



AN OVERVIEW OF SECONDARY IMMUNODEFICIENCY STATES IN CHILDREN ADMITTED TO PAEDIATRIC INTENSIVE CARE UNIT IN A TERTIARY CARE HOSPITAL IN GUNTUR DISTRICT OF ANDHRA PRADESH

Paediatrics

Dr. Tanveer Begum	DNB Paediatrics, DCH. Assistant Professor, Department of Paediatrics, Katuri Medical College and Hospital, Katuri Nagar, Guntur.
Dr. Duppati Dumdi Nandini	Postgraduate In M.D. Paediatrics, Department Of Paediatrics, Guntur Medical College, Guntur,
Dr. Tony B S	Postgraduate In M.D. Paediatrics, Department Of Paediatrics, Guntur Medical College, Guntur,

ABSTRACT

Objective: To review the different causes of secondary immunodeficiencies in children requiring prolonged hospital stay or recurrent hospital admissions and provide clinicians with an updated overview of potential factors that contribute to immunodeficiency in a tertiary care hospital over 18 months. **Background** Immunocompromised status is the common cause of morbidity and mortality in hospital-admitted children. Secondary immunodeficiency contributes to most of the immunocompromised states rather than primary, resulting from a variety of extrinsic factors that can affect a host with an intrinsically normal immune system, including undernutrition, infectious agents, drugs, metabolic diseases, and environmental conditions. In routine clinical practice, these arise from a number of conditions, such as treatment with glucocorticoids and immuno-modulatory drugs, surgery and trauma, extreme environmental conditions, and chronic infections, such as those caused by HIV. The most common cause of immunodeficiency is malnutrition, affecting many communities around the world with restricted access to food resources [1]. **Methods** This is a retrospective observational study using hospital records of children aged 1 month to 12 years, admitted to PICU from January 2021 to August 2022 in a tertiary care hospital in the Guntur district of Andhra Pradesh, India, who were underweight, or on some immunosuppressive agents and those who had hospital stay lasting more than 14 days and who needed >14 days of intravenous antibiotic. **Results** In children less than 1 year, protein energy malnutrition especially SAM is the most common cause of secondary immunodeficiency. Among children older than 1 year, children using steroids for nephrotic syndrome constitute the major cause. **Conclusion** As secondary immunodeficiency disorders are far more common than primary immunodeficiency disorders. PEM is the most common cause in children less than 1 year, Exclusive breastfeeding should be advised to all children, and attention to nutritional supplementation should be given as early as possible. Even brief exposure to steroids may land children into a state of immunosuppression, so judicious use of steroids is mandatory and regular follow-up is necessary.

KEYWORDS

Breastfeeding, Corticosteroids, HIV, Immunodeficiency disorders, Malignancies, Protein-energy malnutrition.

INTRODUCTION

Immunodeficiency disorders can be primary or secondary depending on their etiology. Primary immunodeficiency disorders result from intrinsic defects in the immune system involving the T cells, B cells, Complement components and Phagocytes, during early childhood, with clinical manifestations presenting in early life.. Secondary immunodeficiency occurs in children and adults without any prior genetic defects and is characterized by the development of repeated, prolonged infections requiring prolonged treatment with antibiotics. These disorders result from the adverse consequences of exposure to a variety of factors including infectious agents, drugs, metabolic diseases, and environmental conditions. They are far more common than primary immunodeficiencies caused by genetic defects [2]. Children on drugs like steroids, cyclophosphamide, azathioprine, mycophenolate, methotrexate, leflunomide, ciclosporin, tacrolimus, and rapamycin, which affect the functions of both T and B lymphocytes are also prone to have recurrent infection. Viral infections like HIV is a known cause of acquired immunodeficiency state as it mainly affects CD4+T cells and downregulates cellular immune responses that produce opportunistic infections and cancers, which are threatening to human health [3].

