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Definition of *primary immunodeficiency* in 2011: a "trialogue" among friends

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There is no clear consensus about the definition of the term *primary immunodeficiency* in 2011. Although there is general agreement that defects in both adaptive and innate immunity should be included, issues related to the frequency of primary immunodeficiencies, the modes of inheritance, the other types of cells involved, and the required clinical phenotype are more contentious. Three friends with an interest in both the clinical and scientific aspects of primary immunodeficiency carried out a discussion or trialogue to address some of these issues.

Keywords: inborn errors of innate immunity; autoinflammatory disorders; population genetics

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Introduction

The field of immunodeficiency is evolving, and perhaps the terms we use to describe this group of disorders need to evolve as well. Do the terms *immunodeficiency* or *immune deficiency* limit us to disorders in which we can identify the absence or reduction of a particular component of the immune system? Most of us would agree that DiGeorge syndrome falls in the category of a primary immunodeficiency, yet the underlying defect is the absence of the support system for educating T cells rather than a defect in T cells. *Wikipedia* defines *immunodeficiency* as "a state in which the immune system's ability to fight infectious disease is compromised or entirely absent." Patients with C1 inhibitor deficiency do not have recurrent or unusual infections, but we would also consider this disorder to be an immunodeficiency. The NIH website defines *primary immunodeficiencies* as "a number of rare diseases (that) feature a heightened susceptibility to infections from childhood onward." This definition seems to exclude patients with common variable immunodeficiency (CVID).

It is worth noting that PubMed identifies the first use of the term *immunodeficiency* in the title of an article called "Report from the WHO Committee on Primary Immunodeficiencies" published in *Pediatrics* in 1971.[1] Agammaglobulinemia, severe combined immunodeficiency and congenital neutropenia, was first recognized in the 1950s when basic tools to evaluate the immune system became available and the widespread use of antibiotics allowed patients to survive their first major infection;[2–4] however, these disorders were not grouped together until later. The authors of the WHO report wrote "primary specific immunodeficiency results from a failure to produce the effectors of immune response, i.e., antibodies and sensitized lymphocytes. Excluded from the definition are hypercatabolic states, immunodeficiency states due to exogenous causes, such as X-ray and cytotoxic drugs, and immunodeficiency states associated with lymphopenia due to intestinal lymphangiectasia, with neoplasia (myelomatosis, leukaemia, and so forth), with complement defects (C3 or C5 abnormality), and with phagocyte dysfunction syndrome."

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This definition specifically excludes defects in innate immunity.

Mary Ellen Conley (MEC)

Are we using the right terms to look at the history of our field? In the 1950s patients who were unusually susceptible to infection were sometimes said to have low resistance syndrome.[5,6] Perhaps more to the point, there is a wonderful book called *Immunologic Deficiency Diseases in Man*, published as part of the Birth Defects Series in 1968.[7] This book, which was one of my favorites when I was a student, was based on a workshop organized by Bob Good to classify and describe the etiology of immunologic deficiency diseases.

Luigi (Gigi) D. Notarangelo (LDN)

There is another term we should consider. The search term *inborn errors of immunity* in PubMed brings up several publications in the 1960s. This term was used to describe chronic granulomatous disease in 1966.[8] In that same year, Klemperer *et al*. reported on hereditary deficiency of the second component of complement (C2) in members of a single family. Paradoxically, the clinical history of the three C2-deficient subjects described in that paper was relatively infection free.[9] Very interestingly, the term *inborn errors of immunity* has been used in the past mostly to refer to defects of innate immunity, which contrasts with the WHO definition of *primary immunodeficiencies* in 1971. Combining defects in adaptive and innate immunity to fit the definition of primary immunodeficiency seems to have come later, perhaps when the same doctors were taking care of these patients and it was not always clear whether infections were due to defects in one arm or the other.

