Advances in management of primary immunodeficiency

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Abstract

Primary Immunodeficiencies (PID) although rare are serious; diagnosis is often delayed due to their non-specific presentation. Heightened clinical suspicion leads to earlier diagnosis and improved outcome. Historically fatal in early childhood recent advances in diagnosis and management mean much improved mortality and morbidity. Antimicrobial prophylaxis and Immunoglobulin substitution intravenously, or increasingly subcutaneously offer excellent improvement in quality of life. Haematopoietic Stem Cell Transplant is now the definitive curative treatment for a wide range of severe PIDs. The success of these treatments, allows more focus on improving longterm quality of life. Gene therapy has had early success but significant complications and remains an ongoing area of research with considerable potential.

Keywords antimicrobial prophylaxis; gene therapy; haematopoietic stem cell transplantation; immunoglobulin replacement; primary immunodeficiency

Diagnosis

Primary Immunodeficiencies (PID) are rare and most commonly present to general paediatricians. Improved survival and outcome seen over the past decade has been in part due to improved and new treatments, but in part due to better recognition of children with a potential underlying immune defect. Nevertheless, delay in diagnosis is common due to the non-specific presentation of many of these conditions resulting in high mortality and morbidity and so aids to better recognition are very much needed.

The National Institute for Health identified 10 warning signs which should alert to the possibility of PID (Table 1). However, they are mainly based on expert opinion and a recent study found only three were significantly more common in children found to have a PID:

- family history
- need for IV antibiotics
- failure to thrive.

Diagnosis relies upon clinical suspicion following thorough history and examination and subsequently appropriate baseline investigations. The history and examination may reveal 'red flags' which may suggest either a risk of PID or a specific defect and some of these are highlighted in Table 2. There have been considerable advances in molecular diagnostic tests and over 150 PIDs can now be diagnosed. However, these are only possible if the child is recognized as potentially having a PID.

Improved identification of genetic defects allows for more accurate prognosis and genetic counselling for families with antenatal diagnosis in some cases. Functional tests of immunity are still important, to assess the nature and severity of the defect (which may vary greatly between patients with the same molecular defect).

Investigations should be focussed towards the category in which the patient's suspected immunodeficiency lies (Table 3).

Severe combined immunodeficiency (SCID), can often be diagnosed by a simple Full Blood Count (FBC) and although the total white cell count is usually normal, if the differential is examined, lymphopenia is present; however in an infant the lower limit of a normal lymphocyte count is between 2.5 and 2.7 $\times 10^9$/litre which is higher than that seen in adults or older children and so can be overlooked. Therefore, in an infant presenting with features of immune dysfunction a lymphocyte count below this on two occasions should lead to consideration of a diagnosis of SCID. Further evaluation of lymphocyte surface markers will confirm the diagnosis. Specific genetic defects have now been identified for many of the subtypes of SCID including adenosine deaminase (ADA), common γ chain and Artemis resulting in better prognostic information and specific targeted treatment.

Identification of specific protein expression in leucocytes may aid both diagnosis and prognosis. For example, Wiskott–Aldrich Syndrome (WAS) protein expression is abnormal in WAS and X-linked Thrombocytopenia (XLT). The amount of protein expression correlates with disease severity and prognosis with absent WASP expression being associated with WAS and a poorer prognosis and normal expression of abnormal protein in XLT resulting in a less severe phenotype.

Assessment of suspected antibody deficiency starts with B cell enumeration and measurement of the levels of IgG, IgA, IgM, IgG subclasses and antibody responses to Hib, tetanus and pneumococcal vaccination; these assays being the most robust and reproducible. They also offer the opportunity to look at the relative strength and responses to different antigens, tetanus being the most powerful and pneumococcus the weakest. Thus a failure to respond to tetanus usually signifies a serious antibody deficiency, whereas poor response to pneumococcal antigen may simply represent 'sluggish' immune maturation although if persistent are more significant. It is now possible to measure serotype specific pneumococcal vaccine responses which are a more accurate measure.