Malnutrition is one of the most important causes of secondary immunodeficiency, protein-energy malnutrition affects cell-mediated immunity and phagocytosis, the microorganisms that enter our body are first taken care of by our innate immune system which is later carried by the antigen-presenting cells to the phagocytes. cells to the phagocytes. In PEM the ability of phagocytic cells to kill intracellular organisms is impaired. Nutritional deficiencies can result from cancer, burns, chronic renal disease, multiple trauma, and chronic infections. Zinc and iron deficiencies have a variety of effects on immunity, including a reduction in delayed cutaneous hypersensitivity. Vitamin supplementation (B6 and B12), selenium, and copper are also important for the normal function of the immune system [4].

Secondary hypogammaglobulinemia (SHG) is also one of the causes of secondary immunodeficiency which is characterized by reduced immunoglobulin levels due to acquired causes of decreased antibody production or increased antibody loss. It should be suspected in

children with protein loss syndromes [5]. Children with nephrotic syndrome have a loss of immunoglobulins and are also on corticosteroid therapy, both of these conditions place them at higher risk of infections. In children with this history, a thorough investigation of potential aetiologies of SHG need to be reviewed and an effective treatment plan focused on the removal of iatrogenic causes (like discontinuation of an offending drug) or treatment of the underlying condition (i.e; management of nephrotic syndrome) should be instituted. When iatrogenic causes cannot be removed or underlying conditions cannot be reversed, therapeutic options are not clearly delineated but include heightened monitoring for clinical infections, supportive antimicrobials, and in some cases, immunoglobulin replacement therapy [6].

MATERIALS AND METHODS

This study was conducted in a tertiary care hospital in the Guntur district of Andhra Pradesh. This study aimed to analyze the different causes of immunocompromised states and the most common presentation of these disorders among children, 1 month to 12 years of age, admitted to a paediatric intensive care unit in a tertiary care centre in Guntur district of Andhra Pradesh from January 2021 to August 2022.

It is a retrospective study where the data of 100 children admitted to PICU with a history of chronic illness like HIV (RVD), Diabetes Mellitus (DM), Nephrotic Syndrome (NS), Malignancy, Severe Acute Malnutrition (SAM), etc. or of those who are on long-term treatment is collected, and their clinical presentation, days of hospital stay, days on antibiotics and investigations are recorded.

Statistical Analysis:

All the data was recorded on an excel sheet and analysis of data was done using SPSS 22.0 software. Student t-tests and chi-square tests were applied. P value was calculated using Pearson correlation coefficients, and a p-value of <0.05 was considered significant.

RESULTS

Table 1: Age Distribution Of Various Immunodeficiency Disorders

Etiology	Age in years													Total
	<1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11	11-12	12	
NEPHROTIC SYNDROME	1	2	3	3	6	-	1	1	2	1	2	5	-	25
Type 1 DM	-	-	-	-	2	1	2	2	2	1	5	4	2	21
RVD	2	2	1	-	-	-	-	1	3	1	3	2	3	18
SAM	9	-	4	2	1	1	1	-	-	-	-	-	-	18
Malignancy	-	-	1	1	1	-	1	1	2	2	1	2	-	11
PRIMARY IMMUNODEFICIENCIES	-	1	1	1	-	-	-	3	-	-	-	-	-	6
OTHERS	-	-	-	-	-	-	-	-	-	-	-	-	1	1
Total	12	5	7	7	10	2	5	8	9	5	11	13	6	100

The most common age of presentation was 11-12 years followed by <1 year of age. The different causes of prolonged hospital stay in the order of frequency were nephrotic syndrome, Type 1 Diabetes with DKA, HIV, SAM, Malignancies, and Primary immunodeficiency. In one case, the cause was presumed to be an inborn error of metabolism where workup was not done due to financial constraints.

Types Of Immunodeficiency Conditions In Children Causing Hospitalization

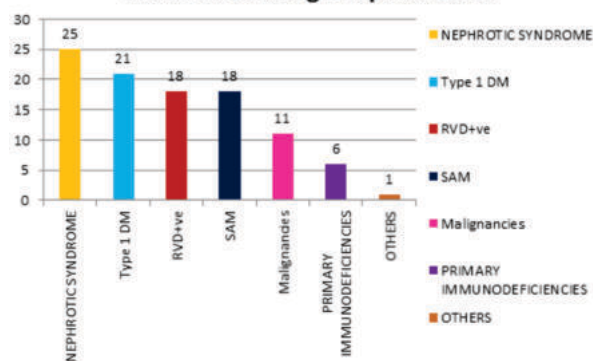


Figure 1: Relative Frequencies Of Various Immunodeficiency Disorders.

