas, is challenging, and even the urban middle classes may experience serious problems in making good use of NBS test results;
- Neonatal care units, especially at the district level, are limited in their availability, with most neonatal care available through specialized tertiary units in urban areas; and,
- Prevalent "misunderstandings" of screening results may prove resistant to typical educational interventions, as interpretations of disease and disease risks are open to cultural influence.

Presently in India, there are no debates in the medical community questioning the benefits of screening; the consensus is that all babies need to be screened, but there is no coherent national strategy for implementing a universal screening program nor guidance on which disorders should be included in the screening panel.

NBS must be considered in the context of competing national healthcare priorities in India. In a country where many people live in extreme poverty (176 million at USD 1.90 or less per capita per day) and access to basic healthcare can be a challenge, where would NBS rank in priority? The answer is, "Not very high"

The 2019 Indian health budget of approximately USD 9 billion allocates USD 6.50 per capita per year. The total cost to perform one screening test for CH, as an example, on one baby on a dried blood spot (DBS) using an enzyme-linked immunosorbent assay (ELISA) is about USD 5.00. Additional tests are approximately USD 1.50 each using ELISA. Assuming all 27 million babies born in a year are screened for CH, the cost is 135 million USD, which is equivalent to 1.2% of the health budget, a significant cost in India. The costs decrease when additional tests are added due to shared consumables and logistics, but the high cost of screening the first disorder can be a barrier to starting a program. The customs duties and taxes levied on equipment and consumables are also substantial (as high as 32%), increasing screening costs.

A critical message to all stake holders is that NBS is a program and does not end with a result of a screening test. The key to success of the program is the continuous follow up with the affected babies. There are cases (especially for births in public hospitals) where the affected baby's health improves and the therapy is discontinued by the parents without the knowledge of the treating physicians. This defeats the purpose of the screening program.

A universal implementation of newborn screening is a challenge in India, but the increasing awareness and programs over the past decade have led to more babies being screened every year. The results of the existing programs suggest to the policy makers in India that there is a benefit in implementing a universal NBS programs. The challenges faced in India, especially financial, make it very difficult to predict when every baby born in India will be screened.

Happy reading on certain issues regarding NBS in India.

Jai IAP!

Dr Jeeson C Unni
Editor-in-Chief

President's Address

Dear friends,

Come September - the Newborn Screening Awareness Month.

There is a lack of awareness of IEMs in the medical community. Feedback received from physicians indicated the lack of emphasis or complete absence of learning of IEMs and their treatments when the physicians were in medical school. Due to this, IEM cases were often misdiagnosed, and unexplained deaths were attributed to sepsis, infection, sudden infant death syndrome, or other causes. An increasing number of Indian physicians are now being trained in institutes where NBS is routine, therefore, expertise has grown and physicians are now able to diagnose and treat these disorders.

India has also lacked a recognized champion who was able to advocate for NBS and had the power to make it a universal benefit in India, comparable to what Dr. C Padilla has been able to accomplish in the Philippines. There have been NBS initiatives announced over the years in the public sphere, but many are yet to be realized.

Private hospitals have taken the lead in NBS in India. These NBS programs, done after consent is obtained, differentiates their service offerings and generates an additional income stream. Most of these are in urban areas with an affluent clientele who understand the benefits of screening.

Public NBS Programs

Screening programs in public hospitals have the potential to achieve universal screening. About 52% of the births in India are in public hospitals where the cost of delivery is less than $60. Since the cost of services in these hospitals, including NBS tests, are free, it is possible to screen all babies born in public hospitals.

The 3 states in India which offer universal NBS, have low infant mortality rates (IMR), well below the Indian average of 33 in 2017. The NFHS 5 data highlights IMR for Goa as 5.6, and Kerala as 4.4 and the 2017 data for Chandigarh was 14 (NFHS 4 & 5 data for Chandigarh are not available). The reason why these states embarked upon the NBS program is because In India, the three leading causes of infant mortality are (a) prematurity and low birth weight, (b) neonatal infections, and (c) birth asphyxia and birth trauma and therefore any further reduction in IMR could be achieved only by addressing neonatal morbidity and mortality.

The importance of NBS programs need to be emphasised and the more widespread its use the less could be the cost implications.

Regards,

Piyush Gupta
National President, IAP 2021

Secretary's Message

Dear All,

"Not all of us can do great things.
But we can do small things with great love."
– Mother Teresa."

Greetings! It has been an eventful month at the IAP Child India in September 2021.

Firstly, it gives me immense pleasure to inform you all that, the process of IAP Election for the year 2022 has begun from the 10th September 2021. A healthy democracy requires a decent society; it requires that we are honourable, generous, tolerant and respectful. Therefore, on behalf of IAP, I urge all esteemed eligible members of IAP to participate in this process of democracy.

We had a very successful IAP Office Bearers Meeting via Video Conferencing on 12th September 2021. My heartfelt thanks to everyone for participating in this meeting.

Early Childhood Development (ECD) is one of the precious and flagship programs of Indian Academy of Pediatrics under the presidential action plan.

Following are some of the major milestones towards the progress of the said program: -

- IAP – UNICEF – WHO Collaborative session on 'Primary Care Interventions for Early Childhood Development' was conducted during on 5th Feb, 2021 at IAP Pedicon program in Mumbai
- Steering committee was made for plan and process of ECD program at country level with Chairpersons as Dr Piyush Gupta (President IAP 2021) and Dr Digant Shastri (President IAP 2019) and Dr Remesh Kumar R (IAP President 2022).
- National consultative meeting along with all partners was conducted from 22nd to 24th March, 2021 at Delhi.
- Virtual launch of the program was conducted on 25th July, 2021 with Dr Rajesh Mehta, Regional Adviser- New born, Child and Adolescent Health, World Health Organization (WHO), Regional Office for South-East Asia as a 'Chief Guest' and was participated by around 70 delegates / partners.
- Zone wise Training of Trainers were conducted under the proactive leadership of respective Vice President of particular zone.
- After successful creation of Master trainers across the country, it is proposed to conduct a total of 200 District Level workshops.

Secretary's Message

We have other committees that met this month like The Meeting of IAP Task Force for School Reopening Guidelines (2.0) on 1st September 2021, and we are happy to inform you that we have published IAP ADVISORY ON SCHOOL REOPENING (Sept 2021) on our official IAP website.

We also had the Periodic Virtual Review Meeting of CIAP staff on 20th September 2021.

We have conducted the South Zone Early Childhood Development ToT physically at Chennai on 5th September 2021. National ToT on Dysbiosis- PG on 15th September 2021via video conferencing. We also conducted 4 Physical NTEP workshops at Ranchi, North Delhi, Rohtak & Chandigarh and 1 Virtual workshop in the month of September 2021.

Mission School Uday is also one of the precious and flagship program of Indian Academy of Pediatrics under the presidential action plan. We have conducted 12 workshops. also we have also conducted 7 Virtual workshops of the CADE Module, 3 Workshops of Immunization Dialog Module across India in the month of September 2021.

Finally sharing the updates on the NRP Projects, we have successfully conducted IAP –NNF Collaborative meeting on 5th September 2021 at Mumbai. IAP NRP Steering Committee Meeting at Delhi on 19th September 2021 as well as meeting of newly appointed Zonal Coordinators along with SAC on the same day at Delhi.

The demand for hybrid Courses is increasing day by day. We have conducted overall 40 NRP courses (Basic, Hybrid and Advance) in the month of September 2021.

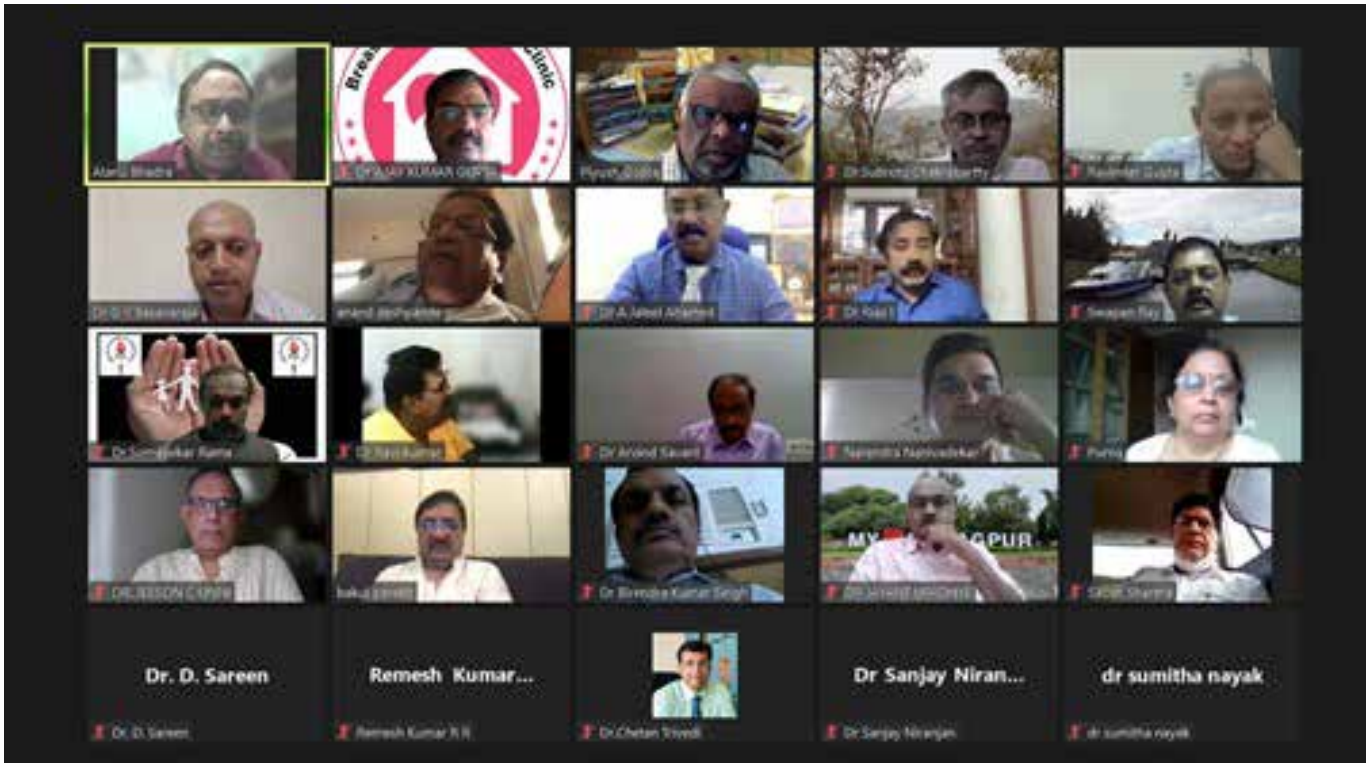
Overall, the month of September 2021 has been very fruitful and focused on academic growth for their members and we look forward to having more such activities in the coming months.

