INDIAN JOURNAL OF PRACTICAL PEDIATRICS

- **IJPP is a quarterly subscription journal of the Indian Academy of Pediatrics committed to presenting practical pediatric issues and management updates in a simple and clear manner**
- **Indexed in Excerpta Medica, CABI Publishing, Scopus**

Vol.23 No.2 **APR.- JUN. 2021**

Dr.S.Thangavelu
Editor-in-Chief

Dr.T.L.Ratnakumari
Executive Editor

CONTENTS

TOPIC OF INTEREST - "IMMUNOLOGY"

GENERAL ARTICLE

Journal Office and address for communications: Dr. S.Thangavelu, Editor-in-Chief, Indian Journal of Practical Pediatrics, 1A, Block II, Krsna Apartments, 50, Thamizh Salai (Halls Road), Egmore, Chennai - 600 008. Tamil Nadu, India. Tel.No. : 044-28190032 E.mail : ijpp_iap@rediffmail.com

FOR YOUR KIND ATTENTION

* The views expressed by the authors do not necessarily reflect those of the sponsor or publisher. Although every care has been taken to ensure technical accuracy, no responsibility is accepted for errors or omissions.
* The claims of the manufacturers and efficacy of the products advertised in the journal are the responsibility of the advertiser. The journal does not own any responsibility for the guarantee of the products advertised.
* Part or whole of the material published in this issue may be reproduced with the note "Acknowledgement" to "Indian Journal of Practical Pediatrics" without prior permission.
* The write up should be in accordance with the recommendations of Central IAP particularly with issues involving National Programmes like Immunization, Public Health Programs and Nutrition.
* NOTE: Many trade names of the vaccines are included in the text for the sake of clarity.

EDITORIAL BOARD

Published by Dr. S.Thangavelu, Editor-in-Chief, IJPP, on behalf of Indian Academy of Pediatrics, from 1A, Block II, Krsna Apartments, 50, Thamizh Salai (Halls Road), Egmore, Chennai - 600 008. Tamil Nadu, India and Printed by Mr. D.Ramanathan, at Alamu Printing Works, 9, Iyyah Street, Royapettah, Chennai - 600 014.

IMMUNOLOGY

APPLIED IMMUNOLOGY AND CLINICAL CLUES FOR INBORN ERRORS OF IMMUNITY

*Geeta M. Govindaraj
**Kalpana George

Abstract: *Primary immune deficiency disorders or inborn errors of immunity are one of the commonest genetic disorders caused by variants in more than 400 genes. This is manifested by susceptibility to severe, persistent, unusual or recurrent infections encompassing a broad or narrow range of pathogens. Autoimmune, allergic and autoinflammatory manifestations and susceptibility to early onset malignancies may be the other manifestations. These disorders are often undiagnosed or misdiagnosed and enhancing awareness among pediatricians is key to improving outcomes, since a high index of suspicion is crucial.*

Keywords: *Primary immune deficiency, Inborn errors of immunity, Autoinflammation.*

* Professor,
Department of Pediatrics

** Associate Professor,
Department of Microbiology,
Government Medical College, Kozhikode, Kerala,
FPID Regional Diagnostic Centre, Kozhikode

email: geetakkumar@gmail.com

Points to Remember

- ***A high index of suspicion is essential to diagnose primary immune deficiency disorders (PIDDs).***
- ***Infections of unusual severity, frequency, etiology and suboptimal response to treatment are the hallmark of these disorders.***
- ***Apart from susceptibility to infections, autoimmune, allergic and autoinflammatory features occur as well as early onset malignancies.***
- ***Important clues from the history include age at onset, types of infections, adverse events following immunization and the family history.***
- ***Examination often reveals valuable clues including syndromic features, paucity or proliferation of lymphoid tissue, other systemic manifestations and failure to thrive.***

References

1. 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.
2. Bousfiha AA, Jeddane L, Ailal F, Benhsaien I, Mahlaoui N, Casanova JL, et al. Primary immunodeficiency diseases worldwide: more common than generally thought. J Clin Immunol 2013; 33(1):1-7.
3. Marshall JS, Warrington R, Watson W, Kim HL. An introduction to immunology and immunopathology. Allergy Asthma Clin Immunol 2018; 14(Suppl2):49.
4. Tasher D, Dalal I. The genetic basis of severe combined immunodeficiency and its variants. Appl Clin Genet 2012; 5:67-80.
5. Kumrah R, Vignesh P, Patra P, Singh A, Anjani G, Saini P, et al. Genetics of severe combined immunodeficiency. Genes Dis 2020; 7(1):52-61.
6. Amado MC. Primary Immunodeficiency Update and Newborn Screening. Mo Med2011; 108(5):350-353.
7. Suri D, Rawat A, Singh S. X-linked Agammaglobulinemia. Indian J Pediatr 2016; 83(4):331-337.
8. Blundell MP, Worth A, Bouma G, Thrasher AJ. The Wiskott-Aldrich Syndrome: The Actin Cytoskeleton

and Immune Cell Function. Dis Markers 2010; 29 (3-4):157-175.

9. Das J, Sharma A, Jindal A, Aggarwal V, Rawat A. Leukocyte adhesion defect: Where do we stand circa 2019? Genes Dis 2020; 7(1):107-114.
10. Arnold DE, Heimall JR. A Review of Chronic Granulomatous Disease. Adv Ther 2017; 34(12):2543-2557.
11. Bustamante J, Boisson-Dupuis S, Abel L, Casanova JL. Mendelian susceptibility to mycobacterial disease: genetic, immunological, and clinical features of inborn errors of IFN-γ immunity. Semin Immunol 2014; 26(6):454-470.
12. Gathmann B, Mahlaoui N, Gérard L, Oksenhendler E, Warnatz K, Schulze I, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J Allergy Clin Immunol 2014; 134(1):116-126.
13. Griffith LM, Cowan MJ, Notarangelo LD, Puck JM, Buckley RH, Candotti F, et al. Improving cellular therapy for primary immune deficiency diseases: recognition, diagnosis, and management. J Allergy Clin Immunol 2009; 124(6):1152-1160.e12.
14. Barron MA, Makhija M, Hagen LE, Pencharz P, Grunebaum E, Roifman CM. Increased resting energy expenditure is associated with failure to thrive in infants with severe combined immunodeficiency. J Pediatr 2011; 159(4):628-632.e1.
15. Hambleton S, Goodbourn S, Young DF, Dickinson P, Mohamad SMB, Valappil M, et al. $STAT_2$ deficiency and susceptibility to viral illness in humans. Proc Natl Acad Sci U S A. 2013; 110(8):3053-3058.
16. Govindaraj GM, Riyaz A, Krishnan C, Scaria. V. Rapid Transition of Facial Features from Early to Mid - Adolescence in Autosomal Dominant Hyper IgE Syndrome with a $STAT_3$ Variation. Indian J Pediatr 2018; 85(7): 595-596.
17. Natkunam Y, Gratzinger D, Chadburn A, Goodlad JR, Chan JKC, Said J, et al. Immunodeficiency-associated lymphoproliferative disorders: time for reappraisal? Blood 2018; 132(18):1871-1878.
18. Carneiro-Sampaio M, Coutinho A. Early-onset autoimmune disease as a manifestation of primary immunodeficiency. Front Immunol 2015; 6:185.
19. DeSanctis S, Nozzi M, Del Torto MD, Scardapane A, Gaspari S, de Michele G, et al. Autoinflammatory syndromes: diagnosis and management. Ital J Pediatr 2010; 36:57.
20. Mayor PC, Eng KH, Singel KL, Abrams SI, Odunsi K, Moysich KB, et al. Cancer in primary immunodeficiency diseases: Cancer incidence in the United States Immune Deficiency Network Registry. J Allergy Clin Immunol 2018; 141(3):1028-1035.

IMMUNOLOGY

LABORATORY CLUES TO PRIMARY IMMUNODEFICIENCY DISORDERS

*Sagar Bhattad
**Rachna Shanbhag Mohite

Abstract: *Primary immunodeficiency disorders are a large group of heterogeneous diseases, which result from defects in the immune system. These defects can either be in the innate or adaptive immunity. As per the latest classification published by the International Union of Immunological Societies expert committee on Inborn Errors of Immunity, around 430 primary immunodeficiency disorders have been recognized and the list is expanding. One in 1000 individuals suffer from a primary immunodeficiency disorder and these diseases are by no means, rare. Yet many patients remain undiagnosed, due to lack of awareness of these conditions. This article highlights the importance of routine tests like complete blood counts and serum immunoglobulin assay in diagnosing patients with these disorders. Along with case-based discussion, simple algorithms have been provided, that can guide a clinician in making a timely diagnosis.*

Keywords: *Primary immune deficiency diseases, Inborn errors of immunity, Laboratory tests.*

* Consultant

** Fellow,
Division of Pediatric Immunology and Rheumatology,
Department of Pediatrics,
Aster CMI Hospital, Bangalore.

email: drsagarbhattad@gmail.com

Points to Remember

- ***PIDs are currently referred to as IEIs.***
- ***One in 1000 individuals suffer from a PID, hence, these diseases are not rare.***
- ***The first step in the diagnosis of PIDs is history and clinical examination and to suspect them in clinical practice.***
- ***Careful analysis of routinely available tests like hemogram provide valuable clues to the underlying PID.***
- ***Neutropenia can be manifestation of a PID and noted in severe congenital neutropenia, cyclic neutropenia, hyper IgM syndrome and many other PIDs.***
- ***Marked neutrophilia must make one think of leukocyte adhesion deficiency.***
- ***Persistent thrombocytopenia in a male child warrants evaluation for possible Wiskott Aldrich Syndrome.***
- ***Serum immunoglobulin assay is a valuable tool in evaluation of patients with suspected PID, which has to be used more often in clinical practice.***
- ***NBT and DHR are simple screening tests for chronic granulomatous disease.***
- ***Once suspected, one must not delay initiation of therapy for want of genetic testing in these patients.***

References

1. McCusker C, Upton J, Warrington R. Primary immunodeficiency. Allergy, Asthma Clin Immunol 2018; 14(2):1-2.
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; 11:1-6.
3. Bousfiha AA, Jeddane L, Ailal F, Al Herz W, Conley ME, Cunningham-Rundles C, et al. A phenotypic approach for IUIS PID classification and diagnosis: guidelines for clinicians at the bedside. J Clin Immunol 2013; 33(6): 1078-1087.

