Severe combined immunodeficiency: recent developments and guidance on clinical management

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ABSTRACT

Severe combined immunodeficiency (SCID) is a rare but important condition. Affected infants are born with profound abnormalities of immune cell function that lead to severe and recurrent infection that are almost always fatal in the first year of life without treatment. Infants with SCID are often initially seen by general paediatricians in the hospital care setting, and the recognition of the cardinal features of the disease and alertness to specific laboratory parameters are important in making an early diagnosis. There is also increasing interest in newborn screening for SCID, which has the potential to significantly improve outcome through early diagnosis and implementation of prophylactic medications. Definitive treatments such as haematopoietic stem cell transplantation and gene therapy have also made major advances over the last decade and again promise to improve the overall outcome for SCID with reduced long-term toxicities. In this review, we highlight some of the major advances in diagnosis and management of the disease, but we also want to emphasise the important role of the general paediatrician in making an early diagnosis and in ongoing management.

INTRODUCTION

Severe combined immunodeficiency (SCID) is a clinical and immunological syndrome that arises from a variety of genetic defects that lead to an absence of lymphocyte development and function, the diagnosis of which constitutes a paediatric emergency.[1] Affected children have extreme susceptibility to infections, which are almost always fatal in the first year of life without treatment.[2] While initial estimates of incidence were thought to be approximately 1 in 100 000 live births, data from newborn screening programmes in the USA over the last five years have shown that this is likely to be a conservative estimate, with the true incidence in the region of 1 in 58 000 live births[3] (although this may be higher depending on the population studied). Continued advances in the understanding of the molecular basis of the different forms of SCID have allowed advances in supportive and definitive therapies that have led to improved outcome for this otherwise devastating condition. This article will summarise some of the recent advances in diagnosis, understanding of the pathogenesis and treatments.

When to suspect SCID

As there is currently no newborn screening programme in the UK for SCID, the age of presentation is variable. Those with a positive family history can be tested antenatally if the genetic mutation is known, or at birth where the infant's lymphocyte numbers and function can be tested. Otherwise of the majority of affected infants, presentation tends to occur at 3–6 months as the protective effects of maternal immunoglobulin, transferred to the infant transplacentally and through breast milk, are diminishing.[4]

Typical characteristics are of an infant who has recurrent, severe or opportunistic infections. This can also be accompanied by failure to thrive with persistent diarrhoea. While oral candida is a common finding in normal neonates, candida that does not resolve with simple treatments or comes back as soon as topical treatments discontinue should raise suspicion.

Omenn's syndrome is a variant of SCID and has a clinical phenotype of erythrodermic rash, lymphadenopathy, hepatosplenomegaly and diarrhoea. In these individuals, unlike typical SCID cases, there is development of abnormally activated autoreactive lymphocytes, which have high affinity for the skin, gut and liver, leading to a reaction similar to graft-versus-host disease (GvHD). Unlike the classical finding of low lymphocyte counts seen on the white cell count differential in typical SCID forms, full blood counts from those with Omenn's syndrome reveal normal or raised lymphocytes with a high eosinophil count. A similar picture can be seen in cases of maternal engraftment, which is caused by maternal lymphocytes that have crossed the placenta and engraft in a SCID infant with a GvHD response.

Most of the genetic defects responsible for SCID are inherited in an autosomal-recessive fashion and so are more common in infants born to consanguineous parents. Sometimes, there is no positive family history of SCID, but further questioning of the family history, sometimes on more than one occasion, may reveal deaths in infancy of unknown cause.

It is important to remember that not all children with SCID will present with failure to thrive. Other features such as recurrent infections or low lymphocyte count should still raise suspicion and warrant further investigation.

Diagnosis

SCID is generally defined by a profound defect of lymphocyte development or function. However, the different forms of SCID can have different patterns of lymphocyte (T, B and natural killer (NK) cells) development. Nearly all SCIDs have absent T cells, but are then further divided by the presence or absence of B and NK cells.

There are two main types of T cells; T-helper cells and cytotoxic T cells. T-helper cells are

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responsible for coordinating immune responses by stimulating B cells to produce antibodies and by activating other T cells. Cytotoxic T cells and NK cells are responsible for identifying and destroying infected cells.