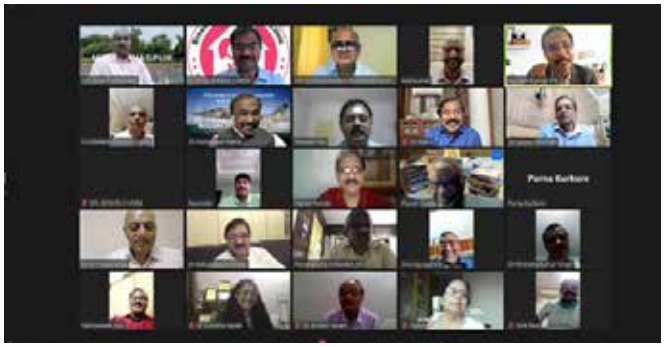
Jai IAP!! Jai Hind!!

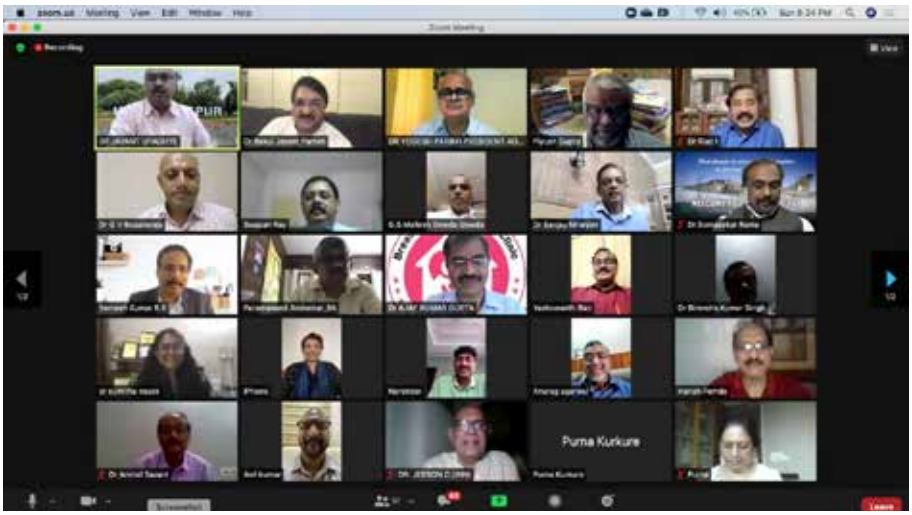
Sincere Regards,

Dr G V Basavaraja
Hon. Secretary General 2020 & 21

National IAP EB meeting on 22.8.2021







Newborn Hearing Screening Programme

Dr. Abraham K. Paul MD, DCH, FIAP, FNNF
Consultant Pediatrician, Indira Gandhi Co-Operative Hospital, Cochin
Convenor, NBHSP, IAP Kerala
Lead Expert- WHO-NBHSP South East Asia

Hearing impairment is one of the most critical sensory impairments with significant social and psychological consequences. Failure to detect children with congenital or acquired hearing loss may result in lifelong deficits in speech and language acquisition, poor academic performance and personal-social and behavior problems. Deficits in speech and language lead to lack of stimulation, which adversely affects the structure of the synaptic junction. Lack of auditory stimulation leads to retrograde degeneration in the cell body and axon.

Apart from the biological evidence, the data on congenital disabilities indicate that hearing loss has a substantially high incidence with congenital hearing loss affecting 30 per 10,000 children. Significant hearing loss is the most common disorder, occurring in 1 to 2 newborns per 1000 in the general population, and 2% to 3% of newborns admitted to neonatal intensive care unit. Vocabulary of a 3-year-old child with hearing impairment if remediated at birth is 300-700 words; if re mediated at 6 months is 150-300 words and if remediated at 2 years is 0-50 words, respectively; as compared to vocabulary of a 3-year-old child with normal hearing which is 500-900 words. This is enough reason for early identification and remediation.

Early Screening

Critical period for identification and remediation of hearing loss is before the age of 6 months. Since the pediatrician is the primary care provider for the child during the first few days of life, it is the sole responsibility of the pediatrician (or the primary physician) to evaluate the child for hearing loss. It has been observed that practice of neonatal screening has dramatically lowered the age of diagnosis of deafness from 1 ½ -3 years to less than 6 months of age. Screening should ideally be 'universal' ie., every baby is screened before discharge from hospital.

Causes of hearing loss are summarized in Box 1. These can be classified as: Conductive, Cochlear (ie., Sensory defect in the cochlea) and Neural: defect in the cranial auditory nerve, Retrocochlear (ie., defect at the level of auditory nerve, brainstem auditory pathway or both) und Central (ie., defect in the auditory area in cerebral cortex).

Sensorineural hearing loss is most relevant and cochlear causes of sensorineural hearing loss are more common. Many risk factors for hearing loss have been identified and are listed in Box 2.

BOX 1 – CAUSE OF HEARING LOSS

- Causes in ear canal/Conductive (e.g., congenital atresia, wax, foreign body, trauma, external otitis, stenosis
- Causes in middle ear Conductive (e.g., acute and chronic otitis media, perforation of tympanic membrane, congenital defects, trauma, malformations either hereditary or familial)
- Causes in the cochlea/Cochlear (e.g., ototoxic drugs, stay in neonatal intensive care unit due to jaundice or other causes, neonatal infections, head injury, noise).
- Causes in auditory nerve/Retrocochlear (e.g., problems in cochlear nerve, auditory pathway or cortex like tumors, trauma, de myelination).
- Intrauterine infections (tetanus, toxoplasma, rubella, cytomegalovirus and herpes or TORCH group of infections) can be classified as cochlear or retrocochlear causes of Sensorineural hearing loss.

BOX 2 -. RICK FACTORS FOR HEARING LOSS

- Family history of hereditary childhood sensorineural hearing impairment
- Intrauterine infection (TORCH)
- Craniofacial anomalies
- Birth weight less than 1500 gram
- Hyperbilirubinemia at a serum level requiring exchange transfusion
- Ototoxic medications used in multiple courses, or in combination with loop diuretics.
- Bacterial meningitis
- APGAR scores 0-4 at 1 minute or 0-6 at 5 minute
- Mechanical ventilation for 5 days or longer
- Sigmata of other findings associated with a syndrome known to include sensorineural and/or conductive hearing loss

Congenital rubella syndrome, Usher syndrome and Jervell and Lange-Nielsen (JLN) syndrome have been noted to be associated with hearing loss, few other syndromes include Treacher-Collins syndrome, Apert syndrome, Alport syndrome, Neurofibromatoas syndrome, Achondroplasia, CHARGE syndrome, Brachio Oto Renal syndrome, Chodley McCullough syndrome and Golden Har syndrome.

Screening for newborn hearing loss

In India, majority of hospitals do not conduct universal or high-risk screening. In such a situation, a centralized facility catering to all hospitals in a city is a practical option, A two-stage screening protocol can be made, in which infants are screened first with otoacoustic emissions (OAE). Infants who fail the OAE are screened with Auditory Brainstem Response (ABR). In this two-tier screening program, the second tier being ABR (which is more expensive) is required only for a select few, making the program more practical and viable.

Otoacoustic emissions (OAE) are quicker methods (as compared to electrophysiologic methods like ABR) for assessing hearing in newborns via a simple set-up. Otoacoustic emissions (OAEs) are sounds of cochlear origin recorded in the auditory meatus, produced by the movement of healthy outer hair cells.

Method

The probe tip is kept in baby's ear and machine switched on. Click sounds produced by

machine traverse to cochlea and causes outer hair cells to move. The sound produced by outer hair cells is picked up by the probe kept in baby's ear and we get a tick mark, indicating normal outer hair cell (cochlear) functioning.

Procedure takes 1-2 minutes only. As mentioned earlier OAE tests only cochlear function. (majority of hearing loss is secondary to cochlear outer hair cell damage).it is advisable to do the test on the day of discharge since false positive results are maximum on first few days of life (cerumen in external auditory canal and fluid in middle ear). If abnormal , repeat test at 6 weeks when baby comes for first immunization. If again abnormal, do ABR which is confirmatory. All NICU babies should have ABR to rule out Auditory Neuropathy and Auditory dyssynchrony.

Test can be done bedside during natural sleep it done on first few weeks of life . if done later, may require sedation . no need for a sound proof room.

PROTOCOL FOR NEWBORN HEARING SCREENING.

- A two-stage screening protocol with OAE as the first screen, followed by ABR for those who fail the OAE screen. This is 99% specific.
- It is advisable that all hospitals with level-3 neonatal care have OAE and ABR facilities. If not feasible, a centralized hearing screening with a portable OAE is suggested and all abnormal cases can be referred for ABR to the nearest Centre.
- The program may be coordinated by an Audiologist and weekly assessment meeting convened with the staff to discuss and sort out the issues, if any (held by the convenor). Usual issues could include non compliance by parents to bring the child for repeat OAE or ABR. This usually can be tackled by phone calls made by screening personnel, coordinator, or in rare instances by the convenor himself. Screening personnel need not to be an Audiologist.


Test done bed side during natural sleep

- Personnel with basic knowledge in computer and good communication skills may be chosen. They should be provided basic training in hearing screening and also skills to gather information on high-risk criteria, if any, from parents/hospital staff/hospital records. This training can be provided over one day.
- The screening personnel should visit each hospital daily/on alternate days/twice a week/weekly depending upon the number of births in that particular hospital. Daily screening may be carried out in hospitals which have more than 200 births, alternate day screening in hospitals with 100-200 births and twice weekly or weekly screening in hospitals with births less than 100 per month.
- All screeners should maintain a register of all cases screened and those with abnormal results. Neonates with abnormal screening results should be evaluated. It is the duty of the screeners to call back all abnormal cases for follow up, with the help of a coordinator. (Number of hospitals covered by a screener depends on the number of cases in a particular hospital and proximity of the hospitals)
- If abnormal OAE is detected, it is repeated at 6 weeks on the 1st immunization visit. If again abnormal, ABR is done for confirmation followed by full audiological evaluation and remediation with hearing aids (cochlear implant may be required in cases of profound hearing loss or poor response to hearing aids for six months).
- All NICU babies undergo ABR testing to rule out auditory dyssynchrony/ auditory neuropathy. They will require ABR after each NICU admission.
- In babies with abnormal ABR, detailed enquiry is made to identify and record risk factors. If any baby missing screening before hospital discharge is called for OAE test on the first immunization visit
- All babies with abnormal ABR should undergo detailed ENT evaluation hearing- aid fitting and auditory rehabilitation before 6 months of age. Systematic evaluation for ruling out syndromic associations such as ophthalmic, paediatric and cardiac assessments should be conducted.
- Children with neonatal meningitis should be treated as a special category and need investigations including imaging and intervention like cochlear implant (if needed) on a semi-emergency basis. Delay can result in cochlear ossification which may preclude subsequent intervention like a cochlear implant.

Goal of NBHSB

The goal is to screen newborn babies before 1 month of age, diagnose hearing loss before 3 months of age and start intervention before 6 months of age. Hurdles experienced in the screening process include: less motivated pediatricians; lack of awareness among parents/ community; non-compliance by the family for evaluation, and stigma attached to hearing aids.

