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Druggable monogenic immune defects hidden in diverse medical specialties: Focus on overlap syndromes

Valentina Boz, Chiara Zanchi, Laura Levantino, Guglielmo Riccio, Alberto Tommasini

Abstract

In the last two decades two new paradigms changed our way of perceiving primary immunodeficiencies: An increasing number of immune defects are more associated with inflammatory or autoimmune features rather than with infections. Some primary immune defects are due to hyperactive pathways that can be targeted by specific inhibitors, providing innovative precision treatments that can change the natural history of diseases. In this article we review some of these “druggable” inborn errors of immunity and describe how they can be suspected and diagnosed in diverse pediatric and adult medicine specialties. Since the availability of precision treatments can dramatically impact the course of these diseases, preventing the development of organ damage, it is crucial to widen the awareness of these conditions and to provide practical hints for a prompt detection and cure.

Key Words: Inborn errors of immunity; Primary immunodeficiency diseases; Precision treatments; Immunodysregulation; Autoimmunity; Overlap syndromes
Core Tip: High-throughput genetic testing have allowed to describe monogenic immune disorders, characterized by combinations of infective, inflammatory, autoimmune, lymphoproliferative, neoplastic features. The term “inborn errors of immunity” (IEIs) is increasingly proposed instead of “primary immunodeficiency” to include defects with a prevalently dysregulatory pathogenesis, resulting in autoimmunity, inflammation, lymphoproliferation, risk of malignancies. It is crucial to widen the awareness of these disorders, as they may mimic multifactorial disorders (rheumatology, gastroenterology, hematology, dermatology, allergology) and some of these are druggable. The awareness of druggable IEIs is the focus of this review, with the aim of favoring a prompter diagnosis and a better cure.

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INTRODUCTION

Primary immunodeficiencies are a growing group of monogenic disorders related to dysregulated immune processes, which can result in autoinflammation, autoimmunity, lymphoproliferation and/or risk of malignancy in addition to the paradigmatic recurrent infections: In this sense, the term “inborn errors of immunity” (IEIs) has recently been proposed to underline the heterogeneous phenotype of immune deficiencies[1,2].

Improved diagnostics of monogenic immune disorders, together with the availability of medications acting on disease-related mechanisms recently led to the development of precision therapies which can improve or correct the phenotype of some IEIs[3-6]. The mutations involved in these disorders are usually associated with gain-of-function (GOF) of proteins (often kinases) or hyperactivity of pathways, which can be targeted by specific medications and thus sometimes referred to as “druggable”. For concision, we indicate IEIs with druggable pathogenic mechanisms as druggable IEI (D-IEIs).

Of note, since immunodeficiency may develop significant organ damage due to infection or autoimmunity, early detection of D-IEIs is crucial to benefit from appropriate treatments[7]. Although a deep clinical-laboratory evaluation can help an experienced immunologist to concentrate suspicion on one of these disorders, the use of next generation sequencing (NGS) offers a powerful tool to diagnose D-IEIs, allowing to examine all the candidate genes at once[8-10]. However, due to the wide heterogeneity of IEIs, it may be difficult to select patients for genetic analysis.

In fact, from a phenotypic point of view, due to their origin from general disturbances in immune regulation, D-IEIs tend to affect multiple organs and systems, composing complex clinical pictures that overlap disorders of distinct medical specialties, and tend to fully manifest over the time, with the definition of typical clinical pictures only in adults. Thus, patients with D-IEI can initially be diagnosed especially in pediatric age - with common multifactorial disorders, pertaining to various medical specialties and displaying atypical clinical presentations such as unusual age of development, multiorgan involvement and response to therapies. These factors are congruent with the immune dysregulation theory.

In light of this, the aim of this review is to widen the awareness of “druggable” IEIs which may be hidden in various medical specialties, in order to promote an earlier diagnosis and a better therapy in this field.

