SEVERE COMBINED IMMUNODEFICIENCY. KING HUSSEIN MEDICAL CENTER EXPERIENCE

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ABSTRACT

Objective: To describe the clinical experience of a single center in severe combined Immunodeficiency.

Methods: A total of 14 patients who were admitted to the Pediatric Department at King Hussein Medical Center with a probable diagnosis of severe combined immunodeficiency over 6 years duration were studied. The study described patients' population, clinical presentations, family history, laboratory and radiological investigations, treatment options and prognosis.

Results: Twelve (86 %) patients were males and two (14 %) were females. Median age at presentation was 21 weeks. They all showed the same clinical presentation with few exceptions. We demonstrated maternofetal engraftment in two (14 %) patients. Unusual post vaccination poliomyelitis type II was demonstrated in one patient. Skin abscess and deep-seated ulcers were seen in one patient. One patient with Viral Associated Hemophagocytosis Syndrome Dead siblings with similar illness were retrieved in most patients. All patients had anemia, lymphopenia, and severe pan-hypogammaglobulinemia at time of presentation. We confirmed neutropenia in only three (21%) patients. Blood cultures revealed heavy growth of Klebsiella and Pseudomonas organisms in nine (64%) patients. We found that intravenous immunoglobulins administration was partially useful. Bone marrow transplant was not done for any patient. One patient was under preparation for autologous bone marrow transplantation. Eleven patients died after a mean of four months after diagnosis. Two patients were in a relatively acceptable condition, and that last one was suffering from fulminant sepsis.

Conclusion: The awareness of the referring physicians to immunodeficiency is sub optimal. Pediatricians are urged to pay attention to persistent Lymphopenia as a helpful clue for the diagnosis of severe combined Immunodeficiency in infants with unusual infections especially in families with positive family history. Live attenuated viral or bacterial immunization is contraindicated in suspected immunodeficiency. Health education of families is an essential part of management of these patients.

Key words: Combined, Severe, Immunodeficiency, Jordan

JRMS June 2005; 12(1): 5-9

Introduction

Severe Combined Immunodeficiency (SCID) comprises a collection of genetic defects involving both humoral and cellular immunity (Table I) [1-4]. The most common is the X-Linked Severe Combined Immunodeficiency (XL-SCID), which incidence varies between in 50, 000 to 1 in 100,000 live births, while other varieties are very rare [1-4]. It is characterized by early presentation in infancy, failure to thrive, unusually persistent infection with low virulence opportunistic organisms (Candida, Pneumocystis Carini, Cytomegalo virus) and early death in untreated patients [1,5]. Laboratory investigations showed profound abnormalities of Cellular Mediated Immunity (CMI); antibody deficiency and lymphopenia particularly of the lymphocytes [2,3,5]. We report our experience of Severe Combined Immunodeficiency (SCID) at the pediatric immunology clinic at King Hussein Medical center (KHMC) between 1997 to 2003.

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Manuscript received July 12, 2003. Accepted January 8, 2004.

Methods

Fourteen patients were admitted to the Pediatric Department at KHMC with a probable diagnosis of SCID between July 1997 and July 2003. The SCID diagnosis was based on WHO criteria (Table I, II) [1-4]. Data included in the study were; demographic features, clinical presentation, family history, laboratory investigations (absolute lymphocytes, and neutrophils counts, HIV screening, serum immunoglobulin assay, flow cytometry-based T, B, NK enumeration, and blood culture), and radiological investigations. Lymphopenia and neutropenia were considered when absolute lymphocyte and neutrophils count are below 3000/mm^3, 1500/mm^3 respectively [3,5]. Since these findings required differentiation from infant with AIDs, we screened all patients for HIV infection [6,7]. We used ELISA technique and when positive, results were confirmed with Western Blot and PCR. We used Flow Cytometry for lymphocyte phenotype assay and absolute count. Mutation analysis and in-vitro T-cell function is not available at our center.

Results

Twelve (86%) patients were males and 2 patients (14%) were females. Median age at presentation was 21 weeks (Table III). They all showed the same clinical presentation with few exceptions. Two patients (14 %) had grown normally. Chest infection was demonstrated either clinically or radiologically in another 2 patients (14 %) patients. Widespread infection and sepsis was clinically diagnosed in 10 patients (71%). We demonstrated maternofetal engraftment in 2 (18%) patients. Diagnosis was made on clinical basis in non-transplanted, non-transfused infants. They had high unrelenting fever, a morbilliform maculopapular erythematous rash, and severe diarrhea. Viral associated hemophagocytosis in one patient. Unusual post vaccination adverse side effect was demonstrated in one patient out of 3 who were given the first dose of conventional vaccination. It was proved to be poliovirus II by stool examination. This patient showed severe neurological consequences of polio disease. Skin abscess and deep-seated ulcers were seen in one patient. Family history of dead siblings with similar illness was positive in 10 patients (71%), with an average of 2 patients for each family (Table III). All patients had anemia and lymphopenia at time of presentation. We confirmed neutropenia in 3 patients (21 %). All patients had severe pan-hypogammaglobulinemia, while only 2 patients (18%) had normal IgM at time of presentation. Blood cultures revealed heavy growth of Klebsiella and Pseudomonas organisms in 9 patients (64%). Microbiological diagnosis of viral and other opportunistic infections like Pneumocystis Carini was difficult to be documented. Presumptive diagnosis was made on clinical and radiological basis. We found that Intravenous Immunoglobulins (IVIG) administration is only partially useful for short period of time before bone marrow transplantation. Bone marrow transplantation was not done for the study group. Only one is under preparation for autologous bone marrow transplantation. Eleven patients died after a mean of 4 months after diagnosis. Two were in a relatively acceptable condition and the last patient is suffering from fulminant sepsis in the Intensive Care Unit (ICU).

