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Adult-Onset Presentations of Genetic Immunodeficiencies: Genes Can Throw Slow Curves

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Abstract

Purpose of Review—The molecular and genetic mechanisms behind adult presentations of primary immunodeficiency diseases are examined, with particular emphasis on cases where this was heralded by severe, recurrent or opportunistic infection.

Recent Findings—A detailed analysis over the last two decades of the relationship between genotype and clinical phenotype for a number of genetic immunodeficiencies has revealed multiple mechanisms that can account for the delayed presentation of genetic disorders that typically present in childhood, including hypomorphic gene mutations and X-linked gene mutations with age-related skewing in random X-chromosome inactivation. Adult-onset presentations of chronic granulomatous disease, X-linked agammaglobulinemia, interleukin-12/T helper 1/interferon-gamma and interleukin-23/T helper 17/interleukin-17 pathway defects, and X-linked lymphoproliferative disorder are used to illustrate these mechanisms. Finally, certain genetic types of common variable immunodeficiency are used to illustrate that inherited null mutations can take decades to manifest immunologically.

Summary—Both genetic mechanisms and environmental factors can account for adult-onset infectious and non-infectious complications as manifestations of disorders that typically present in childhood. This emphasizes the potential complexity in the relationship between genotype and phenotype with natural human mutations.

Keywords

Primary immunodeficiency; adult-onset; hypomorphic mutations

Introduction

Adult patients with recurrent or severe non-opportunistic infections who lack co-morbid conditions or anatomic abnormalities may have contributing immune defects, and, in some instances, this can have a genetic basis [1]. Opportunistic infection in adult patients can also be a presentation of genetic immunodeficiency rather than acquired immunodeficiency or

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iatrogenic immunosuppression or a result of autoantibodies that inhibit cytokines. Examples of the latter include anti-interferon-gamma (IFN- γ) antibodies in previously healthy adults presenting with severe non-tuberculous Mycobacteria (NTM) infection [2], and antibodies to interleukin-17 (IL-17) and IL-22 that are associated with chronic mucocutaneous candidiasis [3**]. Importantly, diverse non-infectious disorders, such as atypical hemolytic uremic syndrome, Crohn's disease, and pulmonary alveolar proteinosis [4*] can also be presentations of adult-onset genetic immunodeficiency, although this review will focus on presentations with infection.

Epidemiology of primary immunodeficiency disorders

Human primary immunodeficiency (PID), in which the underlying defect is intrinsic to the immune system, comprises 150 disorders, including 142 that have a defined genetic basis [5]. The prevalence of PIDs in the general population has generally been assumed to be rare, but a telephone survey of 10,000 households estimated that 1:2000 persons in the United States had a PID [6]. A recent population-based cohort study showed that the incidence of PIDs in Olmstead County, Minnesota, including for adults, increased markedly from 2.4 per 100,000 person-years from 1976 through 1980 to 10.3 per 100,000 person-years from 2001 through 2006 [7**]; it remains unclear if this was due to improved diagnostic capabilities, physician awareness or other factors.

Genetics of primary immunodeficiency disorders

Most PIDs are due to single-gene defects that can affect diverse biological processes, including immune cell development, effector function, homeostasis, and negative regulation of inflammation and effector function. Recessive single-gene defects can be either encoded on the X-chromosome, in which case males are predominantly affected, or on autosomes, with both sexes equally affected [5]. In females, random X-chromosome inactivation occurs in human embryogenesis at approximately the 14–16 precursor cell stage [8], and female carriers of X-chromosome encoded mutations can be affected with disease if there is markedly skewed inactivation of the X-chromosome encoding the wildtype allele rather than a mutant allele. Autosomal dominant disorders, in which heterozygous mutations cause disease, are particularly frequent in cases of proteins that function in complexes, such as receptors and certain intracellular signaling/transcriptional regulatory molecules. For example, many members of the STAT (Signal Transduction and Activator of Transcription) family mediate their effects on transcription as homodimers. Thus, in a heterozygous individual, STAT complexes formed between a normal and an abnormal (mutated allele-derived) STAT protein can impair complex function. This mechanism applies to the autosomal-dominant form of the hyperimmunoglobulin E syndrome due to heterozygous missense STAT3 mutations [9*].

