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RESEARCH ARTICLE

SPECTRUM OF PRIMARY IMMUNODEFICIENCY DISORDERS IN CHILDREN IN KASHMIR

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Abstract

Primary immunodeficiency disorders (PIDs) are a genetically heterogeneous group of disorders that affect distinct components of the innate and adaptive immune system. To date, more than 300 different PIDs have been identified, most of these manifesting by 1 year of life. Recognition of these disorders by the clinician is important because appropriate therapy will not only prevent death but also reduce the long-term morbidity from recurrent infections. There is often under diagnosis of these conditions or a delay in the diagnosis of treatable conditions. Delay in the diagnosis of PID disorders is not only evident in undeveloped or developing countries, but is also reported in developed countries. On the other hand, early diagnosis and easy access to care and treatment play key roles in improving the survival, quality of life, and prognosis of patients with these disorders. Evaluation of immune function should be initiated for children with clinical manifestations for a specific immune disorder or with unusual, chronic, or recurrent infections such as systemic bacterial infections, serious respiratory bacterial infections, liver or brain abscesses, infections with unusual pathogens, and infections with common childhood pathogens but of unusual severity. No study regarding the pattern of diseases, clinical profile, complications and outcomes of primary immunodeficiency diseases has been done in Kashmir, which is **geographically, socially, culturally, and ethnically a unique population.** This study will through some light on the spectrum of primary immunodeficiency Disorders (PID) in this part of the world and help policy makers to set up an ideal platform for the management of these comparatively ignored but important diseases.

Aims And Objectives: To study the clinical profile, disease complications and short-term outcomes of patients over a period of two years with Suspected primary immunodeficiency Disorders (PID); to ascertain the association of immunoglobulin levels and CD counts with PID.

Materials And Methods: This Prospective observational study was conducted in the Department of Pediatrics, Government Medical College, Srinagar. A detailed history was taken from each patient's attendant after confirming the reliability of the attendant (ideally mother or father) with special reference to the presence/ absence of manifestation of Primary immunodeficiency disorders. A thorough clinical examination was done after obtaining written informed consent

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from all patients for their inclusion in the study. In this study, 30 patients ,0-18 years of age, who met the inclusion criteria were included.**:** The duration of the study was two years and three months starting from September 2020-December 2022 (The first 3 months for patient recruitment). Data was compiled using Microsoft 2016 Excel spreadsheet and analyzed by IBMSPSS V.23. Descriptive statistics was computed to describe the sociodemographic characteristics of participants and to summarize the distribution of each of the dependent (outcome) and independent variables.

Results: In this study, 30 patients with suspected Primary immunodeficiency disorders (PIDs) were recruited for three months and each patient was followed for two years as per study protocol. About 47% of the patients were products of 3rd degree consanguineous marriage, 33.3% of patients had a family history of Primary immunodeficiency disorders and 6.7% had received blood transfusions presently or in the past.Serum immunoglobulins profile was deranged in more than half of the patients. IgM was seen to be low in 60% of the patients, IgG and IgA were low in 36.7 % of the patients and IgE was high in 26% of the patients with suspected primary immunodeficiency disorder. CD4 and CD19 counts were seen to be low in 20% of patients and 16.7% of patients reported low CD8 count. Other diagnostic tests like Broncho-alveolar lavage (BAL) showed growth in 3.3% of patients, WAS protein was low in 16.7 % of the patients.The association of CD4 Counts was found to be statistically significant with p value <0.002 by Fisher's Exact test. Patients with low CD4 count had 83.3% mortality as compared to those having normal counts. There was a strong association seen in patients with low CD8 counts with mortality among PID patients and p valve was highly significant (p valve <0.0005).

