Severe combined immunodeficiency: A cohort of 40 patients

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Severe Combined Immunodeficiency (SCID) consists of a heterogeneous group of genetic disorders characterized by an arrest in T lymphocyte development which is variably associated with an abnormal differentiation of B and NK cells. In order to depict the clinical state of Iranian patients with SCID, records of forty patients were reviewed. Patients were classified based on the flow cytometry data in two groups of B− and B+. In thirty two families (80%) parents were consanguine and in 17 families (50%) there were affected members other than proband. We showed that autosomal forms of SCID might be more frequent due to higher rate of consanguineous marriages. Alongside several infective complications, complicated Bacillus Calmette-Guérin (BCG) vaccination was documented in 18 cases (45%) following the routine vaccination at birth. BCG immunization is still a part of standard vaccination for newborns in developing countries; whereas in communities with a better health condition it could be held for a few months and performed for kids whose immune system sounds intact. We discuss where consanguine mating is common, a test of screening should be run timely. A complete blood count of cord blood could reveal lymphocytopenia at birth; this helps early diagnosis. Genetic consultation would help the families with affected members preventing new SCID offspring.

Severe combined immunodeficiency (SCID) consists of a heterogeneous group of genetic disorders characterized by an arrest in T-lymphocyte development. It is variably associated with an abnormal differentiation of B and NK cells. Overall incidence is estimated to be 1 in 75,000 births and several different molecular defects resulting in an SCID have been described so far (1). Having an abnormal adaptive immunity, SCID patients are susceptible to multiple microorganisms. Infants with untreated SCID do not usually live for a longtime (2); SCID is a medical emergency. SCID was the first disease to be effectively treated by allogenic hematopoietic stem cell transplantation and also the first to be subjected by gene therapy, successfully (1). SCID patients are classified according to their peripheral B-lymphocyte population as T−B+ and T−B− (3).

X-linked T−B+ SCID (XL-SCID) is the most commonly reported form of SCID, and is due to mutations in the γc chain which is shared by the receptors for IL-2, IL-4, IL-7, IL-9, and IL-15. Autosomal recessive forms of T−B+ SCID are due to mutations in JAK3, deficiencies or abnormalities of CD3 subunits and IL-7 receptor α chain (4).

The molecular defects producing a T−B− SCID phenotype includes adenosine deaminase (ADA) deficiency, RAG1/RAG2 mutations and defects in the Artemis gene.

Some patients with T−B− SCID have symptoms similar to graft versus host disease in the neonatal period. This has been termed ‘Omenn's
Syndrome; the disease is not, however, due to engraftment of maternal cells.

Other rare causes of SCID have been attributed to defects in signaling molecule CD45, DNA ligase IV, and Orai1 (1, 5).

Objectives

During the last decade, a considerable progress has been made in early diagnosis and management of patients with humoral and phagocytic defects in our country (6, 7). The Iranian Primary Immunodeficiency Association (IPIA) activities and establishment of Iranian Primary Immunodeficiency Registry (IPIDR) have been playing a big role in this regard. Meanwhile, cellular immunity defects and particularly SCID, still make a great fraction of mortality among PID patients. It is needed then, to depict the current status of SCID population as a step to increase awareness of physicians and health policy makers on this issue. An improvement in timely diagnosis and effective treatment is critical. In present report, we have reviewed the clinical and laboratory data of 40 SCID patients extracted from the IPIDR.

Patients and methods

The IPIDR

The IPIDR was established in 1999 (8). A questionnaire was developed to contain all the patient’s demographic information, the diagnosis of PID, first clinical presentation, age at onset, age at diagnosis, family history of immunodeficiency and/or recurrent infections, basic immunologic laboratory tests, and follow-up information. This questionnaire was sent to the university centers participating in the IPIDR. The initial survey, which included patients, diagnosed from 1981 onward, covered seven universities from five major states of Iran. A computerized database program was designed for data entry of all the recorded information and direct statistical analysis of data. A recent report has presented the new statistics of the IPIDR (9).

Patients

We performed a retrospective study. Medical records of 40 patients from 34 unrelated families with the diagnosis of SCID were selected from the registry. Only patients with well-established immunodeficiency and the clinical manifestations compatible with their diagnosis were included in the study. Laboratory analysis included complete blood count and differentials, serum immunoglobulin levels, and immunophenotyping of peripheral blood lymphocytes. There were, however, some missing laboratory data in the records. Currently none of patients in this series is alive and the molecular diagnosis is not possible.

Results

Forty patients of 34 unrelated families with a diagnosis of SCID were enrolled. Twenty-four of them were boys (60%) and 16 were girls (Table 1). Twenty (58.8%) of 34 families had only male affected members. In thirty-two families (80%) parents were consanguine and 17 families (50%) had a positive family history, indicating an inherited disorder; four families had an X-linked pattern of inheritance.

The mean age at onset was 68 days (s.d. ± 13 days). The mean age at diagnosis was 5 months (s.d. ± 20 days). 72.5% of patients showed their first manifestation of the disease before 4 months of age; in one case the evaluations were performed at birth because of his strong family history. The most common presenting manifestations were recurrent oral candidiasis, failure to thrive, diarrhea, and pneumonia (Table 2). Disseminated Bacillus Calmette-Guérin (BCG) infection was documented in 18 cases (45%) following vaccination. Pneumonia was due to different microorganisms including Cytomegalovirus, Adenovirus, and Pneumocystis jiroveci. In six patients skin lesions as furuncles, abscesses, or neonatal rash were of the first presentations.