IEI may present druggable autoimmune, inflammatory and/or lymphoproliferative manifestations

We present a list of druggable IEIs, with prevalent autoimmune, inflammatory and/or lymphoproliferative aspects, which may mimic common multifactorial disorders, and therefore are at risk of being missed, until significant organ damage manifests. Since effective treatments are now available for immune disorders, it is of crucial importance to consider the possibility of a primary immune defect in subjects presenting with clinical pictures suggestive of immune dysregulation, particularly those that overlap distinct rheumatological, gastroenterological, endocrinological and dermatological/allergic disorders (Table 1). As described elsewhere, there is now a trend of anticipating the time of genetic analysis, reserving more in-depth immunological investigations for a later time, with the aim of determining the role of any variants of uncertain significance found in candidate genes[7].

IPEX is a monogenic immune disorder (due to mutations in FOXP3) characterized by an impaired development of Treg cells, resulting in failure of peripheral immune tolerance, with autoimmunity and allergic manifestations[11-13]. The disease typically presents in infancy with enteropathy, cutaneous disorders with eczema and nail changes, and endocrinopathies [e.g., type 1 diabetes mellitus (T1DM), thyroiditis]. Several other autoimmune manifestations may also be found. The treatment may benefit from sirolimus or tacrolimus, in addition to nutrition and glucocorticoids, but only hematopoietic stem
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| DADA2    | ADA2                      | Reduced activity level of the adenosine deaminase 2                               | Hypogammaglobulinemia; increases macrophage release of TNF-α; upregulation of neutrophil activity; upregulation of pro-inflammatory cytokines; upregulation of type 1 interferon | Vasculitis, immunodeficiency; autoimmune neutropenia; autoimmune cytopenia | Splenomegaly; lymphadenopathy; hepatomegaly | Verruca; herpes virus infections; increased | Anti-TNF treatment (etanercept, infliximab,adalimumab); high-dose of glucocorticoids; HSCT; immunosuppressive drugs in isolated cases (mycophenolate, ...
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cell transplantation allows a cure, the success of which is related to an early diagnosis\[14-16\]. Proof of concept for immunoregulation with abatacept was obtained in scurfy mice, which are considered a good animal model for the IPEX\[17,18\].

APECED is a monogenic immune disorder (due to mutations in \textit{AIRE}) characterized by an abnormal presentation of self-antigens in the thymus, resulting in the failure of central immune tolerance, with autoimmunity\[19-21\]. The disease usually presents in infancy with recurrent and severe candidiasis (with susceptibility associated to IL17-neutralizing antibodies) and parathyroid and adrenal autoimmunity, but over time other autoimmune disorders (e.g., hepatitis, thyroiditis, vitiligo, alopecia, gastritis) are also observed\[22,23\]. Even if there is still no precision therapy for APECED, it is important to make an early diagnosis to establish a proper follow-up with prompt detection of new autoimmune phenomena, infections and malignancies\[24,25\].

CTLA4 and LRBA deficiencies are monogenic immune disorders associated with an impaired regulation of lymphocyte activation and development, resulting in autoimmunity and lymphoproliferation, but also infections\[26-30\]. Clinical features include hepatosplenomegaly, enteropathy, eczema, autoimmune cytopenia, arthritis, lupus-like features, hypogammaglobulinemia recurrence of infections and risk of malignancies (particularly due to chronic EBV infection). Hematopoietic stem cell transplantation (HSCT) can cure the disease, however the treatment of milder cases may benefit from the use of CTLA4-Ig (abatacept)\[28,30,31\].

APDS (type I and II) are monogenic immune disorders associated with an impaired regulation of T and B cells maturation and survival, resulting in lymphoproliferation, autoimmunity and infections\[32-35\]. Clinical features include recurrent infections (especially respiratory, often complicated by the development of bronchiectasis and cutaneous) lymphoproliferative manifestations with risk of lymphoma\[36-38\], enteropathy and systemic lupus erythematosus (SLE)-like features. The immune defect is complex, with hypogammaglobulinemia with normal or increased IgM, reduced number of recent thymic emigrants and accumulation of senescent CD8 T cells. The pathogenic mechanisms can be partially reversed with drugs inhibiting the PIK3delta kinase, with a great potential in reducing the disease severity\[39\].