IgG subclass measurement remains controversial. Some argue that low levels of subclasses on their own are not clinically

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The 10 warning signs of PID

- Eight or more new ear infections within 1 year
- Two or more serious infections within 1 year
- Two or more months on antibiotics with little effect
- Two or more episodes of pneumonia within 1 year
- Failure of an infant to gain weight or grow normally
- Recurrent deep skin or organ abscesses
- Need for intravenous antibiotics to clear infections
- Persistent thrush in mouth or fungal infection on skin
- Two or more deep seated infections e.g. sepsis, meningitis
- A family history of PID

Table 1

relevant, however when there is concomitant IgA deficiency or poor response to vaccination with polysaccharide antigens such as pneumococcus they probably are significant. Thus a low IgG_2 in a child with recurrent infection should prompt careful evaluation of IgA and specific vaccine responses. Once an antibody problem has been identified the specific diagnosis can be made either by looking for lack of protein expression and/or for a gene defect such as Bruton Tyrosine Kinase (BTK.)

Investigations for disorders of neutrophil function and number begin with repeat neutrophil counts and if there is a cyclical pattern, these should be performed 2–3 times a week for 3–4 weeks. The Nitroblue Tetrazolium Reduction (NBT) test is commonly used to diagnose Chronic Granulomatous Disease (CGD), although usually diagnostic it is prone to observer error. The FACS based Dihydrohodamine Reduction (DHR) test is more clear cut and is superceding the NBT, but an abnormal DHR is also found in myeloperoxidase deficiency which unlike CGD is only rarely associated with significant infection.

Complement deficiencies are rare, but when suspected should be investigated by testing the whole classical and alternate pathways using the CH100 and AP100 tests. If these are abnormal then individual components should be assayed.

Red flags of PID

Red flag	Condition
Microbial clues	
Meningococcal (>1 episode, unusual serotype, or +ve family history)	Complement deficiency
Pneumococcus (recurrent)	Asplenia, complement deficiency, antibody deficiency
Invasive *Aspergillus*	CGD
Staphylococcus	CGD, Hyper IgE
Respiratory clues	
Pneumatocoeles	Hyper IgE
Persistent bronchiolitis	SCID
Interstitial pneumonitis	SCID, CD40L, NEMO, MHC II deficiency
Recurrent pneumonia	Antibody deficiency
Bronchiectasis	Antibody deficiency
Gastrointestinal clues	
Sclerosing cholangitis	CD40L deficiency
Liver abscess	CGD
Failure to thrive	SCID

Table 2

Newborn screening

Newborn screening programmes are widespread in the developed world, enabling early diagnosis and better treatment before complications develop for conditions such as Cystic Fibrosis. SCID fulfils many of the required criteria for newborn screening; it is serious, identifiable with new techniques and earlier diagnosis has a significant impact on outcome (see later). Screening has now been introduced in many states in the US and has been shown to be highly specific and sensitive and therein clinical consensus is that this should be added to the UK newborn screening programme. Screening tests for conditions such as X-linked Agammaglobulinaemia are also being developed.

Management

Antimicrobials

The evidence base for prophylactic antibiotics in PID patients is sparse; however, they are used widely. Practices are based upon consensus, what is known about likely infecting organisms and more recently from trials involving associated conditions such as HIV.

Most patients with PID receive antibiotic prophylaxis, either longterm or whilst awaiting definitive treatment such as Haemopoietic Stem Cell Transplantation (HSCT). The type of PID impacts upon whether and what prophylaxis is required.

Patients with defects in neutrophils function or number, have a high incidence of significant bacterial infection. Patients with CGD are known to be at particular risk with infections from *Staphylococcus aureus*, *Nocardia* and *Burkholderia* species. Cotrimoxazole (septrin) is therefore, commonly used in CGD, one of the few situations where there is clear evidence to support its use in reducing episodes of infection.