The 'combined immunodeficiency' in SCID refers to the combined absence of lymphocyte subtype function. It is important to remember that although some forms of SCID have near normal B cell numbers, these are unable to function due to the absence of T cell help.

X-SCID was previously thought to be the most common form of SCID accounting for ~45% of cases,[5] although the results from newborn screening suggest that this proportion may be a significant overestimate.[3] It results in the deficiency of the gamma chain cytokine receptor subunit, which results in a complete block of T and NK cell development.[5] It differs from other forms of SCID by having an X-linked rather than autosomal-recessive inheritance.

Recent studies suggest that defects in the recombinase-activating genes (RAG) lead to the second most common form of SCID.[3] These genes are essential for the process of splicing together immunoglobulin genes (a process known as VDJ recombination) and their absence leads to abnormalities of T and B cell receptor expression and consequently T and B cell development. NK cells do not express immunoglobulin-like receptors, and so their development is not affected (thereby giving a T-B-NK+ form of SCID).

Adenosine deaminase (ADA)-SCID is the next most common form accounting for ~15% of cases.[5] It results from the deficiency of ADA, an intracellular enzyme of purine metabolism causing toxic accumulation of the metabolic substrate precursors deoxyadenosine (dAdo) and deoxyadenosine triphosphate (dATP), which are particularly toxic to lymphocytes and lymphocyte precursors.[6]

Never ignore a low lymphocyte count in an infant…

T cells usually comprise ~70% of the circulating lymphocytes, so the reduced number of T cells in children with SCID usually results in lymphopaenia.[7] The normal range for absolute lymphocyte count in healthy term neonates is 3400–7600 cells/mm.[3] Preterm infants may have lower absolute lymphocyte counts that gradually rise over time.[8] If the absolute lymphocyte count is low, the first thing to do is to recheck the count, which may in some cases be suppressed due to infection or severe systemic problems. However, a persistently low count or a low count in a well child requires further investigation. Lymphocyte subset analysis can confirm the presence or absence of T, B and NK cells, which give clues as to the likely form of SCID (see figure 1). Further investigations are then carried out at specialist laboratories that can perform appropriate functional and genetic assays.

It is important to remember, however, that not all children with SCID will have a low lymphocyte count and the index of suspicion should remain high when other features are present (see box 1). Infants with JAK3 or X-SCID may have near normal absolute lymphocyte counts (because of the presence of B cells) and those with Omenn's syndrome will have raised absolute lymphocyte counts (see above). Regardless of the number of lymphocytes, infants with SCID will have absent in vitro response to mitogens such as phytohaemagluttinin (PHA), which makes up another important diagnostic test.

Early diagnosis is crucial as outcomes are significantly improved if treatment can commence prior to onset of infections.[1]

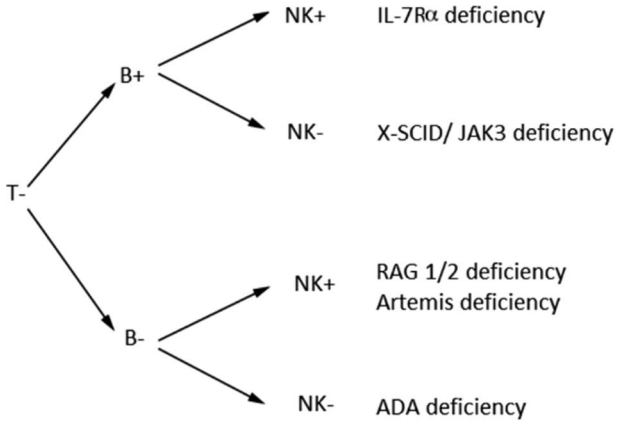

Figure 1 Some of the more common immunophenotypes in SCID. ADA, adenosine deaminase; IL, interleukin; NK, natural killer; RAG, recombinase-activating gene; SCID, severe combined immunodeficiency.