Genetic mechanisms accounting for adult presentations

Hypomorphic mutations, in which there is retention of some functional protein expression, may cause PIDs that characteristically present in childhood to have a milder phenotype and present in later life [1], as opposed to null mutations, which lack any gene function, and usually present earlier. Hypomorphic mutations may be due to missense mutations that result

in amino acid substitutions that alter but do not ablate protein function and that do not markedly destabilize the protein. Small deletions of coding sequences can be hypomorphic provided that there is no downstream alteration of the open reading frame used for mRNA translation. A common mechanism for hypomorphic mutations is splice donor or acceptor site mutations that flank exons and that perturb mRNA splicing and processing [10], but that often allow some “leaky” production of normal mRNAs. Mutations in promoter or other non-coding transcriptional regulatory regions of the gene may decrease mRNA expression, and can act as hypomorphic mutations if mRNA expression is not severely impaired [11]. In X-linked carriers of null mutations, progressive skewing of X-chromosome inactivation of hematopoietic cells that often occurs with ageing [12] can reduce the frequency of normal functioning cells below a critical level resulting in clinical disease. Lastly, even null mutations may allow sufficient residual activity of an effector pathway or involve pathways with some genetic redundancy, allowing for delayed clinical presentation until adulthood. Clinical examples of late-onset chronic granulomatous disease (CGD), X-linked agammaglobulinemia (XLA), interleukin-12 (IL-12)/T helper 1 (Th1)/interferon-gamma (IFN- γ) and IL-23/Th17 defects will be used to illustrate these genetic mechanisms.

Chronic granulomatous disease

CGD, which affects about 1 in 250,000 individuals, is caused by mutations in the five genes that encode the proteins of the NADPH phagocyte oxidase (Phox) complex, namely gp91-*phox*, p22-*phox*, p47-*phox*, p67-*phox*, and 40-*phox* [13]. The Phox is essential for killing pathogens phagocytosed by neutrophils, particularly catalase positive bacteria, such as *Staphylococcus aureus*, *Burkholderia cepacia*, and gram-negative enterobacteriaceae, and fungi, especially *Aspergillus* [13, 14]. CGD classically presents with severe or deep-seated infections, e.g., hepatic abscess, with these microorganisms. Inflammatory tissue responses, such as granulomas, also afflict a substantial frequency of patients, including a type of inflammatory bowel disease (IBD) that closely resembles Crohn's disease [15]. X-linked CGD is due to mutations in *CYBB* gene that encodes for the gp91-*phox* component, whereas mutations in the other four genes (*CYBA* encoding p22-*phox*, *NCF1* encoding p47-*phox*, *NCF2* encoding p67-*phox*, and *NCF4* encoding 40-*phox*) result in autosomal recessive CGD [16]. The only reported case of 40-phox deficiency [17] presented with IBD rather than severe or opportunistic infection.

Although CGD classically presents in early childhood, adult onset disease can occur, even in the elderly. For example, a 67 year-old man who developed *B. cepacia* sepsis was found to have X-linked CGD due to a single base pair splice site mutation in the *CYBB* gene that resulted in an aberrant transcript that encoded a stable protein lacking 10 amino acids of the normal gp91-*phox* sequence [18]. A *CYBB* splice site mutation also accounted for X-linked CGD presenting in a 40 year-old man with a *S. aureus* liver abscess [19].