4. Modell V, Gee B, Lewis DB, Orange JS, Roifman CM, Routes JM, et al. Global study of primary immunodeficiency diseases (PI)-diagnosis, treatment, and economic impact: an updated report from the Jeffrey Modell Foundation. Immunol Res 2011; 51(1):61-70.
5. Parvez Y, Mathew AG. Hyperleukocytosis in newborn: a diagnosis of concern. Indian J Hematol Blood Transfus 2014; 30(1):131-132.
6. Michniacki TF, Walkovich KJ. Leukocytosis. In: Nelson Textbook of Pediatrics. Kliegman RM, St Geme JW, Blum NJ, Shah SS, Tisker RC, Wilson KM, Eds, 21st Edn, Vol.1. Philadelphia: Elsevier; 2020; pp1147-1149.
7. Kwan A, Church JA, Cowan MJ, Agarwal R, Kapoor N, Kohn DB, et al. Newborn screening for severe combined immunodeficiency and T-cell lymphopenia in California: results of the first 2 years. J Allergy Clin Immunol 2013; 132(1):140-150.
8. Celkan T, Koç B. Approach to the patient with neutropenia in childhood. Turk Pediatri Ars 2015; 50(3):136-144.
9. Welte K, Zeidler C, Dale DC. Severe congenital neutropenia. Semin Hematol 2006; 43(3):189-195.
10. Skokowa J, Germeshausen M, Zeidler C, Welte K. Severe congenital neutropenia: inheritance and pathophysiology. Curr Opin Hematol 2007; 14(1):21-28.
11. Berliner N, Horwitz M, Loughran TP Jr. Congenital and acquired neutropenia. Hematology Am Soc Hematol Educ Program 2004:63-79.
12. Dale DC, Hammond WP . Cyclic neutropenia: a clinical review. Blood Rev 1988; 2(3):178-185.
13. Rezaei N, Farhoudi A, Ramyar A, Pourpak Z, Aghamohammadi A, Moham- madpour B, et al. Congenital neutropenia and primary immunodeficiency disorders: A survey of 26 Iranian patients. J Pediatr Hematol Oncol 2005; 27:351-356.
14. Schmutz N, Henry E, Jopling J, Christensen RD. Expected ranges for blood neutrophil concentrations of neonates: the Manroe and Mouzinho charts revisited. J Perinatol 2008; 28:275-281.
15. Calhoun DA, Kirk JF, Christensen RD. Incidence, significance and kinetic mechanism responsible for leukemoid reactions in patients in the neonatal intensive care unit: a prospective evaluation. J Pediatr 1996; 129:403-409.
16. Nittala S, Subbarao GC, Maheshwari A. Evaluation of neutropenia and neutrophilia in preterm infants. J Matern Fetal Neonatal Med 2012; 25(Suppl 5):100-103.
17. Bosticardo M, Marangoni F, Aiuti A, Villa A, Grazia Roncarolo M. Recent advances in understanding the pathophysiology of Wiskott-Aldrich syndrome. Blood 2009; 113(25):6288-6295.
18. Zinkernagel RM. Maternal antibodies, childhood infections, and autoimmune diseases. N Engl J Med 2001; 345(18):1331-1335.
19. Battersby AC, Cale AM, Goldblatt D, Gennery AR. Clinical manifestations of disease in X-linked carriers of chronic granulomatous disease. J Clin Immunol 2013; 33(8):1276-1284.
20. Jirapongsananuruk O, Malech HL, Kuhns DB, Niemela JE, Brown MR, Anderson-Cohen M, et al. Diagnostic paradigm for evaluation of male patients with chronic granulomatous disease, based on the dihydrorhodamine 123 assay. J Allergy Clin Immunol 2003; 111(2):374-379.

IMMUNOLOGY

INNATE IMMUNE DEFECTS

*Akshaya Chougule
*Vaishnavi V. Iyengar
**Vijaya Gowri
***Prasad Taur
****Mukesh M. Desai

Abstract: *The innate immune system is a phylogenetically ancient, germline-encoded system that enables eukaryotes to defend themselves against infections. It is "inborn" and does not require a developmental phase and forms the first line of defense against foreign material. It has an immediate or near immediate effect. Innate immune defects can be broadly classified as predisposition to invasive bacterial infections, predisposition to parasitic and fungal infections, Mendelian susceptibility to mycobacterial disease and predominant susceptibility to viral infections. Each defect has a narrow spectrum of infections and knowledge of the specific causative organism in each case helps in early diagnosis and therapeutic decision making.*

Keywords: *Inborn errors of immunity, Innate immunity, Toll-like receptor pathway, Mendelian susceptibility to mycobacterial disease.*

* Clinical Fellow,
** Consultant,
*** Scientific Officer,
**** Head of Department Immunology,
Department of Pediatric Immunology,
Bai Jerbai Wadia Hospital for Children,
Parel, Mumbai,
Maharashtra, India.
email: mmdesai006@gmail.com

Points to Remember

- ***Innate immune defects can be broadly classified as predisposition to invasive bacterial infections, predisposition to parasitic and fungal infections, Mendelian susceptibility to mycobacterial disease and predominant susceptibility to viral infections.***
- ***Interleukin 1 Receptor Associated Kinase 4 (IRAK4), Myeloid differentiation factor 88 (MyD88) and toll-interleukin 1 receptor (TIR) domain containing adaptor protein (TIRAP) deficiencies are associated with invasive bacterial infections.***
- ***Chronic mucocutaneous candidiasis is caused by defects in the IL-17 pathway, whereas defects in phagocytic defects and CARD9 deficiency cause invasive fungal infections.***
- ***Inborn errors in IFN-γ cause MSMD.***
- ***Errors in TLR3 signaling pathway and Type-1 Interferons lead to predisposition to viral infections and Type-1 Interferon pathway defects are also associated with severe COVID-19.***

References

1. Turvey SE, Broide DH. Innate immunity. J Allergy Clin Immunol 2010; 125(2):S24-32.
2. Hoffmann J, Akira S, Hoffmann J. Innate immunity editorial overview. Curr Opin Immunol 2013; 25(1):1-3.
3. Takeda K, Akira S. Toll-like receptors in innate immunity. Int Immunolog 2005; 17(1):1-14.
4. Sifers TM, Sampath V. Monogenic Defects of Toll-Like Receptor Signaling and Primary Immunodeficiency. In:Immunity and Inflammation in Health and Disease. Eds: Chatterjee S, Jungraithmayr W, Bagchi D. Academic Press Massachusetts 2018; 165-174.
5. 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; 11:1-16.
6. Boisson B. The genetic basis of pneumococcal and staphylococcal infections: inborn errors of human TLR and IL-1R immunity. Human Genetics 2020; 139(6):981-991.
7. Wong T, Yeung J, Hildebrand KJ, Junker AK, Turvey SE. Human primary immunodeficiencies causing defects in

innate immunity. Curr Opin Allergy Clin Immunol 2013; 13(6):607-613.

8. Puel A, Cypowyj S, Maródi L, Abel L, Picard C, Casanova J-L. Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis. Curr Opin Allergy Clin Immunol 2012; 12(6):616-630.
9. Glocker E-O, Hennigs A, Nabavi M, Schäffer AA, Woellner C, Salzer U, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. N Eng J Med 2009; 361(18):1727-1735.
10. Zheng J, van de Veerdonk FL, Crossland KL, Smeekens SP, Chan CM, Al Shehri T, et al. Gainoffunction STAT1 mutations impair STAT3 activity in patients with chronic mucocutaneous candidiasis (CMC). Eur J Immunol 2015; 45(10):2834-2846.
11. Joshi PP, Shegokar VR, Powar RM, Herder SR, Salkar HR, et al. Human trypanosomiasis caused by Trypanosoma evansi in India: the first case report. Am J Trop Med Hyg 2005; 73(3):491-495.
12. Bustamante J, Boisson-Dupuis S, Abel L, Casanova JL. Mendelian susceptibility to mycobacterial disease: genetic, immunological, and clinical features of inborn errors of IFN-γ immunity. Semin Immunol 2014; 26(6):454-470.
13. Taur PD, Gowri V, Pandrowala AA, Iyengar VV, Chougule A, Golwala Z, et al. Clinical and Molecular Findings in Mendelian Susceptibility to Mycobacterial Diseases: Experience From India. Front Immunol 2021; 12:426-438.
14. Casanova J-L, Abel L. Genetic dissection of immunity to mycobacteria: the human model. Annu Rev Immunol 2002; 20(1):581-620.
15. Bustamante J. Mendelian susceptibility to mycobacterial disease: recent discoveries. Human Genetics 2020; 139(6):993-1000.
16. Sancho-Shimizu V, de Diego RP, Jouanguy E, Zhang S-Y, Casanova J-L. Inborn errors of anti-viral interferon immunity in humans. Curr Opin Virol 2011; 1(6):487-496.
17. Ciancanelli MJ, Huang SXL, Luthra P, Garner H, Itan Y, Volpi S, et al. Life-threatening influenza and impaired interferon amplification in human IRF7 deficiency. Science 2015; 348(6233):448-453.
18. Duncan CJA, Mohamad SMB, Young DF, Skelton AJ, Leahy TR, Munday DC, et al. Human IFNAR2 deficiency: Lessons for antiviral immunity. Sci Transl Med 2015; 7(307):307ra154-162.
19. Zhang Q, Bastard P, Liu Z, Le Pen J, Moncada-Velez M, Chen J, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science 2020; 370(6515):eabd4570.
20. Hernandez PA, Gorlin RJ, Lukens JN, Taniuchi S, Bohinjec J, Francois F, et al. Mutations in the chemokine receptor gene CXCR4 are associated with WHIM syndrome, a combined immunodeficiency disease. Nat Genet 2003; 34(1):70-74.
21. 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.

IMMUNOLOGY

PRIMARY ANTIBODY DEFICIENCIES

*Sathishkumar Loganathan
*Murugan Sudhakar
**Pandiarajan Vignesh
*** Surjit Singh

Abstract: *Primary antibody deficiencies are a group of primary immunodeficiency disorders characterized by a marked reduction or absence of serum immunoglobulins due to intrinsic genetic defects in B-cells or impaired interaction between B-cells and T- cells. Clinical symptoms first manifest usually around 6-12 months of life when maternally acquired antibody levels are waning. The sine qua non of antibody deficiency syndromes is recurrent sino-pulmonary infections, especially with encapsulated organisms.Replacement with intravenous immunoglobulin is the mainstay of treatment in primary antibody deficiencies.*

Keywords: *Agammaglobulinemia, Primary immunodeficiency, Recurrent infections, Hypogammaglobulinemia.*

* Senior Resident

** Assistant Professor

*** Head - Department of Pediatrics, Professor In-Charge, Allergy Immunology Unit, Department of Pediatrics, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India.

email: vigimmc@gmail.com

Points to Remember

- ***Primary B-cell disorders/ primary antibody deficiency disorders (PADs) are the most common primary immunodeficiency disorders (PID) accounting for approximately 50% of all PID cases.***
- ***Recurrent infections with typical microorganisms and predilection for specific organ systems (sino-pulmonary system, gastrointestinal tract and bloodstream infections) are important clinical pointers to suspect PADs.***
- ***Absent tonsils and non-palpable lymph nodes are simple bedside clues to clinch the diagnosis of X-linked Agammaglobulinemia.***
- ***Compliance with regular intravenous immunoglobulin (IVIg) replacement and prophylactic antimicrobial agents remains the standard of care, with proven benefits in both morbidity and mortality.***
- ***Autoimmunity in the setting of underlying PADs (especially common variable immunodeficiency) has a heterogeneous spectrum of clinical manifestations and needs a high index of clinical suspicion to recognise.***
- ***Appropriate disease specific vaccination plan, genetic counselling and attempts for antenatal diagnosis for monogenic defects are crucial.***

References

1. Abolhassani H, Azizi G, Sharifi L, Yazdani R, Mohsenzadegan M, Delavari S, et al. Global systematic review of primary immunodeficiency registries. Expert Rev Clin Immunol 2020;16(7):717-732. doi: 10.1080/1744666X.2020.1801422. PMID: 32720819.
2. Plebani A, Soresina A, Rondelli R, Amato GM, Azzari C, Cardinale F, et al. Clinical, immunological, and molecular analysis in a large cohort of patients with X-linked agammaglobulinemia: an Italian multicenter study. Clin Immunol 2002; 104(3):221-230. doi: 10.1006/clim.2002.5241. PMID: 12217331.
3. Conley ME, Rohrer J, Minegishi Y. X-linked agammaglobulinemia. Clin Rev Allergy Immunol 2000;19(2):183-204. doi: 10.1385/CRIAI:19:2:183. PMID: 11107501.