Newborn screening

Infants with SCID are unable to fight infections until they have restored immune function. When diagnosis is delayed, onset of infections leads to end-organ damage. This means that a significant number of infants die before a definitive treatment such as haematopoietic stem cell transplant (HSCT) can be undertaken. Furthermore, infants who come into HSCT with ongoing infection or organ damage have a poorer outcome.[9]

Siblings found to have SCID at birth following testing because of a positive family history have considerably better outcomes compared with the first presenting family member.[10] Whereas normally, best outcomes from HSCT are seen from matched sibling donors, it has been demonstrated that outcomes from donors that are not matched siblings were associated with excellent survival among infants with SCID who were diagnosed before the onset of infection (emphasising the importance of early diagnosis). In fact, all available graft sources are expected to lead to excellent outcomes in asymptomatic infants.[11]

Early diagnosis allows the advent of supportive treatments with prophylactic antibiotics, antifungal treatments and immunoglobulin replacement therapy. It also means that early searches for matched donors can begin.

Although there is limited experience in transplanting newborns where the effects of conditioning with chemotherapy are more likely to be unpredictable, data from transplants in the first month of life are associated with ~92% chance of survival regardless of donor type or type of SCID.[10] Long-term immune reconstitution is also better when transplanted in the first month of life.[9] For these reasons, there has been considerable interest

Box 1 Clinical features of severe combined immunodeficiency

Failure to thrive
Persistent diarrhoea
Persistent oral thrush
Recurrent, severe or opportunistic infections
Lymphadenopathy
Hepatosplenomegaly
Erythrodermic rash (see Omenn's syndrome)
Lymphopaenia

in identifying a biomarker that could be used to identify all forms of SCID at birth.

Normal T cell development requires production of precursor T cells in the bone marrow and processing in the thymus. During normal thymic processing, T cells undergo T cell receptor gene splicing and rearrangement with a resultant DNA by-product, the T cell receptor excision circle (TREC). These do not replicate when the cells divide, and so are only found in recent thymic emigrants and act as a marker of naive T cells and a surrogate marker of thymic activity. Since all patients with SCID have reduced normal T cell development, it follows that the detection of low numbers of naive T cells (by low TRECs) can aid SCID diagnosis. The level of TRECs can be easily quantified by PCR reactions on DNA extracted from the blood spot on routine Guthrie cards.

Newborn screening for SCID in the USA began in 2008 in Wisconsin and has now been extended to 23 states.[3] It is the first condition being screened for that can actually be cured. Data from the first five years of screening in the USA (11 screening programmes) reported an incidence of 1 in 58 000 live births with overall survival of 87% 2008–2013.[3] Specificity was high at >99.8%[3], and in addition to SCID cases, other additional cases of non-SCID T cell lymphopaenia were identified, allowing them to avoid live vaccines and receive appropriate infection prophylaxis and follow-up.[8]

There had been concerns about increased anxiety among parents with false positive results, but some studies have shown that actually parents welcome extension of the newborn blood screening and false positives are considered a relatively minor issue.[12] Potential anxiety can be effectively managed with improved training on counselling about results prior to blood sampling. Although newborn screening is not currently routinely taking place in Europe, this is being actively discussed in a number of countries including the UK.

Making a genetic diagnosis

Making a genetic diagnosis is important in understanding and preparing the family for the potential future outcomes of their child once treated with HSCT[7] and whether there are likely to be associated problems such as the hearing and behavioural issues associated with ADA-SCID. It also allows for genetic counselling and ability to carry out first trimester testing in future pregnancies with termination where desired. Certain genetic diagnoses may be eligible for treatment with gene therapy if a matched donor for HSCT is not available (see below), which is another important advantage of making a genetic diagnosis. Currently, ~10% of infants with SCID still have unknown genetic defects.[3]

Until recently, genetic diagnosis has relied upon the sequencing of individual genes. However, given that there are over 18 different genes associated with SCID and the immunological phenotype can overlap between different forms, the time to establish a diagnosis can be delayed. The remarkable advances in gene sequencing technology now allow the simultaneous sequencing of large number of genes or indeed whole exome or genome sequencing. Some studies show that targeted next-generation sequencing has sensitivity and specificity of >99% in detecting point mutations and 100% sensitivity and specificity of exonic deletions.[13] In this particular approach, accurate simultaneous detection of mutations in 161 of 170 known primary immunodeficiency (PID)-related genes was possible, meaning that screening for genetic mutations can be rapidly carried out where such conditions are suspected.[13]

More detailed genetic analyses will generate further insight into the genotype–phenotype correlations for different PID disorders.