Monoallelic GOF mutations in \textit{STAT1} are associated with susceptibility to infections from bacteria and fungi, autoimmune disorders and rheumatologic manifestations, due to increased activation of interferon stimulated genes\[40,41\]. Since hyperactive \textit{STAT1} still depends on the trigger from Janus kinases, the use of JAK inhibitors can partially restore a physiological balance with great clinical benefit both on inflammatory and on infectious symptoms\[42,43\]. In a recent report, treatment with JAK
inhibitors led to the reversal of autoimmune diabetes in a boy with STAT1 GOF[40].

Monoallelic GOF mutations in STAT3 are associated with autoimmune and lymphoproliferative disorders[44]. Patients may present autoimmune enteropathy, celiac disease-like changes in the jejunum, eczema, autoimmune polyendocrinopathy, lymphoproliferation with increased CD4-CD8-double negative T cells and risk of hematologic malignancies and hypogammaglobulinemia with recurrent infection. The use of JAK inhibitors can lead to significant clinical improvement in this case too[45].

DADA2 deficiency is a combined immunodeficiency due to the defective function of the adenosine deaminase-2 enzyme. The disease is associated with lymphoproliferation, variable hypogammaglobulinemia and susceptibility to infection, arthritis, livedo reticularis, erythema nodosum, purpura and vasculitis with a picture of polyarteritis nodosa and ischemic strokes[46,47]. The main complaints of the disease are driven by TNF-alpha: Thus, there is a formal recommendation to start anti-TNF treatment as early as possible[48].

A20 haploinsufficiency is a monogenic immune disorder (due to mutations in TNFAIP3) characterized by an abnormal activation of NF-kB signalling, resulting in a phenotype similar to Behcet’s disease (BD)[49]. Indeed, clinical features include uveitis, recurrent oral and genital ulcerations, rash, abscesses and periodic fever. However, some patients may present with ulcerative colitis or with signs of SLE-like autoantibodies, increased production of interferons, autoimmune cytopenias and sometimes nephritis[50-52]. Anti-TNF treatment has been proven of great efficacy in several patients, even if it could be ineffective on lupus-related complaints[53].

There are many other rare IEIs that may present with complex features of immune dysregulation, such as lymphoproliferation, autoimmunity, inflammation, and risk of malignancies. However, the therapeutic implications of diagnosing these IEIs are not as straightforward as those for druggable diseases.
Figure 1 Symptoms and laboratory findings supportive of druggable inborn errors of immunity in various medical specialties.

616414), which can benefit from JAK inhibitors[42,69]. Other rare monogenic causes of arthritis in children include immune dysregulation disorders like CTLA4 or LRBA deficiency[30,70], which can be effectively treated by abatacept[30,70], Blau disease and LACC1 deficiency, which present some overlap with sarcoidosis-like granulomatous disorders[71,72].

Gastroenterology

IBD: IBD can occur at any age, however cases with very early onset are more likely due to monogenic defects[73,74]. Although the majority of monogenic IBD cases occur in children diagnosed before 6 years of age (prevalence of 7%-10%), recent reports suggest the presence of rare variants causing monogenic IBD also in children diagnosed older than 6-years of age. Several genes involved in monogenic IBD were identified, classified in six categories based on action mechanisms, namely defects in the epithelial barrier, T- and B-cell defect, hyperinflammatory and autoinflammatory disorders, phagocytic defects and immunoregulation defects, included IL-10 signaling defects[75].