4. Conley ME, Howard V. Clinical findings leading to the diagnosis of X-linked agammaglobulinemia. J Pediatr 2002;141(4):566-571. doi: 10.1067/mpd.2002.127711. PMID: 12378199.
5. Lederman HM, Winkelstein JA. X-linked agammaglobulinemia: an analysis of 96 patients. Medicine (Baltimore) 1985; 64(3):145-156. PMID: 2581110.
6. Ochs HD, Smith CI. X-linked agammaglobulinemia. A clinical and molecular analysis. Medicine (Baltimore) 1996; 75(6):287-299. doi: 10.1097/00005792-199611000-00001. PMID: 8982147.
7. Bonagura VR, Marchlewski R, Cox A, Rosenthal DW. Biologic IgG level in primary immunodeficiency disease: the IgG level that protects against recurrent infection. J Allergy Clin Immunol 2008;122(1):210-212. doi: 10.1016/j.jaci.2008.04.044. PMID: 18602574.
8. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol 1999; 93(3):190-197. doi: 10.1006/clim.1999.4799. PMID: 10600329.
9. Al-Herz W, Bousfiha A, Casanova JL, Chapel H, Conley ME, Cunningham-Rundles C, et al. Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. Front Immunol 2011; 2:54. doi: 10.3389/fimmu.2011.00054. PMID: 22566844; PMCID: PMC3342372.
10. Aghamohammadi A, Allahverdi A, Abolhassani H, Moazzami K, Alizadeh H, Gharagozlou M, et al. Comparison of pulmonary diseases in common variable immunodeficiency and X-linked agammaglobulinaemia. Respirology 2010; 15(2):289-295. doi: 10.1111/j.1440-1843.2009.01679.x.Epub 2009 Dec 27. PMID: 20051045.
11. Aghamohammadi A, Abolhassani H, Moazzami K, Parvaneh N, Rezaei N. Correlation between common variable immunodeficiency clinical phenotypes and parental consanguinity in children and adults. J Investig Allergol Clin Immunol 2010; 20(5):372-379. PMID: 20945602.
12. Ogershok PR, Hogan MB, Welch JE, Corder WT, Wilson NW. Spectrum of illness in pediatric common variable immunodeficiency. Ann Allergy Asthma Immunol 2006; 97(5):653-656. doi: 10.1016/S1081-1206(10)61096-4. PMID: 17165275.
13. Douglas SD, Goldberg LS, Fudenberg HH. Clinical, serologic and leukocyte function studies on patients with idiopathic "acquired" agammaglobulinemia and their families. Am J Med 1970; 48(1):48-53. doi: 10.1016/0002-9343(70)90097-5. PMID: 5308993.
14. Bonilla FA, Barlan I, Chapel H, Costa-Carvalho BT, Cunningham-Rundles C, de la Morena MT, et al. International Consensus Document (ICON): Common Variable Immunodeficiency Disorders. J Allergy Clin Immunol Pract 2016; 4(1):38-59. doi: 10.1016/j.jaip.2015.07.025. Epub 2015 Nov 7. PMID: 26563668; PMCID: PMC4869529.
15. Seidel MG, Kindle G, Gathmann B, Quinti I, Buckland M, van Montfrans J, et al. The European Society for Immunodeficiencies (ESID) Registry Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity. J Allergy Clin Immunol Pract 2019; 7(6):1763-1770. doi: 10.1016/j.jaip.2019.02.004. Epub 2019 Feb 15. PMID: 30776527.
16. Albin S, Cunningham-Rundles C. An update on the use of immunoglobulin for the treatment of immunodeficiency disorders. Immunotherapy 2014; 6(10):1113-1126. doi: 10.2217/imt.14.67. PMID: 25428649; PMCID: PMC4324501.
17. Seidel MG, Kindle G, Gathmann B, Quinti I, Buckland M, van Montfrans J, et al.The European Society for Immunodeficiencies (ESID) Registry Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity. J Allergy Clin Immunol Pract 2019; 7(6):1763-1770. doi: 10.1016/j.jaip.2019.02.004. Epub 2019 Feb 15. PMID: 30776527.
18. Picard C, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Conley ME, et al. Primary Immunodeficiency Diseases: an Update on the Classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency 2015. J Clin Immunol 2015; 35(8):696-726. doi: 10.1007/s10875-015-0201-1. Epub 2015 Oct 19. PMID: 26482257; PMCID: PMC4659841
19. Doğu F, Ikincioğullari A, Babacan E. Transient hypogammaglobulinemia of infancy and early childhood: outcome of 30 cases. Turk J Pediatr 2004; 46(2):120-124
20. Morell A. Clinical relevance of IgG subclass deficiencies. Ann Biol Clin (Paris) 1994; 52(1):49-52. PMID: 8210074.

IMMUNOLOGY

NEUTROPHIL DISORDERS

***Nancy Hilda J**
****Aishwarya Venkataraman**

Abstract: *Neutrophils play an important role in recognition and killing of infectious pathogens. Disorder of neutrophil production, emigration, chemotaxis and function can cause a spectrum of immune defects, which are characterized by recurrent and serious invasive infections. This article is an overview of the common neutrophil disorders.*

Keywords: *Neutrophils, Phagocytes, Neutropenia, Hyper IgE, CGD, Chediak Higashi syndrome.*

* Scientist B

** Scientist E,
ICMR-National Institute for Research in Tuberculosis, Chetpet, Chennai.

email: aishwarya.v@nirt.res.in

Points to Remember

- ***Neutrophil disorders are a rare, but important reason of morbidity and mortality in infants and children.***
- ***Neutrophil disorders should be considered when a child presents with serious or recurrent infections and in those who are being investigated for immunodeficiency.***
- ***Appropriate and prompt investigations can lead to definite diagnoses, and specific management measures can reduce both mortality and morbidity.***

References

1. Summers C, Rankin SM, Condliffe AM, Singh N, Peters AM, Chilvers ER. Neutrophil kinetics in health and disease. Trends Immunol 2010; 31:318-324.
2. Rosales C. Neutrophil: A Cell with Many Roles in Inflammation or Several Cell Types? Front Physiol 2018; 9:113. doi.org/10.3389/fphys.2018.00113
3. Mayadas TN, Cullere X, Lowell CA. The multifaceted functions of neutrophils. Annu Rev Pathol 2014; 9: 181-218.
4. Giaglis S, Hahn S, Hasler P. "The NET Outcome": Are Neutrophil Extracellular Traps of Any Relevance to the Pathophysiology of Autoimmune Disorders in Childhood? Front Pediatr 2016; 4:97.
5. Kobayashi SD, Malachowa N, DeLeo FR. Neutrophils and Bacterial Immune Evasion. J Innate Immun 2018; 10: 432-441.
6. Dinauer MC. Disorders of neutrophil function: an overview. Methods Mol Biol 2007; 412:489-504.
7. Lakshman R, Finn A. Neutrophil disorders and their management. J Clin Pathol 2001; 54:7-19.
8. Bernini JC. Diagnosis and management of chronic neutropenia during childhood. Pediatr Clin North Am 1996; 43:773-792.
9. Rebuck N, Finn A. Polymorphonuclear granulocyte expression of CD11a/CD18, CD11b/CD18 and L-selectin in normal individuals. FEMS Immunol Med Microbiol 1994; 8:189-195.
10. Roos D. Chronic granulomatous disease. Br Med Bull 2016; 118:50-63.

11. Mills EL, Quie PG. Congenital disorders of the function of polymorphonuclear neutrophils. Rev Infect Dis 1980; 2:505-517.
12. Weening RS, Adriaansz LH, Weemaes CM, Lutter R, Roos D. Clinical differences in chronic granulomatous disease in patients with cytochrome b-negative or cytochrome b-positive neutrophils. J Pediatr 1985; 107: 102-104.
13. Forrest CB, Forehand JR, Axtell RA, Roberts RL, Johnston Jr RB. Clinical features and current management of chronic granulomatous disease. Hematol Oncol Clin North Am 1988; 2:253-266.
14. Borges WG, Augustine NH, Hill HR. Defective interleukin-12/interferon-gamma pathway in patients with hyperimmunoglobulinemia E syndrome. J Pediatr 2000; 136:176-180.
15. Grimbacher B, Holland SM, Gallin JI, Greenberg F, Hill SC, Malech HL, et al. Hyper-IgE syndrome with recurrent infections-an autosomal dominant multisystem disorder. N Engl J Med 1999; 340:692-702.
16. Kyono W, Coates TD. A practical approach to neutrophil disorders. Pediatr Clin North Am 2002; 49:929-971, viii.
17. Barrat FJ, Auloge L, Pastural E, Lagelouse RD, Vilmer E, Cant AJ, et al. Genetic and physical mapping of the Chediak-Higashi syndrome on chromosome 1q42-43. Am J Hum Genet 1996; 59:625-632.
18. Kaplan J, De Domenico I, Ward DM. Chediak-Higashi syndrome. Curr Opin Hematol 2008; 15:22-29.
19. Haddad E, Le Deist F, Blanche S, Benkerrou M, Rohrlich P, Vilmer E, et al. Treatment of Chediak-Higashi syndrome by allogenic bone marrow transplantation: report of 10 cases. Blood 1995; 85:3328-3333.

IMMUNOLOGY

COMPLEMENT DEFICIENCY IN SYSTEMIC AUTOIMMUNE DISEASES

*Madhubala Sharma
**Sumit Goel
***Aaqib Zaffar Banday
****Amit Rawat

Abstract: *Complement is an important part of the innate immune pathway. It involves over 20 serum proteins, most being synthesized in liver. These proteins are initially inactive precursors which get activated later by different stimuli. All the three pathways of complement activation i.e., classical, alternative and lectin converge to produce membrane attack complex or terminal complex which leads to lysis of the target pathogen. Activity of complement is controlled by regulatory proteins that prevent host cell damage and lysis caused by inadvertent binding of activated complements. Complement deficiency results in autoimmune diseases. Early complement deficiency results in monogenic lupus and infections due to encapsulated bacteria whereas late complement component deficiency causes neisserial infections. Complements can be assessed by various tools like enzyme-linked immunoassays, flow cytometry, and next-generation sequencing.*

Keywords: *Early-onset systemic lupus erythematosus, Complement, Classical pathway, Autoimmune diseases, Atypical hemolytic uremic syndrome, Alternative pathway.*

* Ph.D., Scholar
** Senior Research Fellow
*** Senior Resident
**** Professor,
Allergy Immunology Unit, Department of Pediatrics,
Advanced Pediatrics Centre,
Postgraduate Institute of Medical Education
and Research, Chandigarh.
email: rawatamit@yahoo.com

Points to Remember

- ***Complement plays a key role in pathogenesis of autoimmune and inflammatory diseases.***
- ***Monogenic lupus can be due to defects in components of classical pathway.***
- ***Complement deficiency results in a predisposition to infections primarily from encapsulated bacteria.***
- ***Defective regulation of complement system can result in atypical hemolytic uremic syndrome or paroxysmal nocturnal hemoglobinuria.***
- ***Excessive alternative pathway activation can cause lupus nephritis or antiphospholipid antibody syndrome.***

References

1. Kaufmann SH. Immunology's foundation: the 100-year anniversary of the Nobel Prize to Paul Ehrlich and Elie Metchnikoff. Nat Immunol 2008; 9:705-712.
2. Varela JC, Tomlinson S. Complement: an overview for the clinician. Hematol Oncol Clin North Am 2015; 29: 409-427.
3. Lintner KE, Wu YL, Yang Y, Spencer CH, Hauptmann G, Hebert LA, et al. Early Components of the Complement Classical Activation Pathway in Human Systemic Autoimmune Diseases. Front Immunol 2016; 15:36.
4. Ballanti E, Perricone C, Greco E, Ballanti M, Muzio GD, Chimenti MS,et al. Complement and autoimmunity. Immunol Res 2013; 56:477-91.
5. Vignesh P, Rawat A, Sharma M, Singh S. Complement in autoimmune diseases. ClinChimActa 2017; 465:123-130.
6. Sharma M, Vignesh P, Tiewsoh K, Rawat A. Revisiting the complement system in systemic lupus erythematosus. Expert Rev Clin Immunol 2020; 16:397-408.
7. Lo MS. Insights Gained From the Study of Pediatric Systemic Lupus Erythematosus. Front Immunol 2018; 9:1278.
8. Bryan AR, Wu EY. Complement deficiencies in systemic lupus erythematosus. Curr Allergy Asthma Rep 2014; 14:448.
9. Macedo AC, Isaac L. Systemic Lupus Erythematosus and Deficiencies of Early Components of the Complement Classical Pathway. Front Immunol 2016; 7:55.