Types of Immunodeficiencies in different Age Group Children

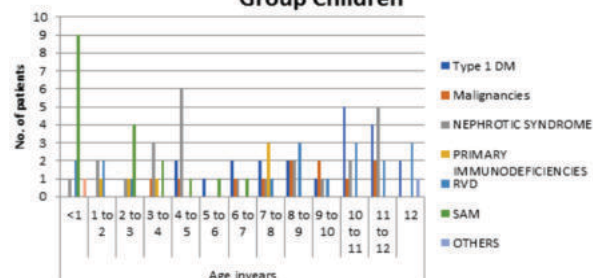


Figure 2: Distribution Of Children With Immunodeficiency With Respect To Age And Aetiology.

Out of 100 children studied, 43 were girls and 57 boys.

The most common age of presentation of NS is 4-5 years. Among the various immunodeficient states without considering age, the most common cause was Nephrotic Syndrome, and the second most common was DM. Whereas in children less than 1 year, malnutrition was found to be the most common cause of an immunodeficient state with a p-value <0.05.

The most common clinical presentation was different, in different conditions. In children with Nephrotic syndrome, the most common presenting symptom was abdominal distension associated with fever, secondary to spontaneous bacterial peritonitis followed by lower respiratory tract infection, whereas children with DM were admitted with Diabetic ketoacidosis with secondary infection and sepsis. The third most frequent illness is severe acute malnutrition and HIV. Overall, the most common presentation was lower respiratory tract infection which is pneumonia.

Eleven children out of a hundred were suffering from malignancies, Acute lymphoblastic leukemia was the most common malignancy. Four out of eleven were suffering from ALL on treatment, three cases were of brain tumours, two cases of Wilms tumour, and one lymphoma. The most common cause of prolonged hospital stay was recurrent pneumonia.

As evidenced by genetic studies, six out of a hundred cases were diagnosed with primary immunodeficiency disorders.

One case was presumed to be due to inborn errors of metabolism but workup was not done due to financial constraints.

Overall, the most common presentation was lower respiratory tract infection, followed by prolonged diarrhoea or persistent diarrhoea. The average duration of hospital stay was 22 days, with antibiotic use for more than 14 days for recovery. Each child was admitted 3-4 times a year.

DISCUSSION

Immunodeficiency disorders can be primary or secondary. Primary immunodeficiency disorders are caused due to defective development of the immune system due to some genetic defect, whereas secondary immunodeficiency disorders are caused by conditions like diabetes, malignancies, certain drugs like corticosteroids [7], immunomodulatory drugs [8], radiotherapy, and states of malnutrition. Secondary immunodeficiencies are far more common than primary disorders [9]. There are reports that say that malnutrition is the most cause of secondary immunodeficiency. In our country, PEM starts from birth with a birth weight <2.5 kgs placing these children at risk for malnutrition [10]. Exclusive breastfeeding for the first six months of life is an important intervention in the prevention of malnutrition [11]. Protein-calorie malnutrition is the biggest global cause of sudden infant death syndrome (SIDS) which can affect up to 50% of the population in some communities of the developing world [12]. In PEM, T cell number and function are depressed which places the child at risk for various infections. Even the present study states that PEM is the major cause of recurrent infection in children less than one year of age placing the child in threat of further malabsorption and further PEM. In the present study respiratory infections followed diarrhoea were the major causes of recurrent admission. This can be resolved if malnutrition is treated. The next major cause of an immunodeficient state is drugs like corticosteroids for nephrotic syndrome. This is seen in the 4-5 years age group of children.

Besides malnutrition and drugs, there are chronic infections like HIV which affect the T cell number as well as its function. The virus attacks CD4+ T cells, which play a critical role in preventing infection, and gradually depletes their numbers. Once the T cell count is less than 200 cells per decilitre, the child is at high risk of recurrent infections that will eventually lead to death if not treated appropriately [13]. The present study also states that HIV is one of the causes of prolonged duration of infection. These children need treatment with antiretroviral drugs. Screening of all pregnant women and giving ART to all those infected is an important factor affecting the outcome of children born to HIV-positive mothers [14].