Humoral immunodeficiencies represent a more diverse group of patients with differing needs with regards to prevention of bacterial infection. The spectrum of disease is broad and the need for prophylaxis beyond the use of replacement immunoglobulin, depends upon the specific condition. This group of patients is particularly at risk of lung damage and the prevention of bronchiectasis, if not already established, is in part the reason for aiming to prevent infection. Once bronchiectasis is established, this increases risk of infections such as pseudomonas and non-tuberculous mycobacteria which are not covered by traditional prophylactic antibiotics. The role of azithromycin is of increasing interest, as it not only covers the aforementioned organisms, but its anti-inflammatory properties have been shown to improve lung function in both Cystic Fibrosis (CF) and non-CF bronchiectasis making its use as a prophylactic agent even more attractive. Azithromycin may also be very helpful in patients with Hyper IgE syndrome who are very prone to lung infection.

Primary T cell immunodeficiencies include infants with SCID through to children with DiGeorge Syndrome who have widely varying immune defects. Patients with SCID have severe deficiencies

Investigations for potential PID

Potential immunodeficiency	1st Line investigations	2nd Line investigations
Combined immunodeficiency	• FBC — particularly looking for lymphopenia • Lymphocyte subsets • Immunoglobulins	• Naive/memory T cells • Proliferative responses • Functional molecular tests • Specific protein assays • ADA and PNP enzyme levels
Antibody deficiencies	• FBC • B cell markers • Immunoglobulin levels • Vaccine responses	• Specific protein assays • IgG subclasses • Isohaemagglutinins • Bone marrow structure or precursor B cells • Molecular tests
Neutrophil disorders	• FBC — repeated • Flow cytometric assessment of neutrophil burst	• BM assessment • Specific protein assays • NBT
Complement disorders	• Assessment of classic and alternative complement pathway (CH100/AP100)	• Individual complement component assays

Table 3

and few would challenge the use of prophylactic co-trimoxazole, due to the high risk of Pneumocystis Jeroveci (formerly Pneumocystis Carinii). Antibiotic prophylaxis is not always required in patients with DiGeorge Syndrome and the decision should be based upon the degree of compromise and the individual patient.

Consideration has been given to whether alternating the agent used as prophylaxis has greater benefit. There is even less evidence for the use of alternating antibiotic regimens. In fact, what little evidence is available suggests that this increases the prevalence of resistance organisms without improving infection rates.

In the absence of well powered, randomized control trials, single agent antibiotic prophylaxis seems best, directed at the most likely organisms. In most situations, this agent will be co-trimoxazole but it is worth considering if the anti-inflammatory properties of azithromycin may be beneficial.

Antifungals

Antifungal prophylaxis is limited to those considered to be at high risk of invasive fungal infection, namely CGD. The use of itraconazole in CGD patients significantly reduces the rate and severity of fungal infection in this group. The development of oral antifungal agents with good bioavailability has provided an extra dimension to antifungal prophylaxis. Posaconazole is increasingly being demonstrated as a useful agent in both treatment of invasive fungal infection and as a prophylactic agent. Palatability is also an important factor in paediatric prescribing and posaconazole is reported to be superior in this domain as well.

Diagnosis of fungal infection remains a challenge. It was anticipated that the introduction of galactomannan measurement may aid in the early diagnosis of Invasive Aspergillosis as initial findings in immunosuppressed adults were promising. Unfortunately, this has not been the case in paediatrics and in the post-HSCT setting, their measurement demonstrated a low specificity and poor positive predictive value.

Immunoglobulin replacement

Immunoglobulin (Ig) has been used to treat hypogammaglobulinaemia since the 1950s and more recently for some patients with combined immunodeficiencies and partial antibody deficiency. Efficacy and safety have been well demonstrated, with improved life expectancy, a reduction in the number of infections, and much less lung damage. Ig is a blood product and blood borne infection is a potential risk. However, current purification methods have all but eliminated this risk.

