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Early vs. Delayed Diagnosis of Severe Combined Immunodeficiency: A Family Perspective Survey

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Abstract

Infants affected with severe combined immunodeficiency (SCID) are susceptible to severe and recurrent infections and do not survive unless provided with immune reconstituting treatments. In the absence of population-based newborn screening, infants with SCID who do not have an affected older relative are ascertained only after they have developed infections. However, only limited data are available from the perspective of patients and families to indicate what proportion of SCID cases might benefit from earlier detection by pre-symptomatic screening, whether adequate treatment facilities are available, and how screening could improve SCID treatment outcomes. A survey of parents of children with SCID evaluated family history, pre- and post-diagnosis events, outcomes, and impact of SCID on families. Affected infants diagnosed with SCID as neonates had better survival, demonstrating the potential benefit of universal newborn screening.

Keywords

severe combined immunodeficiency (SCID); family survey; bone marrow transplantation; newborn screening; primary immunodeficiency; early diagnosis

Introduction

Severe combined immunodeficiency (SCID) encompasses a heterogeneous collection of genetic disorders causing profound defects in adaptive cellular and humoral immunity [1]. Patients affected with SCID are highly susceptible to severe and recurrent infections and do not survive infancy unless provided with immune reconstituting treatments. The diagnosis is often delayed due to the lack of a recognized family history, absence of distinguishing physical characteristics and the fact that infections are common in the general pediatric population. Unfortunately, it is only after a patient suffers cumulative and often serious infections that the possibility of a defect in host defenses is contemplated by medical providers. If these patients are not identified early, they are at risk of acquiring an infection

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at their well-child checkup, by inadvertently receiving a live-attenuated rotavirus vaccine by two months of age [2,3].

When SCID patients are diagnosed, immune reconstituting therapy such as transplantation with allogeneic hematopoietic stem cells from an unaffected donor, enzyme replacement, or gene therapy can rectify the immune defect and allow patients to lead long and healthy lives [4,5]. The prognosis of successful hematopoietic stem cell transplantation (HSCT) is excellent if patients are diagnosed early in life and transplanted prior to 3.5 months of age [6–9]. Not only do such patients have a better survival rate compared to those recognized only after suffering serious infections, but they also have fewer clinical complications, such as poor initial engraftment requiring a subsequent booster transplant [10]. Moreover, long term disability from pre-transplant events, such as meningitis, is avoided [7].

Unfortunately, infants with SCID who do not have an affected older sibling or other known affected relative are usually ascertained only after they have already suffered from multiple infections. These infections can be fatal in some cases, but in all cases they have a significant impact on the immediate medical management, burden on the family and long term morbidity. Therefore, the concept of population-based newborn screening for infants with profound T cell immunodeficiencies has been put forward, so that infants with SCID could be identified prior to repeated infections or death [1,11].

Evidence from prior studies concerning the impact of SCID and other primary immunodeficiencies has generally come from physicians' perspectives [12] as well as the perspectives of SCID transplant centers, as described above [10]. However, only limited data are available from the perspective of patients and families to indicate what proportion of SCID patients might benefit from early detection by screening, whether adequate treatment facilities are available, and how screening could improve SCID treatment outcomes. In this study, conducted by the Immune Deficiency Foundation, surveys were completed by parents of children with SCID to evaluate the impact of SCID on families.

Methods

Invitations to complete a survey were sent to parents from the Immune Deficiency Foundation (IDF) patient database, to subscribers of the SCID Forum database, and to members of the SCID Angels for Life Foundation. There were 208 families who identified themselves as having a member affected with SCID or Omenn Syndrome. The survey was sent by mail or email to the participants. Data were collected from January 13 through 30 of 2009 by IDF. All potential respondent information was requested on strictly a volunteer basis. The survey contained a total of 19 questions primarily focused on the impact of illness on the family. The questions addressed the number of children in the family, whether or not there was a positive family history, age at diagnosis, medical events occurring pre and post diagnosis, and for deceased patients the age of death relative to receiving treatment. (see Appendix for questionnaire). Data were collected in an anonymous and confidential manner and then tabulated and reported in the aggregate. Survey response tracking software was used to assure that responses were not linked back to an identifiable individual; identifiers were held separate and distinct from the collected survey data. Because of the nature of the survey, comparisons to medical records for validation were not possible. Duplicate responses were eliminated by crosschecking the month and year of patient birth, the age in weeks of SCID symptom onset and the city and state where the patient first showed symptoms of SCID. The maximum expected sampling error is 9 percentage points at the 95% confidence level for the full sample of 126 cases.