Primary immunodeficiency disorders comprise about 6% of children with a prolonged hospital stay. All these children should be screened appropriately.

CONCLUSION

The secondary immunodeficiency state is one of the common causes of prolonged hospital stays causing a lot of burden on the families of these children as well as the society. Due attention should be given to all the children suffering from malnutrition, nephrotic syndrome, malignancies, diabetes and HIV, and their parents should be informed of the varied causes of prolonged hospital stay in these children, and proper counselling should be given.

Acknowledgment:

We acknowledge the hospital staff and other colleagues who helped us in drafting the paper.

Conflict Of Interest: nil

Funding: nil

REFERENCES

- Nelson textbook of pediatrics. 21st edition. Part XIII. Immunology. 4625-5139.
- Textbook: Roitt, Brostoff, Male Immunology. 6th edition. Chapter 20. pp. 313-321.
- Rocklin RE. Use of transfer factor in patients with depressed cellular immunity and chronic infection. Birth Defects Orig Artic Ser. 1975;11(1):431-5. [PubMed]
- Rehman AM, Woodd SL, Heimbürger DC, et al. Changes in serum phosphate and potassium and their effects on mortality in malnourished African HIV-infected adults starting antiretroviral therapy and given vitamins and minerals in lipid-based nutritional supplements: secondary analysis from the Nutritional Support for African Adults Starting Antiretroviral Therapy (NUSTART) trial. Br J Nutr. 2017 Mar;117(6):814-821.
- Otani IM, Lehman HK, Jongco AM, et al. Practical guidance for the diagnosis and

- management of secondary hypogammaglobulinemia: A Work Group Report of the AAAAI Primary Immunodeficiency and Altered Immune Response Committees. *J Allergy Clin Immunol.* 2022 May;149(5):1525-1560. doi: 10.1016/j.jaci.2022.01.025. Epub 2022 Feb 14. PMID: 35176351
6. Lee SJ, Chinen J, Kavanaugh A. Immunomodulator therapy: Monoclonal antibodies, fusion proteins, cytokines, and immunoglobulins.
 7. Annane D, Bellissant E, Bollaert PE, Briegel J, Confalonieri M, De Gaudio R et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. *JAMA* 2009; 301:2362–75. [PubMed: 19509383].
 8. Tan HP, Smaldone MC, Shapiro R. Immunosuppressive preconditioning or induction regimens, evidence to date. *Drugs* 2006; 66:1535–45. [PubMed: 16956302].
 9. Justiz Vaillant AA, Qurie A. Immunodeficiency. [Updated 2022 Jul 8]. In: StatPearls [Internet].
 10. Black RE, Allen LH, Bhutta ZA, et al. Maternal and Child Undernutrition Study Group. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet* 2008; 371:243–60. [PubMed: 18207566]
 11. Lewis DB. Development of the fetal and neonatal immune system: Rich RR, editor. *Clinical immunology. Principles and practice.* 3rd ed. Philadelphia: Elsevier Saunders; 2008 p. 493–502.
 12. Abdelkawy RFM, Abo-Shanab AM. Immunological Markers in Children with Genetic Disorders and Recurrent Respiratory Tract Infections. *Open Access Maced J Med Sci* [Internet]. 2020 Feb. 5 [cited 2023 Jan. 27];8(B):104-8.
 13. Brenchley JM, Schacker TW, Ruff LE, Price DA, Taylor JH, Beilman GJ, Nguyen PL, Khoruts A, Larson M, Haase AT, Douek DC. CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. *The Journal of experimental medicine.* 2004 Sep 20;200(6):749-59.
 14. Hoffman R, Black V et al. Effects of highly active antiretroviral therapy duration and regimen on risk of mother to child transmission of HIV in Johannesburg, South Africa. *Journal of acquired immunodeficiency syndromes* (1999). 2010 May 5;54(1):35.