At first Ig was given intramuscularly but this is both painful and less effective at achieving good serum IgG levels. Intravenous Ig (IVIg) or subcutaneous Ig (SCIg) are now given. Both have well demonstrated efficacy and safety. There is a trend towards greater use of SCIg, not least as this enables home-delivered care with a 1 hour infusion each week via an easily sited fine bore needle, whereas venous access and a 3–4 hour infusion is necessary for IVIG. Concern that trough levels of Ig after SC administration would be too low has been unfounded and in fact, SCIG provides a more consistent level of immunoglobulin with trough levels that are similar or higher compared with IVIG. A number of studies have shown that higher trough levels of Ig will result in fewer infections and this is particularly important in patients with bronchiectasis, lung damage and conditions which predispose to this.

SCIG has the advantage that IV access is not required and serious adverse reactions are also less common with SCIG. Home administration of immunoglobulin via the SC route has repeatedly been demonstrated to be preferred by patients. Further improvements may include a shift towards rapid push rather than an infusion which may improve this route more by reducing the time required for each infusion. The concentration may also be increased, reducing the volume of SCIG required. The differences between IVIG and SCIG are shown in Table 4. Adverse reactions are uncommon and most can be managed by a reduction in the

Comparison of subcutaneous and intravenous immunoglobulin

	SCIG	IVIG
Dose	0.1—0.2g/kg	0.2—0.6 g/kg
Frequency	Weekly	Every 3 weeks
Duration of infusion	Over 1 hour	Typically 3—4 hours
Home administration	Commonly arranged	Unlikely
Adverse effects	• No serious adverse reactions • Local adverse reactions (mild)	• Serious adverse reactions rare
Access	No venous access required	Venous access required
Serum Ig levels	More constant	Peaks and troughs

Table 4

rate of infusion. Alteration in manufacturer's preparation of immunoglobulin or by changing the product may affect how it is tolerated. These changes can lead to higher rates of adverse reactions even in cohorts who have previously tolerated IVIG. If a change is necessary then premedication with antihistamine and paracetamol reduces adverse reactions, but where possible the same manufacturer's product should be used (Table 5).

HSCT

HSCT successfully cures a widening range of Primary Immunodeficiencies. Advances have lead to such an improved survival rate that quality of life longterm post transplant has now become a vital consideration. Advances include a greater awareness of PID leading to earlier diagnosis and referral to specialist centres, precise molecular diagnoses, refinement of HLA tissue typing, increased availability of unrelated donors (currently over 18 million registered with the bone marrow donors worldwide registry), alternative sources such as cord blood (over 0.5 million registered), less toxic conditioning regimens, molecular detection of viral infection enabling preemptive antiviral treatment before end-organ damage supervenes and improved prophylaxis for prevention of Graft Versus Host Disease (GVHD). The aim of a transplant is to provide stable donor stem cell engraftment after partial or total ablation of the recipient's marrow and immune system using a combination of chemotherapy, antibodies and a graft versus marrow effect from donor cells. Unlike children receiving a transplant for a haematological malignancy where a graft versus leukaemia effect is useful to eradicate the underlying disease, GVHD confers no advantage to children with PID. In the UK Newcastle upon Tyne and Great Ormond Street Hospitals are the two designated supraregional centres for transplanting children with PID as well as autoimmune gut disease and juvenile idiopathic arthritis.

The don'ts of immunoglobulin replacement

- Give intramuscular replacement
- Too long a gap between infusions
- Infuse too quickly
- Give infusions in acutely infectious patients
- Initiate home infusions without adequate training
- Change product unless no alternative

Table 5

SCID

SCID is usually fatal by 1 year of age unless an infant receives a new immune system. In the most recent analysis of 699 SCID patients transplanted across Europe there was a survival of 90% for those transplanted with a genoidentical sibling donor and nearly 70% for those receiving a matched unrelated donor. The outcome for those without pre-existing infection such as those diagnosed at birth is even better: in the UK series the survival for those transplanted having being diagnosed at or before birth was 91.5% compared to 61% for those transplanted having being diagnosed at a median age of 143 days and a significant number of these children died from infection before reaching transplant. These data show that neonatal screening programmes which are being introduced in North America should be made widely available.