Discussion

Failure to recognize immunodeficiency as the underlying cause of severe diarrhea, pneumonia, septicemia, fungal infections or failure to thrive is evident in families' histories of many large kindred in which male infants have died in several generations [1-3,8]. Often in the past, the patients were mistakenly diagnosed as having dietary intolerance or cystic fibrosis because of pulmonary infections and diarrhea with weight loss [8,9]. Early diagnosis of SCID is essential to enable referral for bone marrow transplantation before the occurrence of infection-induced major organs failure [8,9]. All patients in our study except patient number 4 were referred after the age of 4 months (Table III). Literatures referred to a median delay of 7 weeks between the first abnormal lymphocyte count and diagnosis. We received most of them in poor general condition. Referring physicians spent considerable time in treating proposed sepsis or retrieving other more common diagnoses like cystic fibrosis, tuberculosis, and gastrooesophageal reflux or milk intolerance [2,3,5]. Few of the referring physicians had taken the bad family history into consideration; when most of these patients positive had at least one of their siblings died few months after birth with the same clinical presentations. Persistent absolute lymphopenia was overlooked in all patients [8,9]. This indicates that the awareness of the general practitioners and pediatricians toward early diagnosis of immunodeficiency is suboptimal. Almost all the patients had the same spectrum of clinical presentations with few exceptions. Patient's number 1 and 6 had grown normally at time of presentation. Patients number 8, 11 were not found severely ill, they did not have either clinical or radiological evidence of pneumonia. Maternofetal engraftment was demonstrated in 2 patients (18%). Diagnosis was made on clinical basis in non-transplanted, non-transfused infants. They had high unrelenting fever, a morbilliform maculopapular erythematous rash, and severe diarrhea. They respond partially to Intravenous Immunoglobulins infusion (IVIG) [10,11]. In the absence of proper genetic study, Omenn (leaky SCID) syndrome could not be ruled out. Even though, non of our patients had received blood transfusions, but transfusion of non-irradiated blood may show same clinical presentation. This encourages the avoidance of unnecessary blood transfusion or using irradiated blood when it is needed. The last patient (14) was proved to have Viral Associated Hemophagocytosis by bone marrow study. Three of the patients referred to

our center were found to be vaccinated up to the age. One of them presented with typical neurological complication of post-vaccine polio disease. This was proved by stool culture to be Poliovirus type II. The other patients were not vaccinated not because of known diagnosis but due to high fever documented at the time of scheduled vaccination. This indicates that the referring physicians were not aware of the serious sequences of live attenuated viral and bacterial vaccination in patients with possible immunodeficiency, which is considered an absolute contraindication. Oral thrush, diaper Candida infection, absent tonsils, persistent infection despite long treatment and chronic diarrhea were consistent findings in all patients. Family history of one or more siblings died undiagnosed shortly after birth was obtained in 10 patients (71%). Fever was a universal symptom in all patients regardless the general condition and the out come of the blood, CSF, and urine cultures. We found that all patients had persistent lymphopenia was present (<3000/mm) in all readings. This was also found in available old files of dead siblings. We concluded that absolute lymphopenia is a good marker of severe combined Immunodeficiency [1,2,9]. We advise considering it as a screening marker early in the neonatal period especially in families with Combined Immunodeficiency (CID) in other siblings [1,2,9]. This will ensure early diagnosis and treatment. Anemia due to chronic disease, increased loss and decrease intake was confirmed in all patients at the time of diagnosis. We demonstrated neutropenia in 2 patients who were proved to have GVHD [1,3,5]. All patients had their serum IgG, IgA more than 2 SD below the norm for age. Two patients had normal IgM [1-4]. Flow Cytometry-based phenotype assay facilitates more definite diagnosis and classification [4,9]. Absence of thymus shadow was demonstrated in all patients by lateral chest X-ray [1]. This might be considered as a non-reliable finding in patients above the age of 4 months especially with evidence of severe infection [1]. Positive blood cultures were found in 7 patients, the isolates were Klebsiella and Pseudomonas. Microbiological diagnosis of viral and other opportunistic infections like Pneumocystis Carinii was difficult to be documented. Presumptive diagnosis was made on clinical and radiological basis. Immunoglobulins administration and antibiotics were found partially useful [10,11]. Bone marrow transplantation was not done in any of these patients either due the bad general condition of the patients, lack of compatible donor or because of a written refusal by the family [12,13]. All patients died within 4 months after diagnosis. Early referral before infection is a problem to maximize the chances of bone marrow transplantation is important. Kane, *et al* found that early postnatal bone marrow transplantation should be the preferred option in neonatal SCID [14]. We conclude that the awareness of the referral physicians to immunodeficiency is suboptimal. Most of the patients were referred in poor general condition that makes more definite treatment like bone marrow transplant unfeasible. Lymphopenia should be included in the neonatal screen for SCID especially in families with positive family history [1-3,5]. Family education is an essential part of these patients [12, 13].