CONCLUSIONS

As normal hearing is critical for speech and language development, it is recommended that during first 6 months of life, clinicians identify infants with hearing loss, preferably before 3 months of age. Other important issues are:

- Evaluate all infants before discharge from nursery.
- Universal neonatal screening and not targeted 'high risk' screening is ideal since about 50% of infants with hearing loss have no known risk factors for hearing loss and are discharged from well-baby nursery
- Delayed onset hearing loss should be considered and followed up (if presence of language delays, infections, head trauma,

stigmata of syndromes, ototoxic medications, recurrent otitis media, intrauterine infections, neurofibromatosis type II)

- Prevalence of hearing loss is more than twice that of the other newborn disorders combined.
- Never delay hearing assessment in any baby; no baby is too young to be tested or too young to be evaluated
- Never resort to rudimentary tests of hearing (like clapping hands) as confirmatory tests, and reassure parents that their child's hearing is normal.

Universal Newborn Hearing Screening (UNHS) has become a standard practice in most developed countries. The identification of all newborns with hearing loss before six months has now become an attainable and realistic goal. A concept of a centralized newborn hearing screening model existing in Ernakulam District to cater to all hospitals in the district is worth replicating. It takes away the financial burden of each hospital investing for the screening equipment. Follow up of positive cases and drop-outs are made easier with the central reporting and monitoring system. With unified strength of pediatricians, IAP city/district branches could take initiative to replicate this model in their respective towns or districts and by collaborating with government agencies involved in implementation of Rashtriya Bal Swasthya Karyakram. Now that Kerala State is declared Hearing Friendly on 20th December 2020, we have the responsibility to see to it that all babies borned in our State is screened for Hearing Loss before discharge.

Newborn hearing screening will help to identify hearing loss at an earlier age and alleviate the double tragedy of inability to hear and speak. Forming a consensus and national level guidelines for hearing screening is very important to construct a healthy independent society. Early intervention is mandatory for best prognostic outcomes.

Challenges in Newborn screening in India

DR. ANIL JALAN MD DCH
Pediatrician and Metabolic Physician
NIRMAN Metabolic Centre, Mumbai

DR. KETKI KUDALKAR
MSc (Biotechnology) PhD (Biochemistry)
Lab In Charge, NIRMAN Metabolic Centre, Mumbai

New born screening is the most important cost effective preventive public health program. It is implemented in majority of the developed countries. Currently there is no government funded universal neonatal screening program in India. About 27 million babies are born every year in our country. Approximately 4:1000 and 5:1000 are estimated to have hearing defects and congenital heart abnormalities, respectively, whereas the incidence of IEMs in India is estimated to approximately 1:1000 (1). This high incidence is due to high prevalence of consanguinity in our country. Many of the NICU admissions are expected to be due to IEMs. If undiagnosed and untreated many children develop mental retardation, learning disabilities, autism, dyslexia, behavioral abnormalities, and scholastic backwardness later in life. There is also considerable burden – financial and emotional on the parents to diagnose, treat, and manage these children (1). The most rational and cost-effective way of preventing such tragedies would be to have a NBS program which will detect most of the preventable or treatable, if not all IEMs and other disorders. Awareness of benefits of NBS is increasing and this could lead to the creation of one national NBS program. Although universal screening is a cost-intensive program, the benefits outweigh the cost as it helps in reducing the mortality and morbidity in these diseases.

Despite the benefits and absolute need for screening program in India, implementing it has its own challenges. NBS is not a test, it's a program. It needs more than just equipment and kits. It needs proper planning, proper commissioning, proper follow-up and confirmatory testing, adequate dietary and medical help and expert genetic pre- and post- test counseling. Developed countries where NBS has been introduced decades ago still face lot of problems and resolving such problems is a day-to-day affair. In developing countries like India, such problems are bound to be more due to many factors and we need to be cautious. In this article we will not be discussing actual NBS testing but some common problems that NBS program is like to stumble upon.

Achieving the goals of newborn screening is, as for any screening, a balancing act: getting maximum benefit from screening while producing the minimum harm. The obvious potential harms from screening and those most discussed, arise from the occurrence of false positive and false negative results, and the cost of the program (2). We herewith discuss some of the challenges that we face while implementing and carrying out new born screening at our facility.

- **Awareness :** Newborn screening is not known to many medical professionals including nurses and doctors in India. Also, the awareness among general public is very low. Many physicians may also feel distrustful about new born screening due to the misconceptions about the further costs involved, like, confirmatory tests, treatment expenses and outcome of the treated children. (Currently there is no policy or recommendation or

national guidelines for universal newborn screening by the state governments or Indian Association of Pediatrics (IAP)). Hence many hospitals (even in big cities and metros) have their own NBS programs with no consensus of the disorders screened. A harmonized policy regarding screening for rare diseases is highly desirable.

- **Pre-test counseling and Consent:** It is our experience that many a times blood sample is collected either by cord blood or on 2nd day of life but parents are rarely informed about the need and importance of NBS. There is a lack of pre- test counseling at majority of the hospitals carrying out NBS programs and in most of hospitals, NBS is done on verbal consent obtained from the parents. One reason could be large number of deliveries and very limited consultation time, but this can be overcome by appointing trained nurses who can discuss NBS with couples on one- to- one basis or even in groups. It is very essential to explain about NBS to the parents in simple words in local language and provide literature with pictures to make it simple. Same way once the results arrive, experienced staff should explain to the parents what the results really mean. As we deal with genetic counseling and positive cases on a day-to-day basis, in our experience most of the patients are under stress due to some "screen positive" results. Most of the general population have not even heard of disorders like MSUD and it is difficult for them to understand screen positive for the disease. If we have already done pre-test counseling, it becomes easy for them to understand the difference between screen positive and a confirmed case. Since there is no national policy in India an informed consent must be obtained before collecting blood for NBS. The consent form must include issues like storage and duration of storage of the NBS samples, policy for reporting of results (including positive and negative screen results), performing other tests like 2nd tier testing, confirmatory tests, DNA studies which may be relevant in the future (3,4).
- **Selection of disorders:** Not all countries carrying out NBS screen for the same disorders. There are some countries screening for 55 disorders where as some countries adopt more cautious approach (5). Every country and every ethnic group have different load of genetic disorders. Due to the ethnic diversity every region in India has a different set of prevalent disorders, which can make implementing a national policy difficult. While deciding which disorders to include in our panel of NBS, probably the most important criteria will be cheap and effective treatment available for everyone at no or minimal cost. Based on personal experience, we can recommend a panel of 4 common disorders that one can screen all over India.

1. Hypothyroidism
2. G6PD deficiency
3. Galactosemia
4. Biotinidase deficiency

- **Cost and budget:** Screening program in India is currently not funded by the Central Government or the State Government at most of the places. Many private and government hospitals provide NBS at cost. Disorders like congenital hypothyroidism (CH), Glucose 6 phosphatase dehydrogenase (G6PD) deficiency, galactosemia, cystic fibrosis (CF), congenital adrenal hyperplasia (CAH) and diseases screened by tandem mass spectrophotometry (TMS) are included in these programs. Every hospital has its own policy for funding and selection of disorders to be screened. This can make collection of data on a nation- wide basis and arriving at a consensus for a national screening program difficult.

While considering the costs involved in NBS programs one should also not neglect other factors like the cost of re-call, confirmatory tests,

treatment, manpower and genetic counselling.

- Using NBS as a diagnostic tool: The current scenario in India has many primary care providers using NBS as a diagnostic tool for all IEMs rather than a screening program. Many of the doctors use NBS for diagnosis in symptomatic children due to the lower costs involved than the extensive diagnostic work-up. However, awareness needs to be spread in our country that NBS cannot diagnose many IEMs like NKH, Respiratory chain defects, proximal urea cycle defects, and many more.
- Reporting results and post-test counseling: Performing NBS tests and understanding and reporting of NBS results require a trained staff. Education of all the staff involved in NBS program is very essential for the successful implementation of the program. Right from the collection of samples to conveying of results to the parents should be done according to a protocol. Person conveying the results of NBS to the parents must be a qualified geneticist and trained personal who is capable of explaining the results, implications of the results, need for further testing if any and also capable of solving queries of the parents and calming their anxieties regarding the results. Post- test counseling is a very important part of the program which can make the NBS program a great success.
- Providing treatment: The most important aim of any NBS program is to identify the metabolic disorders so that treatment can be initiated before the appearance of symptoms. Approximately 1 in 3,000 infants detected by expanded NBS requires dietary modification. In our experience, annual cost for such dietary treatment and other medical expenses including follow-up studies in India comes to approx. 1,50,000/- INR. This cannot be covered by the government alone or by insurance companies alone. We need some system in place whereby we can procure diets at a much lesser cost, partly or fully supported by government. Even today our patients have to import many of these special medicines (e.g. NTBC, Carbaglu, Sodium Phenylbutyrate etc.) from western world at a very high cost and at times custom's duty also. Hence it is very essential to make such diets and drugs available on regular basis from the companies or hospitals in India.
- Efficiency of NBS: There are 4 disorders where outcome studies have confirmed the efficacy of NBS beyond doubt (2)–

1. MACD Deficiency
2. Phenylketonuria
3. Congenital Hypothyroidism
4. Cystic fibrosis.

However, there are some disorders in which efficiency of screening is low. Disorders with probably no clinical significance like Histidinemia and SCADD have been removed from the list of NBS disorders in many developed countries (6).

Apart from the disorders selected, there are also some other factors which can affect the efficiency and success of a Newborn screening program.

1. Delay in test results: Delay in the NBS test results can cause unnecessary anxiety for the parents as well as a risk of delay in diagnosis. If a baby has a positive NBS result this needs to be followed up very quickly to avoid delay in treatment.
2. Sample recalls: Screen positive results must be re- checked by means of a sample recall before confirming the diagnosis. Certain disorders require samples to be collected after adequate milk feeds for e.g. galactosemia. These recalls can further delay the diagnosis of a child with IEM.

   Impact of a screening recall on the family is also substantial, even after normal retesting, a screening recall often results in increased anxiety over a child's health, altered parent child relationship and increased

hospitalizations for unrelated illness (7).

3. High false positivity rates: False positivity is part and parcel of the whole program. Increased numbers of disorders tested for will inevitably lead to an increase in the number of false positive test results [although impact of this on parents may have been over estimated] (8). However, as the false positivity rate goes down, the sensitivity also may be significantly reduced. Therefore, we need to strike a balance between false positivity and sensitivity. It has been shown that there is increased parental stress and anxiety following an abnormal result even after this was shown to be falsely positive, the authors also found that such stress was less in parents who were well informed about newborn screening (8). It was shown that false positive results by expanded screening may cause disruption of the family life through a combination of unnecessary hospitalization, high parental stress, and parent – child relationship dysfunction (7). Some metabolites- propionyl carnitine, isobutyryl carnitine, tyrosine and methionine are more likely to cause false positive results and increase the recall rates (7).