Inclusion as a true SCID or Omenn syndrome case for the purpose of this study required one or more of the following: (i) a specified SCID gene defect; (ii) immunologic diagnosis and treatment at an immunodeficiency center; (iii) autopsy results provided to the family that confirmed SCID; and (iv) absence of a documented non-SCID immune disorder. For families with more than one affected child, questions regarding diagnosis and treatment were based on either the oldest living child in the family or, if there were no surviving children, on the oldest deceased child.

PASW Statistics 18 (SPSS Inc., Chicago, IL) was used for calculating the descriptive statistics and for the bivariate analysis using the Fisher exact test, which was used to compare the relationship between primary immunodeficiency disease testing and non-testing interventions on infant mortality and to compare the relationship between subject mortality and the average age at the time of HSCT or other immunoreconstituting intervention.

Results

Of the 208 families invited to participate, 134 (64%) provided responses within five weeks (Fig. 1). Eight of those responses were eliminated because they had either a non-SCID diagnosis (n=1) or insufficient clinical features to be typical of a SCID diagnosis (n=7). Clinical features not consistent with SCID included symptom onset older than six years of age or survival for more than three years without immune reconstituting therapy such as HSCT, enzyme therapy or gene therapy. Our analysis included 126 families with 158 SCID cases (Fig 1). The SCID families resided in 32 states across the United States. The various genetic types of SCID represented in our population were similar to other reported cohorts including publications from the Jeffrey Modell Foundation and Duke University [10,12]. Nearly half of our surveyed population had an X-linked defect in the IL-2 receptor common γ chain, and smaller proportions had other types of SCID (Table 1).

Among the 158 SCID infants in this survey, 61 were reported to have died, giving an overall survival rate of 61% (95% CI 54–69%). As illustrated in Fig. 2, approximately half of the deaths (51%) occurred in diagnosed infants after receiving HSCT or enzyme replacement. Twelve infants (20%) did not receive definitive treatment, but did have a diagnosis prior to their death, and 17 of the 61 deceased infants (29%) had their diagnosis made only after their death.

Overall survival rate of treated patients, 81.4%, was comparable to that reported in studies published by referral centers [8,10,13–15]. Figure 3A illustrates the survival curves of treated patients according to their birth year. While infants born in 2000 or later had somewhat higher survival, 87.2%, as compared to those born earlier, the differences between birth cohorts were not significant. When stratified by type of treatment (Fig. 3B), there were no significant differences between groups except for the expected better survival of recipients of transplants from HLA-matched siblings (93.8% survival, n=16), as compared to transplants from unrelated adult or cord blood donors (66.7% survival, n=19) (Fig 3B).

Another concern our survey addressed was whether the lack of treatment was due to impeded access to specialized centers or the high cost of the therapy. The majority of patients were treated for their SCID (87%, 95% CI 81 – 93%). Of the remainder who were not treated, none of the respondents listed denied access to specialized treatment centers or financial constraint as a barrier (Fig. 4). Moreover, lack of a suitable HSCT donor was not a factor in receiving treatment (Fig. 4). However, 57% and 29% of SCID cases diagnosed but not treated, did not receive treatment because, respectively, they had already died, or had become too ill at the point of diagnosis to receive a transplant or ADA enzyme replacement.

Since major reasons cited for a SCID infant to remain untreated were patient death or being too ill at diagnosis to be treated (Fig. 4), the timing of diagnosis was hypothesized to have a significant impact on survival. A positive family history can raise awareness and lead to prompt diagnosis; however, only one in five affected infants was born into a family with prior experience with a SCID-affected child. In these families, most (75%) (95% CI- 62.5 to 86.4%) tested subsequent children in the family for SCID either prenatally or at birth (data not shown).

The majority of families (80%, 95% CI 73–87%) had only one member diagnosed with SCID in our survey. Excluding those infants who had a positive family history at the time of their birth, the mean age of onset of symptoms was approximately 11 weeks (95% CI 9 to 14 weeks, median 8 weeks) (Table 2). The diagnosis of SCID was not made until these infants reached a mean of age of 26 weeks (95% CI 23 to 30 weeks, median 24 weeks), a delay of 3.5 months from their first symptoms. Most SCID infants (91%) were diagnosed at a specialized pediatric medical center after a varying duration of symptoms. Fifty-four percent (95% CI 45 to 65%) of the families had to travel to a different city from where they lived, and 20% (95% CI 12 to 28%) traveled to a different state (data not shown).