Female carriers of *CYBB* mutations are well known to frequently develop cutaneous discoid lupus (skin rashes and photosensitivity), oral ulcers, and arthralgias [20], but they can also present with adolescent- or adult-onset CGD due to extreme skewing of X-chromosome inactivation (for example, see [21–23]). The frequency of skewed X-chromosome inactivation, which has been defined as a ratio of greater than or equal to 3:1, has been

reported to occur in about 9% of newborn females and increases with ageing [24], with an occurrence of 38% in healthy females over the age of 60 [12,25], with little or no fluctuation [26]. Although there remains some controversy as to the extent of such skewing with aging [27], a plausible scenario for adult-onset X-linked CGD in carrier females is progressive age-related X-chromosome skewing in the hematopoietic cell lineage and a reduction in the frequency of neutrophils with Phox activity below a critical level required for host defense. However, establishing a firm protective level that is clinically useful may prove difficult without study of additional cases; infectious complications have been reported with X-linked carriers of *CYBB* mutations who, based on the dihydrorhodamine flow cytometry assay, have had oxidative burst positive neutrophils as high as the 5–10% range [28]. Interestingly, there is a single example of adult-onset X-linked CGD from progressive X-chromosome inactivation skewing in a 66 year-old female who had a somatic mutation of the *CYBB* gene affecting hematopoietic cells, and who lacked a germ-line mutation [29].

Another important consideration in adult-onset CGD are null mutations of the p47-*phox* gene, which allows low but clearly uniformly detectable amounts of residual Phox activity by neutrophils [16,30]. One particular null allele, Δ GT, in which there is a GT deletion in exon 2 of the *NCF1* gene (75_76delGT) resulting in a frameshift and premature stop codon, occurs at a high frequency in the gene pool due to its ready generation by a gene conversion event involving a neighboring pseudogene, Ψ *NCF1* [31]. Homozygous Δ GT *NCF1* mutations account for 97% of p47-*phox* CGD and % of autosomal recessive CGD. Thus, this mutation is an especially important consideration for females who present with suggestive infectious complications but have no male relatives with CGD. Although most cases of p47-*phox* deficiency present in childhood the residual neutrophil Phox activity makes adult-onset CGD reasonably common. This is demonstrated by three unrelated and previously healthy women who presented at 25 years of age with a pyogenic liver abscess [32], at 46 years of age with a liver abscess due microaerophilic streptococcus [33], and at 22 years of age with *Aspergillus fumigatus* pneumonia and an extensive contiguous neck tissue phlegmon (our unpublished observations). Also notable is a case of a 53-year old woman who was diagnosed with p47-*phox*-deficient CGD after having had suffered from Crohn's disease since 8 years of age, and two episodes of hepatic abscess at the age of 5 years and 27 years [34]. Thus, a careful patient history reviewing unusual or deep seated infections is important in all patients with inflammatory bowel disease, particularly Crohn's disease.

X-linked agammaglobulinemia

XLA (Bruton's agammaglobulinemia) is due to mutations in the *Btk* gene encoded in the Xq22 region. Btk is a cytoplasmic tyrosine kinase that is required for early B-cell maturation, with null mutations resulting in a maturational arrest of bone marrow B-lineage cells at the pre-B-cell stage, markedly reduced levels of circulating mature B cells, and hypogammaglobulinemia that is typically severe. Clinical manifestations typically include recurrent sinopulmonary infections due to encapsulated bacteria, especially *Streptococcus pneumoniae*, during infancy. Less frequent presentations include infection of the joints with genital-type mycoplasma organisms (*Mycoplasma hominis* and *Ureaplasma urealyticum*) and persistent central nervous infections with non-polio enteroviruses. Although more than

600 mutations in the *Btk* gene have been identified [35], there has not been a clear correlation between clinical phenotype and the location of amino acid substitution missense mutations within the *Btk* gene. In general, mutations that would be expected to allow some production of functional Btk (amino acid substitution mutations and splice site mutations, especially those that involve conserved but not invariant residues of the splice site consensus) have often been associated with higher numbers of circulating B cells, higher immunoglobulin levels and an increased age at the time of diagnosis but there are many exceptions [36, 37].

