

## From idiopathic infectious diseases to novel primary immunodeficiencies

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Primary immunodeficiencies are typically seen as rare monogenic conditions associated with detectable immunologic abnormalities, resulting in a broad susceptibility to multiple and recurrent infections caused by weakly pathogenic and more virulent microorganisms. By opposition to these conventional primary immunodeficiencies, we describe nonconventional primary immunodeficiencies as Mendelian conditions manifesting in otherwise healthy patients as a narrow susceptibility to infections, recurrent or otherwise, caused by weakly pathogenic or more virulent microbes. Conventional primary immunodeficiencies are suspected on the basis of a rare, striking, clinical phenotype and are defined on the basis of an overt immunologic phenotype, often leading to identification of the disease-causing gene. Nonconventional primary immunodeficiencies are defined on the basis of a more common and less marked clinical phenotype, which remains isolated until molecular cloning of the causal gene reveals a hitherto undetected immunologic phenotype. Similar concepts can be applied to primary immunodeficiencies presenting other clinical features, such as allergy and autoimmunity. Nonconventional primary immunodeficiencies thus expand the clinical boundaries of this group of inherited disorders considerably, suggesting that Mendelian primary immunodeficiencies are more common in the general population than previously thought and might affect children with a single infectious, allergic, or autoimmune disease. (J Allergy Clin Immunol 2005;116:426-30.)

**Key words:** Primary immunodeficiency, infectious diseases, idiopathic infections, inborn errors, Mendelian disorders, predisposition to infection

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An immunologic definition and classification of primary immunodeficiencies currently prevails and is expected to do so for the foreseeable future.<sup>1</sup> Unfortunately, this has resulted in studies of otherwise healthy patients with specific infectious clinical diseases but no overt immunologic phenotype being largely neglected. The attention of most investigators and clinicians has remained focused on the tip of the iceberg: those rare patients with a noisy clinical phenotype (multiple, recurrent, and severe infections) and a visible immunologic phenotype (defining the primary immunodeficiency). The most striking example of such conventional primary immunodeficiencies is reticular dysgenesis, an exceedingly rare disorder associated with agranulocytosis and alymphocytosis, resulting in early-onset vulnerability to virtually all microorganisms and a rapidly fatal outcome in the absence of hematopoietic stem cell transplantation.<sup>2</sup> Immunodeficiency is commonly ruled out in patients with a single severe infectious disease (even if recurrent or life-threatening) and normal routine immunologic workup (searching for signs of inherited or acquired immunodeficiency). Self-contradictory titles in the medical literature, such as "Fatal infection in an immunocompetent individual," remain common. Unusual infectious diseases are often described as idiopathic, demonstrating caution and a desire to avoid the direct incrimination of the patient's genetic background. However, some infections typically caused by weakly virulent (opportunistic) microbes have been found to be associated with a high frequency of familial forms, parental consanguinity, or both, suggesting Mendelian predisposition. This group of nonconventional primary immunodeficiencies is characterized by a very narrow spectrum of opportunistic infections limited to one microbial genus or species possibly, but not necessarily, recurrent in otherwise healthy patients with no detectable immunologic abnormality on initial investigation.<sup>3</sup> These diseases do not fit easily into the classical classification of primary immunodeficiencies.

Nonconventional primary immunodeficiencies include the syndromes of Mendelian susceptibility to mycobacterial diseases (OMIM 209950,<sup>4</sup> first described in 1951) in patients with mutations in the IL-12/23-IFN- $\gamma$  circuit (first identified in 1996)<sup>5-8</sup>; recurrent invasive disease caused by *Neisseria* species in patients with mutations affecting the terminal components of complement (C5 to C9) forming the membrane attack complex (first described

in 1974)<sup>9,10</sup>; isolated chronic mucocutaneous candidiasis (OMIM 114580, first described in 1969), which remains unexplained genetically<sup>11,12</sup>; epidermodysplasia verruciformis with disseminated warts caused by human papillomaviruses belonging to group B1 (OMIM 226400, first described clinically in 1922 and subsequently shown to be a Mendelian trait [1939] conferring susceptibility to papillomaviruses [1946-1966]) in patients with mutations in EVER1 and EVER2 (first described in 2002)<sup>13,14</sup>; and X-linked lymphoproliferative syndrome caused by Epstein-Barr virus (OMIM 308240, first described in 1975) in patients with mutations in SAP (first described in 1998).<sup>15,16</sup> Needless to say, the dichotomy between conventional and nonconventional conditions is somewhat artificial because there is really a continuum between these 2 extremes.<sup>17</sup> Patients with a recently described conventional primary immunodeficiency, IL-1 receptor-associated kinase 4 deficiency, are particularly susceptible to *Streptococcus pneumoniae*,<sup>18,19</sup> and conversely, patients with mutations in the IL-12-IFN- $\gamma$  axis are also susceptible to *Salmonella* species.<sup>20</sup> In any event, neither the identification of a cellular phenotype nor that of the causal gene suggested the existence of an underlying primary immunodeficiency in patients with nonconventional primary immunodeficiencies. Instead, primary immunodeficiency diagnosis was based on the relatively low virulence of the microbe and the seemingly Mendelian inheritance of predisposition to severe disease.