I must say that while I like the notion that primary immunodeficiency disease (PID) should be defined functionally as causing impaired resistance to infections, it would be disrespectful of the homeostatic role of the immune system to dismiss the many genetic disorders that cause autoimmunity or exaggerated inflammatory responses. I would propose that we keep these important defects within the definition of PIDs. And do we really think that primary immunodeficiencies are rare? (LDN smiles at JLC)

Jean-Laurent Casanova (JLC)

Of course I disagree with the "rarity" concept, which merely stems from the fact that only a few PIDs are known (cars were rare circa 1900)! As noted above, the field began with three or four PIDs; we now count at least 300 disorders. The genetic characterization of known phenotypes and the search for inborn errors of immunity underlying new phenotypes are both accelerating.[10,11] Whole-exome and whole-genome sequencing will probably reveal thousands of PIDs in the next decade. With about 25,000 coding and RNA genes, a conservative estimate of 5% of genes involved in host defense and tolerance, and at least two types of alleles per locus (say, heterozygous versus homozygous, or loss-of-function versus gain-of-function, or hypomorphic versus amorphic, not to mention the various types of hypomorphs), my prediction is that we will count up to 3,000 PIDs in 2021.

MEC

Jean-Laurent suggests that all of us have an immunodeficiency (not me! I never get sick!!). We agree that an infection is the result of a particular set of genes functioning in a particular environment. Is there a continuum of frequency and/or severity of infections?—perhaps with a small peak at one end with frequent, severe infections in patients with classic disorders, and a broad peak with the rest of humanity? Where do we draw the line? What is normal? What is abnormal?

JLC

You are completely wrong Mary Ellen! Even though you think you do well (that you don't have a PID), this is an illusion, because you wash your hands (and live in a nice area, free of many bugs), you have been vaccinated (a lot), and you have received antibiotics (a lot). Most immunologists think like you, but if you drop them without any medicine in the forests of Africa (Congo) or South America (Brazil), I can assure you that they will be less proud of their immune system.

The bottom line is that life expectancy in truly natural conditions (without medicine) is about 20 years at birth. It has been so for 200,000 years worldwide, and this has been thoroughly documented. Half (yes, half) of the children died of infection before the age of 15 years. By far, the greatest

burden was infection (war and starvation, by comparison, were minor contributors). You may look up the great book by John Cairns (*Matters of Life and Death*).[12] We extracted some of his data, and, together with WHO curves, we made a global figure representing human mortality curves throughout prehistory and history.[13] For example, Pasteur lost 3 of his 5 children to fever, and Darwin lost 3 of his 9 children to fever. So, yes, immunodeficiency is the rule, if one accepts the very reasonable definition that death caused by an infection results from an immunodeficiency (a conservative definition, as near-lethal infections and phenotypes other than infections may also be caused by immunodeficiencies). A more debatable question is whether these immunodeficiencies are inherited or acquired.

MEC

I want to defend my immune system! After all Mathusale lived to be 969 years old before the days of antibiotics and the hygiene concept.[14] You tell us that life expectancy at birth in natural conditions is about 20 years. However, this can be explained, at least in part, by the high infant mortality. Plenty of people lived into old age even in the Neolithic age. Jean-Laurent's figure shows that the median survival was about 40–50 years old.[13] My father's great aunts Alice and May, who were born in the 1840s, died in their 90s without the benefit of modern medicine. Maybe genetic defects that are detrimental to the immune system are common; but not everyone has an immunodeficiency!! I am saving money for a long retirement.