Management

General principles

Although management varies among countries and institutions, some common principles of conservative management are described below that revolve around reducing infection and associated end-organ damage prior to definitive treatment.

Isolation of SCID infants: Infants with SCID are most likely to stay in hospital between diagnosis and treatment. Where discharge has been recommended, it is important to keep affected infants away from other children, infected individuals, large groups of individuals and closed environments including public transport, in order to reduce exposure to pathogens.

Vaccinations: Live vaccines must be avoided and those who have already received Bacillus Calmette–Guérin vaccine (BCG) prior to diagnosis will need to start antituberculosis treatment. It is recommended that *siblings* of those with SCID should also not receive the rotavirus vaccine.[5] Although routine vaccinations are unlikely to cause harm, they are unlikely to confer any additional benefit as they will not be effective.

Nutrition: Nasogastric tube feeding or parenteral nutrition may be required in order to optimise nutrition. Hydrolysed formulae are generally better tolerated, particularly in those with Omenn's syndrome with marked gut inflammation, as they are better absorbed.

Prophylaxis: *Pneumocystis Jirovecii pneumonia* prophylaxis should start with co-trimoxazole and additional antiviral and antifungal cover given depending on local guidelines and clinical circumstances.

Immunoglobulin replacement: Replacement immunoglobulins should be given intravenously or subcutaneously every two to three weeks depending on response.

Organism surveillance: Some centres conduct weekly screening of infants for herpes viruses (adenovirus, Epstein–Barr virus and cytomegalovirus (CMV)) as well as for respiratory and stool organisms. Early detection allows for intervention prior to end-organ damage and improved outcomes.[14]

Breast feeding: Due to the increased risk of CMV transmission through breast milk, breast feeding is discouraged until the mother and infant's CMV status is known.[15]

Chicken pox: Early intervention with use of varicella zoster-specific immunoglobulin in those who have been in contact with the virus and treatment with Aciclovir in those with suspected infection are essential to avoid disseminated infection.

Blood products: All blood products will need to be CMV negative, irradiated and leucocyte depleted in order to prevent donor T cells from attacking the infant and to prevent interference with future HSCT.

Immunosuppression: Infants with Omenn's syndrome or maternal engraftment (see above) are likely to require immunosuppressive treatment such as systemic steroids and possibly ciclosporin in order to control the inflammatory reaction.

Enzyme replacement: In ADA-SCID, enzyme replacement therapy (ERT) can provide initial benefit in reducing the toxic accumulation of metabolites. Unfortunately, there are no equivalent agents to aid other forms of SCID.

Haematopoietic stem cell transplant

Since all mature blood cells and their progenitors are derived from haematopoietic stem cells, it follows that giving donor cells that are rich in stem cells to infants with SCID would have

the ability to restore normal lymphocyte number and function from the genetically normal blood cells.

Donor grafts are available from bone marrow and mobilised peripheral blood from related or unrelated donors or umbilical cord samples from unrelated newborns. In order to allow the donor stem cells to undergo normal haematopoiesis, some chemotherapy is normally needed to destroy native bone marrow and make room for donor cells to engraft. Myeloablative conditioning generally leads to the highest levels of donor engraftment, and although myeloablative regimen previously used caused significant morbidity and some mortality, current reduced intensive regimens cause much less toxicity.[16] The conditioning process also results in an extremely vulnerable period where the recipient bone marrow has been destroyed but donor stem cells have not yet started to produce functioning cells, thus leaving the transplant recipient extremely susceptible to infection. After engraftment takes place, reactions between graft and host (GvHD) can develop, which can in severe cases have major consequences. More commonly, it causes ongoing inflammation with a need for immunosuppression with corticosteroids, which in itself can lead to associated problems such as poor growth, osteopaenia and susceptibility to infection, especially if used long term.