10. Picard C, Lega JC, Ranchin B, Cochat P, Cabrera N, Fabien N, et al. Anti-C1q autoantibodies as markers of renal involvement in childhood-onset systemic lupus erythematosus. Pediatr Nephrol 2017; 32:1537-1545.
11. Ling GS, Crawford G, Buang N, Bartok I, Tian K, Thielens NM, et al. C1q restrains autoimmunity and viral infection by regulating $CD8^+$ T cell metabolism. Science 2018; 360:558-563.
12. Schejbel L, Skattum L, Hagelberg S, Ahlin A, Schiller B, Berg S, et al. Molecular basis of hereditary C1q deficiency - revisited: identification of several novel disease-causing mutations, Genes Immunol 2011; 12:626-634.
13. Truedsson L. Classical pathway deficiencies - A short analytical review. Mol Immunol 2015; 68:14-19.
14. Macedo AC, Isaac L. Systemic lupus erythematosus and deficiencies of early components of the complement classical pathway. Front Immunol 2016; 7:55.
15. Ram S, Lewis LA, Rice PA. Infections of people with complement deficiencies and patients who have undergone splenectomy. Clin Microbiol Rev 2010; 23:740-780.
16. KislaEkinci RM, Altun I, Bisgin A, Atmis B, Altintas DU, Balcý S. Recurrent macroscopic hematuria in a pediatric patient: is it early to diagnose as having type I hereditary C2 deficiency? CEN Case Rep 2020; 9:344-346.
17. Miller EC, Atkinson JP. Overcoming C2 deficiency. Clin Immunol 2012; 144:269-271.
18. Bathia JN, Pal P, Roy M, Guha S. Hereditary Homozygous C3 Deficiency. Indian J Pediatr 2017; 84:643-644.
19. Wu YL, Hauptmann G, Viguier M, Yu CY. Molecular basis of complete complement C4 deficiency in two North-African families with systemic lupus erythematosus. Genes Immun 2009; 10:433-445.
20. Li N, Zhang J, Liao D, Yang L, Wang Y, Hou S. Association between C4, C4A, and C4B copy number variations and susceptibility to autoimmune diseases: a meta-analysis. Sci Rep 2017; 16:42628.
21. Afzali P, Isaeian A, Sadeghi P, Moazzami B, Parvaneh N, Robatjazi M, et al. Complement deficiency in pediatric-onset systemic lupus erythematosus. J Lab Physicians 2018; 10:232-236.
22. Würzner R. Deficiencies of the complement MAC II gene cluster (C6, C7, C9): is subtotal C6 deficiency of particular evolutionary benefit? Clin Exp Immunol 2003; 133: 156-159.
23. Hoare S, Shazali OE, Clark JE, Fay A, Cant AJ. Investigation for complement deficiencey following meningococcal disease. Arch Dis Child 2002; 86:215-217.
24. Mayilyan KR. Complement genetics, deficienceis, and disease associations. Protein Cell 2012; 3:487-496.
25. Hodeib S, Herberg JA, Levin M, Sancho-Shimizu V. Human genetics of meningococcal infections. Hum Genet 2020; 139:961-980.
26. Lisa A, Ram S. Complement interactions with the pathogenic Neisseriae: clinincal features, deficiency states, and evasion mecahnisms. FEBS Letters 2020; 2670-2694.
27. Kavanagh D, Goodship T. Atypical hemolytic uremic syndrome, genetic basis, and clinical manifestations. Hematology 2011; 2011:15-20.
28. Nilsson B, Ekdahl KN. Complement diagnostics: concepts, indications, and practical guidelines. Clin Dev Immunol 2012; 2012:962702.
29. Prohászka Z, Nilsson B, Frazer-Abel A, Kirschfink M. Complement analysis 2016: Clinical indications, laboratory diagnostics and quality control. Immunobiology 2016; 221:1247-1258.
30. Thurman JM, Yapa R. Complement Therapeutics in Autoimmune Disease. Front Immunol 2019; 10:672.
31. Galindo-Izquierdo M, Pablos Alvarez JL. Complement as a Therapeutic Target in Systemic Autoimmune Diseases. Cells 2021; 10:148.
32. Pugh D, O'Sullivan ED, Duthie FA, Masson P, Kavanagh D. Interventions for atypical haemolyticuraemic syndrome. Cochrane Database Syst Rev 2021; 3(3): CD012862.
33. Risitano AM, Marotta S, Ricci P, Marano L, Frieri C, Cacace F, et al. Anti-complement Treatment for Paroxysmal Nocturnal Hemoglobinuria: Time for Proximal Complement Inhibition? A Position Paper from the SAAWP of the EBMT. Front Immunol 2019; 10:1157.

IMMUNOLOGY

SEVERE COMBINED IMMUNE DEFICIENCY

*Ankita Singh
**Kanika Arora
***Pandiarajan Vignesh

Abstract: *Severe combined immune deficiency is a disorder characterized by defective production or function of lymphocytes resulting in early-onset severe infections in infants. It is a medical emergency and needs to be recognized early for optimal treatment outcomes. Opportunistic infections are the hallmark clinical manifestation and presence of lymphopenia in complete blood counts is a vital clue for diagnosis. Diagnosis can be confirmed by lymphocyte subset analysis with flow cytometry. Hematopoietic stem cell transplantation is the treatment of choice. Establishment of genetic diagnosis is needed for counselling of the affected families.*

Keywords: *Severe combined immune deficiency, Infections, Pneumonia, BCG, Flow cytometry.*

* Senior Resident (DM)

** PhD fellow,
Pediatric Clinical Immunology and Rheumatology

*** Assistant Professor - Pediatrics,
Allergy Immunology Unit, Department of Pediatrics,
Advanced Pediatrics Centre,
Postgraduate Institute of Medical Education
and Research, Chandigarh.

email: vigimmc@gmail.com

Points to Remember

- ***Severe Combined Immune Deficiency (SCID) is a severe form of primary immunodeficiency disorder characterised by defective lymphocyte production or function.***
- ***Clinical manifestations in SCID usually start from early infancy. These include opportunistic infections which are recurrent and severe.***
- ***In countries where universal BCG vaccination at birth is practiced, disseminated BCGosis remains a major concern in children with SCID.***
- ***Presence of lymphopenia (absolute lymphocyte counts in infants <3000/mm^3) is an important laboratory clue.***
- ***Flow cytometry enumeration of lymphocyte subsets helps in diagnosing and categorising subtype of SCID.***
- ***Hematopoietic stem cell transplantation (HSCT) is the definitive mode of therapy for children with SCID.***
- ***Early identification and timely HSCT results in successful outcomes in SCID.***

References

1. Glanzmann E, Riniker P. Essential lymphocytophthisis; new clinical aspect of infant pathology. Ann Pediatr 1950; 175(1-2):1-32.
2. Giblett ER, Anderson JE, Cohen F, Pollara B, Meuwissen HJ. Adenosine-deaminase deficiency in two patients with severely impaired cellular immunity. Lancet 1972; 2(7786):1067-1069.
3. 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.
4. Ryser O, Morell A, Hitzig WH. Primary immunodeficiencies in Switzerland: first report of the national registry in adults and children. J Clin Immunol 1988; 8(6):479-485.
5. Stephan JL, Vlekova V, Le Deist F, Blanche S, Donadieu J, De Saint-Basile G, et al. Severe combined immunodeficiency: a retrospective single-center study of

clinical presentation and outcome in 117 patients. J Pediatr 1993; 123(4):564-572.

6. Kwan A, Abraham RS, Currier R, Brower A, Andruszewski K, Abbott JK, et al. Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. JAMA 2014; 312(7): 729-738.
7. Shahbazi Z, Yazdani R, Shahkarami S, Shahbazi S, Hamid M, Sadeghi-Shabestari M, et al. Genetic mutations and immunological features of severe combined immunodeficiency patients in Iran. Immunol Lett 2019; 216:70-78.
8. Al-Mousa H, Al-Dakheel G, Jabr A, Elbadaoui F, Abouelhoda M, Baig M, et al. High Incidence of Severe Combined Immunodeficiency Disease in Saudi Arabia Detected Through Combined T Cell Receptor Excision Circle and Next Generation Sequencing of Newborn Dried Blood Spots. Front Immunol 2018; 9:782. doi: 10.3389/fimmu.2018.00782. PMID: 29713328; PMCID: PMC5911483.
9. Chien YH, Chiang SC, Chang KL, Yu HH, Lee WI, Tsai LP, et al. Incidence of severe combined immunodeficiency through newborn screening in a Chinese population. J Formos Med Assoc 2015; 114(1):12-16.
10. Vignesh P, Rawat A, Kumrah R, Singh A, Gummadi A, Sharma M, et al. Clinical, Immunological, and Molecular Features of Severe Combined Immune Deficiency: A Multi-Institutional Experience From India. Front Immunol 2021; 11:619146. DOI=10.3389/fimmu.2020. 619146
11. Fischer A. Severe combined immunodeficiencies (SCID). Clin Exp Immunol 2000; 122(2):143-149.
12. Norouzi S, Aghamohammadi A, Mamishi S, Rosenzweig SD, Rezaei N. Bacillus Calmette-Guérin (BCG) complications associated with primary immunodeficiency diseases. J Infect 2012; 64(6):543-554.
13. Meggetto F, Muller C, Henry S, Selves J, MariamÝB, Brousset P, et al. Epstein-Barr Virus (EBV)-Associated Lymphoproliferations in Severe Combined Immunodeficient Mice Transplanted With Hodgkin Disease Lymph Nodes: Implication of EBV-Positive Bystander B Lymphocytes Rather Than EBV-Infected Reed-Sternberg Cells. Blood 1996; 87(6):2435-2442.
14. Monforte-Muñoz H, Kapoor N, Saavedra JA. Epstein-Barr virus-associated leiomyomatosis and posttransplant lymphoproliferative disorder in a child with severe combined immunodeficiency: case report and review of the literature. Pediatr Dev Pathol 2003; 6(5):449-457.
15. Lee PPW, Lau YL. Endemic infections in Southeast Asia provide new insights to the phenotypic spectrum of primary immunodeficiency disorders. Asian Pac J Allergy Immunol 2013; 31(3):217-226.
16. Gupta K, Rawat A, Agrawal P, Jindal A, Nada R, Saikia B, et al. Infectious and non-infectious complications in primary immunodeficiency disorders: an autopsy study from North India. J Clin Pathol 2018; 71(5):425-435.
17. Villa A, Santagata S, Bozzi F, Giliani S, Frattini A, Imberti L, et al. Partial V(D)J recombination activity leads to Omenn syndrome. Cell 1998; 93(5):885-896.
18. Aluri J, Gupta MR, Dalvi A, Mhatre S, Kulkarni M, Desai M, et al. Lymphopenia and Severe Combined Immunodeficiency (SCID) - Think Before You Ink. Indian J Pediatr 2019; 86(7):584-589.
19. Dvorak CC, Cowan MJ. Radiosensitive severe combined immunodeficiency disease. Immunol Allergy Clin North Am 2010; 30(1):125-142.
20. Grunebaum E, Mazzolari E, Porta F, Dallera D, Atkinson A, Reid B, et al. Bone marrow transplantation for severe combined immune deficiency. JAMA 2006; 295(5):508-518.
21. Carbonaro DA, Zhang L, Jin X, Montiel-Equihua C, Geiger S, Carmo M, et al. Preclinical demonstration of lentiviral vector-mediated correction of immunological and metabolic abnormalities in models of adenosine deaminase deficiency. Mol Ther 2014; 22(3):607-622.
22. Touzot F, Moshous D, Creidy R, Neven B, Frange P, Cros G, et al. Faster T-cell development following gene therapy compared with haploidentical HSCT in the treatment of SCID-X1. Blood 2015; 125(23):3563-3569.
23. Sobh A, Bonilla FA. Vaccination in Primary Immunodeficiency Disorders. J Allergy Clin Immunol Pract 2016; 4(6):1066-1075.
24. Puck JM. Newborn Screening for Severe Combined Immunodeficiency and T-cell Lymphopenia. Immunol Rev 2019; 287(1):241-252.
25. Gerstel-Thompson JL, Wilkey JF, Baptiste JC, Navas JS, Pai S-Y, Pass KA, et al. High-throughput multiplexed T-cell-receptor excision circle quantitative PCR assay with internal controls for detection of severe combined immunodeficiency in population-based newborn screening. Clin Chem 2010; 56(9):1466-1474.

