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Ten warning signs of primary immunodeficiency: a new paradigm is needed for the 21st century

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The 10 warning signs of primary immunodeficiency are being promoted as a screening tool for use by both the general public and physicians. A recent study, however, shows that except for family history, need for intravenous antibiotics and failure to thrive, the 10 warning signs are not a useful screen of primary immunodeficiency diseases (PIDs). Over the last few decades, there has been a revolution in our understanding of PID. The 10 warning signs do not take into account the fact that PIDs now include diseases that present with sporadic infections, autoimmunity, autoinflammation, and malignancy. This review focuses on the advances in our understanding of PID, the current limitations of the 10 warning signs, and recommendations to ensure that patients with PID are diagnosed in a timely fashion in the future.

Keywords: primary immunodeficiency; autoimmunity; atopic dermatitis; cancer; family history

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First studies characterizing primary immunodeficiency diseases

The first primary immunodeficiency diseases (PIDs) were identified 50–60 years ago, at a time when immunoglobulin was first measured and isolated from serum[1,2] and the function of lymphocytes as an important component of the immune system was recognized.[3] The earliest PID to be described included disorders of neutrophils (chronic granulomatous disease),[4] T lymphocytes (severe combined immunodeficiency ["Swiss-type"]),[5] Wiskott Aldrich syndrome,[6] and B lymphocytes (Bruton's agammaglobulinemia).[7] Along with this expansion in our understanding of the immune basis of PID, new therapies were being developed, including the introduction of immunoglobulin replacement (1952) and bone marrow transplantation (1957).[8] The molecular etiology of 150 different PIDs have now been defined. The spectrum of clinical presentations of PID is now recognized to include autoinflammation, autoimmunity, and neoplasia as well as serious, recurrent, or unusual infections. Changes to the way we promote awareness of PID among the medical profession and sectors of the general public are required if premature death and serious morbidity due to late diagnosis of the wider spectrum of PID are to be avoided.

The development of the 10 warning signs of primary immunodeficiency

The first PIDs to be discovered were manifest by a propensity to recurrent severe or unusual infections. Attending physicians learned to recognize patterns of clinical disease that suggested the patient may have an underlying primary immune defect.[9–11] Over the last few decades, the number of clinicians and scientists involved in the diagnosis and management of PID has expanded exponentially, initially in western Europe (European Society for Immunodeficiencies) and the United States (United States Immunodeficiency Network; http://www.usidnet.org/), and more recently in

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eastern Europe (J Project),[12] the Middle East (Asian Society for Primary Immunodeficiency), northern Africa (African Society for Immunodeficiency), South America (Latin American Group for Primary Immunodeficiencies), and other parts of the world. Better training of physicians has led to diagnosis of more patients with PID.[13] The prevalence of PID is currently estimated to be 1/10,000 people in the Western world.

A number of nonprofit organizations (Jeffery Modell Foundation, International Patient Organisation for Primary Immunodeficiencies, Primary Immunodeficiency Association) provide valuable support for families with PID as well as health care professionals looking after these patients. Recently, these organizations have become increasingly vocal in promoting public awareness of PID at a government level as well as among the general public. The 10 warning signs of primary immunodeficiency, based largely on clinical presentation of antibody immunodeficiencies in adults[14] and expert opinion, are now heavily promoted as a way of making people aware of PID, most recently through World Primary Immunodeficiency Week 2011 (www.worldpiweek.org/). The clinical features focus on the occurrence of recurrent upper and lower respiratory tract infections (sinus, ear, and chest), persistent superficial fungal infections, or more deep-seated infections (localized abscesses or disseminated blood-borne infections). The need for intravenous antibiotics or prolonged courses of oral antibiotics, failure to thrive in infancy, and a family history of PID are also included (Table 1).

Table 1. Ten warning signs of primary immunodeficiency

1	≥4 ear infections in one year
2	≥2 serious sinus infections in one year
3	≥2 pneumonias in one year
4	Recurrent, deep skin or organ abscesses
5	Persistent thrush in mouth or fungal infection on skin
6	≥2 deep-seated infections including septicemia
7	≥2 months on antibiotics with little effect
8	Need for intravenous antibiotics to clear infections
9	Failure of an infant to gain weight or grow normally
10	Family history of primary immunodeficiency

NOTE: If you or someone you know is affected by ≥2 warning signs, speak to a physician about the possible presence of an underlying primary immunodeficiency; www.info4pi.org/aboutPI/index.cfm?section=aboutPI&content=warningsigns, accessed July 18, 2011.