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Introduction:-

Primary immunodeficiency disorders (PIDs) are a genetically heterogeneous group of disorders that affect distinct components of the innate and adaptive immune system, such as neutrophils, macrophages, dendritic cells, complement proteins, natural killer cells, and T and B lymphocytes. Most primary immunodeficiencies are genetic disorders; the majority are diagnosed in children under the age of one year, although milder forms may not be recognized until adulthood (1, 2).PIDs are distinct from acquired, secondary, transient, or stable immunodeficiency states including, but not limited to, those of iatrogenic or viral (e.g. HIV in particular, influenza and measles viruses) etiology, as well as those resulting from splenectomy or autoinflammatory disorders such as type 2 diabetes mellitus.

To date, more than 300 different PIDs have been identified (3). The data from two large claims databases from 2001 to 2007 have reported the prevalence in children with PIDs has increased from 38.9 to 50.5 per 100,000 among privately insured and from 29.1 to 41.1 per 100,000 among publicly insured persons. [3A]. As per the Indian Society for Primary Immune Deficiency, the prevalence rates for diagnosed PIDs have been estimated to be 1 in 2,000 for children, and 1 in 1,200 for all based on a population-based survey in the United States. The prevalence of all PIDs per 100,000 was reported to be 66.6, 82.2, 97.4, and 126.8 in 2003, 2006, 2009, and 2012, respectively in the United States. The highest prevalence was among children 0-5 years of age (56%) as compared to other age groups and the overall mortality was 2% (3A). In India, a study conducted about 50 years ago reported an incidence of around **1.5 per 100,000 live births** (3B).

Recognition of these disorders by the clinician is important because appropriate therapy will not only prevent death but also reduce the long-term morbidity from recurrent infections (4). There is often under diagnosis of these conditions or a delay in the diagnosis of treatable conditions. Delay in the diagnosis of PID disorders is not only evident in undeveloped or developing countries, but is also reported in developed countries. On the other hand, early

diagnosis and easy access to care and treatment play key roles in improving the survival, quality of life, and prognosis of patients with these disorders (5). Recent advances in molecular biology have led to the identification of molecular defects for a number of PIDs, which has led to the development of new diagnostic tools with the prospect of new therapies for these disorders (6, 7-8). Because PIDs occur infrequently and are highly heterogeneous in nature, relatively few centers gain extensive experience in the diagnosis management and applied research of these disorders (6,9-11). Extensive use of antibiotics by physicians has masked the classic presentation of many of the primary immunodeficiency diseases. Evaluation of immune function should be initiated for children with clinical manifestations for a specific immune disorder or with unusual, chronic, or recurrent infections such as systemic bacterial infections, serious respiratory bacterial infections, liver or brain abscesses, infections with unusual pathogens, and infections with common childhood pathogens but of unusual severity (12).

A generally accepted classification of PID includes antibody deficiency, cellular deficiency, combined (humoral and cellular) immunodeficiency, phagocytic disorders, and complement deficiency. Apart from infectious complications, patients with PID are also predisposed to several non-infectious complications such as autoimmune diseases and malignancies (13). The international union of immunological societies (IUIS) expert committee for primary immunodeficiency has classified all PIDS under 9 different subheadings.

1. Immunodeficiencies affecting cellular and humoral immunity (e.g., SCID)
2. Combined Immunodeficiencies with associated or syndromic features (e.g., Wiskott Aldrich syndrome, hyper IgE syndrome, and DNA repair defects such as ataxia telangiectasia)
3. Predominantly antibody deficiencies (e.g., X- linked and autosomal recessive agammaglobulinemia and CVID)
4. Diseases of immune dysregulation (e.g., familial hemophagocyticlymphohistiocytosis)
5. Congenital defects of phagocyte number, function, or both (e.g., neutropenia, chronic granulomatous disease and leucocyte adhesion defect)
6. Defects in intrinsic and innate immunity (e.g., mendelian susceptibility to mycobacterial disease, STAT 1 deficiency, STAT1 gain of function and IL- 17 deficiency; the majority of them also predispose to CMC)
7. Autoinflammatory disorders (e.g., Familial Mediterranean fever, neonatal-onset multisystem inflammatory disease [NOMID], and disorders with sterile inflammation involving skin, bone and joints that may manifest as sterile pustular eruptions such as deficiency of IL- 1 receptor antagonist [DIRA], deficiency of IL-36 receptor antagonist [DITRA], and neonatal inflammatory skin and bowel disease)
8. Complement deficiencies (e.g., C1q deficiency presenting as early-onset lupus and C1 inhibitor deficiency presenting as hereditary angioedema)
9. Phenocopies of PID (e.g., antibodies to IL17 or IL-22 presenting as CMC and antibodies to C1inhibitir presenting as angioedema)