IMMUNOLOGY

DISORDERS OF IMMUNE REGULATION

*Sathish Kumar
**Anu Punnen

Abstract: *Inborn errors of immunity are genetic disorders with broad clinical manifestations, ranging from increased susceptibility to infections to significant immune dysregulation. As per 2019 Update of the International Union of Immunological Societies expert committee's classification, there are now 430 single-gene inborn errors of immunity. Primary immune regulatory disorders are a growing subset of diseases referred to as inborn errors of immunity. Unlike classical primary immune deficiency disorders that typically present with severe, recurrent, or unusual infections, the clinical manifestations of primary immune regulatory disorders are dominated by immune-mediated diseases (autoimmunity, autoinflammation/ hyperinflammation, lymphoproliferation, malignancy, and severe atopy). In this article we will discuss in detail about disorders of immune regulation with phenotypical presentation and associated genetic defects.*

Keywords: *Immune deficiency, Inborn errors of immunity, Primary immune regulatory disorders, Autoimmunity.*

* Professor of Pediatrics

** Associate Professor,
Pediatric Rheumatology,
Department of Pediatrics,
Christian Medical College,
Vellore.

email: sathishkumar@cmcvellore.ac.in

Points to Remember

- ***PIRD predominantly have clinical features of autoimmunity, hyperinflammation, lympho-proliferation, malignancy and severe atopy with less dominant features of immunodeficiency and infection.***
- ***Genetic causes of PIRD function in immune pathways that regulate the various types of immune responses.***
- ***The treatment is challenging, as it requires careful balancing of immunosuppression in subjects at increased risk of infections.***
- ***Treatment for PIRD are directed at the specific genetic defect, and HCT can be a curative therapy for some cases***

References

1. Tangye SG, Al-Herz W, Bousfiha A,Chatila T, Rundles CC, Etzioni, 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; 40:24-64.
2. Chan AY, Torgerson TR. Primary immune regulatory disorders: a growing universe of immune dysregulation. Curr Opin Allergy Clin Immunol 2020; 20(6):582-590.
3. Chandrakasan S, Chandra S, Davila Saldana BJ, Torgerson TR, Buchbinder D. Primary immune regulatory disorders for the pediatric hematologist and oncologist: A case-based review. Pediatr Blood Cancer 2019; 66(5):e27619.
4. Matson DR, Yang DT. Autoimmune Lymphoproliferative Syndrome: An Overview. Arch Pathol Lab Med 2020 Feb;144(2):245-251.
5. Oliveira JB. The expanding spectrum of the autoimmune lymphoproliferative syndromes. Curr Opin Pediatr 2013; 25:722-729.
6. Takagi M, Shinoda K, Piao J, Mitsuiki N, Takagi M, Matsuda K, et al. Autoimmune lymphoproliferative syndrome-like disease with somatic KRAS mutation. Blood 2011; 117:2887-2890.
7. Nabhani S, Schipp C, Miskin H, Levin C, Postovsky S, Dujovny T, et al. STAT3 gain-of-function mutations associated with autoimmune lymphoproliferative syndrome like disease deregulate lymphocyte apoptosis and can be

targeted by BH3 mimetic compounds. Clin Immunol 2017; 181:32-42.

8. Park JH, Lee KH, Jeon B, Ochs HD, Lee JS, Gee Hy, et al. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome: A systematic review. Autoimmun Rev 2020; 19(6):102526.
9. Verbsky JW, Chatila TA. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) and IPEX-related disorders: an evolving web of heritable autoimmune diseases. Curr Opin Pediatr 2013; 25: 708-714.
10. Zhang Y, Ma CA, Lawrence MG, Break TJ, O'Connell MP, Lyons JJ, et al. PD-L1 up-regulation restrains Th17 cell differentiation in STAT3 loss-and STAT1gain-of-function patients. J Exp Med 2017; 214:2523-2533.
11. Yazdani R, Habibi S, Sharifi L, Azizi G, Abolhassani H, Olbrich P, et al. Common Variable Immunodeficiency: Epidemiology, Pathogenesis, Clinical Manifestations, Diagnosis, Classification, and Management. J Investig Allergol Clin Immunol 2020; 30(1):14-34.
12. Bergsten E, Horne A, Arico M, Astigarraga I, Egeler RM, Filipovich AH, et al. ´Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. Blood 2017; 130(25):2728-2738.
13. Ehl S, Astigarraga I, von Bahr Greenwood T, Hines M, Horne A, Ishii E, et al. Recommendations for the use of etoposide-based therapy and bone marrow transplantation for the treatment of HLH: consensus statements by the HLH Steering Committee of the Histiocyte Society. J Allergy Clin Immunol Pract 2018; 6(5):1508-1517
14. Chellapandian D, Das R, Zelley K, Wiener SJ, Zhao H, Teachey DT, et al. EBV-HLH Rituximab Study Group. Treatment of Epstein Barr virus-induced haemophagocytic lymphohistiocytosis with rituximab-containing chemo-immunotherapeutic regimens. Br J Haematol 2013; 162(3):376-382
15. Walter JE, Farmer JR, Foldvari Z, Torgerson TR, Cooper MA. Mechanism-based strategies for the management of autoimmunity and immune dysregulation in primary immunodeficiencies. J Allergy Clin Immunol Pract 2016; 4:1089-1100
16. Bakhtiar S, Fekadu J, Seidel MG, Gambinieri E. Allogeneic hematopoietic stem cell transplantation for congenital immune dysregulatory disorders. Front Pediatr 2019; 7:461.

IMMUNOLOGY

UTILITY OF GENETIC TESTS IN PRIMARY IMMUNODEFICIENCY DISORDERS

*Abhinav Jain
**Vinod Scaria

Abstract: *Genetic testing plays a crucial role in the field of primary immunodeficiency. It provides the confirmatory molecular diagnosis to the affected patient. This helps the family in prenatal diagnosis, personalized treatment, embryo implantation during in-vitro fertilization and family screening. In this review, we have broadly discussed the widely used genetic tests in the clinical setting for primary immunodeficiency. We have also described the most appropriate genetic testing approach for different types of primary immunodeficiency. the utility of genetic testing to the affected patients and their family members is also discussed.*

Keywords: *Primary immunodeficiency, Genetic testing, Molecular diagnosis, Personalized treatment.*

* Senior Research Fellow

** Principal Scientist,
CSIR-Institute of Genomics and Integrative Biology,
Mathura Road, New Delhi and
Academy of Scientific and Innovative Research (AcSIR),
Ghaziabad, Uttar Pradesh.

email: abhinavjj@gmail.com

Points to Remember

- ***Genetic testing provides the confirmatory diagnosis for the patients affected with primary immunodeficiency that has a heterogeneous array of symptoms.***
- ***The identification of the variant helps the clinicians in tailoring the treatment of the patient according to the genetic condition.***
- ***Variant identification helps in prenatal diagnosis, embryo pre implantation, family and community screening.***
- ***Choosing the most appropriate genetic test for diagnosis of different types of PID is based on the patient's clinical characteristics and immunological investigations.***

References

1. Vetrie D, Vorechovský I, Sideras P, Holland J, Davies A, Flinter F, et al. The gene involved in X-linked agammaglobulinaemia is a member of the src family of protein-tyrosine kinases. Nature 1993; 361(6409):226-233.
2. 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.
3. Boyle JM, Buckley RH. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. J Clin Immunol 2007; 27(5):497-502.
4. World PI Week. What is Primary Immunodeficiency (PI)? [Internet]. Available from: http://www.worldpiweek.org/what-is-primary-immunodeficiency-pi/Accessed on 12th April 2021.
5. Seidel MG, Duerr C, Woutsas S, Schwerin-Nagel A, Sadeghi K, Neesen J, et al. A novel immunodeficiency syndrome associated with partial trisomy 19p13. J Med Genet 2014; 51(4):254-263.
6. Stray-Pedersen A, Sorte HS, Samarakoon P, Gambin T, Chinn IK, Coban Akdemir ZH, et al. Primary immunodeficiency diseases: Genomic approaches delineate heterogeneous Mendelian disorders. J Allergy Clin Immunol 2017; 139(1):232-245.

7. Thaventhiran JED, Lango Allen H, Burren OS, Rae W, Greene D, Staples E, et al. Whole-genome sequencing of a sporadic primary immunodeficiency cohort. Nature 2020; 583(7814):90-95.
8. Massaad MJ, Zhou J, Tsuchimoto D, Chou J, Jabara H, Janssen E, et al. Deficiency of base excision repair enzyme NEIL3 drives increased predisposition to autoimmunity. J Clin Invest 2016; 126(11):4219-4236.
9. Abbott S, Fairbanks DJ. Experiments on Plant Hybrids by Gregor Mendel. Genetics. 2016; 204(2):407-422.
10. Immune Deficiency Foundation (IDF). Primary immunodeficiency diseases in America: 2007. Available from: https://primaryimmune.org/wp-content/uploads/2011/04/Number-59-Fall-2008.pdf. Accessed on 12th April 2021.
11. Centers for Disease Control and Prevention (CDC). Update on overall prevalence of major birth defects-Atlanta, Georgia, 1978-2005. MMWR Morb Mortal Wkly Rep 2008; 57(1):1-5. Available from https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a2.htm. Assessed on 12th April 2021.
12. Thauvin-Robinet C, Munck A, Huet F, Génin E, Bellis G, Gautier E, et al. The very low penetrance of cystic fibrosis for the R117H mutation: a reappraisal for genetic counselling and newborn screening. J Med Genet 2009; 46(11):752-758.
13. Manchanda R, Loggenberg K, Sanderson S, Burnell M, Wardle J, Gessler S, et al. Population testing for cancer predisposing BRCA1/BRCA2 mutations in the Ashkenazi-Jewish community: a randomized controlled trial. J Natl Cancer Inst 2015; 107(1):379.
14. Jain A, Sharma D, Bajaj A, Gupta V Scaria V.Founder variants and population genomes-Toward precision medicine. Adv Genet 2021; 107:p.121-152.
15. Touitou I. The spectrum of Familial Mediterranean Fever (FMF) mutations. Eur J Hum Genet 2001; 9(7):473-483.
16. World Health Organization. Children: improving survival and well-being https://www.who.int/news-room/fact-sheets/detail/children-reducing-mortality. Accessed on 24th Mar 2021.
17. Bousfiha AA, Jeddane L, El Hafidi N, Benajiba N, Rada N, El Bakkouri J, et al. First report on the Moroccan registry of primary immunodeficiencies: 15 years of experience (1998-2012). J Clin Immunol 2014; 34(4): 459-468.
18. Jain A, Bhoyar RC, Pandhare K, Mishra A, Sharma D, Imran M, et al. IndiGenomes: a comprehensive resource of genetic variants from over 1000 Indian genomes. Nucleic Acids Res 2021; 49(D1):D1225-1232.
19. Jain A, Gandhi S, Koshy R, Scaria V. Incidental and clinically actionable genetic variants in 1005 whole exomes and genomes from Qatar. Mol Genet Genomics 2018; 293(4):919-929.
20. Buckley RH, Win CM, Moser BK, Parrott RE, Sajaroff E, Sarzotti-Kelsoe M. Post-transplantation B cell function in different molecular types of SCID. J Clin Immunol 2013; 33(1):96-110.
21. Cowan MJ, Gennery AR. Radiation-sensitive severe combined immunodeficiency: The arguments for and against conditioning before hematopoietic cell transplantation-what to do?. J Allergy Clin Immunol 2015; 136(5):1178-1185.

