Advances in primary immunodeficiencies

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Abstract

Primary Immunodeficiencies (PID) although rare are serious; diagnosis is often delayed due to their non-specific presentation. The concept of PID has changed in recent years to a broader clinical phenotype, including autoimmunity, malignancy, immune dysregulation and allergy. Improved genetic diagnostics has greatly improved both our understanding of PID and our approach to diagnosis, enabling more accurate delineation. Haematopoietic Stem Cell Transplantation (HSCT) is an increasingly successful curative treatment for a widening range of severe PIDs; survival following HSCT is now 90% due to better preparation, less toxic chemotherapy, improved donor matching, better manipulation of stem cells and improved management of complications. Quality of life for PIDs such as Chronic Granulomatous Disease (CGD) is markedly better after HSCT than with supportive care. This article outlines the advances made in this rapidly advancing field in the last decade and offers practical advice on investigation and management of suspected or confirmed PID for the general paediatrician.

Keywords autoimmunity; HSCT; primary immunodeficiency

Introduction

Individual primary immunodeficiencies (PID) are rare but together affect 1 in 500 to 1 in 2000 children. PIDs are serious and present throughout childhood, most commonly to a general paediatrician outside a specialist centre. Early diagnosis improves outcome as it allows early treatment and prevention of infectious and inflammatory complications.

The number of children diagnosed with PID is increasing in part due to greater awareness and more accurate genetic testing allowing more careful delineation of condition and in part due to a change in concept of what PID encompasses.

Changes in the concept of PID

Initially PIDs were defined by an increased susceptibility to infection due to defective immunity. Our understanding of how the immune system functions at a molecular and cellular level renders this too simplistic, as we recognize a broader clinical phenotype, overlapping with disorders of immune dysregulation, autoimmunity and recurrent infection. Children present not solely as infection, but also with allergy, inflammation, autoimmunity, immune dysregulation and unusual malignancy at some point as illustrated by more recently discovered or defined diseases such as DOCK8 deficiency. The pattern of clinical findings can give important clues which allow a more efficient order to investigation (Figure 1).

The child with severe eczema or atopy and decreased immune response

Eczema is a common childhood complaint. Nonetheless, it is an early manifestation of the allergic phenotype and represents an important clue if the child also has faltering growth and suspected immunodeficiency. Its incidence is increased in association with many primary immunodeficiencies including DOCK8 deficiency, Wiskott–Aldrich Syndrome (WAS) and Job's syndrome.

Patients with DOCK8 deficiency often have severe eczema, asthma and food allergies/anaphylaxis as well as very severe warts, Molluscum contagiosum, recurrent pneumonia leading to bronchiectasis and unusual CNS infection (Figure 2).

The child with suspected or confirmed malignancy

In Wiskott–Aldrich Syndrome (WAS) the immunodeficiency and effect of infections is complicated by a risk of malignancy and autoimmune complications. These complications may prompt earlier curative treatment such as haematopoietic stem cell transplantation (HSCT). The same is increasingly true of X-linked thrombocytopenia (XLT). XLT was considered the milder form of WAS, caused by less severe mutations and in the same gene results, however, the tendency towards malignancy and autoimmunity remains. The change in concept of PID prompts us to consider if XLT should be, in fact, also treated more aggressively with earlier consideration of HSCT.

Inducible Tyrosine Kinase deficiency (ITK) may present early with lymphoma as the result of EBV exposure and highlights the overlap of a dysfunctioning immune system, which is unable to control the ubiquitous EBV, resulting in malignancy. Unusual presentations of lymphoma at a young age should prompt consideration of PID and in particular ITK deficiency.

The child with autoimmune disease affecting multiple systems

Where autoimmunity appears to be affecting multiple systems and progressing rather than remaining isolated, a diagnosis of PID should be considered. Gain of function mutations in STAT3 may present with features of autoimmune disease, lymphoproliferation, alongside problematic infection, particularly with bronchiectasis. Autoimmune enteropathy, diabetes and thyroid disease are all seen. The defect lies in the phosphorylation of the STAT3 molecule.

Loss of function mutations in *STAT3* have a different, but equally severe, clinical phenotype recognized for many years as Job's syndrome. There remains an increased risk of infection, but candida is the significant pathogen. Other features include pneumonia, significant dermatitis, hyper IgE and musculoskeletal anomalies.