- Improving quality and performance of NBS: There are many strategies to improve performance of NBS. Proper selection of disorders and systematic implementation are the first requirements, but once the program starts, there are many difficult areas which need special attention. To further improve the performance following steps may be required:

1. Participation in Quality assurance program: Most of the NBS programs participate in CDC or ERNDIM QC/PA programs. In common with other laboratories, most errors (missed cases) are not due to inaccurate or imprecise laboratory tests, they are due to problems in laboratory processes (9). We need to standardize and control such laboratory processes.
2. Proper guidelines: Written guidelines and protocols are very important for any NBS lab.
3. Established protocols and standards: The quality of screening and follow-up can be improved by the use of diagnostic protocols and algorithms, particularly rarer disorders and those in which diagnosis is complex (9).
4. Rechecks to reduce recall rates: To reduce the number of recalls, we have implemented many strategies at our institute. Screen positive samples are re- run to exclude any analytical errors. Also, continuous evaluation of cutoffs helps in reducing the recall rates. At our institute we constantly evaluate the cutoffs of all the parameters examined. For e.g. Revising the cutoffs of C0 as per the CDC guidelines (from 12 µmol/L to 8.6 µmol/L, reduced our false positivity rate for this parameter from 2% to 0.8%. (10)
5. 2nd tier testing and multiple markers: New born screening diagnoses many new borns with Inborn errors of metabolism in the pre-symptomatic phase but is it has also increased a lot of costly, stress producing, false positive results (7). To reduce the number of false positives, 2nd tier testing is very essential. 2nd tier testing is performing a second analysis for the suspected disorder from the same new born screening sample. For many disorders this approach is used

a. T4 and TSH for Hypothyroidism
b. Galactose and GALT Enzyme for Galactosemia
c. IRT and DNA studies for Cystic Fibrosis
d. MMA and 3- hydroxypropionate for C3 elevation
e. Pivaloyl carnitine for elevated C5
f. Homocysteine for high methionine
g. Alloisoleucine for high leucine (Figure 1)
h. Succinylacetone for high tyrosine
i. ADA and PNP for SCID
j. C26 for X-ALD

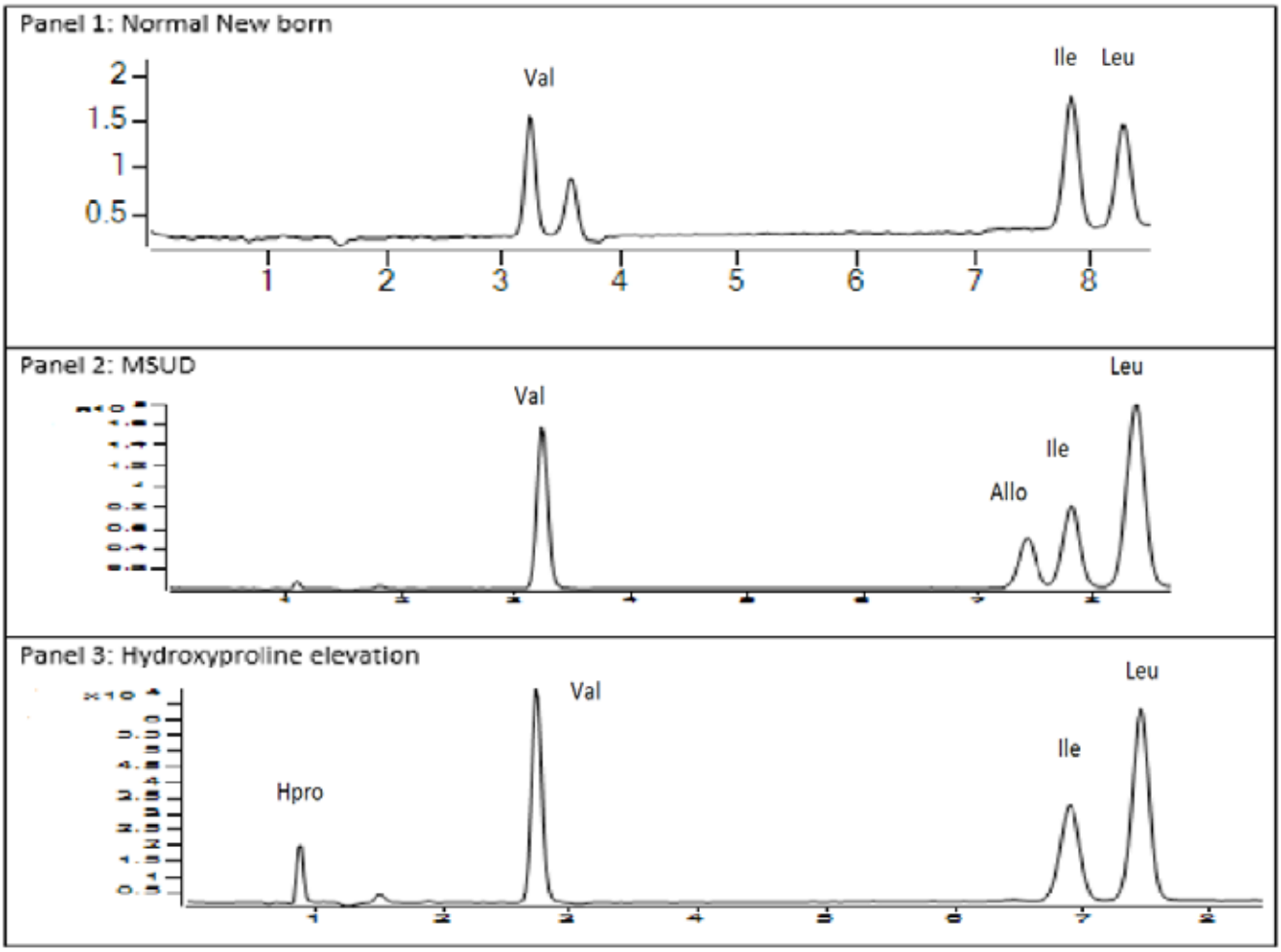


Figure 1: 2nd tier testing for Leucine elevation on NBS. Panels show Alloisoleucine estimation by LC/MS/MS. Panel 1 shows a normal individual (for comparison) with no presence of allosioleucine. Panel 2 shows presence of Alloisoleucine suggesting MSUD. Panel 3 shows presence of Hydroxyproline, which gives high Leucine on NBS (TMS).

They can be used one after another (two tier approach) or simultaneously (multiple markers for one disease approach). This increases the cost, but also improves the performance and reduces chance of missing any case or false positivity. Another advantage is that the second-tier tests are performed in the same NBS samples and this can reduce the recall rates considerably.

6. Training: NBS programs need special training of all the staff in understanding all the problems associated with testing and interpretation of the results. Training is an integral part of the whole system. Unfortunately, such specialized training is not easily available in developing world. We have provided training to many newcomers in this field. Excellent training is available in many European centers and also in USA and UK.

7. Facilities for confirmation and follow-up: The main aim of NBS is to pick up rather asymptomatic or pre- symptomatic cases and treat them. However, every screen positive baby needs proper follow-up and confirmatory testing, sometimes enzyme assays or even molecular studies. Such centers must be affiliated from the very beginning and their expertise in actual management of rare inborn errors must be utilized properly. In our experience many centers do offer newborn screening as "tests" and when something comes screening positive have difficulty in directing parents to proper centers. It is

always better to properly record such referrals and also provide information on information page that is handed over to parents, so that they know whom to contact in case of screen positive results. This will definitely reduce their anxiety.

References

1. Jalan AB, Kudalkar KV. New Born Screening. Need of the hour. Karnataka Pediatric J. 2021; 36 (1): 35-41.
2. Bridget Wilcken, Expanded newborn screening: reducing harm, asserting benefit, J Inherit Metab Dis (2010) 33 (Suppl 2); S205-S210.
3. Akkad A, Jackson C, Kenyon S, Dixon woods M, Taub N, Habiba M, Patients's perception of written consent questionnaire study, BMJ (2006); 333; 528.
4. Jean-Luois Dhondt, Expanded newborn screening: social and ethical issues, J Inherit Metab Dis (2010) 33 (Suppl 2); S211-S217.
5. Bodamer OA, Hoffmann GF, Lindner M, Expanded Newborn Screening in Europe 2007, J Inherit Metab Dis (2007); 30: 439-444
6. Widhalm K, Virmani K, Long Term follow-up of 58 patients with Histidinemia treated with a histidine restricted diet; no effect of therapy. Pediatrics (1994) 94: 861-866.
7. La Marca, Malvagia S, Pasquini E, Innocenti M, Donati MA, Zammarchi E, et al. Rapid 2-nd tier test for measurement of 3-OH propionic acid and methylmalonic acid in dried blood spots: reducing the false- positive rate for propionylcarnitine during expanded new born screening by liquid chromatography- tandem mass spectrometyr. Clin Chem 2007; 53(7): 1364-1369.
8. Prosser LA, Ladapo JA, Rusinak D, Waisbern SE, Parental tolerance of the false positive newborn screening results, Arch Pediatr Adolesc Med (2008); 162 : 870 – 876
9. D Webster, Quality performance of newborn screening systems: Strategies for improvement. J Inherit. Metab Dis (2007) 30: 576 – 584.
10. Umamaheshwari B, Susmitha T, Prakash A, Binu N, Sowmya K, Jalan A, Kudlakar K. New born screening for Inborn Errors of Metabolism (IEM) - 5 years' experience from a tertiary care neonatal unit. Abstract No: P-01. Presented at ISIEM 2021, August 2021.

Neonatal screening for primary immunodeficiency diseases

PROF. AMIT RAWAT
Professor of Pediatrics

POOJA MALHOTRA, AAQIB ZAFFAR BANDAY
Allergy Immunology Unit, Department of Pediatrics,
Advanced Pediatrics Center (APC),
Post Graduate Institute of Medical Education and Research (PGIMER)
Chandigarh

Introduction

Establishment of a new born screening (NBS) program allows for the recognition of various disorders in the asymptomatic infant enabling early diagnosis, prompt initiation of appropriate therapy and favourable outcomes. Primary immunodeficiency diseases (PIDs), also called inborn errors of immunity (IEIs), are an ever expanding group of about 500 monogenic disorders that are associated with significant morbidity and mortality, especially in undiagnosed/untreated individuals (1). These disorders result in a significantly increased risk of development of infections, often complicated by the development of autoimmunity and at times malignancy (2). The cumulative incidence and prevalence of IEIs is estimated to be up to 1 in 4000 and 1 in 1000, respectively (3, 4) which is similar to various inborn errors of metabolism for which NBS has been widely utilized (5). Herein, we briefly review the application of NBS in reference to IEIs.

Severe combined immune deficiency (SCID)

SCID, the most severe form of primary immune deficiency, is one of the very few immunological emergencies in pediatric clinical practice. The outcome of usual forms of SCID is universally fatal in the absence of definitive treatment. Most untreated patients fail to survive beyond infancy (hence 'severe') due to profound dysfunction of both cellular and humoral arms of the immune system (thus 'combined') (6). Currently, pathogenic gene variants in more than 20 different genes, which primarily regulate T-cell (± B-cell) development and function, have been reported to cause SCID (7). These children may suffer from overwhelming infections with any pathogen including the live attenuated vaccines like Bacillus Calmette–Guérin (BCG), oral polio, rotavirus and measles vaccines. Hematopoietic stem cell transplantation (HSCT) is the curative treatment for most forms of SCID; however, gene therapy has also been employed for few SCID due to a defect in adenosine deaminase (8). The outcome of HSCT is excellent with >90-95% overall survival in patients transplanted within the first 3–4 months of life in an infection-free state (9). Occurrence of infections in patients with SCID, which often correlates with delays in treatment, drastically reduces the overall and event-free survival. Hence, early detection of SCID in an infection-free young infant or neonate becomes inevitable meriting the need for NBS.

