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CLINICAL PRACTICE ARTICLE

Severe Combined Immune Deficiency Syndrome

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ABSTRACT

Objective: To determine the clinico-demographic features and laboratory parameters of children with severe combined immunodeficiency (SCID).

Study Design: Case series.

Place and Duration of Study: Department of Paediatrics and Child Health, the Aga Khan University, Karachi, from July 2006 to July 2011.

Methodology: Thirteen infants who were discharged with a diagnosis of SCID were inducted in the study. Their clinico-demographic features and laboratory parameters were determined. Descriptive statistics has been used for computing frequency and percentage.

Results: The median age at diagnosis was five months; 5 infants presented within 3 months of life. Three-fourth (77%) were males. Most of the infants were severely malnourished (85%) at the time of presentation. More than two-thirds (69%) were products of consanguineous marriages. All subjects had severe lymphopenia {absolute lymphocyte count (ALC) ranging between 170 – 2280} and low T and B lymphocyte counts.

Conclusion: SCID should be considered in infants presenting with severe and recurrent infections. Low ALC (< 2500/mm^3), is a reliable diagnostic feature of SCID. These infants should be promptly referred to a facility where stem cell transplant can be done.

Key Words: *Severe combined immune deficiency (SCID). Absolute lymphocyte count (ALC). Recurrent infections. Infants. Lymphopenia.*

INTRODUCTION

Severe combined immune deficiency syndrome (SCID) is an inherited immune disorder characterized by lack of cellular and humoral immunity leading to severe and recurrent infections. Clinical features include recurrent or persistent severe infections starting from the first few months of life, which results in progressive failure to thrive and death during infancy if left untreated.[1] Early stem cell transplant therapy within the first 3 months of life has upto 95% chance of success, however, the success rate progressively decreases with the increase age.[2,3]

The global incidence of SCID is estimated to be 1 per 40,000 – 75,000 newborns.[4] There are no published data regarding the incidence of SCID in Pakistan. SCID is more common in countries where consanguineous marriage rates are high;[1,5] and Pakistan has one of the highest reported consanguineous rate in the world with approximately two thirds of all marriages being consanguineous.[6]

An excellent screening test for SCID is the absolute lymphocyte count (ALC), which can be easily calculated with the help of routine complete blood count with manual differentiation in an infant. A bedside calculation of ALC < 2500/mm^3 in the neonatal period or infancy should alert the physician towards the possible diagnosis of SCID and further evaluation should be done. Confirmatory tests include flow cytometry, which shows very low B and T cell subsets, low immunoglobulin levels, and mitogen stimulation assay that detect abnormal or dysfunctional lymphocytes.[7]

There is a complete dearth of knowledge regarding the incidence of SCID in Pakistan. With the high rate of consanguineous marriages, the incidence is likely to be high. However, if children with SCID are to be successfully treated with early stem cell transplant, the health care community needs to be sensitized about the prevalence and early diagnosis of this disorder.

The aim of this study was to describe the clinical characteristics and laboratory features of SCID in infants admitted at the study centre.

METHODOLOGY

This is a case series of infants with discharge diagnosis of SCID at the Aga Khan University Hospital (AKUH), Karachi, during five years (June 2006 till July 2011). Patients were identified by health information management system using coded discharge diagnosis of combined immunity deficiency (ICD9 CM 279.2). This coding contains SCID.

Features including the age on admission, gender, anthropometry, past admissions, family history of early

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deaths and miscarriages, patient microbiological and immunological profile (ALC, cluster of differentiation (CD) markers count; serum immunoglobulin levels; HIV) and duration of hospitalization were recorded. The ALC was calculated from the first available complete blood count that could have been done prior to, or at the time of hospitalization.