In 1990, the Jeffrey Modell Foundation (an international nonprofit organization established for the welfare of individuals and families affected by PIDs) proposed 10 warning signs (14) to help physicians suspect the diagnosis of PID which are line listed below:

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in the mouth or fungal infection on the skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including septicemia.
10. A family history of PID

Delay in diagnosis and inadequate management may lead to permanent organ damage, such as bronchiectasis and bronchiolitis obliterans, or even death from overwhelming sepsis (15).

To our best knowledge, no study regarding the pattern of diseases, clinical profile, complications and outcomes of primary immunodeficiency diseases has been done in Kashmir, which is **geographically, socially, culturally, and ethnically a unique population.** This study will through some light on the spectrum of primary immunodeficiency Disorders (PID) in this part of the world and help policy makers to set up an ideal platform for the management of these comparatively ignored but important diseases.

Aims:-

To study the clinical profile, disease complications and short-term outcomes of patients over a period of two years with Suspected primary immunodeficiency Disorders (PID).

Objectives:-

Primary Objective:

1. To assess the pattern of primary immunodeficiency Disorders in Kashmir.
2. To study the clinical profile, disease complications and short-term outcomes of patients over a period of two years of primary immunodeficiency Disorders in Kashmir.

Secondary Objectives:

1. To determine the association of Immunoglobulins with primary immunodeficiency Disorders.
2. To determine the association of CD Counts with primary immunodeficiency Disorders.

Materials And Methods:-

Study design:

This Prospective observational study was conducted in the Department of Pediatrics, Government Medical College, Srinagar. A detailed history was taken from each patient's attendant after confirming the reliability of the attendant (ideally mother or father) with special reference to the presence/ absence of manifestation of Primary immunodeficiency disorders. A thorough clinical examination was done after obtaining written informed consent from all patients for their inclusion in the study. In this study, 30 patients who met the following inclusion criteria were included.

Inclusion Criteria

1. Age group 0 months to 18 years
2. Four or more new ear infections within 1 year
3. Two or more serious sinus infections within 1 year
4. Two or more months on antibiotics with little effect
5. Two or more episodes of pneumonia within 1 year
6. Failure of an infant to gain weight or grow normally
7. Recurrent, deep skin or organ abscesses
8. Persistent thrush in the mouth or fungal infection on the skin
9. Need for intravenous antibiotics to clear infections
10. Two or more deep-seated infections including septicemia
11. A family history of PID

Exclusion Criteria

1. Secondary immunodeficiency disorders
2. Cancers of the immune system like leukemia
3. Patients who are on chemo and Radio therapy
4. HIV positive cases
5. Diabetes
6. Malnutrition
7. Downs syndrome
8. Aplastic anemia
9. Tuberculosis
10. Nephrotic syndrome

Study Duration:

The duration of the study is two years and three months starting from September 2020-December 2022 (The first 3 months for patient recruitment). During the first 3 months data was collected and follow-up was done for two years for each patient. Although permission from the institutional ethical committee was obtained in November, we were piloting from September 2020 for the validation of the study instrument. As per the study design the 2-year follow-up of the patients was mandatory, so we also included the patients recruited in the pilot study, to have a good sample

size. The data entry, analysis, and write-up were carried out one month after the completion of the follow-up of all the patients.