The defects in STAT3 highlight the delicate balance the immune system is constantly achieving when functioning normally,

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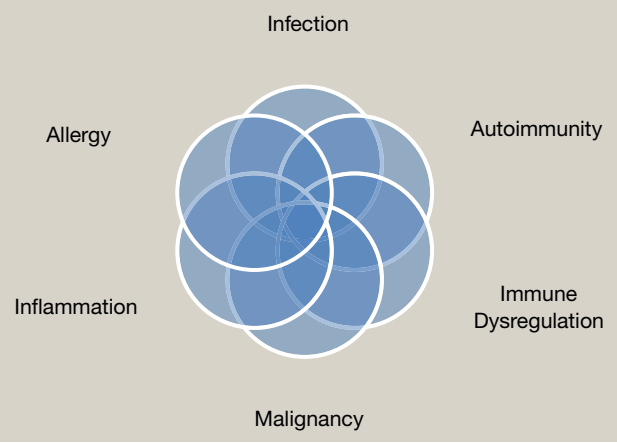

Figure 1 The many faces of PID, more than just increased infection risk.

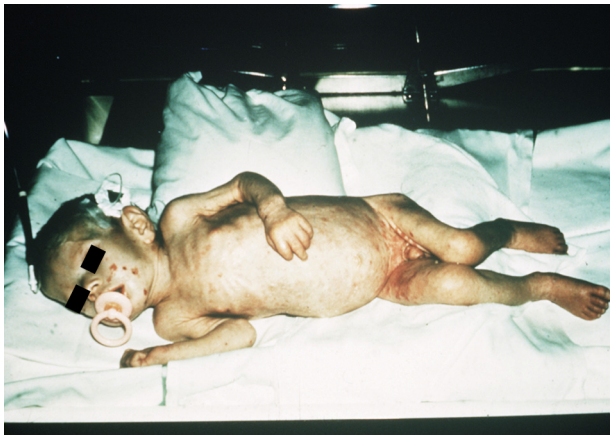

Figure 2 A child with severe candida and SCID (severe combined immunodeficiency).

as both loss and gain of function mutations result in abnormal immune function with severe clinical consequences but with differing phenotypes.

Cytotoxic T-Lymphocyte-Associated Protein-4 (*CTLA-4*) mutations cause disease because haploinsufficiency (loss of gene function) results in insufficient *CTLA-4* for normal function. The combination of severe enteropathy and cytopaenias should prompt the consideration of immune dysregulation, particularly if there is a family history of unexplained early death or immune deficiency. *CTLA-4*, like other immune defects inherited in an autosomal dominant manner, has a variable clinical presentation. There may be early onset and severe disease, or the progress may be more insidious. Indeed, some affected family members may be almost asymptomatic. Knowledge about disease progression is important.

As has been shown, there are varying clinical phenotypes even when the genetic defect is the same. This has also been recently demonstrated in the women who carry the gene for XL-CGD, many of whom suffer from autoimmunity and gastrointestinal symptoms akin to that seen in the CGD patients. These women have a reduced rather than absent respiratory oxidative burst, but again this suggests that when the balance of the immune system is disrupted, clinical features, albeit to a greater or lesser degree may be present.

Overall, PID should be considered as a diagnosis in a broader remit than simply recurrent infection. Where there is autoimmunity, malignancy or features of immune dysregulation, a diagnosis of PID should be sought.

Diagnostic advances

Screening

The advent of new-born screening for SCID allows diagnosis to be made within the first few days of life. This has been introduced in many states of the US and in Norway. Screening is via the new-born blood spot and has been shown to be highly specific and sensitive. Work continues in the UK to demonstrate cost effectiveness and clinical necessity for the introduction of new-born screening for SCID. Screening tests for conditions such as X-linked Agammaglobulinaemia are also being developed. These allow treatment before damaging infection and greatly improve prognosis.

Diagnostic approach

The formula of history, examination and investigations remains as the fundamental approach to PID diagnosis.

History and family history are crucial in PID. Family history has been shown consistently important in diagnosis of PID. Given our change in understanding in PID, family history must also focus on inflammation, autoimmunity and unusual predisposition to malignancy within the immediate and wider family.

Examination of the child with a potential PID should actively seek to examine for lymphadenopathy, hepatosplenomegaly, signs of autoimmunity or poor growth. Basic investigations form the first line and should include looking for autoimmunity in other organs, including thyroid.

Immunological investigations will target specific categories of diagnoses. The International Union of Immunological Societies recently updated their classification of PIDs. This provides a useful framework for all paediatricians to work from and guides investigations. It incorporates information about the newer PIDs and serves as a useful reference point.

Table 1 summarizes initial investigations in PID:-

First line investigation for combined immunodeficiency involves a simple FBC. In severe combined immunodeficiency (SCID) 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 confirms the diagnosis.

Suspected antibody deficiency investigation should start 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