Cases were diagnosed on the basis of clinical presentations and laboratory investigations; ALC < 2500/mm^3, low serum immunoglobulin levels (according to age) and extremely low B and T cell subsets {suggestive clinical presentation - recurrent diarrhea, pneumonia and pyogenic infections; failure to thrive (FTT), family history of sibling death due to recurrent infections, oral thrush and absence of lymphoid tissue}.[1,8]

Descriptive statistics has been used for computing frequency and percentage. The Ethical Review Committee of the AKU granted an exemption for this study (1950-Ped-ERC-11).

RESULTS

Among the 13 SCID infants, the mean age was 143 ± 70 days (median 154 days). Males (n = 10, 77%) were predominant. Eleven (85%) were severely malnourished (weight/age < 3 SD). Fever (n = 7; 54%), respiratory distress (n = 7; 54%), persistent cough (n = 5; 38%), poor oral intake (n = 4; 31%) and loose stools (n = 4; 31%) were the presenting complaints. Parents of nine infants had consanguineous marriage. More than half (n = 7, 54%) of the patients had family history of infant deaths of undiagnosed cause while 3 (23%) had family history of recurrent miscarriages. The ALC ranged between 170 – 2280/mm^3 (Table I). CD counts and serum immunoglobulin levels were not available for 3 patients. The diagnosis of these patients was made on their clinical presentation (recurrent infections and failure to thrive), as well as supportive lab investigations including low ALC, low lymphocyte subsets and immunoglobulin levels. HIV status was checked for 5 patients and found to be negative. Mean length of hospitalization was 10.9 ± 10 days. Three children had positive bacterial cultures. Table II shows the spectrum of microorganisms isolated from blood, urinary, respiratory and from the stool of the patients.

DISCUSSION

SCID is a genetic disease with severe abnormalities of immune function and development. Infants with SCID usually appear normal and healthy at birth but within 1 – 2 months, the transplacentally acquired immunity (immunoglobulin) starts waning, and infants develop

Table I: Demographic and immunological profile of SCID patients.

Patient	Age at presentation (days)	Gender	Anthropometry			CD4/CD8 ratio	Absolute lymphocyte count (ALC)*	CD3 (2800-3500)	CD4 (1700-3500)	CD8 (800-1100)	CD19 (1000-1700)	CD 56 (300-800)	IgG	IgM	IgA	HIV status checked
			Wt.	Lgt.	FOC											
1	177	F	Δ	-	-	Reversed	393	-	-	-	-	-	0.07	0.36	0.11	No
2	49	M	-	-	-	Maintained	747	-	-	-	undetectable	-	0.07	6.26	0.94	No
3	82	M	-	-	-	--	297	Severely decreased	Severely decreased	Severely decreased	undetectable	Relatively increased	0.23	3.07	0.13	Yes
4	195	M	Δ	-	-	Reversed	2100	Severely decreased	Severely decreased	Severely decreased	Mildly low	-	0.66	0.07	0.33	Yes
5	184	M	Δ	-	-	--	413	31	-	-	2	-	-	-	-	No
6	90	M	Δ	Δ	Δ	Reversed	282	Severely decreased	290	543	undetectable	15	-	-	-	No
7	90	F	Δ	-	Δ	--	1400	-	-	-	-	-	0.07	1.91	0.23	Yes
8	150	M	Δ	-	-	Maintained	393	-	-	-	-	-	0.6	0.1	94	No
9	240	M	Δ	-	-	Maintained	340	180	203	144	1	46	0.07	0.44	0.06	Yes
10	37	M	Δ	Δ	Δ	Maintained	170	195	41	18	13	28	3.51	0.11	0.13	No
11	120	M	Δ	-	-	Maintained	2280	430	255	196	143	4	-	-	-	No
12	150	M	Δ	-	-	Reversed	1270	37	31	27	9	800	-	-	-	No
13	268	F	Δ	-	-	Reversed	478	31	23	30	364	9	-	-	-	Yes

*M = male; F = female; CD = Cluster of differentiation; *ALC = calculated from the first ever complete blood count; Wt. = weight; Lgt. = length; FOC = Fronto-occipital circumference; Δ = < 3 SD - severely malnourished.*

Table II: Microorganisms isolated in SCIDS patients.