SCID is the prototype IEI for which NBS has been developed and validated. It is now routinely been

performed in many developed countries of the world. The primary tool currently been utilized for NBS of SCID is quantitative estimation of T-cell receptor excision circles (TRECs) by quantitative polymerase chain reaction (qPCR) (10). TRECs are circular, extrachromosomal DNA fragments that are generated as result of unique somatic recombination of T-cell receptor gene segments of developing T lymphocytes in the thymus. Currently, it is the most suitable method for NBS of SCID and is performed on dried blood spots blotted on Guthrie cards. This facilitates NBS of SCID in conjunction with other genetic diseases (11). Patients with abnormal TREC assay are further evaluated by a detailed lymphocyte immunophenotyping (example, enumeration of absolute CD3+ T-cell counts, estimation of naïve T-cells, etc). Finally, genetic testing is performed to confirm the diagnosis of SCID in patients with abnormal lymphocyte immunophenotyping. However, the cut-off for an abnormal TREC assay is variable among different countries employing NBS for SCID. Nonetheless, patients with <4 TREC copies per µL are often referred to as 'urgent positive' as they have the highest risk of having underlying SCID (12, 13). Such infants require immediate evaluation for definitive diagnosis of SCID. Given the substantial risk of infection in patients with SCID and subsequent dismal prognosis, it may be prudent to start broad-spectrum antimicrobial prophylaxis and avoid live vaccines in such healthy infants till accomplishment of a definitive diagnosis.

It is noteworthy to mention that patients with other primary and secondary causes of T-cell lymphopenia may also have low TRECs. These include other combined immunodeficiencies (like Wiskott-Aldrich syndrome, DOCK8 deficiency), genetic syndromes associated with immune deficiency (like Di-George syndrome, ataxia-telangiectasia, Kabuki syndrome), chromosomal anomalies (like trisomy 21), prematurity, HIV infection, maternal use of glucocorticoids and intestinal lymphangiectasia amongst others (12). In case of deficiency of metabolic enzymes resulting in SCID or SCID-like phenotype, namely, adenosine deaminase and purine nucleoside phosphorylase, combining TREC assay with tandem mass spectrometry can enable further delineation of the IEI (14, 15). In addition to its role in facilitation of early diagnosis, NBS has provided more accurate estimates of the incidence of SCID. Besides, it has resulted in the discovery of new genetic etiologies of T-cell immune deficiency. It has also shed light on immunological phenotype of various disorders (like ataxia telangiectasia, trisomy 21) in the neonatal period (16).

Antibodies deficiencies Primary antibody deficiencies, as the name suggests, are a group of IEIs characterised by lack of circulating protective antibodies, of which X-linked agammaglobulinemia (XLA) is the prototype. It is caused by pathogenic variants in Bruton tyrosine kinase (BTK) gene which is required for downstream signalling events of the pre-B-cell receptor complex. Mutations in the BTK gene lead to developmental arrest of B-cells in the bone marrow resulting in absence of circulating B-cells, low to undetectable levels of immunoglobulins, and predisposition to bacterial and enteroviral infections in the affected males (17). These children suffer from recurrent, severe pulmonary and gastrointestinal infections and development of pulmonary complications such as bronchiectasis is common. Although affected children usually present after 6 months of age (by virtue of circulating protective maternal antibodies), they are at risk of fatal infections from the oral polio vaccine (OPV). Early identification of this disorder can, hence, prevent the administration of OPV (multiple doses of which are given in early infancy) and prompt initiation of immunoglobulin replacement therapy, thus preventing pulmonary and other infectious complications. Similar to TRECs generated in T-cells, κ-deleting recombination excision circles (KRECs) are generated during B-cell receptor rearrangements in developing B lymphocytes in the bone marrow. Analogous to SCID, NBS

by qPCR-based KREC assay is a cost-effective method for detection of B-cell lymphopenia and, hence, facilitates the diagnosis of XLA and other antibody deficiencies (18). KREC assay can also be used for screening of autosomal recessive forms of agammaglobulinemia which result from mutations in various proteins/enzymes involved in B-cell development (19).

Complement and granulocyte disorders

Screening for deficiencies of different complement proteins and for granulocytic defects using protein-based assays represents a further expansion in the number of PIDs which can be detected by NBS. In contrast to T- and B-cells which are components of the adaptive immune response, complement proteins and granulocytes are integral constituents of the innate immune system. Deficiencies of complement proteins predispose an individual to autoimmunity, renal disease, and recurrent, serious bacterial infections especially from encapsulated organisms (20). Defects in granulocyte function (like chronic granulomatous disease) and number predispose individuals to develop bacterial and fungal infections. Using fluorescence-based suspension bead array technology specific complement and granulocytic proteins can be eluted and captured from dried blood spots, enabling identification of infants with low or absent complement/granulocytic proteins (21). Whole genome sequencing (WGS) technology has also been utilized in identification of complement component deficiency in newborn screening programs (Reference).

The use of newer techniques such as bead array technology, targeted sequencing, protein-based assays, and next generation sequencing (NGS) technologies have expanded the ambit of disorders which could potentially be included for newborn screening programmes.

Role of multiple qPCRs for NBS

Multiplexing of qPCRs has been utilized for screening of inversion mutations resulting in type 3 familial hemophagocytic lymphohistiocytosis along with T and B cell immunodeficiencies (22). A similar strategy of multiplexing qPCRs with TREC/KRES assay has been used to identify deletion mutations resulting in spinal muscular atrophy (23).

Next-generation sequencing (NGS) as a screening tool for IEIs

Whole exome/genome or target gene panel sequencing in case of IEIs is an upcoming modality for screening of IEIs. However, the significant difficulty in interpreting variants of unknown significance is the major hindrance to this approach (24, 25). However, given the diverse nature and ever expanding number of PIDs being identified, no single technique except NGS has the potential to identify all forms of PID. Besides, NGS has the potential to identify and, hence, serve as a screening tool for majority of the genetic disorders Given the improvements in NGS technology, progressive reduction in costs, greater accessibility, development of fully automated bioinformatics pipelines, and ever-increasing variant information, NGS may soon become the first-line screening strategy for genetic disorders including IEIs (25). Incorporation of NGS in NBS programs would be one of the most important milestones in the history of medicine; however, large scale studies are needed to validate this approach.

References

1. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, et al. The Ever-Increasing Array of Novel Inborn Errors of Immunity: an Interim Update by the IUIS Committee. J Clin Immunol. 2021;41(3):666-679.

2. Bousfiha A, Jeddane L, Picard C, Al-Herz W, Ailal F, Chatila T, et al. Human Inborn Errors of Immunity: 2019 Update of the IUIS Phenotypical Classification. J Clin Immunol. 2020;40(1):66-81.
3. Al-Herz W, Al-Ahmad M, Al-Khabaz A, Husain A, Sadek A, Othman Y. The Kuwait National Primary Immunodeficiency Registry 2004-2018. Front Immunol. 2019;10:1754.
4. Boyle JM, Buckley RH. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. J Clin Immunol. 2007;27(5):497-502.
5. Green NS, Dolan SM, Murray TH. Newborn screening: complexities in universal genetic testing. Am J Public Health. 2006;96(11):1955-1999.
6. Fischer A, Notarangelo LD, Neven B, Cavazzana M, Puck JM. Severe combined immunodeficiencies and related disorders. Nat Rev Dis Primers. 2015;1:15061.
7. Tangye SG, Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, Etzioni A, et al. Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2020;40(1):24-64.
8. Booth C, Romano R, Roncarolo MG, Thrasher AJ. Gene therapy for primary immunodeficiency. Hum Mol Genet. 2019;28(R1):R15-R23.
9. Pai SY, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, et al. Transplantation outcomes for severe combined immunodeficiency, 2000-2009. N Engl J Med. 2014;371(5):434-46.
10. van der Spek J, Groenwold RH, van der Burg M, van Montfrans JM. TREC Based Newborn Screening for Severe Combined Immunodeficiency Disease: A Systematic Review. J Clin Immunol. 2015;35(4):416-30.
11. King JR, Hammarström L. Newborn Screening for Primary Immunodeficiency Diseases: History, Current and Future Practice. J Clin Immunol. 2018;38(1):56-66.
12. Currier R, Puck JM. SCID newborn screening: What we've learned. J Allergy Clin Immunol. 2021;147(2):417-426.
13. El-Sayed ZA, Radwan N. Newborn Screening for Primary Immunodeficiencies: The Gaps, Challenges, and Outlook for Developing Countries. Front Immunol. 2020;10:2987.
14. la Marca G, Giocaliere E, Malvagia S, Funghini S, Ombrone D, Della Bona ML, et al. The inclusion of ADA-SCID in expanded newborn screening by tandem mass spectrometry. J Pharm Biomed Anal. 2014;88:201-6.
15. la Marca G, Canessa C, Giocaliere E, Romano F, Malvagia S, Funghini S, et al. Diagnosis of immunodeficiency caused by a purine nucleoside phosphorylase defect by using tandem mass spectrometry on dried blood spots. J Allergy Clin Immunol. 2014;134(1):155-9.
16. Puck JM. Newborn screening for severe combined immunodeficiency and T-cell lymphopenia. Immunol Rev. 2019;287(1):241-252.
17. Bearden D, Collett M, Quan PL, Costa-Carvalho BT, Sullivan KE. Enteroviruses in X-Linked Agammaglobulinemia: Update on Epidemiology and Therapy. J Allergy Clin Immunol Pract. 2016;4(6):1059-1065.
18. Nakagawa N, Imai K, Kanegane H, Sato H, Yamada M, Kondoh K, et al. Quantification of κ-deleting recombination excision circles in Guthrie cards for the identification of early B-cell maturation defects. J Allergy Clin Immunol. 2011 Jul;128(1):223-225.e2.
19. Cardenas-Morales M, Hernandez-Trujillo VP. Agammaglobulinemia: from X-linked to Autosomal Forms of Disease. Clin Rev Allergy Immunol. 2021 Jul 9:1–14. Epub ahead of print. doi: 10.1007/s12016-021-08870-5.
20. Schröder-Braunstein J, Kirschfink M. Complement deficiencies and dysregulation: Pathophysiological consequences, modern analysis, and clinical management. Mol Immunol. 2019;114:299-311.
21. Dezfouli M, Bergström S, Skattum L, Abolhassani H, Neiman M, Torabi-Rahvar M, et al. Newborn Screening for presymptomatic Diagnosis of Complement and Phagocyte Deficiencies. Front Immunol. 2020;11:455.
22. Borte S, Meeths M, Liebscher I, Krist K, Nordenskjöld M, Hammarström L, et al. Combined newborn screening for familial hemophagocytic lymphohistiocytosis and severe T- and B-cell immunodeficiencies. J Allergy Clin Immunol. 2014;134(1):226-8.
23. Gutierrez-Mateo C, Timonen A, Vaahtera K, Jaakkola M, Hougaard DM, Bybjerg-Grauholm J, et al. Development of a Multiplex Real-Time PCR Assay for the Newborn Screening of SCID, SMA, and XLA. Int J Neonatal Screen. 2019;5(4):39.
24. Bodian DL, Klein E, Iyer RK, Wong WS, Kothiyal P, Stauffer D, et al. Utility of whole-genome sequencing for detection of newborn screening disorders in a population cohort of 1,696 neonates. Genet Med. 2016;18(3):221-30.
25. King JR, Notarangelo LD, Hammarström L. An appraisal of the Wilson & Jungner criteria in the context of genomic-based newborn screening for inborn errors of immunity. J Allergy Clin Immunol. 2021;147(2):428-438.