Validity of the 10 warning signs in predicting the likelihood of PID in children

It remains the role of specialists who treat patients with PID to ensure that promotional material is accurate and up to date in relation to the rapid advances in the field of immunodeficiency. As the effectiveness of the 10 warning signs as a screening test of PID had not previously been formally assessed, early in 2011 we evaluated the presenting symptoms of 563 children attending two tertiary pediatric immunology centers in the north of England.[15] Ninety-six percent of the children with PID were referred by hospital clinicians, indicating that the most important group to target regarding awareness and education of PID are hospital doctors who are most likely to be called on to manage children at presentation. The strongest identifier of PID in our study was a family history, with use of intravenous antibiotics for sepsis in children with neutrophil PID and failure to thrive in children with T lymphocyte PID of secondary importance. Using these three signs, 96% of patients with neutrophil and complement deficiencies and 89% of children with T lymphocyte PID could be correctly identified. The results indicated that as well as hospital physicians, education and particularly genetic counseling of families who have had a child with a PID are important.

The 10 warning signs leaflet advises that if two or more warning signs are present, PID should be considered. We therefore performed additional analyses to determine whether two or more warning signs are more common in children with defined PID compared with those where no PID is found. Two or more warning signs identified children with neutrophil PID but not those with complement, B cell or T cell PID (Table 2).

Evolving concepts of infectious diseases that may herald PID

It is now recognized that PID may not only present with recurrent or unusual infections, but that one-off infections with common pathogens may also herald a life-threatening PID. To delay considering the diagnosis of PID for the appearance of subsequent

Table 2. Frequency (percentage) of ≥2 warning signs in children with and without PID

	<2 Warning signs	≥2 Warning signs	Relative risk (95% CI) compared with no PID
No PID	70 (52%)	63 (48%)	–
Any PID	163 (38%)	267 (62%)*	1.8 (1.2–2.7)
Neutrophil PID	10 (14%)	63 (86%)*	7.0 (3.3–14)
Complement PID	9 (41%)	13 (59%)	1.6 (0.6–4.0)
B cell PID	42 (40%)	63 (60%)	1.7 (1.0–2.8)
T cell PID	102 (44%)	128 (56%)	1.4 (0.9–2.1)

*Significant at $P < 0.01$ by Chi-square, compared with the group that did not have a PID.

infections as suggested by the 10 warning signs may be courting disaster, for instance, in patients with toll-like receptor (TLR) pathway PID. Defects in the IRAK4 and MyD88 genes are associated with life-threatening/fatal infections with *Staphylococcus aureus* and *Streptococcus pneumoniae*.[16] Fifty percent of children with IRAK4/MyD88 were dead by the age of eight years, most before the age of two years. Mutations in TLR3 and downstream signaling molecules have been associated with herpes simplex encephalitis, which is often either fatal or leads to severe neurological disability.[17,18] Although naivety of young children's immune system explains why some develop infectious diseases, there is now a growing recognition that an underlying PID should be considered when children present with infections with certain common pathogens.[19,20] In these children, the 10 warning signs fail to provide appropriate warning.

PID presenting with noninfectious diseases

The 10 warning signs make no mention of autoimmune or malignant manifestations of PID, which may be the presenting clinical feature (Table 3).[13,21–23] Our recent study assessing the usefulness of the 10 warning signs of PID[15] excluded 20% of patients with PID in whom their clinical presentation did not involve infectious diseases (autoimmune lymphoproliferative disease [ALPS], familial hemophagocytic histiocytosis, hereditary angioedema, immunodysregulation polyendocrinopathy enteropathy X-linked [IPEX], IL-10 receptor deficiency, and periodic fever syndromes). Thus, in our north of England cohort, at least one in five patients with PID would be missed if the 10 warning signs were used as a screen.

To illustrate this point further, a classic example of a PID disease, where presentation is usually with noninfectious features, is IPEX syndrome due to mutations in the *FOXP3* gene. IPEX is due to a deficiency of T regulatory cells, and children present with severe, often unremitting autoimmune enteropathy, endocrinopathies, such as thyroid disease and diabetes mellitus, autoimmune cytopenias, and eczema. Recurrent infections may or may not occur as part of the clinical course.[24] Even some of the earliest PIDs to be described, for example chronic granulomatous disease[25] and Omenn syndrome, may present with prominent autoinflammatory features involving the gut, skin, and other organs. Periodic fever syndromes are now recognized within the wider PID classification. Autoinflammation in this group of conditions can affect bones and joints, brain, eyes and ears, skin, and serous membranes.[26] Malignancy is also a presenting feature of some PIDs. Patients with X-linked lymphoproliferative disease[27] and IL-2-inducible T cell kinase deficiency[28] may present with lymphoproliferative disease/lymphomas. Patients with DNA repair enzyme defects, such as Nijmegen breakage syndrome, may also present with cancer, particularly non-Hodgkin lymphoma.[29,30] These PIDs are examples of which delayed diagnosis is common and the 10 warning signs of yesteryear are least useful. Curative treatment is available for a number of these disorders and outcome is better where the diagnosis is made before the development of extensive disease and end-organ damage.