In males who present with recurrent sinopulmonary infections, particularly pneumonia and bronchiectasis, it is important to distinguish between late-onset XLA and common variable immunodeficiency (CVID), one of the most frequent forms of primary immunodeficiency with a prevalence of approximately 1 in 50,000 and a median age of onset in the third decade for men and women [38, 39]. CVID also typically includes hypogammaglobulinemia, particularly for IgG and IgA, which can be severe. However, unlike XLA, B-cell numbers are substantially decreased in only about 10% of cases of CVID, and, even in these cases, the numbers of peripheral blood B cells are substantially higher than is observed in XLA. In males with XLA diagnosed in adulthood, many had IgG levels that were only moderately depressed or even normal [40], which may account for the delay in presentation, but, even in cases of relatively high immunoglobulin levels, the number of peripheral B cells was clearly markedly depressed [37, 41, 42]. Minimal hypomorphic *Btk* mutations are likely clinically silent, as these have only a subtle impact on peripheral B-cell number [43]. Particularly striking are cases where two or more affected males within a family having the same *Btk* mutation had markedly different clinical presentations. For example, a man who was diagnosed at age 72 years who had a brother who died in infancy of sepsis [44], suggesting that important environmental factors and/or modifying genes influence the phenotype. Although extraordinarily rare, female carriers of *Btk* mutations with skewed X-chromosome inactivation can develop XLA [45], and this would be a reasonable concern in a woman with presenting with recurrent sinopulmonary infections along with a family history of *Btk* deficiency.

Interleukin-12/Th1/interferon-gamma and interleukin-23/Th17 pathway defects

The IL-12/Th1/IFN- γ pathway involves the IL-12-dependent generation of pathogen-specific T helper 1 (Th1) cells [46, 47]. Th1 cells secrete IFN- γ that binds to target cells, such as mononuclear phagocytes, enhancing their microbicidal activity against intracellular pathogens, especially Mycobacteria. In the IL-23/Th17 pathway, IL-23 augments the accumulation of Th17 cells, which secrete IL-17 (A and F), and IL-22 that enhance neutrophil-mediated control of extracellular bacteria and the antimicrobial and barrier function of epithelial cells. IL-12 is a heterodimeric cytokine that consists of p35 and p40 subunits encoded by the *IL12P40* and *IL12P35* genes, respectively. IL-12 is mainly produced by dendritic cells and activated mononuclear phagocytes and promotes Th1 differentiation by binding to activated naïve CD4 T cells with high-affinity IL-12 receptors. The IL-12 receptor is a heterodimer of a $\beta 1$ and a $\beta 2$ chain encoded by *IL12RB1* and *IL12RB2*. IFN- γ that is secreted by Th1 cells and other cell types binds to target cell surface IFN- γ receptors, which are heterodimers encoded by *IFNGR1* and *IFNGR2*, resulting in the

activation of STAT1 homodimers that mediate transcription. IL-23, which consists of the same IL12 p40 subunit utilized by IL-12 and a distinct p19 subunit encoded by *IL23A*, is also produced by dendritic cells, but probably acts at a later stage than IL-12 does to promote Th17 immunity. Thus, in the case of human gene defects in *IL12P40* or *IL12RB1* or, infections indicative of both Th1 and Th17 deficiency would be expected [48].

Of interest is a recent report of a 22 year-old male with disseminated recalcitrant coccidioidomycosis beginning at 10 year of age who was found to have autosomal dominant IFN- γ R1 deficiency due to gene defect that resulted in the accumulation of defective receptors on the cell surface [49]. This extends the importance the Th1 pathway in humans to *Coccidioides*, and also supports a potential benefit of adjunctive therapy with IFN- γ in cases of *Coccidioides* that are refractory to conventional anti-fungal agents.