Clinical profile of Glucose-6-phosphate dehydrogenase deficiency (G6PD) in Indian neonates : Need for a universal screening in India

Preeti Deswal[1] Haseena Sait[2] BK Thelma[3] Seema Kapoor[4]

ABSTRACT

Objective: To study clinical and molecular profile of G6PD deficiency in neonates born in North India

Design: Cross sectional study

Setting: Tertiary care centre in North India

Participants: Newborns born in 20 hospitals participating in newborn screening project between November 2014-2016

Methods: All neonates were screened at 24-48 hours of life for G6PD deficiency. G6PD was measured by the semiautomated platform using Victor 2D in the first year of study and later by completely automated platform using Genomic Screening Processor and value <2.2 U/g Hb and < 16 IU/dL was considered as suspected positive respectively. Confirmation was done by spectrophotometric analysis using RBC lysate.

Results: Prevalence of G6PD deficiency was 1:195 (1043/203385 screened neonates). Males constituted 71.6% of the study population. 49 % of the G6PD deficient neonates developed jaundice with 18% requiring intervention. No correlation was observed between severity of jaundice and enzyme levels.

Conclusion: High prevalence of G6PD deficiency in our population warrants universal newborn screening and proper triaging of the jaundiced neonates for better neurodevelopment outcome.

Introduction

Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency is the most common human enzyme deficiency affecting more than 400 million people worldwide. Its prevalence is especially high in tropics and subtropics synchronizing with malarial endemicity [1]. Recent meta-analysis revealed that the prevalence of G6PD deficiency was 8.5% with a higher frequency in Northern

1. *Preeti Deswal, MD Pediatrics, Senior Resident, Department Of Pediatrics, Maulana Azad Medical College, New Delhi*
2. *Haseena Sait, DM (Medical Genetics) student, Ex Senior Resident Dept of Pediatrics, Maulana Azad Medical College, New Delhi*
3. *BK Thelma, Professor (Human Genetics), University of Delhi South Campus, New Delhi*
4. *Seema Kapoor, Director Professor, Division of Genetics, Dept of Pediatrics, Maulana Azad Medical College, New Delhi*

and Western parts of India [2]. While the clinical manifestations of its deficiency are thought to involve red cells exclusively, recent advances in biology has also emphasized the role of G6PD in causation of neurodegenerative disorders [3]. Neonatal hyperbilirubinemia remain the most important condition requiring identification of G6PD deficiency in the neonatal period. While severe hyperbilirubinemia is rarely associated with mortality in developed countries, the condition still remains a significant cause of neonatal mortality in populations with high G6PD deficiency and survivors who experienced delays in receiving phototherapy and, or, exchange transfusion are commonly associated with diverse long-term neurodevelopmental impairments.

Thus, we aimed at studying the clinical profile of the neonates with G6PD deficiency detected through newborn screening from North India.

Methodology

This cross-sectional study was conducted from November 2014-2016 in a tertiary care centre in Delhi. All the neonates were screened at 24-48 hours of life as a part of new-born screening programme by dried blood spot sample (DBS). Institutional ethical committee approval was taken from all the 20 participating hospitals. The demographic information containing gender, ethnicity, consanguinity, gestational age, birth weight and presence of cephalohematoma and other risk factors contributing to hyper-bilirubinemia were recorded.

The G6PD phenotype is primarily described in terms of G6PD activity normalized for hemoglobin or red blood cell count. The classification of the G6PD status of an individual is defined as the percentage of a normal value determined by the regional laboratory as it is challenging to define a single universal normal (100%) G6PD activity value. Male neonates with less than 30% activity are considered as deficient and >30% activity as normal and females with less than 30%, 30–80%, and greater than 80% G6PD activity are considered G6PD deficient, intermediate, and normal, respectively [4].

G6PD was measured by the semiautomated platform using Victor 2D (Perkin Elmer) in the first year of study and later by completely automated platform using Genomic Screening Processor (Perkin Elmer, Finland). To determine G6PD activity levels, the fluorescence of NADPH is measured using an excitation wavelength of 340 nm and emission wavelength of 460 nm. With the fully automated measurement by fluro immunoassay, a novel measurement technology enabled the measurement of wells with floating disks. After punching of the samples and reconstitution of the NADP substrate, the assay was run in a semiautomated platform and fully automated form from plate loading to completion. The assay time for one plate is 1 hour 22 minutes and a batch of 24 plates can be run in 10 hours 12 minutes. G6PD values of <2.2U/g Hb and < 16IU/dL was considered as suspected positive by victor 2D and completely automated GSP respectively. A repeat test was performed using fresh DBS sample.

For those neonates whose values still remained below the cut off, confirmation was done by the quantitative spectrophotometric analysis using RBC lysate. This quantitative tests measure G6PD activity in terms of units. One International Unit (U) is the amount of G6PD activity that will convert 1 micromole of NADP+ per minute under predetermined substrate and reaction conditions. Activity was expressed in either a standard number of cells (U/1012 red blood cells) or amount of hemoglobin (U/g Hb). G6PD deficiency has been defined as a percentage of normal G6PD activity. The cut offs for deficiency are variable and 10% to 30% G6PD activity cut-off were considered acceptable. The levels differed in male hemizygotes and female heterozygotes.

The G6PD deficiency confirmed neonates were followed up during first week of life to identify those who develop hyperbilirubinemia and amongst them, information regarding need for phototherapy and duration and/or need for exchange transfusion was recorded.

Parents of all deficient neonates who got traced were given a disease information booklet, which enlists all the offending diets and drugs which have a potential to cause hemolysis if ingested. They were advised to take this booklet to any hospital they would visit for intercurrent illness.

Statistical analysis: The entire analysis was done using STATA 11 software. Gestation , birth weight and G6PD levels were expressed as mean and standard deviation. Kruskal-Wallis equality-of-populations rank test was used to compare the enzyme levels in all the mutational variants.

Results

From a total of 203385 neonates screened by two methods, 1431 were screen positives. With repeat testing followed by confirmatory test, 1043 were found to be G6PD deficient. Considering this, the prevalence of G6PD deficiency in our population was 1:195. Males constituted 71.6% of the study population. The demographic data of the study population is provided in Table 1.

Phenotype of the G6PD deficient neonates

Amongst the 1043 confirmed G6PD deficient neonates, phenotypic ascertainment could not be done in 57 neonates due to early discharges and expiry. Parents of neonates born in other hospitals (n=795) were contacted telephonically to enquire regarding the development of jaundice and any intervention that was provided. Intramural neonates (n=191) were followed up for jaundice and the intervention provided was recorded.

Amongst the 191 intramural neonates, 83 developed jaundice and 28 of them required phototherapy and 5 required exchange transfusion. Amongst the 795 extramural neonates, 48 required phototherapy and 9 required exchange transfusion. The details regarding the same is provided in table 2.

Consanguinity was present in 260 parents of G6PD deficient neonates (25%). No correlation was observed between severity of jaundice and the enzyme levels. Amongst the intramural

Table 1 -Demographic variables of G6PD deficient neonates

VARIABLES	VICTOR 2D (U/gm Hb)	GSP (mIU/dL)
Overall mean (SD) enzymatic level	Males 5.6 (1.4) Females 5.7 (1.3)	Males 53.2 (14) Females 52.4(13.9)
No. of G6PD deficient (%)	Males n-545 (71.6) Females n-216 (28.4)	Males n- 202 (71.6) Females n-80 (28.4)
Gestational age in weeks Mean (SD)	37.9 (1.4)	
Gestation	Preterm n-178 (17%) Term n-865 (83%)	
Birth weight in grams Mean (SD)	2622.5 (503.3)	

Table 2-Phenotype of the G6PD deficient neonates

Variables	Intramural neonates (n)	Extramural neonates (n)	Total
G6PD deficient	191	795	986
Presence of Jaundice	83	400	483 (49%)
Phototherapy required	28	48	76 (15.7%)
Exchange transfusion required	5	9	14 (2.9%)

births, 2 neonates had cephalohematoma while in the remaining, no other risk factors for jaundice were present.

Discussion

The prevalence of G6PD deficiency in our study population was 1:195. Males constituted 71.6% of the study population and 83% of them were term gestation. Clinical jaundice was present in 49% of the study population and intervention in the form of phototherapy or exchange transfusion was required in 18.6% of the neonates with jaundice. No correlation was obtained between the severity of jaundice and enzyme levels.

While the prevalence of G6PD deficiency varies between different regions, recent meta-analysis revealed a higher magnitude of G6PD deficiency (8.5%) [2]. The frequency of G6PD deficiency is also considered to be comparatively higher in North and West India. These results were concordant with our observation showing higher prevalence of G6PD deficiency in our study population.

Males are hemizygous for the G6PD gene but females can have normal gene expression, be heterozygous, homozygous or compound heterozygous for two mutations on the G6PD gene [5]. It has been reported that the frequency of the G6PD-deficient allele is very high in sub-tropical region and females can be homozygous or compound heterozygous and can present with the same clinical manifestations as hemizygous males [6]. This emphasizes need for universal screening considering a high gene pool in the population (28.4% of the G6PD deficient neonates were females)

The incidence of development of jaundice in G6PD deficiency varied between different studies. While we observed the incidence of jaundice in 49% of the G6PD deficient neonates, it was 23.8 % in the study by Bisoi [7] and 48.7% in the study by Verma [8]. This implies that a considerable number (51%) of asymptomatic G6PD deficient newborns run a greater risk of unexpected hemolytic anemia if they unknowingly get exposed themselves to hemolytic triggers later in life. Hence, early detection and initiation of treatment is required to reduce or eliminate morbidity of the disease.

Studies have also found that G6PD deficient neonates tend to have low haemoglobin and haematocrit levels and the severity of jaundice and the intervention needed in much higher in the G6PD deficient group than the G6PD normal jaundiced neonates [9,10]. In developing regions, access to phototherapy and exchange transfusions is often limited. Despite these simple and accessible treatments, up to 6.6% of G6PD-deficient babies will develop kernicterus even in developed countries [11] and 12-50% of G6PD-deficient infants [12] with kernicterus will die. It is impossible to prevent kernicterus by conventional treatments especially in cases where an acute hemolytic event in G6PD-deficient infants triggers rapid rise of bilirubin

concentration in the brain. Furthermore, exchange transfusion leads to adverse events in 5% of infants, and death in 0.4% of infants [13]. Thus, knowing the G6PD status would help us in triaging those neonates who develop jaundice and a closer surveillance will help in preventing kernicterus and its long term neurodevelopmental sequalae. This stresses the need for a urgent universal newborn screening program for G6PD deficiency and it should be considered for inclusion in the core panel of disorders considering its prevalence across all states and the significant sequale which the family has to face.