The clinical picture can be indistinguishable from IBD, however the presence of consanguinity, family history of autoimmune diseases and some histological and clinical features associated with extraintestinal manifestations, should raise the suspicion of an IEI. For example, autoimmune enteropathy and eosinophilic infiltrates may support the diagnosis of an underlying inborn immune defect. On a clinical ground, the presence of lymphoproliferative signs, the association with autoimmune phenomena in other organs, the increased burden of infections and the refractoriness to conventional therapies should prompt considering an IEI. The finding of lymphopenia, neutropenia or hypogammaglobulinemia can help address the suspicion of specific conditions. Eosinophilia can also be of great clinical significance. Some typical immunodeficiencies should be considered in cases with very early onset in infancy: Wiskott Aldrich Syndrome may present in the first days of life with inflammatory colitis, thrombocytopenia and infectious or inflammatory complaints; chronic granulomatous disease can mimic an IBD even before the occurrence of serious infections; combined immunodeficiency can present with intestinal inflammation and failure to thrive. Severe perianal disease, folliculitis and arthritis in early infancy suggest the presence of IL-10 signaling defects[76]. It is crucial to consider all these possibilities, as the diagnostic workload can be quite straightforward, if we pay attention to blood cell count, platelet count and volume, lymphocyte subsets and basic functional assays like the study of the oxidative burst in neutrophils or the dihydorhodamine assay[7]. Various recent experiences proved the utility of performing high throughput genetic testing in children with very early onset IBD or in those with complex clinical pictures supportive of widespread immunodysregulation, with the aim of planning appropriate and targeted treatment[77].
**Autoimmune enteropathy:** Autoimmune enteropathy is a rare disorder characterized by intractable diarrhea, growth failure, presence of anti-enterocyte autoantibodies and typical mucosal changes with lymphocyte infiltrates and increased apoptotic cells[78,79]. Most cases occur during the first year of life with severe primarily secretory diarrhea[78]. The association with extra-intestinal diseases like insulin-dependent diabetes, thyroiditis, membranous glomerulopathy, interstitial nephritis and the presence of numerous autoantibodies (e.g., antinuclear, anti-smooth-muscle, anti-parietal cells, pancreatic islets...), should raise suspicion of IPEX syndrome. Furthermore, early diarrhea and malabsorption can occur in up to 25% of patients with APECED, due to the destruction of intestinal endocrine cells; in these cases, small bowel biopsies show mild damage, in contrast with the inflammation present in autoimmune enteropathy. An early enteropathy with a relative paucity of inflammatory cells in a patient with a history of recurrent infections should be suspicious for CVID[80,81]. Recent literature reports a series of patients with both LRBA deficiency and CTLA-4 haploinsufficiency with gastrointestinal manifestations, including autoimmune enteropathy, lymphocytic duodenitis resembling celiac disease and autoimmune gastritis[82,83].

Parenteral nutrition, steroids and immunosuppressants like cyclosporin A and tacrolimus are the cornerstones of the therapy. If an IEI can be found in a significant proportion of children with early onset IBD, this is even more true for autoimmune enteropathy[78]. In most cases underpinned by IEIs, HSCT can be the treatment of choice. However, when HSCT is not possible or has to be delayed, a treatment with abatacept or sirolimus may be a valuable option for CTLA4 and LRBA deficiency or for IPEX respectively[30].

**Atrophic autoimmune gastritis:** Atrophic autoimmune gastritis is an autoimmune disorder associated with chronic gastric autoimmunity, vitamin B12-dependent anemia and increased risk of developing gastric cancer[84]. This condition is often found associated with other immune disorders like common variable immunodeficiency, autoimmune thyroid disease and T1DM[85]. However, some patients may initially present only gastrointestinal complaints with gastritis[83]. Considering that this is a rare disorder in children, the likelihood of finding a monogenic cause is high, and an immunologic and genetic workup should be carried out before the patient develops further autoimmune phenomena. APECED, IPEX and immune dysregulatory disorders are examples of monogenic diseases that can present with autoimmune atrophic gastritis, even if it is rare for autoimmune gastritis to be the sole complaint[83,86,87].