In some cases of SCID, HSCT can be undertaken without the need for any chemotherapy. In particular, X-SCID and ADA-SCID forms have significant benefit and good immune recovery after unconditioned transplants from matched family donors.[17] In other SCID forms, unconditioned transplants are associated with suboptimal immune reconstitution that may be problematic in the long term.

The first transplant for SCID was carried out in 1968.[18] Since then there has been much research into how to make the process safer and survival from HSCT has improved.[16] It is now increasingly common to see that children treated with HSCT are going on to achieve educational goals and some children have been able to produce children of their own (not possible with the earlier myeloablative chemotherapy regimens).[19–21]

With concentration of HSCTs in a few centres of excellence and pooling of data, combined experience allows development of safer procedures. The European cohort follows >1500 patients who have undergone HSCT for PIDs. This allows sharing of lessons learned between centres of excellence, with analysis of this large data pool leading to development of guidelines for best practice (European Bone Marrow Transplant guidelines).

Data published by Gennery *et al* in 2010[16] on long-term outcomes for patients treated between 1968 and 2005 in European centres show that survival following HSCT for SCID from a genoidentical donor after 2000 is 90%. Survival following transplant from other donor sources has also improved over time. Absence of respiratory impairment or viral infection before transplant and younger age at transplant was associated with better prognosis on multivariate analysis.

Box 2 Advances in haematopoietic stem cell transplant

Less toxic conditioning regimens
More detailed tissue typing
Greater use of unrelated and cord donors
Graft-versus-host disease prophylaxis
Molecular detection of viral infections

The advances in HSCT identified from the cohort[16] leading to improved outcomes are summarised in box 2.

The use of less toxic conditioning regimens results in reduced chemotherapy-induced end-organ damage and has allowed children who are more unwell and would previously have been deemed not fit for chemotherapy to undergo transplantation.

Improved methods for more detailed tissue typing and greater use of unrelated and cord donors have increased the chances of finding a matched donor, which together with the introduction of GvHD prophylaxis have reduced the burden of GvHD and need for long-term corticosteroid use.

In utero HSCT

There is not currently thought to be any benefit of in utero HSCTs. It is not possible to deliver chemotherapy to the fetus without harming both the mother and fetus, which means that engraftment is likely to be difficult. The procedure itself would be associated with high risk of fetal loss and after the procedure there would be no way to monitor for GvHD. When outcomes from early infant transplants are so good, the rationale for in utero transplantation is limited.

Gene therapy

The last decade has witnessed substantial progress of gene therapy using autologous gene-corrected haematopoietic stem cells for two types of SCID: ADA deficiency and X-SCID. ADA-SCID was the first molecularly diagnosed SCID in 1972,[22] and the first treatment with gene therapy was initiated for ADA-SCID in the early 1990s.[23]

Although HSCT is the mainstay of definitive treatment of children with SCID, the outcome is dependent on the availability of a human leucocyte antigen-matched donor.[24] Those with ADA-SCID can continue with ERT, which has been shown to offer good metabolic correction; however, the immunological recovery is variable with decreasing T cell numbers over time and the loss of thymic function.[25–27] Adverse effects of ERT also include haemolytic anaemia, chronic pulmonary insufficiency, lymphoproliferative disorders and rarely hepatocellular carcinoma.[6]

In ADA-SCID, although some conditioning is still needed to ensure engraftment,[28] this is usually at much lower doses than regimens used for HSCT and so has reduced organ toxicity. As autologous cells are used, there is no risk of GvHD and no immunosuppressive prophylaxis is needed.[15] Over 50 patients worldwide with ADA-SCID have been treated by gene therapy with encouraging results. There has been 100% survival and 75% of patients have been able to discontinue ERT long term, suggesting that immune recovery has resulted from the use of gene therapy alone (ref. 15 and unpublished data).