The limitation of the study was that long term follow up of these neonates was not feasible to study the chronic complications like non spherocytic haemolytic anaemia which could have helped us in understanding the actual burden of the disease. Data regarding the confounding factors for jaundice could not be obtained from neonates who were delivered in other hospitals.

In conclusion, the high prevalence of G6PD deficiency warrants implementation of an urgent universal newborn screening. The benefits of such screening would also extend well beyond the neonatal period.

References

1. Allison AC. Malaria and glucose-6-phosphate dehydrogenase deficiency. Nature. 1963;197:609.
2. Pradeep Kumar, Upendra Yadav, Vandana Rai. Prevalence of glucose-6-phosphate dehydrogenase deficiency in India: An updated meta-analysis. Egypt J Med Hum. 2016;17:295–302.
3. Tiwari M. Glucose 6 phosphatase dehydrogenase (G6PD) and neurodegenerative disorders: Mapping diagnostic and therapeutic opportunities. Genes Dis. 2017;4:196-203.
4. Anderle A, Bancone G, Domingo GJ, Gerth-Guyette E, Pal S, Satyagraha AW. Point-of-Care Testing for G6PD Deficiency: Opportunities for Screening.Int J Neonatal Screen. 2018;4(4):34.
5. Broek L, Heylen E, Akker M. Glucose-6-phosphate dehydrogenase deficiency: not exclusively in males. Clinical case reports. 2016;4:1135-7.
6. Mehta A, Mason P.J, and Vulliamy T.J. Glucose-6-phosphate dehydrogenase deficiency. Baillieres Best Prac. Res. Clin. Haematol. 2000;13:21–38.
7. Bisoi S, Chakraborty S, Chattopadhyay D, Biswas B, Ray S. Glucose-6-phosphate dehydrogenase screening of babies born in a tertiary care hospital in West Bengal. Indian J Public Health. 2012;56:146-8.
8. Verma M, Singla D, Crowell SB. G6PD deficiency in neonates: a prospective study. Indian J Pediatr. 1990;57:385-8.
9. Çelik HT, Günbey C, Ünal Ş, Gümrük F, Yurdakök M. Glucose-6-phosphate dehydrogenase deficiency in neonatal hyperbilirubinaemia: Hacettepeexperıence. J Paediatr Child Health. 2013;49:399-402.
10. Hasan M. Isa, Masooma S. Mohamed, Afaf M. Mohamed, Adel Abdulla, Fuad Abdulla. Neonatal indirect hyperbilirubinemia and glucose-6-phosphate dehydrogenase deficiency. Korean J Pediatr. 2017;60: 106–11.
11. Weng Y-H, Chiu Y-W. Clinical Characteristics of G6PD Deficiency in Infants With Marked Hyperbilirubinemia: J Pediatr Hematol Oncol. 2010;32(1):11–14.
12. 46. Kaplan M, Bromiker R, Hammerman C. Severe Neonatal Hyperbilirubinemia and Kernicterus: Are These Still Problems in the Third Millennium? Neonatology. 2011;100(4):354–362.
13. Muchowski KE. Evaluation and treatment of neonatal hyperbilirubinemia. Am Fam Physician. 2014;89(11):873–878.

Newborn Screening Program in India

Dr Jeeson C Unni
Editor-in-Chief, IAP Drug Formulary
Sr Consultant, Dept of Child And Adolescent Health
Aster Medcity, Kochi

Newborn screening is a public health program that tests spots of blood from all newborns for certain conditions that are not noticeable at the time of birth, but that can cause serious disability or even death if not identified and treated early. Infants with these conditions may seem perfectly healthy and frequently come from families with no previous history of the condition.

Screening occurs within the first 24 to 48 hours after delivery. A "heel stick" provides blood drops that are collected on sterile, absorbent filter paper. Most states also include a hearing test in newborn screening, and many states also measure the amount of oxygen in a baby's blood to identify infants who need to see a heart specialist immediately; neither test requires a bloodspot. To ensure accuracy, some states require a second blood test when an infant is 10 days to 2 weeks old.

The overwhelming recommendation is to universally screen for congenital hypothyroidism (CH) in India, because it is easy and inexpensive to treat, with excellent outcomes. It would also be beneficial to consider screening universally for glucose-6-phosphate dehydrogenase deficiency due to its high incidence and ease of treatment. Finally, sickle cell disease should be screened in those areas in India where it is prevalent due to the costs associated with universal screening.

Evolution of NBS Screening Tests in India

In 2004, Lal Path Labs, New Delhi, started offering screening tests for a comprehensive panel of disorders with the commissioning of a tandem mass spectrometer (MS/MS). This was the first organization in India to offer screening for a wide range of inborn errors of metabolism (IEMs). They were pioneers in offering commercial NBS services, but the market, unfortunately, was not ready for it.

In 2007, the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, started offering screening for disorders by tandem mass spectrometry. The hospitals and physicians who were aware of IEMs started using these services for diagnosis as opposed to screening and, therefore, this did not achieve the benefits associated with pre-symptomatic treatment.

Today, there are numerous NBS laboratories, public and private, in India offering NBS tests. Some of them offer comprehensive NBS panels, resembling the Recommended Universal Screening Panel (RUSP) in the US or a subset of it. Many, but not all, of them participate in the Newborn Screening Quality Assurance Program (NSQAP) offered by the Centers for Disease Control and Prevention (CDC), US.

Three regional screening programs, Chandigarh, Goa, and Kerala could serve as models for other NBS programs in India. The evolution and progress of these programs will be discussed.

Chandigarh's NBS program is concentrated in four urban government hospitals, screening about 15,000 births per year; Goa screens approximately 12,500 births per year in 13 government hospitals, and Kerala screens more than 140,000 births per year in over 90 government hospitals. None of these programs screen births in private hospitals. All the Govt sector programs screen for panels of disorders that doctors in the health sector are well versed with regarding diagnosis and treatment. Disorders screened by MS/MS (fatty acid oxidation disorders, organic acid disorders, and amino acid disorders) are not part of the screening panels due to resource constraints (significant capital costs, few experts, lack of treatment facilities, and high cost of diets). There are also other NBS programs, but these three are unique in their longevity. The success of these 3 programs lies in the fact that, the institutional birth rates for these regions are over 95%, which makes the task of universal screening easier. All these programs offer free screening for births in the government hospitals. It is important to note that none of these public programs were started based on the results of pilot programs and were then translated into public health policy based on the benefits of screening. They were started for other reasons, identified in the program descriptions detailed below.

The Chandigarh Program

In 2007, the union territory (UT) of Chandigarh in India started a program to study the prevalence of three disorders (CH, CAH, and G6PD deficiency) in the territory. This effort is the pioneering public NBS program in India and continues to this day with the addition of other government hospitals in the UT and the testing of additional disorders. The success of the program is based on a team that is passionate about NBS, a small number of births (~15,000 in the public hospitals in 2016), close to 100% institutional births, and a small geographical area that optimizes logistic efficiency. The screening tests are performed in the NBS laboratory operated by the Government of Chandigarh. The laboratory participates in NSQAP.

The Goa Program

The Goa 1.0 NBS Program (2008 to 2013) was initiated based on the desire of the state government to improve neonatal care. Since health policy in India has an emphasis on IMR and incentivizes reducing it, it was believed that NBS could be a factor in improving this statistic in Goa. The NBS program screened every baby born in a public hospital (~48,000), about 50% of the births in Goa in the five-year period. The disorders selected were a comprehensive panel of more than 50 disorders. This program followed a public–private partnership (PPP) model that was financially beneficial to the state government since their investment was minimal. All aspects of the program, other than sample collection, through the delivery of the screening report were handled by the PPP. The program laboratory participated in NSQAP. Follow-up and treatment were the responsibility of the state government. The program was successful in identifying disorders in Goa and raising NBS awareness in India. It also identified issues that needed to be overcome for a successful NBS program run by any state governments in India. Subsequent public programs have referred to the Goa NBS program to justify screening initiatives in their states. The program also pointed out shortcomings in an NBS program, primarily in follow up and treatment resources (both in expertise and in availability and access to diets). One of the disappointments was there were not many success stories to showcase the benefits due to the lack of a treatment infrastructure. In 2013, the program was terminated for political reasons with a change in the government.

Nevertheless, this program is a precursor to a successful universal screening program in India. The Goa 2.0 NBS Program started in Aug 2018, incorporating the learnings from Goa 1.0. All births in government hospitals are screened and, once again, following the PPP model. The panel was reduced to six disorders (CH, CAH, G6PD, galactosemia (GALT), biotinidase deficiency and cystic fibrosis). There are adequate resources to treat these disorders. High-risk deliveries and all neonatal intensive care unit (NICU) admissions are screened for over 50 disorders, including those by MS/MS. The shortcomings of the previous program were addressed, and more emphasis was placed on follow-up activities, access to experts, and availability of diets. Political will ensured the success of the program, and its progress is monitored at the highest levels of government.

The Kerala Program

The Public Health Laboratory in Kerala submitted a proposal to the central government for a pilot NBS program in 2011, which was funded. The program was launched in 2012, screening for four disorders. Since then, the program has grown and aimed to screen all births (~140,000) in government hospitals in 2018. The program screens for CH, CAH, G6PD, and GALT in four laboratories spread across the state. None of the state screening laboratories participate in NSQAP. After the program meets the goal of screening all the births in the government hospitals (25% of all births in Kerala per year), the program plans to extend screening to the private hospitals, which account for the remaining 75% of the births (~400,000). In the upcoming phase of the NBS program, 300,000 births per year in the next two years, are planned to be screened. The program is streamlining the collection and transport of samples. The testing infrastructure is in place and samples are processed in a reasonable timeframe. Even though the expertise is available to treat affected babies, the communication of positive results, follow-up, and treatment are areas that need to improve. It will take time to work out the shortcomings in the program, but Kerala is the best positioned among all the large states in India to implement a universal screening program. Many private hospitals in the state already perform their own NBS program. The samples re sent ato private labs after obtaining consent as the program in these hospitals are done not free of cost.

Kerala State has the distinction of being declared, on Dec 20th 2020, as the first Hearing friendly State in India. All babies born in Govt health services and cooperative hospitals in Kerala get their 1st otoacoustic emission (OAE) free of cost before discharge and facilities for the same have been made available for all private hospitals too. Reporting of follow up procedures in Govt facilities is awaited. Data for Universal Newborn Hearing Screening (UNHS) is available for Ernaklulam District, according to Dr Abraham K Paul, where the 2nd OAE at 6 weeks for babies who fail OAE, the follow up ABR where required is ensured. Some private hospitals outside Ernakulam district are reporting their 1st OAE data but the confirmation of follow up is awaited.