IMMUNOLOGY

FOOD DEPENDENT EXERCISE INDUCED ANAPHYLAXIS

Major K. Nagaraju

Abstract: *Food dependent exercise induced anaphylaxis is an uncommon condition in childhood and occurs during exercise, preceded by ingestion of culprit food, which used to be independently tolerated. Wheat gluten is the commonest food responsible for food dependent exercise induced anaphylaxis. Diagnosis is mainly by evaluation of clinical history. As allergy tests do not give accurate results, modified exercise challenge tests are needed. Accurate diagnosis definitely helps the patient to return to exercise with confidence. Patient should avoid exercise for 4-6 hours after consuming the offending food but can take other foods without any restriction. Parents should be educated about the importance of carrying epinephrine for emergency.*

Keywords: *Food dependent exercise induced anaphylaxis, Cofactors, Challenge test, Wheat dependent.*

* Professor of Pediatrics,
Division of Allergy and Clinical Immunology,
Saveetha Medical College and Hospital,
Chennai.

email : majorknr@yahoo.in

Points to Remember

- ***FDEIA is a special type of food allergy, where symptoms are triggered by consumption of causative food combined with exercise.***
- ***Pathophysiological mechanism of FDEIA is not fully understood.***
- ***Exercise tolerance test combining aspirin along with suspected food allergen can establish the diagnosis and can exclude other causes.***
- ***Omega 5 gliadin is the preferred marker for diagnosing wheat dependent exercise induced anaphylaxis.***
- ***Children with FDEIA should avoid eating the causative food 4 hours before any exercise/exertion.***

References

1. Maulitz RM, Pratt DS, Schocket AL. Exercise-induced anaphylactic reaction to shellfish. J Allergy Clin Immunol 1979; 63:433-434.
2. Robin M, Karadan U. Nonspecific food dependant exercise-induced anaphylaxis with seizure: a case report. Asian J Med Sci 2020; 11:94-97.
3. Asaumi T, Ebisawa M. How to manage food dependent exercise induced anaphylaxis (FDEIA). Curr Opin Allergy Clin Immunol 2018; 18(3):243-247.
4. Paula RA, George DT. Pathophysiology, diagnosis and management of exercise-induced anaphylaxis. Curr Opin Allergy Clin Immunol 2010; 10:312-317.
5. Barg W, Wolanczyk-Medrala A, Obojski A, Wytrychowski K, Panaszek B, Medrala W. Food-dependent exercise-induced anaphylaxis: possible impact of increased basophil histamine releasability in hyperosmolar conditions. J Investig Allergol Clin Immunol 2008; 18(4):312-315.
6. Cooper DM, Radom-Aizik S, Schwindt C, Zaldivar F Jr. Dangerous exercise: lessons learned from dysregulated inflammatory responses to physical activity. J Appl Physiol 2007; 103(2):700-709.
7. Tam CJ, John RM. Food-Dependent Exercise-Induced Anaphylaxis: A Review. J Nurse Pract 2017; 13(5):313-321
8. Christensen MJ, Eller E, Mortz CG, Brockow K, Bindslev-Jensen C. Wheat-Dependent Cofactor-Augmented Anaphylaxis: A Prospective Study of Exercise,

Aspirin, and Alcohol Efficacy as Cofactors. J Allergy Clin Immunol Pract 2019; 7(1):114-121.

9. Rosier SE, Otten R, Brugts JJ, Hoek AE. Allergic acute coronary syndrome in exercise-induced anaphylaxis. Neth J Med 2018; 76(9):411-414.
10. Toit GD. Food-dependent exercise-induced anaphylaxis in childhood. Pediatr Allergy Immunol 2007; 18:455-463.
11. Morita E, Matsuo H, Chinuki Y, Takahashi H, Dahlström J, Tanaka A. Food-dependent exercise-induced anaphylaxis -importance of omega-5 gliadin and HMW-glutenin as causative antigens for wheat-dependent exercise-induced anaphylaxis. Allergol Int 2009; 58(4):493-498.
12. Thongngarm T, Wongsa C, Pacharn P, Piboonpocanun S, Sompornrattanaphan M. Clinical Characteristics and Proposed Wheat-Cofactor Challenge Protocol with a High Diagnostic Yield in Adult-Onset IgE-Mediated Wheat Allergy. J Asthma Allergy 2020; 13:355-368.
13. Dreborg S, Foucard T. Allergy to apple, carrot and potato in children with birch pollen allergy. Allergy 1983; 38:167-172.
14. Pacharn P, Jirapongsananuruk O, Daengsuwan T, Vichyanond P, Visitsunthorn N. Wheat-dependent, exercise-induced anaphylaxis in Thai children: a report of 5 cases. Asian Pac J Allergy Immunol 2009; 27(2-3):115-120.
15. Sugimura T, Tananari Y, Ozaki Y, Maeno Y, Ito S, Yoshimoto Y, et al. Effect of oral sodium cromoglycate in 2 children with food-dependent exercise-induced anaphylaxis (FDEIA), Clin Pediatr (Phila) 2009; 48(9):945-950.
16. Peroni DG, Piacentini GL, Piazza M, Cametti E, Boner AL. Combined cetirizine-montelukast preventive treatment for food-dependent exercise-induced anaphylaxis. Ann Allergy Asthma Immunol 2010; 104(3):272-273.
17. Bray SM, Fajt ML, Petrov AA. Successful treatment of exercise-induced anaphylaxis with omalizumab. Ann Allergy Asthma Immunol 2012; 109(4):281-282.
18. Noh G, Lee JH. Specific Oral Tolerance Induction Using IFN-Gamma in 2 Cases of Food-Dependent Exercise-Induced Anaphylaxis. Case Rep Med 2013; 2013:259692.
19. Caminiti L, Passalacqua G, VitaD, Ruggeri P, BarberioG, Pajno GB. Food-exercise-induced anaphylaxis in a boy successfully desensitized to cow milk. Allergy 2007; 62(3): 335-336.

IMMUNOLOGY

HEREDITARY ANGIOEDEMA

***Archan Sil**
****Ankur K. Jindal**

Abstract: *Hereditary angioedema is an uncommon disorder with autosomal dominant mode of inheritance and is clinically characterized by recurrent episodic swelling of face, limbs, genitals, airway and gastrointestinal tract. Because of lack of awareness, most patients with hereditary angioedema remain undiagnosed and untreated. Swelling episodes in patients with hereditary angioedema are mediated by bradykinin. Excess bradykinin due to defective C1 inhibitor protein is the basic fault. While in type 1 HAE, C1 inhibitor protein levels are low, HAE type 2 is characterized by normal levels of C1 inhibitor protein that is functionally defective. C1 inhibitor protein levels. and function are normal in type 3 hereditary angioedema Treatment of acute attacks, short term prophylaxis and long-term prophylaxis are the mainstay in management. C1 inhibitor protein concentrate is the preferred treatment for patients with hereditary angioedema in the developed countries. However, because of non-availability of this drug in India and many other developing countries, most patients are treated with fresh frozen plasma, attenuated androgens and tranexamic acid. In this review, we update on the pathogenesis, clinical features, diagnosis and management of hereditary angioedema.*

Keywords: *Hereditary angioedema, Bradykinin, C1 inhibitor, Acute attacks, prophylaxis, Attenuated androgens, Tranexamic acid.*

* Senior Resident, (DM-Pediatric Clinical Immunology and Rheumatology),

** Assistant Professor of Pediatric Clinical Immunology and Rheumatology,
Allergy Immunology Unit, Department of Pediatrics,
Advanced Pediatrics Centre,
Post Graduate Institute of Medical Education and Research, Chandigarh.

email: ankurjindal11@gmail.com

Points to Remember

- ***Hereditary angioedema (HAE) is an uncommon disorder characterized by episodic edema.***
- ***Because of lack of awareness, the disease remains undiagnosed for several years.***
- ***HAE should be suspected in all patients who present with episodic edema without urticaria.***
- ***In patients with suspected HAE, C4, C1-INH levels and C1-INH function should be assessed.***
- ***Most patients have diseases onset in childhood. Hence, pediatricians have an important role to play in the early diagnosis of HAE.***
- ***Patients with HAE in most of the developing countries including India are managed using fresh frozen plasma, attenuated androgens and tranexamic acid because all 1st line treatments are not available.***

References

1. Nussberger J, Cugno M, Amstutz C, Cicardi M, Pellacani A, Agostoni A. Plasma bradykinin in angio-oedema. Lancet 1998; 351:1693-1697.
2. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. J Allergy Clin Immunol 2012; 130(3):692-697.
3. Reshef A, Kidon M, Leibovich I. The story of angioedema: from Quincke to bradykinin. Clin Rev Allergy Immunol 2016; 51:121-39.
4. Donaldson VH, Evans RR. A biochemical abnormality in hereditary angioneurotic edema: absence of serum inhibitor of C2 1-esterase. Am J Med 1963; 35:37-44.
5. Maurer M, Magerl M, Ansotegui I, Aygören-Pürsün E, BetschelS, Bork K, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-the 2017 revision and update. Allergy 2018; 73:1575-1596.
6. Schmaier AH. The contact activation and kallikrein/kinin systems: pathophysiologic and physiologic activities. J Thromb Haemost 2016; 14(1):28-39. doi: 10.1111/jth.13194. Epub 2016 Jan 11. PMID: 26565070.
7. Kaplan AP, Joseph K. Pathogenesis of hereditary angioedema: the role of the bradykinin-forming cascade. Immunol Allergy Clin North Am 2017; 37: 513-525.

8. Frank MM. Complement disorders and hereditary angioedema. J Allergy Clin Immunol 2010; 125:S262-S271.
9. Kaplan AP, Joseph K. Complement, kinins, and hereditary angioedema: mechanisms of plasma instability when C1 inhibitor is absent. Clin Rev Allergy Immunol 2016; 51:207-215.
10. Sharma J, Jindal AK, Banday AZ, Kaur A, Rawat A, Singh S, et al. Pathophysiology of Hereditary Angioedema (HAE) Beyond the SERPING1 Gene. Clin Rev Allergy Immunol 2021 Jan 14. doi: 10.1007/s12016-021-08835-8. Epub ahead of print. Erratum in: Clin Rev Allergy Immunol 2021; PMID: 33442779.
11. Banday AZ, Kaur A, Jindal AK, Rawat A, Singh S. An update on the genetics and pathogenesis of hereditary angioedema. Genes Dis 2019; 7(1):75-83. doi: 10.1016/j.gendis.2019.07.002. PMID: 32181278; PMCID: PMC7063419.
12. Pappalardo E, Cicardi M, Duponchel C, Carugati A, Choquet S, Agostoni A, et al. Frequent de novo mutations and exon deletions in the C1 inhibitor gene of patients with angioedema. J Allergy Clin Immunol 2000; 106:1147-1154.
13. Jacques L, Couture R, Drapeau G, Regoli D. Capillary permeability induced by intravenous neurokinins. Receptor characterization and mechanism of action. Naunyn Schmiedebergs Arch Pharmacol 1989; 340:170-179.
14. Busse PJ, Christiansen SC. Hereditary Angioedema. N Engl J Med 2020; 382(12):1136-1148. doi: 10.1056/NEJMra1808012. PMID: 32187470.
15. Saltoun C. Urticaria, angioedema, and hereditary angioedema. In: Grammer LC, Greenberger PA, eds. Patterson's allergic diseases. 8th ed. Philadelphia: Wolters Kluwer, 2018; pp689-708.
16. Zuraw BL, Bernstein JA, Lang DM, Craig T, Dreyfus D, Hsieh F, et al. A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency and angiotensin-converting enzyme inhibitor-associated angioedema. J Allergy Clin Immunol 2013; 131:1491-1493.
17. Khan DA. Hereditary angioedema: historical aspects, classification, pathophysiology, clinical presentation and laboratory diagnosis. Allergy Asthma Proc 2011; 32: 1-10.
18. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. J Allergy Clin Immunol 2012; 130: 692-697.
19. Aabom A, Bygum A, Koch C. Complement factor C4 activation in patients with hereditary angioedema. Clin Biochem 2017; 50:816-821.
20. Zuraw BL, Christiansen SC. Hereditary angioedema and bradykinin-mediated angioedema. In: Adkinson NF Jr, Bochner BS, Burks AW, Busse WW, Holgate ST, Lemanske RF, O'Hehir R, editors. Middleton's allergy: principles and practice. 8th edn. Philadelphia: Elsevier Saunders, 2014; pp588-600.
21. Jindal AK, Rawat A, Kaur A, Sharma D, Suri D, Gupta A, et al. Novel SERPING1 gene mutations and clinical experience of type 1 hereditary angioedema from North India. Pediatr Allergy Immunol 2021; 32(3):599-611. doi: 10.1111/pai.13420. Epub 2020 Dec 5. PMID: 33220126.
22. Betschel S, Badiou J, Binkley K, Borici-Mazi R, Hébert J, Kanani A, et al. The International/Canadian Hereditary Angioedema Guideline. Allergy Asthma Clin Immunol 2019 Nov 25; 15:72. doi: 10.1186/s13223-019-0376-8. Erratum in: Allergy Asthma Clin Immunol 2020; 16:33. PMID: 31788005; PMCID: PMC6878678.
23. Busse PJ, Christiansen SC, Riedl MA, Banerji A, Bernstein JA, Castaldo AJ, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. J Allergy Clin Immunol Pract 2021; 9(1):132-150.e3. doi: 10.1016/j.jaip. 2020.08. 046. Epub 2020 Sep 6. PMID: 32898710.
24. Bork K, Staubach P, Hardt J. Treatment of skin swellings with C1-inhibitor concentrate in patients with hereditary angio-oedema. Allergy 2008 Jun; 63(6):751-757. doi:10.1111/j.1398-9995.2007.01577.x. PMID:18445189.
25. Craig TJ, Levy RJ, Wasserman RL, Bewtra AK, Hurewitz D, Obtu³owicz K, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. J Allergy Clin Immunol 2009; 124(4):801-808. doi: 10.1016/j.jaci.2009.07.017. Epub 2009 Sep 19. PMID: 19767078.
26. Lumry WR, Li HH, Levy RJ, Potter PC, Farkas H, Moldovan D, et al. Randomized placebo-controlled trial of the bradykinin B_2 receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. Ann Allergy Asthma Immunol 2011; 107(6):529-537. doi: 10.1016/j.anai.2011.08.015. Epub 2011 Oct 5. PMID: 22123383.
27. Cicardi M, Levy RJ, McNeil DL, Li HH, Sheffer AL, Campion M, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. N Engl J Med 2010; 363(6):523-531.
28. Jindal AK, Reshef A, Longhurst H, GEHM workgroup (Global Equity in HAE Management). Mitigating Disparity in Health-care Resources Between Countries for Management of Hereditary Angioedema. Clin Rev Allergy Immunol 2021. doi: 10.1007/s12016-021-08854-5. Epub ahead of print. PMID: 34003432.
29. Prematta M, Gibbs JG, Pratt EL, Stoughton TR, Craig TJ. Fresh frozen plasma for the treatment of hereditary angioedema. Ann Allergy Asthma Immunol 2007; 98(4):383-388. doi: 10.1016/S1081-1206(10)60886-1. PMID: 17458436.
30. Bork K, Hardt J, Staubach-Renz P, Witzke G. Risk of laryngeal edema and facial swellings after tooth extraction