Matched unrelated donors give good results, but the time taken to work up an adult unrelated donor can be detrimental to an infected patient and cord bloods can be procured more quickly. For those without an HLA-identical relative or matched unrelated donor a mismatched relative can be used. New methods of depleting T lymphocytes from such donors such CD3/CD19 depletion or CD34 positive selection are successful. A recent European study compared mismatched related donor HSCT to unrelated donor cord HSCT in children with severe T cell deficiencies: no significant difference in survival was found, but cord blood recipients had a higher frequency of complete donor chimerism at day 100 and faster total lymphocyte recovery.

The use of cytoreductive conditioning before HSCT for SCID is much debated. There is general agreement that recipients of HLA-identical sibling HSCT, those with severe infection and ADA SCID babies do not need this. However without conditioning donor B cells rarely engraft resulting in many patients requiring lifelong immunoglobulin replacement with a greater risk of infective lung damage. Conditioning also leads to better quality T cell reconstitution with improved thymic output, important for ensuring a longterm broad T cell repertoire. Failure of thymopoiesis may lead to T lymphocyte senescence in the longterm. B— SCID patients have an overall worse outcome than B+ SCIDs and need conditioning to obtain good quality immune reconstitution. NK cells may contribute to graft rejection, and double negative T cell precursors in RAG 1, RAG 2 or Artemis deficiencies may also hamper engraftment.

A successful procedure leads to patients leading normal lives usually off all medication. Some sequelae relate to specific genetic defects such as human papillomavirus associated warts in IL-2RG/JAK3 SCID and neuro developmental disorders in ADA deficiency which may not be cured by HSCT.

Other PID

HSCT is now being offered to an increasing number of children with non-SCID Primary Immunodeficiencies firstly because

outcomes have improved, and secondly because of studies of the natural history of patients managed conservatively, for example with CGD high rates of morbidity and mortality are seen in the second and third decades of life without transplant despite prophylaxis: in a UK registry study quality of life was poor with frequent hospital admissions and surgical procedures and only 50% were alive at 30 years of age. Non-SCID disorders that can be cured by HSCT include Wiskott–Aldrich syndrome (WAS), T cell deficiencies such as Omenn syndrome and CD40 Ligand deficiency, Haemophagocytic syndromes such as familial haemophagocytic syndrome and X-linked lymphoproliferative disease and phagocytic cell disorders such as CGD and leukocyte adhesion deficiency. In the European analysis of 783 patients with non-SCID PID the survival for both genoidentical and matched unrelated donor HSCT was between 70 and 80%. T cell depleted mismatched donor HSCT is not so successful in these patients due to their increased ability to reject such grafts compared to SCID patients. Survival for undefined T lymphocyte immunodeficiencies remains poor maybe because without a clear genetic diagnosis patients are not offered HSCT until infection and end-organ damage supervene making the transplant much more difficult, highlighting the importance of precise genetic diagnosis at an early stage.

HSCT for patients with CGD with a matched related or well matched unrelated donor is now widely accepted as the treatment of choice. A recent international study of 194 patients with WAS reported an overall survival of 84% rising to 89% for those transplanted since 2000. Younger age and milder clinical phenotype were associated with better outcome.

Patients with mutations in the WAS protein gene that allows some expression exhibit the milder X-linked Thrombocytopenia (XLT) phenotype. The role of HSCT in these patients remains controversial but a recent multicentre study of 173 patients revealed serious bleeding episodes in 13.9%, life-threatening infections in 6.9%, autoimmunity in 12.1% and malignancy in 5.2% indicating that HSCT may be an option for patients with XLT as well as WAS.