JLC

No one ever said you were normal!! There is evidence coming from a completely distinct set of observations, made from the 1920s onward by population geneticists, suggesting that infectious diseases in past generations were often due to PIDs. Twin studies and adoptee studies provided strong evidence that susceptibility to infection in the general population is inherited. Maybe the most striking paper along these lines is the Sorensen paper in 1988, showing that infection is by far the most genetic human disease (for example, by comparison with cancer).[15] Initially, PIDs were restricted to rare, highly penetrant genetic traits defined by an immunological phenotype (e.g., agammaglobulinemia) and conferring early-onset vulnerability to multiple and recurrent infections. In the last 15 years, it has become apparent that children vulnerable to a single infectious agent (e.g., herpes simplex virus) may suffer from single-gene inborn errors of immunity.[16] Moreover, these infections may strike only once, pointing to the existence of PIDs solely affecting immunity to primary infections, not to latent or recurrent infections.[17] And then, of course, the entire history of PIDs that supports this notion, from X-linked agammaglobulinemia to herpes encephalitis, and more to come. Finally, as Gigi mentioned before, one should add to this extraordinary infectious burden all the diseases that were shown to result from PIDs in the last 50 years—for example, autoinflammation, autoimmunity, angioedema, allergy, some tumors, granulomas, hemophagocytosis, and thrombotic thrombopenia.[18]

LDN

I want to disagree with Mary Ellen on another point. I am not sure that the frequency and/or severity of infections is a continuum (perhaps the frequency is, but severity may not be). Moreover, defining what a severe infection is would take another long discussion (or another chapter). The severity of infections also needs to be seen in a temporal and geographical context, inasmuch as what was very severe 200 years ago, before antibiotics, would no longer be considered severe now. Similarly, some infections may be relatively common in some geographical areas but extremely unusual in other areas (although Quintana-Murci would say that this may also have to do with differences in gene pools and selection![19,20]). This has obvious implications as well for the definition of what is normal and what is not normal.

If I were to define PIDs from an infection standpoint, I would say that any of the following may reflect an underlying immunodeficiency: (1) recurrent, unusually frequent infections due to common pathogens; (2) unusual manifestations due to common pathogens (e.g., liver abscesses or pneumatoceles); (3) infections sustained by unusual pathogens; and (4) unique susceptibility to single agents (or groups of pathogens).

MEC

But you would not say that these circumstances define immunodeficiency, would you? These circumstances should make a physician consider the possibility of immunodeficiency, but certainly many

infants with "unusually frequent infections due to common pathogens" are babies who are exposed to lots of other babies.

JLC

Maybe I can agree with Mary Ellen on this. Regarding the infections, I think we should consider life-threatening infections as the main criterion. It has the advantage of being simple and conservative. If we considered milder infections (e.g., otitis), we would be exposed to severe criticism. Whereas, nobody would argue that bacterial meningitis is a severe infection. Whether such severe infections result from PID or acquired infectious diseases, and whether the PIDs are single-gene inborn errors of immunity or not, is a difficult and largely unanswered question; although I think that pediatric infectious deaths are unlikely to be polygenic and are more probably monogenic.[16] I am therefore uncomfortable with Gigi's four categories because many other children with PIDs would fall between the cracks, and some of the kids you define would not suffer from a PID.

LDN

Let me challenge you both. The main point is that it is very hard (and subjective) to define life-threatening infections. What I tried to say in my previous comment is that this judgment is not (and cannot be) an absolute one, but it depends on time (pneumonia was a life-threatening infection until not too many decades ago!) and environment, not to mention availability of treatment. Herd immunity, for instance, may make one specific infection trivial in a given population and life-threatening in another (or even the same population if immunization coverage drops!).[21] It is not easy (or perhaps not even possible) to define what the specific effect of an infection would be in a naive host (i.e., for example, in the absence of treatment or herd immunity). Furthermore, changes in the social infrastructure (e.g., unplanned urbanization, poverty, mass migrations) are as important as the emergence of antimicrobial resistant strains in determining vulnerability to infections.[22]

That said, I agree that it is easier to take susceptibility to infection as the paradigm of PID phenotype, but this does not mean that what is more simple is necessarily more true. For instance, we all agree that TLR3 defects come under the category of PIDs, even if the ultimate phenotype depends on defects occurring in nonhematopoietic cells, but why would this be different than for manifestations other than infection (such as psoriasis)?