in patients with hereditary angioedema with and without prophylaxis with C1 inhibitor concentrate: a retrospective study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011; 112(1):58-64.

31. Jindal AK, Singh A, Anjani G, Kaur A, Jaiswal M, Chopra S, et al. Successful perioperative management of three patients with hereditary angioedema without C1 esterase inhibitor therapy: A developing country perspective. Immunobiology 2020; 225(6):152022. doi: 10.1016/j.imbio.2020.152022. Epub 2020 Nov 3. PMID: 33197705.
32. Longhurst H, Zinser E. Prophylactic Therapy for Hereditary Angioedema. Immunol Allergy Clin North Am. 2017; 37(3):557-570. doi: 10.1016/j.iac.2017.04.003. PMID: 28687109.
33. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med 2010; 363(6):513-522.
34. Longhurst H, Cicardi M, Craig T, Bork K, Grattan C, Baker J, et al. Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor. N Engl J Med 2017; 376(12):1131-1140. doi: 10.1056/NEJMoa 1613627. PMID: 28328347.
35. Bork K, Bygum A, Hardt J. Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients. Ann Allergy Asthma Immunol 2008; 100(2):153-161. doi: 10.1016/S1081-1206(10)60424-3. PMID: 18320917.

GENERAL ARTICLE

EARLY BEHAVIORAL SIGNS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER: A PRACTICAL GUIDE

*Vijaya Raman

Abstract: *Attention deficit hyperactivity disorder is one of the most common neurobehavioral disorders seen in childhood. It is important to keep a high index of suspicion when parents complain of behavioral issues in young children. Many behavioral changes in early childhood do cease to be of concern when children grow up. There are some definite early indicators of behavioral issues that continue to be problematic and affect the development and later functioning in all areas. This article focuses on early identification of problem behaviors that may lead to negative short and long-term effects on an individual's personal and professional life.*

Keywords: *Early identification, Behavior, Children.*

* Professor of Clinical Psychology,
Department of Psychiatry,
St. John's Medical College,
Bangalore.
email: vijaya.r@stjohns.in

Points to Remember

- ***ADHD is a common neurobehavioral disorder which is often undiagnosed till significant impairment is observed.***
- ***Repeated parental concerns regarding behavior of the child during routine OPD visits should warrant referral rather than reassurance.***
- ***There are early behaviors that can aid in early identification and intervention.***
- ***Early intervention prevents negative impact on the child's development, self-esteem and overall functioning and outcome.***

References

1. Polanczyk G, Silva de Lima M, Lessa Horta B, Biederman J, Rohde LA. The Worldwide Prevalence of ADHD: A Systematic Review and Meta-regression Analysis. Am J Psychiatry 2007; 164:942-948.
2. Suthar N, Garg N, Verma KK, Singhal A, Singh H, Baniya G. Prevalence of Attention Deficit Hyperactivity Disorder in primary school children: A cross - sectional study. J Indian Assoc. Child Adolesc. Mental Health 2018, 14(4):74-88.
3. Rucklidge JJ. Gender differences in attention deficit hyperactivity disorder. Psychiatr Clin North Am 2010; 33(2):357-373.
4. Arnett AB, MacDonald B, Pennington BF. Cognitive and behavioral indicators of ADHD symptoms prior to school age. J Child Psychol Psychiat 2013; 54(12):1284-1294.
5. Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. Molecular Psychiat 2019; 24: 562-575.
6. Dalwai S, Unni J, Kalra V, Singhi P, Shrivastava L, Nair MKC. Consensus statement of the Indian Academy of Pediatrics on evaluation and management of Attention Deficit Hyperactivity Disorder. Indian Pediatr 2017; 54:481-488.
7. Rothbart MK, Bates JE. Temperament. In: W. Damon (Series Ed.), N. Eisenberg (Vol. Ed.) Handbook of Child Psychology: Vol.3. Social, Emotional and Personality development, 6th edn. Hoboken, NJ: John Wiley & Sons, Inc 2012; pp105-176.

8. McIntosh DE, Cole- Love AS. Profile comparisons between ADHD and non-ADHD children on the temperament assessment battery for children. J Psychoeduc Assess 1996; 14:362-372.
9. Foley M, McClowry SG, Castellanos FX. The relationship between attention deficit hyperactivity disorder and child temperament. J Appl Devl Psychol 2008; 29:157-169.
10. Sullivan EL, Holton KF, Nousen EK, Barling AN, Sullivan CA, Propper CB, et al. Early identification of ADHD risk via infant temperament and emotion regulation: a pilot study. J Child Psychol Psychiat 2015; 56(9): 949-957.
11. Kan KJ, Dolan CV, Nivard MG, Middeldorp CM, van Beijsterveldt CE, Willemsen G, et al. Genetic and environmental stability in attention problems across the lifespan: Evidence from the Netherlands twin register. J Am Acad Child Adolesc Psychiatry 2013; 52:12-25.
12. Chen W, Zhou K, Sham P, Franke B, Kuntsi J, Campbell D, et al. DSM IV combined type ADHD shows familial association with sibling trait scores: a sampling strategy for QTL linkage. Am J Med Genet B Neuro Psychiatr Genet 2008; 147B:1450-1460.
13. Fewell RR, Deutscher B. Attention Deficit Hyperactivity Disorder in Very Young Children: Early signs and interventions. Inf Young Children 2002; 14(3):24-32.
14. Craig F, Lamanna AL, Margari F, Matera E, Simone M, Margari L. Overlap between Autism Spectrum Disorders and ADHD: Searching for Distinctive/ Common Clinical Features. Autism Res 2015; 8:328-337.

DRUG PROFILE

IRON CHELATION IN CHILDREN

***Jeeson C. Unni**

Abstract: *Currently, the goal of iron chelation has shifted from treating iron overload to preventing iron accumulation and iron-induced end-organ complications, in order to achieve a complication-free survival and an improved quality of life of children with iron overload. New chelation options increase the likelihood of achieving these goals. Timely initiation, close monitoring and continuous adjustment are the cornerstones of optimal chelation therapy in children. Despite use of iron chelators for more than 60 years, grey areas still remain. The three available iron chelators have been reviewed.*

Keywords: *Iron overload, Iron chelators, Desferrioxamine, Deferiprone, Deferasirox.*

* Editor-in-chief,
IAP Drug Formulary,
Sr. Consultant, Dept. of Child and Adolescent Health,
Aster Medcity,
Kochi, Kerala.
email: jeeson1955@gmail.com

Points to Remember

- ***Uncontrolled transfusional iron overload increases the risks of heart failure, endocrine damage, liver cirrhosis and hepatocellular carcinoma.***
- ***Chelation therapy is an effective treatment modality (but not ideal as yet) in improving survival, decreasing the risk of heart failure and decreasing morbidities from transfusional iron overload and should be started at least within 2 years of starting regular blood transfusions.***
- ***Response to chelation is dependent on the dose and the duration of exposure***
- ***Changes in body iron in response to transfusion and chelation can usually but not always be estimated from the trend in serum ferritin - Liver iron concentration (LIC) is better indicator of total body iron, and serum ferritin is an approximate marker of LIC.***
- ***Iron mediated tissue damage is often irreversible, and removal of iron deposited in tissues by chelation is slow - particularly after it has escaped the liver. Chelation of liver iron is faster than from the myocardium.***
- ***Heart iron accumulates later than liver iron, and is rare before the age of 8 years.***
- ***Over chelation increases side effects from chelation therapy, and doses should therefore be decreased as serum ferritin or liver iron levels fall (demonstrated most clearly with DFO)***
- ***The chelation regime must be tailored for the individual child and will vary with the clinical situation.***
- ***Chelation therapy will not be effective if it is not taken regularly - a key aspect of chelation management is to work with patients to ensure adherence.***

References

1. Porter JB. Practical management of iron overload. British J Haematol 2001; 115:239-252.
2. Esposito BP, Breuer W, Sirankapracha P, Pootrakul P,

Hershko C, Cabantchik Z. Labile plasma iron in iron overload: redox activity and susceptibility to chelation. Blood 2003; 102(7):2670-2677.

3. Taher A, Cappellini MD, Vichinsky E, Galanello R, Piga A, Lawniczek T, et al. Efficacy and safety of deferasirox doses of >30 mg/kg per d in patients with transfusion-dependent anaemia and iron overload. British J Haematol 2009; 147:752-759.
4. Delea TE, Edelsberg J, Sofrygin O, Thomas SK, Baladi JF, Phatak PD. Coates TD. Consequences and costs of noncompliance with iron chelation therapy in patients with transfusion-dependent thalassemia: a literature review. Transfusion 2007; 47:1919-1929.
5. Kwiatkowski JL, Kim HY, Thompson AA, Quinn CT, Mueller BU, Odame I, et al. Chelation use and iron burden in North American and British thalassemia patients: a report from the Thalassemia Longitudinal Cohort. Blood 2012; 119:2746-2753.
6. Bollig C, Schell LK, Rücker G, Allert R, Motschall E, Niemeyer CM, et al. Deferasirox for managing iron overload in people with thalassaemia. Cochrane Database of Systematic Reviews 2017, Issue 8. Art. No.: CD007476. DOI: 10.1002/14651858. CD007476.pub3.
7. Fisher SA, Brunskill SJ, Doree C, Chowdhury O, Gooding S, Roberts DJ. Oral deferiprone for iron chelation in people with thalassaemia. Cochrane Database of Systematic Reviews 2013, 8. Art. No.: CD004839. DOI: 10.1002/14651858. CD004839. pub3.
8. Neufeld EJ, Galanello R, Viprakasit V, Aydinok Y, Piga A, Harmatz P, et al. A phase 2 study of the safety, tolerability, and pharmacodynamics of FBS0701, a novel oral iron chelator, in transfusional iron overload. Blood 2012; 119: 3263-3268.
9. Hamilton JL, Kizhakkedathu JN. Polymeric nanocarriers for the treatment of systemic iron overload. Mol Cell Ther 2015; 3:3. doi:10.1186/s40591-015-0039-1.
10. Hoffbrand AV, Taher A, Capellini MD. How I treat transfusional iron overload. Blood 2012; 120: 3657-3669. doi: 10.1182/blood-2012-05-370098.
11. Chuang T, Li J, Weng T, Wu K, Chao Y. Combined chelation with high-dose deferiprone and deferoxamine to improve survival and restore cardiac function effectively in patients with transfusion-dependent thalassemia presenting severe cardiac complications. Ann Hematol 2020; 99(10):2289-2294.
12. Eghbali A, Shokri P, Afzal BR, Bagheri B. A 1-year randomized trial of deferasirox alone versus deferasirox and deferoxamine combination for the treatment of iron overload in thalassemia major. Transfus Apher Sci 2019; 58(4):429-433.
13. Deferasirox. In: British National Formulary for Children, BMJ group and Pharmaceutical Press, Tavistock Square, London, 2019-20; pp596-597.