Sample size:
The sample size was kept open and all the eligible patients were recruited for 3 months of duration as per the study design. A total of thirty (30) patients were ultimately recruited for the study.

Sample plan:
The selectedPID patients were informed about the objectives of the study. Proper written informed consent was taken from the selected patients who agreed to participate in the study as shown in Annexure in English/ Urdu language. Then the relevant information regarding their socio-demographic variables, and other desired as per the performed questionnaire was obtained. A detailed history was taken and a clinical examination was also done as mentioned earlier.

Participants:
Children between 0 months to 18 years of age

Tools used:
Laboratory monitoring of PID at base line and follow-up will include
1. Complete blood count (CBC) with differential white blood cell count and PBF
2. These tests are of great clinical importance because they allow the physician to know whether the lymphocyte, neutrophil, and platelet counts are normal. Many immune defects can be detected by these simple tests.
3. Serum immunoglobulin (IgG, IgA, IgM, IgE) Levels
4. Myeloperoxidase (MPO) staining
5. Flow cytometry- CD4, CD8, CD11, CD18, CD19 (as and when possible).
6. Complete exome sequencing (as and when possible)
7. X-ray chest

Data Analysis
Data was compiled using Microsoft 2016 Excel spreadsheet and analyzed by IBMSPSS V.23. Descriptive statistics was computed to describe the sociodemographic characteristics of participants and to summarize the distribution of each of the dependent (outcome) and independent variables.

Operational Definitions:
The laboratory tests were done in the Department of Paediatrics, Children Hospital Srinagar, serum immunoglobulin profile and flow cytometry was done in National Accreditation Board for testing and calibration laboratories (NABL) during this study as per the following reference range is given in Tables below:

Complete Blood Count			
S No.	**TEST NAME**	**UNIT**	**REFRENCE RANGE**
1.	HB	g/dl	11.0-17.0
2.	TLC	^{3}/µL	3000-15000
3.	ANC	^{3}/µL	1800-6300
4.	ALC	^{3}/µL	2000-7000
5.	Platelet	^{3}/µL	50000-400000
6.	MPV	Fl	9.0-13.0
7.	ESR	mm/hr.	0-13
8.	AEC	^{3}/µL	150—500
9.	CRP	mg/L	0-10
10.	Peripheral smear	-	-

Immunoglobulin PROFILE			
S.No.	Ig	UNIT	REFRENCE RANGE
1.	IgG	mg/dl	460-1240
2.	IgA	mg/dl	25-160
3.	IgM	mg/dl	45-200

4.	IgE	mg/dl	0-180

FLOW CYTOMETRY			
S No.	**TEST**	**UNIT**	**REFRENCE RANGE**
1.	CD4	µL	1400-3700
2.	CD8	µL	490-1300
3.	CD19	µL	610-2600

Results:-

In this study, 30 patients with suspected Primary immunodeficiency disorders (PIDs) were recruited for three months and each patient was followed for two years as per study protocol. Out of these 30 patients, 25 (83.3%) were males and 5 (16.7%) patients were females. The mean age of the participants was 30.27 months with a minimum age of 2 months and a maximum of 132 months. The mean birth weight of the patients was 2.77+0.19 Kg, with a maximum weight of 3.2 kg and a minimum weight of 2.4 kg. About 47% of the patients were products of 3rd degree consanguineous marriage, 33.3% of patients had a family history of Primary immunodeficiency disorders and 6.7% had received blood transfusions presently or in the past. Most of these patients came with symptoms and signs of respiratory tract infections (43.3%), skin rashes (33.3%), eczema (33.3%), otitis media (26.7%) and osteomyelitis (23.3%). Abscesses, recurrent diarrhea, candidiasis, facial dysmorphisms and lymphadenopathy were other presentations. Tonsillar enlargement (96.7%), splenomegaly (10%) and tachycardia (10%) were noted.