Among all the patients who were treated for their SCID, the average age of treatment was 34 weeks (median 28 weeks, n=98). Those who were diagnosed due to a positive family history had a mean duration of hospitalization that was almost 7 weeks shorter than unsuspected cases (12.2 vs. 18.8 weeks). Those who were treated and survived (n=78) were, on average, treated at 29 weeks of age. Those who were treated but died (n=20) were on average treated at 57 weeks (Fig. 5). There was a statistically significant difference between the mean age of 29 weeks in those who survived and 57 weeks in those who died ($p=0.038$). Seventy-eight percent of survivors continue to be followed by specialist, usually an immunologist (data not shown).

Overall, as shown in Figure 6, infants tested as neonates, or even identified prenatally using mutation information available from affected and carrier relatives, had a higher survival rate compared to those not tested early (85% vs 58%, $p = 0.026$). This improvement in survival rate was not attributable to pre vs. post-2000 transplant (Fig. 3A) or transplant donor type (Fig. 3B).

Discussion

Our survey focused on the impact of an infant with SCID on the family, in contrast to previous reports from the perspective of immunologists and care centers. The overall survival rate of 61% of the 158 individuals with SCID is lower than reported by recent SCID transplant series [8,10,13–15]. The lower survival we found was not attributable to differences in the genetic types of SCID in our population, nor was it explained by the year of the patients' birth or type of therapy received since there were no significant survival differences in our series between pre and post-2000 transplants or type of transplants. Neither families' access to specialized treatment centers nor the affordability of the therapy were cited as reasons that SCID patients were not treated. Lastly, the lack of a donor was also not cited in our surveyed population. Instead, this study suggests that approximately half of the deaths among infants with SCID may be missed in the statistics arising from referral centers since these centers certainly fail to capture patients diagnosed only post-mortem, and may also not include patients too ill to be treated who may not have made it to a referral center. Thus our study design had the unique ability to include a more complete ascertainment of the SCID population than is included in studies from referral centers.

Our survey also identified a mean delay of 3.5 months from the onset of symptoms to diagnosis; this delay provides a window of susceptibility for SCID infants to acquire serious infections. Indeed, surviving infants received therapy when on average half as old as infants who died (29 vs 57 weeks, respectively, Fig. 5). Furthermore, testing of infants at birth had a statistically significant positive impact on survival, with 85% of those tested at birth surviving compared to only 58% of those not tested (Fig 6). Taken together, our results suggest that early diagnosis of SCID is key to overall survival.

One of the limitations of this study was that to maintain anonymity of the participants, the data obtained from the survey were unable to be correlated with medical records. The results presented here were solely from the family perspective. Also, the patients analyzed in this survey were of varying ages and spanned a timeframe when treatment for SCID was evolving (1976 to 2008), though survival differences were not explained by year of birth of our cohort. Furthermore, our survey captured only those families who were in touch with the IDF and patient-based SCID interest groups and who responded to the questionnaire instead of all SCID patients.

Overall, our survey illustrates several features of the impact of SCID on families at a time before population-based newborn screening for SCID was available. Morbidity, delayed diagnosis, increased medical costs and death were potentially avoidable outcomes that might have been prevented had a universal newborn screening test been in place. The death of a prior SCID-affected family member did lead the majority of families to test subsequent children. Having an affected relative increased the likelihood of, but did not guarantee, early diagnosis and prompt, successful treatment of affected children with a positive family history, indicating that genetic diagnosis, awareness and counseling were not completely effective [16,17]. A universal newborn screening test for SCID could afford early diagnostic confirmation and initiation of care and treatment for all families, not just those in which a prior devastating experience had made them alert to the risk in future children.