Although molecular investigation was not available, according to the lymphocyte immunophenotyping profile, we categorized the patients into B+ and B− groups (Table 1). Twenty-three

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>M</th>
<th>F</th>
<th>Lymphocyte count*</th>
<th>CD3*</th>
<th>CD4*</th>
<th>CD8*</th>
<th>CD19*</th>
<th>IgG (mg/dl)</th>
<th>IgM (mg/dl)</th>
<th>IgA (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T−B+</td>
<td>12</td>
<td>11</td>
<td>1893</td>
<td>124</td>
<td>63</td>
<td>187</td>
<td>925</td>
<td>352 ± 180</td>
<td>78 ± 29</td>
<td>24 ± 7</td>
</tr>
<tr>
<td>T−B−</td>
<td>12</td>
<td>5</td>
<td>631</td>
<td>110</td>
<td>50</td>
<td>75</td>
<td>50</td>
<td>202 ± 42</td>
<td>35 ± 18</td>
<td>18 ± 4.8</td>
</tr>
</tbody>
</table>

M, male; F, female; s.d., standard deviation.

*Mean number of peripheral lymphocytes.

Patients

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(57.5%) were B-cell positive and 17 were B-cell negative. Data for NK cells was not available for all the cases: among B⁺ group, eight patients were T⁺B⁺NK⁺, including five males and three females and seven cases were T⁺B⁻NK⁻ (five males and two females). For the remaining eight B⁺ patients the NK cell count was not available.

In B⁻ group, eleven cases (eight males and three females) were T⁻B⁺NK⁺, of whom two infants were clinically diagnosed as Omenn's syndrome, five patients (three males and two females) had no data about NK cells, and one male infant was T⁻B⁻NK⁻.

Serum immunoglobulin levels were abnormal in all patients (Table 1). Mean immunoglobulin levels were higher in B positive group; however, this was not statistically significant. Normal IgG levels could be attributed to the residual maternal IgG and/or intravenous immunoglobulin (IVIG) received before examination.

All the cases were deceased before their first birthday. Most patients received medical treatment including IVIG and antibiotics for somehow 6 months. Twenty-two patients received IVIG for at least 4 months. None of attempts for doing cord blood transplantation in the only three candidates were successful.

Discussion

We reviewed the records of a cohort of 40 SCID cases. Regarding the current 70 million population of Iran we roughly estimate an incidence of at least one out of 70,000–100,000 for SCID in Iran. We believe there are a number of cases who are not registered as SCID or who have not been referred to an immunodeficiency center. There is almost a 3-month lag of diagnosis which is probably due to delayed referring to tertiary centers. This is a warning to improve the knowledge of first line physicians about T-cell deficiencies.

The number of families with only male affected members was pretty lower than in previous reports of SCID patients (2) in which the ratio was over 70 percent. In a series of SCID infants, 53% of 49 males with γc SCID had a positive family history (2). In contrast, in our series we had just four families with an X-linked pattern of inheritance while 50% of patients had a positive family history. Although, XL-SCID is known as the most common form of SCID (1), it is likely that we do not have such a predominance in Iran. Six of eight T⁺B⁻ patients with unknown NK enumeration are females who could hardly be affected by γc mutations. This could be justified by the higher rate of consanguineous mating among our families (10). It can be deduced that autosomal forms of SCID are more frequent in our series than previous reports.

Eleven SCID infants were T⁻B⁻NK⁺ that are presumably caused by defective TCR rearrangement. Two of them were clinically diagnosed as Omenn's syndrome.

Finally, the only T⁻B⁻NK⁻ child was probably affected by the mutation of ADA gene. Unfortunately, the data regarding his clinical features were partly missing. This child died of pneumonia due to *Pneumocystis jirovici*.

Forty-five percent of the patients in this report developed disseminated BCG infection following routine BCG immunization at birth. In an Iranian cohort of children with disseminated bovine mycobacterium infection, eight of 17 patients suffered from SCID (11). There is a common agreement about the protection provided by the first dose of BCG vaccine against severe and disseminated forms of tuberculosis (TB) among children, especially with regard to meningitis and miliary forms (12). However, controversy still exists over the protective efficacy of BCG vaccine against pulmonary TB, a clinical form that has a major impact on TB control (12). In communities with a better health condition, this might be held for a few months and performed for kids whose immune system looks intact.

Regarding the rate of consanguinity, it is suggested that a test of screening should be run timely for selected cases. Buckley et al. reported nine SCID infants with cord blood absolute lymphocyte count ranged from 158 to 2400/mm³ and three infants with persistent lymphopenia in their series which led to early diagnosis (2). A complete blood count of cord blood could reveal lymphocytopenia at birth which helps early diagnosis of SCID. The lower limit of normal cord blood absolute lymphocyte count is 2000/mm³ (2). A diagnosis of SCID urges prompt intervention. Although our experiences for cord blood transplantation were not

| Table 2. Frequency of major initial manifestations among 40 SCID patients |
|--------------------------|--------|
| Persistent               | 23     |
| Candidiasis              | 25     |
| Failure to thrive        | 16     |
| Pneumonia                | 20     |
| Diarrhea                 | 18     |
| BCGosis                  | 10     |
| Gram negative            | 6      |
| Sepsis                   | 3      |
| Skin lesions             |        |
| Organomegally            |        |
successful in three candidates, it is notable that they were not referred in their first months of age. Early diagnosis and achievement of a better transplantation practice increase the survival of patients. However, immune reconstitution is expensive. Developing prenatal diagnosis and genetic consultations for families with a previously affected child is more rewarding to prevent afterward imposed expenses.

References