The decision to transplant needs to be taken on the balance of risk and benefit taking into account the underlying diagnosis, anticipated mortality and morbidity on supportive treatment, comorbidities such as infection and organ damage and quality of donor available. Families need careful counselling in order to appreciate for example a 10% risk of mortality in transplanting a young, well child with CGD with a good matched unrelated donor followed by a normal life, compared to a poor quality of life and risk of death of 50% by the age of 30.

It is important to prepare patients carefully prior to transplant by rigorous attention to detection and treatment of infections, organ damage, inflammation e.g. Colitis in CGD and maximizing nutritional status.

For many years myeloablative chemotherapy with busulphan and cyclophosphamide was given prior to HSCT for PIDs. However this combination is associated with significant toxicity including veno-occlusive disease of the liver despite the use of intravenous busulfan and pharmacokinetic monitoring particularly in those under a year of age who represent a significant proportion of PID patients undergoing HSCT. Reduced intensity conditioning regimens using drugs such as fludarabine and melphalan have diminished treatment-related toxicity but toxicity remains a problem for infants under one year of age. Minimal intensity conditioning with fludarabine, low dose cyclophosphamide and antibodies can reduce toxicity further, but has been associated with poor engraftment of donor myeloid cells [chimerism] or an increased incidence of GVHD. New regimens are being developed that give adequate myeloablation but less toxicity particularly in patients under a year of age such as the combination of treosulfan with fludarabine and Alemtuzumab. By using mobilized donor peripheral blood stem cells rather than bone marrow as the stem cell source the percentage of donor chimerism may be increased which may be important for diseases where donor myeloid chimerism is required such as CGD which is more difficult to achieve than donor lymphoid chimerism required for diseases such as T cell deficiencies. Targeted busulfan in combination with fludarabine is also a promising combination and longterm studies are needed to assess outcome using these regimens and in particular the longterm effects such as infertility.

Gene therapy

HSCT is the treatment of choice for an increasing number of PIDs and morbidity and mortality is constantly improving. However, HSCT is not without risk particularly if there is not a well matched donor available. The genetic defect, usually a single gene, is now known for over 150 PIDs. Gene therapy is the introducing of a functional copy of the defective gene, using a viral vector, into haematopoietic stem cells.

SCID represents an ideal model for gene therapy; particularly if there is only an HLA-mismatched donor or the patient is older at diagnosis and already damaged by infection. Initial results in the X-linked SCID were promising with good production of T lymphocytes, although a lesser response in the B and NK cell lineages. However, these promising results were tempered by the development of leukaemias in five of the first 20 treated due to preferential insertion of the vector at a pro-oncogene locus. These trials were halted due to this finding. A similar problem has occurred in 1 of 10 patients with WAS.

In ADA SCID, gene therapy has demonstrated some success without any cases of leukaemia, although good immune reconstitution was only demonstrated if the patients were conditioned with busulphan prior to treatment. In CGD initial results were very promising but the population of gene corrected cells then either died out or the inserted gene was silenced.

The need for conditioning and the risk of oncogenes mean that gene therapy has not replaced HSCT as the definitive treatment of choice for PID. For patients without a matched donor it may be appropriate and ongoing research appears promising. ◆

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Practice points

- Early diagnosis of PID is key to best outcomes
- Of the 10 warning signs for PID identified, three are the most important; family history, failure to thrive and need for IV antibiotics to clear infection
- Precise molecular diagnosis and knowledge of natural history is pivotal in deciding best treatment
- Higher levels of replacement IG and adjunctive antibacterial therapy may delay chronic lung damage in hypogammaglobulinaemia
- SCIG and IVIG are both equally effective; SCIG is preferred by many patients
- HSCT result have much improved, meaning more PIDs are curable
- Gene therapy is an exciting prospect but technical challenges and complications limit its usefulness at present