By utilizing the dried blood spots already obtained to screen newborns for other conditions, the presence or absence of T cells can be screened for by measuring the number of T cell receptor gene excision circles (TRECs) as a marker of successful development of a diverse T cell repertoire [18]. Peripheral blood with low or undetectable numbers of TRECs, a byproduct of normal T cell maturation, is a characteristic of SCID and all conditions in which T cell production or survival is profoundly impaired [18,19]. The TREC test has already been incorporated into the Wisconsin, Massachusetts, and California newborn screening panels on a pilot basis [19 and unpublished data]. Although no classic case of SCID was detected in the 71,000 infants screened in the first year of testing in Wisconsin, TREC screening did identify prospectively infants with profound T-cell lymphopenia requiring intervention [19]. The Wisconsin pilot program has also achieved a false-positive rate of only 0.03% in term infants and 0.14% in premature infants [20], comparable to other newborn screening tests in the state. It has been shown that false-positive tests can have a significant impact on the perspective of parents, increasing their anxiety and utilization of health care services [21], so the benefits of screening will have to be balanced against risks. In May, 2010, in response to an evidence based review by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, the Secretary of Health and Human Services endorsed addition of SCID to the Recommended Uniform Screening Panel of genetic disorders for which all newborns should be screened [22,23]. Additional states are planning to integrate dried blood spot TREC analysis into their newborn screening panels. Their aim is to make an indication of T cell lymphocytopenia available locally in the neonatal period, so that time to diagnosis and difficulty in establishing the diagnosis of SCID can be decreased, in turn leading to improved prognosis for infants with SCID.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Flow diagram of surveyed patients. This diagram shows the excluded cases, number of families with more than one affected members, and percentage of cases derived from families with 1, 2, or 3 affected members.

Figure 2. Composition of mortality in SCID patients surveyed. Of the 61 deaths, Not Diagnosed were cases of SCID not diagnosed pre-mortem (dark gray); diagnosed cases were separated into those who received (white) and those who did not receive (light gray) transplantation or enzyme replacement.

Figure 3.

Survival of treated SCID patients. (A) Patients grouped by birth year. All treated patients, solid line (81.4%, n=93); born pre-1995, dashed/dotted line (78.6%, n=28); born 1995–1999 dashed, (75%, n=24); born in 2000 or later, with no difference pre or post 2004, dotted (87.2%, n=41). (B) Patients grouped by treatment type (includes only patients reporting a single treatment, since the order of different treatments was not available); HLA matched sibling HSCT, long-dashed line (93%, n=16); haploidentical T-depleted parent HSCT, short dashed (84%, n=50); adult matched unrelated HSCT, dotted (67%, n=9); matched unrelated cord blood, solid (67%, n=9); and PEG-ADA dashed/dotted (80%, n=5).

Figure 4. Percentage of families citing particular reasons for not receiving definitive therapy among patients who were diagnosed with SCID, but died without being treated (n = 14).

Figure 5.

Age at definitive treatment for SCID by mortality. Living (white) and deceased (gray) patient numbers are compared (p=0.038).

Figure 6.

Comparison of infant mortality between those groups of neonates who were not tested (n= 138, left) and tested (n= 20, right) for SCID. Testing was performed only if an affected relative's SCID diagnosis had made parents and medical providers aware of the risk. Proportion of deceased infants is shaded in each pie chart.

Table 1

Distribution of SCID genetic defects in our survey compared to other reported cohorts. Genetic defects are shown in decreasing frequency based on our study.

Genetic Defect	This study (n=126)	JMF survey [ref 11] (n=314)	Duke cohort [ref 7] (n=111)
X-linked, IL-2 receptor γ chain	46%	24%	48%
Adenosine deaminase	13%	14%	14%
Recombinase activating genes 1 or 2	7%	8%	5%
IL-7 receptor α chain	3%	9%	14%
Omenn syndrome	3%	8%	n/a
Zap-70	3%	2%	n/a
Janus kinase 3	2%	3%	5%
CD45	1%	0%	1%
Purine nucleoside phosphorylase	1%	1%	n/a
Other or not known	21%	31%	13%

Table 2

Ages of occurrence of events for infants with SCID with no recognized prior affected family members.*

	Number of Responses	Mean Age (weeks)	Median Age (weeks)
Age at onset of SCID symptoms	103	11	8
Age at diagnosis of SCID	101	26	24
Age at which definitive treatment instituted**	98	34	28
Age at death, if deceased	56	117	45

* These infants became symptomatic prior to diagnosis of their SCID. In some of these families a positive family history was ultimately recognized retrospectively.

** Definitive treatments in these infants included transplantation or enzyme replacement.