Patient	Blood isolates	Urinary isolates	Respiratory isolates	Stool isolates
3	–	*Candida albicans*	–	*Campylobacter jejuni* *Escherichia coli* *Aeromonas* species
7	–	–	–	*Campylobacter jejuni*
9	*Staphylococcus epidermis*	–	–	–
10	*Acinetobacter* species	–	*Escherichia coli*	–
11	*Acinetobacter* species	*Candida tropicalis*	*Klebseilla pneumoniae Candida tropicalis*	–

severe and recurrent life threatening infections.[9,10] The median age of diagnosis worldwide is reported to be 4 – 7 months of age.[4,11] Median age of diagnosis in this cohort was 5 months.

Male infants were predominant in this cohort. The slight male predominance has been reported previously in the literature with M:F ratio varying from 1.5 – 2:1 (12, 13). X-linked SCID is the most common form and accounts for approximately 46%.[7] One possible explanation of the high male predominance in this cohort could be X-linked SCID. The X-linked affected patients have no T cells or NK cells in the peripheral blood, but have normal number of B cells. Their immunoglobulin levels are low or undetectable with absent lymph nodes and tonsils.[8,10] Among the 10 male patients in this cohort, parents of eight had consanguineous marriages and had very low ALC; undetectable to very low NK cells and markedly low serum immunoglobulin levels. While not formally tested, it is probable that many of these had X-linked variation of SCID.

FTT is one the common clinical presentation of infants with SCID. Recurrent gastrointestinal and respiratory infections are the basic reason of FTT in SCID patients. Shah has found 100% FTT in their SCID patients case series from India.[9] Majority of the present study subjects were severely malnourished.

Consanguinity increases the risk of rare inherited disorders.[5,14] Subbarayan *et al*. retrospectively reviewed the clinical features of children diagnosed as primary immunodeficiency at their immunology centres (Manchester and New Castle) and found that 33% (111/334) of children with B and T cell immunodeficiency were Pakistani in origin.[1] This was a significant over-representation compared to the proportion of Pakistani-origin children in their catchment area.

SCID is a medical emergency. The best screening test for SCID is to check the ALC in all neonates and infants. However, this represents a challenge in a country where the majority of births take place at home and newborns are not seen by physicians. In this environment, perhaps a strategy of screening young infants from families having early sibling death may pick-up a substantial SCID cases. The ALC of < 2500/dL should alert the physician towards the possibility of SCID and child should be referred for confirmation (flow cytometry and immunoglobulin level).

The good feature of HSCT therapy for SCID is its easy acceptance in the recipient. Pre-requisites for SCID transplantation require only human leukocyte antigen matching (related or unrelated donor).[15] The biggest challenge is the unavailability of transplant centres and cost of transplantation in developing countries like Pakistan. None of these patients could receive transplantation due to late presentation, lack of transplant set up in neonates at that time, and financial constraints of parents.

To the best of authors' knowledge, this is the first study of any kind about SCID in Pakistan. This study had a few limitations. This is a retrospective chart review of inpatients only and not the outpatients, therefore, the true burden of SCID seen in the hospital is likely to be more than the report based on this inpatient case series. The true confirmatory tests, including molecular testing and mitogen stimulation assay could not be done because of lack of facilities. However, using the current criteria of severe lymphopenia and extremely low B and T cell subsets, the likelihood that our diagnosis was correct is very high.

CONCLUSION

SCID is an important cause of early infant deaths in a country with one of the highest rates of consanguinity. Increased awareness and educating health care providers regarding SCID may lead to earlier diagnosis and potential therapy. Systemic studies documenting the contribution of serious inherited disorders to infant mortality in Pakistan are also needed.

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