Cases of null genetic defects of the IL-12 receptor β 1 chain (*IL12RB1*), which impairs both Th1 [50] and Th17 development [48] but leaves cellular responsiveness to IFN- γ intact, typically present in childhood with BCG-osis, infections with NTM, and extraintestinal Salmonellosis [51]. Recurrent mucocutaneous candidiasis is also increasingly recognized as complication [51], most likely reflecting a deficiency of Th17 immunity. Although most patients present with infectious complications in early childhood, a large proportion of these patients received routine BCG vaccination in infancy, and it is likely that the average age of presentation is substantially older in unvaccinated individuals. Even among genetically affected siblings of index cases in areas with high coverage of BCG vaccine, as many as 20% of *IL12RB1* deficient individuals may remain free of major infectious complications until age 20 [51] or later. For example, a man with a homozygous *IL12RB1* null mutation presented with disseminated *Mycobacterium avium* complex infection at 30 years of age [52].

Markedly delayed penetrance - common variable immunodeficiency

Adults are diagnosed with CVID based on hypogammaglobulinemia and poor antibody responses to vaccines, particularly for pneumococcal polysaccharides, but are also at high risk to develop autoimmune diseases, particularly those that are mediated by antibodies, and lymphoproliferative and granulomatous disorders [53]. As many as 10% of CVID patients may have reduced numbers of B cells, but these are usually still well above the very low or absent levels observed in *Btk* deficiency. Recurrent sinopulmonary infections with encapsulated organisms, especially *Streptococcus pneumoniae*, are characteristic. Most cases of CVID are of unknown genetic cause. A number of sequence variants of *TNFRSF13B* (encoding TACI) are found in about 10% of cases. Two of these alleles (C104A) and (A181E) may substantially increase the risk of CVID [54], although there appears to be substantial clinical heterogeneity [55, 56]. Gene polymorphisms, such as for the mannose-binding lectin opsonin, may also modify disease in CVID, for example by increasing the risk of the development of bronchiectasis [57].

Rarely, homozygous mutations in four genes – *ICOS* (Inducible T-cell Co-stimulator) [58], *TNFRSF13C* (BAFF receptor) [59], *CD19* [60, 61], and *CD81* [62] – can result in a CVID-like phenotype of antibody deficiency syndrome despite substantial numbers of circulating B

cells [55]. In the case of homozygous ICOS deficiency due to the same null large deletion mutation [63], eight patients presented with CVID clinical features as early as 18 months and as late as 27 years of age; one 5 year-old lacked symptoms but was already immunologically affected by hypogammaglobulinemia, suggesting that immunologic dysfunction may precede clinical onset [58**]. As recurrent sinopulmonary infections did not occur until adolescence or adulthood in 5 of the 9 ICOS-deficient patients, this suggests that an important environmental factor or factors is required for expression of the CVID disease phenotype in this rare genetic deficiency and, possibly, idiopathic CVID as well. Only two related patients homozygous for the same BAFF receptor mutation have been identified. A striking feature of BAFF receptor deficiency was that the clinical onset of disease was delayed in one of the individuals until 70 years of age, with the other having asymptomatic immune abnormalities. Based on these two cases, BAFF receptor deficiency might present in CVID patients who have reduced but substantial numbers of circulating B cells that are mainly of the early transitional phenotype, and who have depressed levels of total IgG and IgM but normal levels of serum IgA [59**]. Finally, CD19- and CD81-deficient patients have so far presented with childhood onset hypogammaglobulinemia and recurrent infections; such disorders might also be a consideration in adult-onset symptoms of antibody deficiency, particularly if hypomorphic mutations for these genes are documented to have an impact on immune function.

Summary

PID disorders that ordinarily present during childhood may present in adulthood due to hypomorphic mutation, skewed X inactivation, somatic mutation, and a possible requirement for poorly defined environmental factors for phenotypic expressivity. Disorders of the immune system that are classically identified in childhood have varied presentations in adult patients, including not only severe or recurrent infection, but also autoimmune disease and malignancy. These adult-onset cases of PID emphasize the complex relationship between genotype and phenotype with natural human mutations affecting the immune system.

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