Etiology of Primary Deficiency Disorders among the Patients and their Outcome.					
S No.	**Primary Deficiency Disorders**	**Frequency**	**Percent**	**Expired**	
1	**WISKOTT ALDRICH SYNDROME(WAS)**	7	23.3	2	
2	**BRUTONS AGAMMAGLOBULINEMIA(XLA)**	6	20.0	1	
3	**SEVERE COMBINED IMMUNODEFICIENCY(SCID)**	5	16.7	4	
4	**COHEN'S SYNDROME**	3	10.0	0	
5	**SPECIFIC GRANULE DEFICIENCY**	3	10.0	0	
6	**CHRONIC GRANULOMATOUS DISEASE (CGD)**	2	6.7	0	
7	**IDIOPATHIC CD4 LYMPHOCYTOPENIA**	1	3.3	1	
8	**HYPER IGE SYNDROME**	1	3.3	0	
9	**COMMON VARIABLE IMMUNODEFICIENCY (CVID)**	1	3.3	0	
10	**PRIMARY AUTOIMMUNE NEUTROPENIA**	1	3.3	0	
	Total	**30**	**100.0**	**8**	

The complete blood count of the patients revealed Hemoglobulin <11 gm/dl in 50% of the patients, although TLC was low in only 3.3% of the patients, Absolute neutrophil count was intermittently low in 50 % of the patients. ALC and Eosinophils were low in 16.7% and 3.3% of the patients respectively. Moreover, 40% of the patients reported low platelet count. About 30% of the patients were found to have high CRP. Peripheral blood film revealed Hypo segmented Neutrophils in 6.7% of the patients and Lymphopenia in 3.3% of the patients. The Pus culture was positive for 16.7% of the patients.

Serum immunoglobulins profile was deranged in more than half of the patients. IgM was seen to be low in 60% of the patients, IgG and IgA were low in 36.7 % of the patients and IgE was high in 26% of the patients with suspected primary immunodeficiency disorder. CD4 and CD19 counts were seen to be low in 20% of patients and 16.7% of patients reported low CD8 count. Other diagnostic tests like Broncho-alveolar lavage (BAL) showed growth in 3.3% of patients, WAS protein was low in 16.7 % of the patients. Whole Exome sequence was advised to all 30 patients but only 7 patients were able to do this test at NABL, and was found positive in all the 7 patients (100%)

During the follow-up of the patient for two years 8 patients i.e. (26.7%) mortality was seen. So, the mortality as per Mid-P Exact method was 26.66% with CI (13.22%-44.43%). The Confidence Interval was wide because of less sample size. The mortality was highest among SCID patients (80%). Although there was 100% mortality in Idiopathic CD4 Lymphocytopenia patients but only one patient was recruited in the study. There was 28.5% mortality seen amongst the 7 patients of WAS recruited in the study. The statistical tests were done to find the difference among the subgroups of Primary Immunodeficiency disorders and it was found that there was no significant difference in mortality among the subgroups with p valve <0.15 (Fisher's Exact Test).

The association of CD4 Counts was found to be statistically significant with p value <0.002 by Fisher's Exact test. Patients with low CD4 count had 83.3% mortality as compared to those having normal counts. There was a strong association seen in patients with low CD8 counts with mortality among PID patients and p valve was highly significant (p valve <0.0005). The statistical tests showed no association of CD19 counts with the outcomes in this study and p valve <0.9 was found by Fisher's Exact test. There was an association of low IgM levels with the mortality of the PID patients and p valve <0.05, which was noticed during the statistical analysis. A statistically significant difference in PIDs and IgG levels was found (p valve <0.005). Strong statistically significant difference in PIDs and IgM levels was found (p valve <0.0005). A statistically significant difference in PIDs and IgA levels (p valve <0.0005), and PID and IgM levels (p valve <0.005) was also found.