It would not be wise to limit the group of nonconventional primary immunodeficiencies to these 5 Mendelian syndromes, to patients presenting unexplained infections caused by weakly virulent opportunistic microorganisms, or even to patients with recurrent infections caused by more virulent pathogens. There is good reason to believe that other human conditions reflect currently unknown Mendelian primary immunodeficiencies. First, genetic epidemiologic studies searching for familial forms and parental consanguinity have not been carried out for most infectious, autoimmune, and allergic clinical syndromes. Second, neither the absence of familial cases nor the lack of consanguinity are sufficient to exclude Mendelian defects, and sporadic cases might reflect a genetic lesion, as illustrated by the first genetic lesion discovered in human subjects, trisomy 21, in patients with Down syndrome.<sup>21</sup> Third, the virulence of microorganisms is also a continuum, and many pathogenic microbes, such as *Mycobacterium tuberculosis*, are actually innocuous in most human beings. A number of common infectious diseases are likely to reflect nonconventional primary immunodeficiencies in at least a fraction of patients. Consistent with this view, mycobacterial diseases caused by weakly virulent BCG species were described as idiopathic infections before the identification of defects in the IL-12-IFN- $\gamma$  circuit.<sup>22,23</sup> The identification of these defects has led to the recent description of 3 unrelated families with a purely Mendelian form of predisposition to bona fide tuberculosis,<sup>24-26</sup> following on from the observation that IL-12R $\beta$ 1 deficiency had low penetrance for the case-definition phenotype of clinical disease caused by

weakly virulent mycobacteria.<sup>20,27</sup> Currently unexplained candidate infectious diseases include invasive pneumococcal disease<sup>18,19</sup> and herpes simplex encephalitis,<sup>28,29</sup> which have been diagnosed in at least a few patients with conventional immunodeficiencies. Many life-threatening infectious diseases might well turn out to result from the Mendelian inheritance of a specific predisposition, reflecting a nonconventional primary immunodeficiency.

Nonconventional primary immunodeficiencies are defined on clinical grounds, raising the issue of the classification of primary immunodeficiencies. In fact, there has never been a fully satisfactory classification of primary immunodeficiencies.<sup>1,30,31</sup> This problem has become increasingly acute because of the explosion of knowledge in the field in the last 20 years, with at least 200 conditions described clinically and more than 100 disease-causing genes identified. Moreover, many more conventional and nonconventional primary immunodeficiencies are likely to be identified in the near future. A genetic classification was impossible in the early days before identification of the disease-causing genes. Even today, genetic classification would be hindered by the lack of a well-defined temporal and spatial expression pattern for the disease-causing genes, limiting our understanding of pathogenesis. Furthermore, different clinical syndromes might be caused by different mutations in the same gene, and the same syndrome might be caused by different genetic causes. Even if it were possible, a genetic classification would not actually be sufficient because phenotypes are obviously more important than genotypes; the chief value of a genotype lies in its ability to account for a given phenotype. Accordingly, the McKusick catalog of human genetic disorders is merely a catalog and not a classification.<sup>4</sup> Any classification system for academic and clinical purposes must therefore be primarily phenotypic, although improvements in our understanding of the genetic basis of primary immunodeficiencies might lead to changes in phenotypic classification. The phenotypic definition of primary immunodeficiencies is clearly the necessary starting point for phenotypic classification.

Historically, the identification of agammaglobulinemia in 1952 by Ogden Bruton<sup>32</sup> and the subsequent discovery that its inheritance was X-linked and recessive<sup>33</sup> was the origin of current classifications of primary immunodeficiencies on the basis of a combination of immunologic phenotypes and modes of inheritance.<sup>1,30,31,34-39</sup> Primary immunodeficiencies are commonly classified into disorders of T cells, B cells, phagocytes, and complement. They are then further classified according to the mode of inheritance and, when known, genetic cause. This method of classification poses a serious problem of definition because it tightly links the concept of primary immunodeficiency with the observation of an immunologic phenotype. According to this view, even asymptomatic IgA-deficient individuals are immunodeficient, unlike, paradoxically, patients dying of infectious disease without immunologic abnormality. Moreover, because many disease-causing genes are expressed in different cell types in which mutant alleles might have different effects,

clinical phenotypes, whether infectious, allergic, or autoimmune, are far from being consistent within each of the 4 cell type–based groups. What is the clinical similarity between defects of C1 inhibitor and C9? Conversely, X-linked agammaglobulinemia (primarily, but not exclusively, a B-cell defect) clinically resembles HLA class I deficiency (often improperly classified as a T-cell defect). This situation also results in paradoxical classifications, with an immunologic phenotype attributed to one cell type but a genetic defect actually affecting another cell type. For example, CD40L deficiency is generally described as a B-cell defect because of the hyper-IgM syndrome,<sup>40</sup> but CD40L is expressed on T cells and is involved in the interaction of T cells with both B cells and macrophages–dendritic cells. The focus on certain immunologic phenotypes, such as hyper-IgM syndrome, is misleading in itself: there are more differences than common points between patients with mutations in CD40L (expressed on T cells), AID (expressed in B cells), and NEMO (expressed ubiquitously), all of which can result in hyper-IgM syndrome. The current immunologic classification of primary immunodeficiencies is thus imperfect both immunologically and clinically.