Table I. Severe Combined Immunodeficiency (SCID).

Designation	**Serum/Ig**	**Circulating B cells**	**Circulating T cells**	**Presumed Pathogenesis**	**Inheritance**
T-B+SCID a. X-linked (γc deficiency)	↓	N/↑	↓↓	Mutations in chain of IL 2,4, 7,9,15 receptors	XL
b. AR (Jack3 deficiency)	↓	N/↑	↓↓	Mutation in Jack 3	AR
2. T-B-SCID a. RAG1/2 deficiency	↓	↓↓	↓↓	Mutation in RAG1/2	AR
b. Adenosine Deaminase (ADA) deficiency	↓	↓↓	↓↓	T- and B- cell defects from toxic metabolites (dATP) due to enzyme deficiency	AR
c. Reticular dysgenesis	↓	↓↓	↓↓	Defective maturation of T, B, and myeloid cells (stem cell defect)	AR
Omen's syndrome	↓	↓	Variable	Defective activation or regulation of T-cell proliferation (mutation RAG gene)	AR

T: T cell B: B cell XL: X linked AR: Autosomal recessive
↓: Decreased ↓↓: Marked decrease ↑: Increased. Adapted from reference 2.

Table II. WHO diagnostic criteria for X-linked Severe Combined Immunodeficiency (SCID) and differential diagnosis.

Definitive	Male patients with either (a) engrafment of transplacentally acquired maternal T cells or (b) less than 10% $CD3^+$ T cells, less than 2% $CD16/56^+$ NK cells, and more than 75% $CD19^+$ B cells and who has one of the following: Mutation in the cytokine common gamma chain (γc). Abscent c mRNA on Northern blot analysis of lymphocytes. Abscent c protein on the surface of lymphocytes or lymphocyte cell lines. Maternal cousins, uncles, or nephews with SCID
Probable	Male patient with less than 10% $CD3^+$ T cells, less than 2% CD $16/56^+$ NK cells, and more than 75% $CD19^+$ B cells and who has one of the following: Onset of failure to thrive before 1 year of age. Serum IgG and IgA more than 2 SD below normal for age. Persistent or recurrent diarrhea, URTI, or thrush
Possible	Male patient with greater than 40% $CD19^+$ B cells in the peripheral circulation and one of the following: Engraftment of transplacentally acquired maternal T cells. Maternal cousins, uncles, or nephews with SCID.
Differential Diagnosis	JAK 3 deficiency IL-7Rα deficiency HIV

Adapted from reference 2.

Table III. Clinical presentation of the study group.

Patient number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Sex	M	M	M	M	M	M	M	M	M	M	M	F	F	M
Age (months)	4	4	9	1	9	5	9	4	3	8	6	5	5	11
FTT	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N
Oral Thrush	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Diaper Candida	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Absent Tonsils	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Persistent Infection Despite long treatment	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
FHx	N	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y
Chronic diarrhea	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Respiratory congestion (cough)	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y
Fever	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Pneumonia	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y
Sepsis	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y
Maternofetal Engraftment	N	N	N	N	N	N	Y	N	Y	N	N	N	N	N
Vaccine adverse effects	N	N	N	N	N	N	Y	N	N	N	N	N	N	N

M: Male F: Female Y: Yes N: No ↑: Increased
FTT: Failure to thrive. FH: Family History

Table VI. Laboratory investigations for 11 patients.

Patients Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Anemia	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
ALC<1500	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
ANC<1500	N	N	N	N	N	Y	Y	N	N	N	N	N	N	Y
Low IgG	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Low IgA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Low IgM	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Abscent T/cells	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Abscent B-cells	Y	Y	Y	↑	Y	↑	Y	Y	Y	↑	N	N	Y	N
Abscent NK-cells	N	N	Y	Y	N	N	N	N	N	N	N	N	Y	N
Positive Blood C/S	Y	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y

Y: Yes N: No ↑: Increased

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