There were some important adverse effects of early gene therapy using the initial design of retroviral vectors for X-SCID where an increased incidence of lymphoproliferative disorders was noted.[29] Twenty subjects underwent gene therapy in Paris and London 1999–2006 for X-SCID and showed effective T cell recovery. However, following gene therapy five developed leukaemia of which four children went into remission, but one unfortunately died.[30] The identification of the adverse effects led to detailed characterisation of retroviral vector integration profiles, and a new generation of self-inactivating and lentiviral vectors were designed to address these concerns.[31] To date, no adverse events due to insertional oncogenesis have been reported for the new generation of self-inactivated retroviral or lentiviral vectors for X-SCID,[32 33] and this, coupled with good

Table 1 Features of GvHD

Typical features of GvHD	Atypical features of GvHD
Inflammation of ▶ Skin ▶ Liver ▶ Gut	Cytopaenias Pneumonitis

GvHD, graft-versus-host disease.

T cell recovery, suggests that gene therapy may offer a viable treatment option for patients who lack a well-matched donor.

Studies looking at gene therapy for RAG 1/2 and Artemis deficiencies in mice are promising, and it is likely that clinical trials will commence over the next few years.[15]

Novel approaches using homing endonucleases and zinc finger nucleases to target specific endonucleases that induce site-specific DNA double-strand breaks have been developed, and this can facilitate homologous recombination around target sites to achieve gene correction or gene insertion into safe genomic locations.[34] These technologies are likely to come into the clinical arena in the near future and may have a significant impact on gene therapy as a treatment modality for SCID.

Follow-up

Follow-up will vary between institutions, but in general children are monitored closely by the transplant centre for the first year, after which care is shared with local hospitals supported by six monthly visits at the transplant centre.[7] After the first five years, the frequency of visits to the transplant centre usually drops to yearly.

Reviews look at immune reconstitution and chimerism (what proportion of the child's lymphocytes are native or donor) as well as monitoring for ongoing GvHD. Those with typical or atypical features of GvHD (see table 1) should be referred back to the transplant centre.[7]

Duration and intensity of antimicrobial prophylaxis depends on immune reconstitution as well as their preinfectious and postinfectious disease history.[7] This will be guided by the immunologists, but in general, CD4 counts >300 cells/μL and PHA proliferation of >50% normal are used as cellular immunity parameters to consider discontinuing prophylaxis.[7] Continued need for immunoglobulin replacement (which is IgG replacement) depends on duration of therapy, trough levels and ability to make IgA and IgM. Those on immunosuppressive agents for ongoing GvHD will usually need to continue immunoglobulin replacement.[7] Once IgG replacement has been discontinued, routine vaccinations can then be given.

Box 3 Role of the general paediatrician

Monitor growth and development
Screen for consequences of chemotherapy and long-term corticosteroid use
Support mental health aspects for the child and other family members
Refer back to transplant centre if
- worsening graft-versus-host disease
- onset of recurrent, severe or opportunistic infections
- falling lymphocyte count.

Those with pre-existing infections will require specific treatment until clinical, imaging and laboratory assessments of disease have improved.[7]

Growth and development will need to be monitored carefully (see box 3). If the child received conditioning with chemotherapy or long-term corticosteroids, they should be screened for endocrine problems, neurocognitive delays, osteopaenia and dental problems.[7] It is now increasingly recognised that the effects on mental health, quality of life and well-being of the child and their families should also be monitored. Counselling is routinely offered to parents and siblings before and during the transplant process, particularly when a family donor is used. It is important to remember that sometimes these services need to continue in the longer term, regardless of the clinical outcome of the affected child.

SUMMARY

The last 20 years have shown important changes in how SCID is diagnosed and treated. The use of targeted next-generation sequencing and improved understanding of the molecular basis of the various forms of SCID are aiding the understanding of genotype–phenotype correlation. Overall and disease-free survival are continuing to improve with earlier diagnosis through newborn screening, safer transplants and development of alternative treatments such as gene therapy. We have seen SCID change from a condition that had an extremely poor outcome to one where now early diagnosis can lead to a >90% survival outcome. The next 20 years are likely to continue to contribute to this exciting era of developments in the diagnosis and management of SCID.

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