JLC

Yes, this is true. For the last 60 years immunodeficiency has had a hematopoietic-centered view of immunity. I can easily make the case that nonhematopoietic cells (such as keratinocytes, endothelial cells, and fibroblasts) are essential for host defense: (1) some nonhematopoietic cells secrete as much and as many cytokines as some leukocytes, if not more; (2) many of these nonhematopoietic cells can be infected by microbes and viruses, and use intrinsic pathways for protection; and (3) in some cases these cells are essential and sufficient for host defense, for example, our study of HSV1 immunity in neurons and oligodendrocytes.

MEC

So we are agreed that the definition of primary immunodeficiency ought to extend beyond the limits of classic cellular and humoral immune system. What about addressing the genetics of immunodeficiency? There has been an emphasis on monogenetic defects of the immune system and family history of disease. Arkwright and Gennery (in this volume) suggest that a positive family history is the most reliable way to identify patients with primary immunodeficiencies.[23] Although I am taking their statement out of context (at least a little bit), I think it is worth pointing out that most patients with immunodeficiency don't have a family history of disease. At least half of the patients with X-linked or autosomal-dominant immunodeficiencies have no family history of disease because they are the first manifestation of a new mutation. Some immunodeficiencies, particularly some autosomal-dominant defects (like Fas defects) have incomplete penetrance.[24,25] Patients with autosomal recessive disorders usually have no family history of disease because this requires that both parents have a heterozygous defect in the same gene.

What about monogenetic versus polygenetic disease? The classic immunodeficiency that is not usually a monogenetic disease is CVID, which is probably caused by a combination of susceptibility genes in most patients. This gets us closer to many disorders that are influenced by the immune system

but are not strictly the purview of clinical immunologists, like diabetes, psoriasis, cystic fibrosis, or atherosclerosis. Where do we draw the line?

JLC

I'm inclined to be inclusive. Why would cystic fibrosis not be a PID, besides the historical reasons that led pulmonary doctors and not clinical immunologists to take care of these patients? For the same reason, why would neonatal and type I diabetes, which are both so genetic and so immunological, not be considered PIDs? Likewise, how about pediatric systemic lupus erythematosus, which is now connected with the Aicardi–Goutières syndrome and interferonopathies (Y. Crow, this volume)?[26] We could go on for hours and revisit the whole field of pediatrics. I actually think that the merger between these hitherto separated fields will occur, sooner or later, because this will be in the patients' and clinicians' best interests. This is inevitable and will be beneficial.

LDN

I start worrying now! Shall we really ask PID specialists to take care of all kinds of patients? And how many years will it take for the next generation of immunology fellows to complete their studies?

MEC

Maybe we need different definitions of immunodeficiency for different situations. A clinical immunodeficiency might be defined as a recurrent infection or the appearance of recurrent infections (autoinflammatory disorders) requiring specialty care from a clinical immunologist. A scientific definition of immunodeficiency could be much broader and include any documented abnormality of the immune system that may, or may not, be associated with clinical disease. An example might be BAFF-R defect. This definition would include disorders that are influenced by the immune system like lupus, inflammatory bowel disease, and diabetes.

JLC

Well, I would argue that we don't need a definition. That's the best thing we can propose; this is the best way to keep the field open and inclusive. Each new PID will naturally expand the field, without the need for discussions about the definition. You understand that I say that reluctantly, as I not only enjoyed our discussion but also love definitions. I just don't think the field is ready for a profound reform.

MEC

Part of the appeal of the field of immunodeficiency for many of us is that the field does not limit itself to a single organ system or a single mechanism of disease. Although a high proportion of defects resulting in immunodeficiency are caused by defects in signal transduction, other areas of cell biology, including DNA repair, degranulation, and specialized functions for microbial killing can also be involved. Thus we keep our eyes and ears open about disorders that involve the immune system even if the affected patients do not have susceptibility to infection and would not receive care from a clinical immunologist.

Conflicts of interest

The authors declare no conflicts of interest.

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