A new dimension to PID: epithelial barrier-centered immunodeficiencies

Atopic dermatitis (eczema) affects up to one in five people in Western countries. It is characterized by a propensity to chronic or recurrent viral (eczema herpeticum, eczema vaccinatum, warts and molluscum contagiosum) and bacterial—especially *S. aureus*—infections localized to the skin.[31] Impetigo is a common cause of eczema flares, particularly in children.[32] Thus, atopic dermatitis can be defined as a PID, although until now it has been

Table 3. Groups of PID and example diseases that may be associated with autoimmune/autoinflammatory or malignancy as a presenting feature

	Autoinflammatory	Autoimmune	Malignancy
Familial hemophagocytic lymphohistocytosis, e.g., XLP, XIAP, Griselli, Chediak-Higashi, perforin Munc13–4, Munc 18, and Syntaxin 11	HLH	–	lymphoma
Familial periodic fever syndromes, e.g., TRAPS, HIDS, FMF, CINCA, and Muckel-Wells	polyserositis	–	–
DNA repair/cell cycle disorders,	–	skin, thyroid	lymphoma, other
e.g., ataxia-telangiectasis, Nijmegen-breakage syndrome, ligase IV, and Cernunnos	–	–	–
Omenn syndrome, e.g., RAG deficiency	hepatitis, encephalopathy, pneumonitis, enteropathy	–	–
Complement deficiencies —especially C1q, also HAE, factor H, MCP and factor I, the activator factor B, or the C3 factor	hemolytic-uremic syndrome, angioedema	SLE	–
defects in apoptosis, e.g., ALPS	–	autoimmune cytopenias	lymphoma
APECED	–	organ-specific autoimmunity	–
Defects in nucleic acid disposal —immuno-osteodysplasias, SAMHD1 deficiency, Aicardi–Goutières syndrome	–	SLE-like	–
Reduced T regulatory function, e.g., IPEX, IL-10R deficiency	IBD	cytopenia	–
Other —pulmonary alveolar proteinolysis, haemolytic uremic syndrome	–	–	–

routinely classified as a dermatological or allergic disorder.

There is increasing recognition over the last decade that skin epithelial cells do not just form an inert barrier between the host and its environment but actively respond to surface immunogens and redirect the immune response from one that engulfs and internally digests pathogens (Th1 response), to one that limits exposure/expels them (Th2 response).[33,34] In this regard, surface epithelial cells, although not bone marrow-derived, are an integral part of the immune system. Thymic stromal lymphopoietin (TSLP), an epithelium-derived IL-7–like cytokine is now considered an important master switch and key regulator of epithelium-orchestrated Th2 immunity.[35,36]

Activation of this innate, nonhemopoietic component of the immune system in atopic dermatitis is now known to be a defect in the superficial stratum corneum of the skin, which normally protects the underlying live keratinocytes from exposure to pathogens and allergens. The surface of the stratum corneum consists of a relatively impermeable barrier formed by aggregation of keratin filaments by a filament-aggregating factor, filaggrin. Up to 50% of patients with moderate to severe disease have inherited defects in skin barrier function due to mutations in the filaggrin gene.[37–39] The poor skin barrier results not only in dry ichthyotic skin, dermatitis, and propensity to other allergic diseases[40,41] but also the predisposition to cutaneous infections.[42,43] Thus, eczema occurs not only secondary to rare PIDs such as Wiskott-Aldrich syndrome, Hyper IgE syndrome, and IPEX, but as a primary condition and may well constitute the most common PID.

Recognizing PID: 60 years on

There is no doubt that our understanding of PID has undergone a revolution over the last 60 years. The diagnosis of PID includes not only patients presenting with recurrent severe and unusual infections but also those with sporadic infections, such as herpes simplex encephalitis, as well as autoinflammation and autoimmunity (Table 3). The human adaptive immune system has evolved from the ability to alter the structure of genomic DNA and cancers may also be presenting feature of PID.[44] "A typical PID" may cause just as much morbidity and mortality as PID with a more classical presentation.