An ideal definition and classification of primary immunodeficiencies and inborn deficiencies should evidently rely on clinical phenotype because this best reflects the physiologic effect of any deleterious genotype. Indeed, immunodeficiencies in general, whether inherited or acquired, should be defined clinically, as opposed to immunologically. Would anyone seriously suggest that it would be better to define respiratory failure in terms of epithelial abnormalities rather than the physiologic consequences of insufficient oxygen inhalation? It is certainly useful to assess various parameters in the course of any organ failure, but the definition and monitoring of organ failure must be physiologic. Immunodeficiency is a failure to achieve immune function to provide efficient, self-limited host defense against the biotic and abiotic environment while preserving tolerance to self. Immunodeficiencies are thus best defined in terms of the diverse forms of life-threatening infections, allergies, or autoimmune reactions. The detection of an identifiable immunologic abnormality is less important and depends on the tools available to the investigator. Immunodeficiencies might also be considered in terms of whether they are inherited or acquired. Most immunodeficiencies are actually idiosyncratic, reflecting both nature (genetic background) and nurture (the effect of the environment on the host). An ideal classification of primary immunodeficiencies should take this into account, considering infectious syndromes one by one (and possibly autoimmune and allergic syndromes as well). For example, primary immunodeficiencies associated with mycobacterial<sup>41</sup> or pneumococcal<sup>42</sup> diseases are specifically associated with defects of interaction between T-cells and phagocytes (involving in particular the IL-12/23–IFN- $\gamma$  circuit and the respiratory burst) and bacterial sensing and opsonization (involving mucosal inflammation, complement, carbohydrate-specific antibodies, and splenic macrophages), respectively. This classification is

not operational yet because it awaits investigators in the field to review all pathogens one by one, perhaps in a collaborative effort (eg, primary immunodeficiencies associated with, for example, *Pneumocystis* species infection or *Toxoplasma* species infection). This classification will address the most relevant clinical question at the bedside (Which immunodeficiency should the physician consider in a given infected patient?) and the most relevant immunologic question at the bench (What role does a particular molecule play in immunity to infection *in vivo*?). Of course, the genotype and immunologic phenotype are invaluable both clinically to tailor treatment options to individual patients and immunologically to decipher the molecular basis of immune responses.

A corollary of this purely clinical definition and classification of primary immunodeficiencies is that inborn Mendelian deficiencies of immunity are more common than initially thought. Accordingly, newly described primary immunodeficiencies, such as partial IFN- $\gamma$ R1 and signal transducer and activator of transcription 1 deficiencies, have been shown to be transmitted as autosomal dominant traits in multiplex families, at odds with the classical view that primary immunodeficiencies are necessarily recessive traits because of their severity.<sup>43</sup> Not all severe infectious diseases will be found to reflect a Mendelian primary immunodeficiency or to be due to the inheritance of a major susceptibility gene, as seen in leprosy with mutations in Parkin,<sup>44–46</sup> because predisposition to infection might display truly polygenic determinism. Nevertheless, it will be important in the future to decipher the Mendelian genetic basis of infectious diseases. Studies of autoimmune and allergic syndromes are also likely to reveal novel Mendelian disorders. Once a clinical definition of immunodeficiency is accepted, patients with infectious diseases, allergy, or autoimmunity (in the broad sense of these terms, including angioedema, hemophagocytosis, and autoinflammation) should be considered as potential bearers of Mendelian primary immunodeficiencies. Accordingly, several primary immunodeficiencies were recently shown to present purely as autoimmune,<sup>47</sup> autoinflammatory,<sup>48</sup> and hemophagocytosis<sup>49</sup> syndromes. Intriguingly, only one Mendelian disorder, C1 inhibitor deficiency, has thus far been found to be purely associated with autosomal-dominant angioedema, a syndrome related to (but possibly different from) allergy.<sup>50</sup> Noninfectious immunologic diseases have only recently emerged as a public health problem and do not threaten mankind as acutely as infections. Records show that life expectancy in Western Europe in the 18th century was about 25 years, whereas life expectancy is currently about 40 years in Sub-Saharan Africa, largely because of the burden of infection.<sup>17,51</sup> The current longer life expectancy in developed countries primarily reflects recent developments in hygiene (preventing infection), vaccines (preventing disease), and antibiotics (preventing a fatal outcome), rather than the intrinsic efficiency of our immune system.<sup>51</sup> Although the immune system serves well at the population level, ensuring the reproduction of species, it is the least efficient physiologic system at the

individual level. As indicated by medical and demographic data, most human subjects are immunodeficient and exposed to life-threatening infectious diseases.<sup>51</sup> Many might carry a Mendelian primary immunodeficiency, being thus perhaps the rule rather than the exception and paradoxically raising hope for scientists, physicians, and patients.

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