Discussion:-

PIDs are rare inherited disorders involving the immune system, typically associated with recurrent and severe infection, autoimmune disease, and increased incidences of malignancies. The prevalence of undiagnosed primary immunodeficiency disorders is remarkably high in developing countries and contributes to increasing the rate of morbidity and mortality among this group of patients. Due to the wide spectrum of signs and symptoms, a multi-disciplinary approach is often required to diagnose and manage these disorders promptly. Such facilities are sparse in low/middle-income countries resulting in underdiagnosis. Besides, straightforward cases of PID may remain undiagnosed as underlying immunodeficiency may not be suspected at all as an etiological cause of infection. Even when a diagnosis of PID is attained, pertinent data often remain unpublished due to a lack of large datasets.

Therefore, the present study was conducted to evaluate the relative frequency of primary immunodeficiency disorders in children of our region. Our study highlights that the awareness regarding PIDs amongst the general public and clinicians is increasing in this region.

The total number of children diagnosed to have primary immunodeficiency disorders during the study period was 30 and each patient was followed for two years as per study protocol. We observed a wide spectrum of PIDs in our study ranging from combined immunodeficiency to antibody deficiency to disorders of neutrophil function and number. This includedWiskott Aldrich syndrome(n=7), Bruton's agammaglobulinemia (n=6), Severe combined immunodeficiency (n=5), Cohen's syndrome(n=3), Specific granule deficiency(n=3), CGD(n=2). Other types reported were Idiopathic CD4 Lymphocytopenia, Hyper IgE syndrome, CVID and PAIN. Antibody deficiency was the commonest group of PID diagnosed in this study.

Diagnosis of antibody deficiency may be relatively easier in developing countries as facilities for performing immunoglobulin assays are available and at affordable prices. However, facilities for performing flow cytometry are limited and, when available, costs are huge. Only a basic lymphocyte subset analysis could be performed in most of the patients. Therefore, further delineation of types of antibody deficiency was not possible in many cases. In only a few patients, the diagnosis of PID could be confirmed by genetic testing. Nonetheless, even in the developed regions of the world, antibody deficiencies are the commonest subset of PIDs. Similarly, Wiskott-Aldrich syndrome was a commonly diagnosed PID in our study. Data from recent multicenter data from the rest of India suggest that antibody deficiencies are one of the commonest PIDs diagnosed. Besides, chronic granulomatous disease and SCID are other commonly diagnosed PIDs. The mean age of the participants was 30.27 months with a minimum age of 2 months and a maximum of 132 months. While most SCID patients were affected very early, the affected children above 10 years were the least. In Patients with SCID and other severe forms of PID are likely to be diagnosed the earliest given the severe disease manifestations [39]. Besides, countries employing newborn screening would be able to diagnose severe forms of PIDs soon after birth

Out of the 30 patients, 25 (83.3%) were males and 5 (16.7%) patients were females. The age of onset of the disease was also very early in male children compared to female children. The high rate of occurrence in males could be explained by X -linked diseases such as X- linked CGD, WAS, and X-linked SCID.

An in-depth history revealed consanguinity amongst parents in about 47% of the patients, a family history of Primary immunodeficiency disorders in about 33% and 6.7% having received blood transfusions presently or in the past. Family history of sibling deaths was elicited in1 family.

Most of the patients (43%) presented with symptoms and signs of respiratory infections. Chest X-ray findings for pneumonia were seen in 33.3% of patients. It was followed by rashes (33.3%), ear discharge (26.7%) of the patients, and 23.7% had a history of osteomyelitis or were suffering from the same.

On general examination, patients' weights and heights were within normal limits for their age. Although CVS examination was grossly normal, heart rate was high in 33.3% of the patients. Likewise, in the respiratory system, abnormal breath sounds and respiratory rates were found in 40% of the patients. Respiratory infection was the most common complication including sinusitis, acute otitis, bronchitis, bronchiectasis, and pneumonia. The second common complications were infections of the skin and mucous membranes. Opportunistic infections were the presenting manifestation in most patients. These included pneumonia, diarrhea, oral thrush, BCG site ulceration otitis media and meningitis.