ADOLESCENCE

RELATIONSHIP COUNSELLING

***MKC Nair**
****Shyamal Kumar**
****Riya Lukose**

Abstract: *'Human relationship' has various phases. Counselling being a collaborative effort between the counselor and client, aims at identifying goals and potential solution to problems which causes emotional conflicts. A boy-girl relationship follows certain laws- 'laws of attraction, difference and self-image'. In this context, relationship counseling not only aims at identifying the problems but also provides insight into the type of relationship. Based on this knowledge, one can seek to improve communication and coping skills, strengthen self-esteem and promote behavioural changes and strong inter-personal relationships.*

Keywords: *Relationship, Counselling, Boy-Girl relationship, Love relationship*

Points to Remember

- ***The human relationship counselling model follows Roger's client-centered approach, where the client forms the core part of therapy process.***
- ***A boy-girl relationship follows certain laws- 'laws of attraction, difference and self-image'.***
- ***The boy-girl relationship can be of multiple types, and these have their own set of relationship issues.***
- ***A healthy boy-girl relationship is formed on the grounds of honesty, compassion, finding right balance, talking openly and having mutual respect.***
- ***Physical relationship before marriage can affect post marriage relationship.***

* Director,

** IAP Fellow in Developmental Pediatrics,
NIMS-Spectrum-Child Development Research Centre (CDRC),
NIMS Medicity Campus,
Thiruvananthapuram.

email: cdcmkc@gmail.com

References

1. Miles RE. Human relations or human resources? Harv Bus Rev 1965; 43(4):148-157.
2. Rogers C. The necessary and sufficient conditions of therapeutic personality change. J Consult Psychol 1957; 21(2):95-103.
3. Bratton S, Purswell K, Jayne K. Play therapy - A child centered approach. In: Thompson HP, Fedewa AL. (Editors). Counseling and Psychotherapy with Children and Adolescents. 5th Edn. Hoboken, New Jersey:John Wiley & Sons, Inc; 2015; pp95-97.
4. Okun BF. Effective Helping-The Human Relations Counseling Model' (From Correctional Counseling and Treatment. Peter C Kratcoski See NCJ-74557). United States: Duxbury Press; 1981; pp213-222.
5. Nair MKC. Presenting Family life education. In: MKC Nair, Ranjan K. Pejaver (Eds). Adolescence and Family Life Education. 1st Edn. Bangalore: Prism Books; 2002; pp97-146.
6. Paul KM, Suresh KG. Guidance and Counseling in School setting. In: Nair MKC, Babu George, Indira MS, Leena Sumaraj (Eds). Adolescent Counselling. 1st Edn. New Delhi:Jaypee Brothers; 2016; pp73-87.
7. Nair MKC, Babu George, Leena Sumaraj. Premarital Guidance and support. In: MKC Nair, Paul Russell, Babu George, Leena Sumaraj (Eds). Adolescent Pediatrics. 1st Edn. Delhi: Noble Vision: 2017; pp202-213.
8. Mini G, Asha Kumari, Nair MKC. Development of a tool on partner relationship and estimation of prevalence of marital disharmony among married people. Ph.D Thesis Submitted to University of Kerala, 2020.

CASE REPORT

HYPERTRANSAMINASEMIA MASQUERADING AS WILSON DISEASE

Riyaz A

Abstract: *It is indeed very unfortunate that clinicians occasionally embark on the pursuit of expensive and invasive investigations, including liver biopsy, in the evaluation of children with isolated elevation of transaminases. Many of these children may be subsequently found to have various myopathies, including Duchenne muscular dystrophy. Superfluous testing can be avoided by following the basic principles of medicine like good history taking and meticulous clinical examination followed by relevant investigations.*

Keywords: *Hypertransaminasemia, Wilson disease, Duchenne muscular dystrophy, Gamma-glutamyl transpeptidase, Creatine kinase.*

References

1. Riyaz A. Pediatric Gastroenterology and Hepatology. 4thedn. Hyderabad. Paras Medical publishers; 2019; pp 344-362.
2. Stenhammar L, Klintberg B, Tevebring J, Henriksson KG. Muscular dystrophy misdiagnosed as hepatic disease in a child with celiac disease. Acta Pediatr 1995; 84:707-708.
3. Caropreso M, Fortunato G, Lenta S, Palmieri D, Esposito M, Vitale DF, et al. Prevalence and long-term course of macro-aspartate aminotransferase in children. J Pediatr 2009; 154:744-748.
4. Rosales XQ, Chu ML, Shilling C, Wall RNC, Pastores GM, Mendell JR. Fidelity of Gamma-Glutamyl Transferase (GGT) in Differentiating Skeletal Muscle From Liver Damage. J Child Neurol 2008; 23(7):748-751.
5. Ulgen PA, Dirik E, Ercal D. Letters to the Editor. Indian Pediatrics 2002; 39:210-211.
6. Kohli R, Harris DC, Whitington PF. Relative elevations of serum alanine and aspartate aminotransferase in muscular dystrophy. J Pediatr Gastroenterol Nutr 2005; 41:121-124.
7. McMillan HJ, Gregas M, Darras BT, Kang PB. Serum transaminase levels in boys with Duchenne and Becker muscular dystrophy. Pediatrics 2011; 127:132-136.
8. Wright MA, Yang ML, Parsons JA, Westfall JM, Yee AS. Consider muscle disease in children with elevated transaminase. J Am Board Fam Med 2012; 25:536-540.
9. Veropalumbo C, Del Giudice E, Esposito G, Maddaluno S, Ruggiero L, Vajro P. Aminotransferases and muscular diseases: a disregarded lesson. Case reports and review of the literature. J Pediatr Child Health 2012; 48:886-890.
10. Ramachandran J, Sajith KG All that glitters is not gold: Elevated liver enzymes do not mean liver disease always. Indian J Gastroenterol. 2014; 33(5):476-477.

* Professor & Head of Pediatric Gastroenterology, KMCT Medical College, Calicut, Kerala.
email: riyazped@gmail.com

CASE REPORT

MYXEDEMA COMA IN A CHILD WITH DOWN'S SYNDROME

*Suchitra Sivadas
*Gayathri Sajeevan
*Sajitha S
*Jayakumar C
**Nisha Bhavani

Abstract: *Myxedema coma is a rare condition characterised by severe hypothyroidism leading to depressed mental status, hypothermia and multiorgan dysfunction as a result of reduced circulating levels of thyroid hormones. We present here a boy with Down syndrome who was admitted with progressive lethargy, hypotension, and hypothermia who was diagnosed to have myxedema coma and managed appropriately. Treatment includes ICU care, replacement with thyroxine, intravenous steroids and supportive measures. Worldwide there are only very few case reports of children with Down syndrome presenting as myxedema coma. The condition requires a high index of suspicion, prompt diagnosis and treatment, as it is potentially life threatening.*

Keywords: *Hypothyroidism, Downs syndrome, Child.*

References

1. Jordan RM. Myxedema coma: Pathophysiology, therapy and factors affecting prognosis. Med Clin North Am 1995; 79:185-94.
2. Nicoloff JT, Lo Presti JS. Myxedema coma. A form of decompensated hypothyroidism. Endocrinol Metab Clin North Am 1993; 22:279-90.
3. Kwaku MP, Burman KD. Myxedema coma. J Intens Care Med 2007; 22:224-31.
4. Coleman M. Thyroid dysfunction in Down syndrome: A review. Down Syndrome Research and Practice 1994; 2(3):112-115.
5. Thompson MD, Henry RK. Myxedema coma secondary to central hypothyroidism: A rare but real cause of altered mental status in pediatrics. Horm Res Pediatr 2016; 87: 350-353.
6. Root JM, Vargas M, Garibaldi LR, Saladino RA. Pediatric patient with altered mental status and hypoxemia. Pediatric Emergency Care July 2017; 33(7):486-488.
7. Salomo LH, Laursen AH, Reiter N, Rasmussen UF. Myxedema coma: an almost forgotten, yet still existing cause of multiorgan failure. BMJ Case Rep 2014; 2014:bcr2013203223.
8. Bansal D, Nanda A, Gupta E, Croker M, Williams ML, Bacchus A, et al. Myxedema coma in a patient with Down's syndrome. J Ark Med Soc 2006 Nov;103(5):112-113.

* Department of Pediatrics
** Department of Endocrinology,
Amrita Institute of Medical Sciences,
Kochi.
email : suchudas2482@gmail.com

CASE VIGNETTE

SUBCUTANEOUS ZYGOMYCOSIS

*Ashitha K. Unny
*Siddharth Pandian
**Seyed Rabia
***Gopinathan Kathirvelu
****Senthil G. Kamaraj

References

1. Thotan SP, Kumar V, Gupta A, Mallya A, Rao S. Subcutaneous phycomycosis-fungal infection mimicking a soft tissue tumor: a case report and review of literature. J Trop Pediatr 2010; 56(1):65-66. doi: 10.1093/tropej/fmp049.
2. Mathew R, Kumaravel S, Kuruvilla S, Varghese RG, Shashikala, Srinivasan S, et al. Successful treatment of extensive basidiobolomycosis with oral itraconazole in a child. Int J Dermatol 2005; 44(7):572-575. doi: 10.1111/j.1365-4632.2004.02419.x.
3. Gummadi GK, Pai BS, Nayak UKS, Prakash PY, Pai K. Basidiobolomycosis mistaken for cutaneous tuberculosis. Indian J Dermatol Venereol Leprol 2019; 85(2):236. doi: 10.4103/ijdvl.IJDVL_16_17. PMID: 29536980.

* Pediatric Surgery Resident
** Consultant Pathologist, Department of Lab Services, CHILDS Trust Medical Research Foundation, Kanchi Kamakoti CHILDS Trust Hospital, Chennai.
*** Prof of Radiodiagnosis, Department of Radiodiagnosis, Kilpauk Medical college, Chennai.
**** Senior consultantPediatric Surgeon, Department of Pediatric Surgery, CHILDS Trust Medical Research Foundation, Kanchi Kamakoti CHILDS Trust Hospital, Chennai.
email: ashitha.aku@gmail.com

CASE VIGNETTE

A RARE CAUSE OF OPEN ANTERIOR FONTANELLE IN A TODDLER

***Sridevi A. Naaraayan**
****Sharuka R**

References

1. Bosemani T, Orman G, Boltshaiser E, Tekes A, Huisman TAGM, Poretti A. Congenital abnormalities of posterior fossa. Radiographics 2015; 35(1): 200-220.
2. Knipe H, Thapa S. Tegmento vermian angle. Radiopedia [Internet]. Available from radiopedia.org/articles/tegmentovermian angle. Accessed on 21st May 2021.

* Associate Professor of Pediatrics
** Resident,
Kilpauk Medical College,
Chennai.
email : childdoctorsri@yahoo.co.in