The challenge for physicians is to recognize the diverse ways PID may present if unnecessary deaths are to be avoided in our patients and other affected family members. Nonprofit organizations are right to work with physicians to help promote knowledge of these conditions to those that need it most. There is no doubt that they have contributed to the development and promotion of professional services for patients with PID worldwide. The 10 warning signs are however a relic of yesteryear. They fail to recognize the complexity and diversity of PID as we understand them today and if promoted as the screening test for PID, risk patients with less classical presentations being missed, or their diagnosis being delayed. A new diagnostic paradigm is required for the 21st century.

Recognizing PID in the 21st century

Rather than promoting the 10 warning signs of PID to the general public, consolidating and refining a specialist-led approach to the timely identification of PID would help to focus limited resources available from both health care professionals and support organizations. Optimal detection of PID requires a multipronged approach: (1) ongoing training of clinicians, particularly those involved in secondary and tertiary practice regarding the diverse clinical presentations of PID, as with the J Project in eastern Europe; (2) ensuring that parents who have had a child with PID are provided with genetic counseling and that their family practitioners as well as obstetricians realize the importance of consulting with PID specialists in all future pregnancies; and (3) use of evolving laboratory screening tests as they become available. Success of this model requires the combined and collaborative input of specialists in PID and other disciplines, as well as PID advocacy groups. Early diagnosis ensures a 95% chance of cure and/or long-term survival for many patients with PID.

Training of clinicians managing patients with PID

Ongoing training of clinicians working not only in infectious diseases and immunology, but also general pediatricians and physicians and specialists in intensive care, rheumatology, hematology, oncology, gastroenterology, and neurology is important if the diverse phenotypes that PID patients can present with are to be recognized. Rather than a simple list of warning signs, these specialists require detailed knowledge of clinical presentations as it relates to their speciality and where to seek help and advice regarding the investigation of these diseases. As the majority of patients will initially present to hospital doctors, a focus on hospital specialists rather than the general public and family doctors is likely to be more effective in reducing disease burden, while at the same time avoiding inappropriate referrals and public anxiety. Further prospective studies are, however, needed to confirm this supposition.

Counseling and education of families who have a child with a PID and their personal health care physicians

Family history is the key warning feature of PID.[15] A focus on parents who have a child with a PID

is important if unnecessary morbidity and mortality of affected siblings is to be avoided. Parents should be provided with genetic counseling and be encouraged to discuss future pregnancies with their family doctor and geneticist before, or at least in the early stages of subsequent pregnancies. Using this approach, birth of children with severe PID would potentially be avoided and affected infants treated before they succumb to clinical complications. Parental acceptance of genetic counseling is variable and often depends on their ethnic and social background. Specialists as well as society must meet the challenge of educating and influencing social attitudes in groups where this approach may have greatest impact on disease morbidity and mortality.[45] In regions where specific diseases are high, for example, β-thalassemia in some regions of the Mediterranean region, Government regulations requiring genetic screening and counseling before marriage has been successfully implemented leading to a decline in disease incidence.[46] Support organizations may well be able to provide valuable support and influence.

Worldwide, one billion people live in countries where 20% to more than 50% of marriages are consanguineous, and it is in these societies where the burden of inherited conditions, such as PID, are likely to be highest. However, the promotion of nonconsanguineous unions for genetic reasons needs to be weighed against socioeconomic advantages of such unions, and is therefore as much a sociopolitical as medical issue.[47,48]

Genetic screening and future research

No single screening test will adequately diagnose the diverse group of over 150 PIDs. Progress is being made with neonatal screening for severe combined immunodeficiency. T cell receptor excision circle screening, which detects the absence of functional T cells, has been trialled with some success in the United States.[49,50] Research into this and other aspects of transitional research of PID will no doubt lead to future improvements in the genetic and clinical screening for PID.

Summary

PID is a diverse and complex group of diseases that present with not only superficial or systemic, unusual or recurrent infections but also one-off infections with common pathogens as well as with autoimmunity, autoinflammation, and neoplasia. Use of the 10 warning signs in public and physician-based awareness campaigns is not supported by current evidence or advances in our understanding of diverse presentations of PID. Most PIDs present to hospital physicians. The key useful warning sign is a family history. A more focused approach of educating, training, and counseling hospital doctors and families with patients would target limited resources on those where impact is likely to be greatest. It is also likely to avoid unnecessary concern within the general public and unnecessary referrals to specialists.

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Conflicts of interest

The authors declare no conflicts of interest.

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