Serum immunoglobulins profile was deranged in more than half of the patients. IgM was seen to be low in 60% of the patients, IgG and IgA were low in 36.7 % of the patients and IgE was high in 26% of the patients with suspected primary immunodeficiency disorders

The complete blood count of the patient revealed Hemoglobulin <11 gm/dl in 50% of the patients, although TLC was low in only 3.3%of the patients, and Absolute neutrophil count was intermittently low in 50% of the patients. Moreover, there were 40% of the patients reported low platelet counts. About 30% of the patients were found to have high CRP. Peripheral blood film revealed Hypo segmented Neutrophils in 6.7% of the patients and Lymphopenia in 3.3% of the patients. The Pus culture was positive for 16.7% of the patients.

CD4 and CD19 counts were seen to be low in 20% of patients and 16.7% of patients reported low CD8 count. The CD11 count was normal in all the patients. During the follow-up of the patient for two years 8 patients i.e. (26.7%) mortality was seen. The mortality, as per Mid-P Exact method, was 26.66% with CI (13.22%-44.43%). The Confidence Interval was wide because of less sample size. The mortality was highest among SCID patients (80%). Although there was 100% mortality in Idiopathic CD4 Lymphocytopenia patients but only one patient was recruited in the study. In our study, the majority of the children died due to sepsis. The majority of the SCID children died. Male children are most commonly affected. Children were normal at birth. The diagnosis may be significantly delayed because the complicated infections present in these children may not initially be distinguishable from routine childhood infections. The most common infections are pneumonia, persistent diarrhea, disseminated BCGosis, and candidiasis (oral, esophageal, and perianal). Due to complications of various infections, these infants usually die during the first year of life. Sometimes if such babies are left untreated, they may die within a few months. The treatment of SCID is to treat the existing infections and antimicrobials, antifungals and IVIG prophylaxis are to be given to avoid further infections. Enzyme replacement therapy, gene therapy, and stem cell transplantation are the definitive treatment options available nowadays. Mortality in other etiological groups included (2/7) in WAS, (1/5) in Bruton Agammaglobulinemia and (1/1) in Idiopathic CD4 Lymphocytopenia. There were no deaths fromCGD, Cohen's Syndrome, Hyper IgE Syndrome, and specific granule deficiency.

Limitations

Insufficient understanding of these illnesses leads to delayed referral. As a result, these children pass away before a diagnosis is made.

The current era's improper usage of antibiotics conceals diseases and makes it very challenging to diagnose these conditions.

A significant issue that contributes to the majority of these illnesses going untreated is the lack of diagnostic facilities.

Children who have infections at a very high incidence and who do not respond to the majority of antibiotics die as a result.

Conclusion:-

According to the findings of our investigation, we believe that primary immunodeficiency illnesses are more common than we had anticipated in our nation. Primary immunodeficiency disorders in children with recurrent infections involving different systems, infections by uncommon organisms, delayed umbilical cord separation, poor response to conventional treatment and severe consequences following infections ought to be considered. Simple CBC measurements can provide numerous hints for PID diagnosis. Pediatricians need to be very suspicious of and knowledgeable about these illnesses. This could result in an early diagnosis and suitable treatment, reduce the number of hospitalizations, complications, permanent harm, and PID patients' deaths.

The family would benefit from the diagnosis for prenatal diagnosis for the subsequent pregnancy. It would be beneficial to make diagnosing facilities available in higher centers. The precise prevalence of the disease is unknown because we don't disclose all of the PID cases that are identified. In the future, it will be extremely beneficial to report these illnesses and to exchange data and management expertise regarding these unusual conditions. Improving pediatric HSCT services in our nation and raising awareness of PID among internists and pediatricians are essential needs.

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