Newborn Screening for Sickle Cell Disease in India

In India, sickle cell anemia (SCA) is prevalent among tribal populations who are considered to be the original inhabitants in south Gujarat, Maharashtra, Madhya Pradesh, Chhattisgarh, and western Odisha with a smaller focus in the southern region in Andhra Pradesh, Karnataka, northern Tamil Nadu and Kerala. It is also prevalent in some of the scheduled castes and other backward classes (non-tribal populations) in central India, mainly among the Mahar, Kunbi and Teli. It is estimated that 15% of the world's neonates with SCA are born in India.

There is no National neonatal screening program for SCD as yet and affected children are generally identified when they become symptomatic. However, few newborn screening programs have been initiated in some regions in the last 5 to 6 years.

Summary of newborn screening programs for SCA initiated in India.

State	District	Target Population	Sample	Technology for Screening	No. Screened	No(%)AS	No(%) SCD	Follow Up	Reference
South Gujarat Phase 1	Valsad	All Tribal babies	Heel prick - Dried blood spot	HPLC-Variant NBS machine	5467	687 (12.5 %)	46 (0.8%)	5–6 years	Italia et al., 2015 [18]
South Gujarat Phase 2	Valsad, Bharuch	All Tribal babies	Heel prick - Drie	HPLC-Variant NBS	2944	649 (22.0 %)	76 (2.6%)	2 years	Unpublished

State	District	Target Population	Sample	Technology for Screening	No. Screened	No(%)AS	No(%) SCD	Follow Up	Reference
			d blood spot	machine					
Maharashtra	Nagpur	Largely non-tribal, babies of AS mothers	Cord blood, heel prick	HPLC-Variant Hb Testing System	2134	978 (45.8%)	113 (5.3%)	4-5 years	Upadhye et al., 2016 [19]
Madhya Pradesh	Jabalpur	Tribal, babies of AS mothers	Cord blood, heel prick	HPLC-Variant Hb Testing System	461	36 (7.8%)	6 (1.3%)	1 year	Unpublished
Chhattisgarh	Raipur	Tribal and non-tribal babies	Heel prick - Dried bloo	HPLC-Variant NBS machine	1158	61 (5.3%)	6 (0.5%)	No follow up reported	Panigrahi et al., 2012 [20]

State	District	Target Population	Sample	Technology for Screening	No. Screened	No(%)AS	No(%) SCD	Follow Up	Reference
			d spot						
Odisha	Kalahandi	Tribal and non-tribal babies	Heel prick - Dried blood spot	HPLC-Variant Hb Testing System	1668	293 (17.6%)	34 (2.0%)	No follow up reported	Mohanty et al., 2010 [21]
Odisha	Kalahandi	Tribal babies	Cord blood	HPLC-Variant Hb Testing System	761	112 (14.7%)	13 (1.7%)	No follow up reported	Dixit et al., 2015 [22]
Tripura	Agartala	Tribal & non tribal babies	Cord blood	HPLC-Variant Hb Testing System	2400	15 (0.6%)	0 (0.0%)	Not done	Upadhye et al., 2018 [23]

State	District	Target Population	Sample	Technology for Screening	No. Screened	No(%)AS	No(%) SCD	Follow Up	Reference
Maharashtra	Chandrapur	Tribal and non-tribal babies	Cord blood, heel prick	HPLC-Variant Hb Testing System	1010	85 (8.4%)	4 (0.4%)	Not done	Unpublished

Most of the above were pilot studies undertaken in different states. These studies showed that it was feasible to undertake newborn screening for SCA even in rural areas in India and register affected babies for follow up and comprehensive care although the outcome of the follow up was not reported in all these studies.

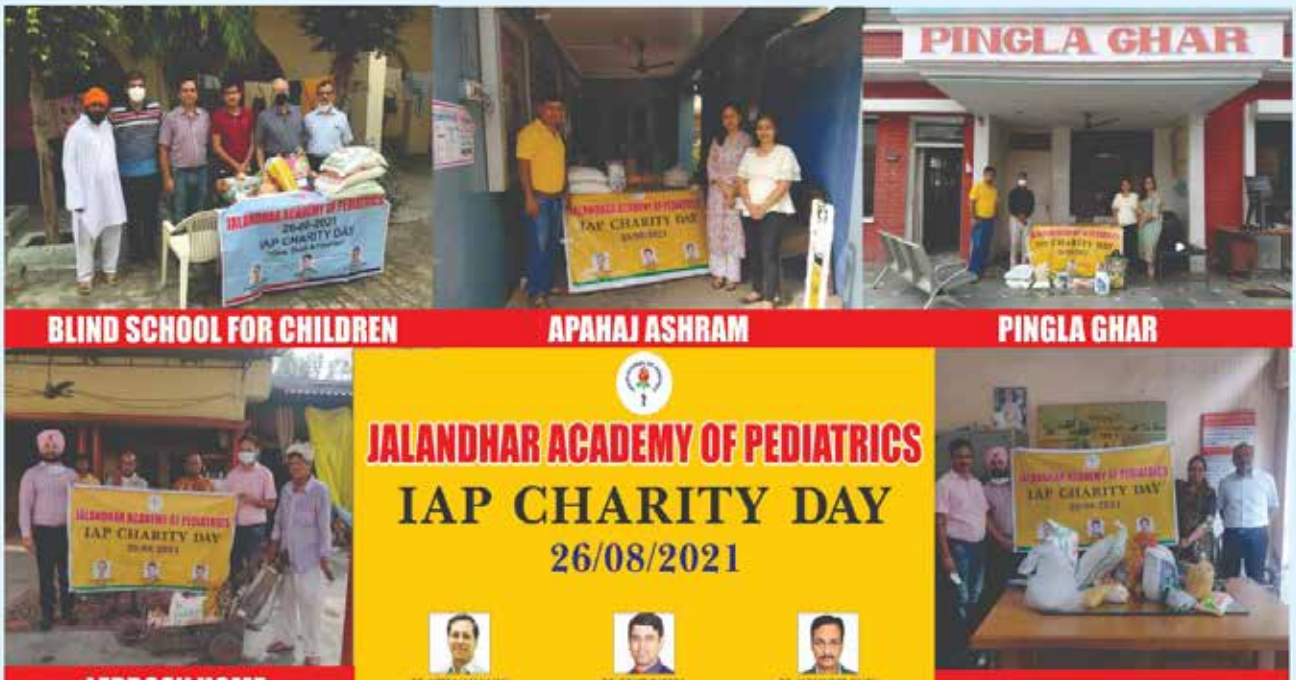
The Indian studies on newborn screening for SCA used HPLC analysis. This was mainly due to two reasons. Automated HPLC machines were already in use at these centers for other programs, hence, no additional cost for infrastructure was required. Secondly, it was felt that these machines would be easier to operate and maintain even in rural areas. The Variant NBS machine (BioRad laboratories, Hercules, CA, USA) has been used for hemoglobin analysis from dried blood spots or the Variant Hemoglobin Testing System (BioRad laboratories) for cord blood samples using either the sickle cell short or the β thal short programs. The β thal short program had the advantage of picking up other hemoglobin abnormalities including some rare non-deletional α chain variants like Hb Fontainebleau, Hb O Indonesia and Hb Koya Dora.

Several point-of-care devices have been developed for screening of SCA, which are either paper-based screening protocols or antibody-based rapid diagnostic devices based on lateral flow immunoassay technologies. These user friendly, relatively inexpensive methods that do not require electricity or specific equipment to run are being validated.

A systematic follow up of SCA babies for around 4 to 5 years had been possible in at least two newborn screening programs in the country in Valsad in south Gujarat and Nagpur in Maharashtra. The findings of these 4-5 year follow ups showed that the clinical presentation of SCA was very variable in different regions. Further efforts and motivation are needed to ensure that the maximum number of babies can be enrolled and continue to receive comprehensive care and follow up for a longer duration.

IAP Jalandhar

JALANDHAR ACADEMY OF PEDIATRICS
CELEBRATING
IAP CHARITY DAY



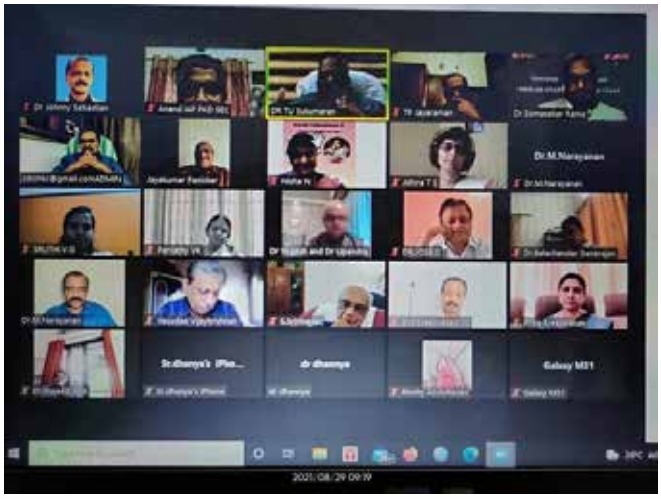
IAP Navi Mumbai

The program was concluded in the presence of RMO Dr. Singh and respected MS Dr. Jawade.

IAP Navi Mumbai

IAP Kerala


IAP KERALA PRESIDENTIAL
ACTION PLAN 2021
PROGRESS
S- SUICIDE PREVENTION IN ADOLESCENTS
Theme :
You want to tell us something,
We have enough time to listen
MID ZONE TOT FOR PEDIATRICIANS
Organised by:
IAP & AHA KERALA & IAP MALANAD
on Tuesday 31st August 2021
8 PM -10 PM




SEASON 4
Hosted by
IAP KOZHIKODE
Moderator
Dr Krishna Mohan R
Scientific Session
Approach to LRTI with wheeze
Speaker:
Dr Subramanya NK
Prof of Pediatrics & Chairperson
IAP National Respiratory Chapter
333 678 2020
IAPCALICUT


PROTECT
BREAST
FEED
ING

IAP Kerala


FILLING THE GAPS IN IMMUNISATION
PRESIDENTIAL ACTION PLAN
Bridging the Gap in Immunisations
Meeting ID: 646 950 4528
Passcode: IAPKERALA
8.00pm Monday, 16.8.21
Welcome Dr. Manoj Mony
President, IAP Kollam
Presidential Address Dr.T PJayaraman
President, IAP Kerala
Felicitations Dr M. Narayanan
IPP, IAP Kerala
Dr Johnny Sebastian
Secretary, IAP Kerala
Dr Gopimohan
Treasurer, IAP Kerala
Vote of Thanks Dr Bidhu P
Secretary, IAP Kollam
Moderator :Dr.M.Narayanan
The Universal Immunization Program comes of age : Introduction of Pneumococcal Vaccine in UIP
Dr. C Prathapachandran.
MD (Ped) , DNB (Ped) Surveillance Medical Officer , World Health Organization , Trivandrum.
Vigilance on VPDs : Fever Rash reporting comes to Kerala
Dr Santhosh Rajagopal
MBBS,DCH ,DCH -UK, Surveillance Medical Officer World Health Organization, Kozhikode.
Sponsored by
IAP Kerala
IAP Kollam


Mission Pink Health

IAP Kerala