**Non celiac flat mucosa:** The main cause of flat mucosa in jejunum is active celiac disease (CD), due to gluten-dependent immune activation in the lamina propria of the intestinal mucosa[88,89]. Similar findings can be found in subjects in whom CD has been ruled out, based on negative testing for antiglutenase antibodies and/or absence of the predisposing HLA haplotypes and/or refractoriness to gluten free diet[83,90]. In these cases, intestinal inflammation may be related to an immune defect like common variable immunodeficiency. A flat jejunal mucosa has been described in subjects with immune dysregulatory diseases including IPEX, CTLA4 and LRB immunodeficiency, often in association with other gastrointestinal immune-mediated diseases, like autoimmune gastritis, autoimmune enteropathy or inflammatory bowel disease[83,91].

**Esophageal candidiasis:** Muco-cutaneous candidiasis is rarely observed in healthy children above the age of 1 year. Seldomly, therapies with oral glucocorticoids may facilitate the development of candidiasis in older children too, however the recurrence of the problem and the extension of the infection to the esophagus should always prompt the suspicion of an underlying immune defect. The underlying causes of chronic muco-cutaneous candidiasis may be monogenic, such as single gene mutations in the autoimmune regulator, signal transducer and activator of transcription-1 (STAT1) and -3 (STAT3), and many others genes (CARD9, TYK2, DOCK8, CD25, IL-1RA, RORC..), or the result of polymorphisms in genes encoding Dectin-1, NACHT LRR and PYD-containing protein 3, protein tyrosine phosphatase non receptor type-22, and Toll-like receptors which contribute to candida infection susceptibility[92-94]. It is worth noting that candida infections can sometimes be misinterpreted as the results of glucocorticoid treatments administered for other immune complaints, as some patients may present SLE-like phenomena (IL12RB1, STAT1 GOF) or autoimmune manifestations (APECED). Indeed, it is uncertain whether severe diffuse mucosal candidiasis reported in a subset of subjects with SLE are the result of immunosuppressive therapy or the marker of a possible underlying immunodeficiency[95].

**Endocrinology**

**Autoimmune polyglandular syndromes:** Endocrine glands are the most typical targets of organ-specific autoimmunity, probably related to the cell-specific expression of proteins involved in the highly specialized machinery of hormone production. Based on distinct patterns of involvement of diverse endocrine systems, autoimmune polyglandular syndromes (APS) have been classified in three groups (APS1-3). Overall, APS have been associated with a general failure of maintaining immune tolerance to specialized tissue. This can be due to a defective presentation of tissue antigens in the thymus during lymphocyte development (as in APECED), improper control of autoreactive lymphocytes in target organs (as in IPEX and IPEX-like disorders) or to breakdown of tolerance by medications (as with...
checkpoints inhibitors used to induce anti-cancer immunity). The combination of hypoparathyroidism and adrenal insufficiency (APS1) with mucocutaneous candidiasis and ectodermal dystrophy is typical of APECED, however patients may initially present only with a single autoimmune disease. In these cases, the search for autoantibodies can help anticipate further autoimmune disorders, avoiding the risks of a hyperacute onset of disease. APS2 is characterized by T1DM, autoimmune thyroiditis and Addison Disease and is considered a multifactorial disorder associated with the HLA class II locus. APS3 is characterized by T1DM and autoimmune thyroiditis and can be either due to monogenic druggable immune defects (IPEX-like disorders) or to multifactorial causes including HLA class II variants. The presence of dermatitis, autoimmune cytopenia or lymphoproliferation in addition to autoimmune endocrine diseases should always raise suspicion of a monogenic immune dysregulation disorder.

The therapy is mainly based on the replacement of defective hormones. However, in cases associated with significant immune dysregulation, a prompt immune modulation can prevent the development of further autoimmune or infectious diseases, in particular in the cases of druggable IEIs responsive to abatacept and/or sirolimus.

Hematology

Evans syndrome: Evans syndrome is characterized by the association of autoimmune hemolytic anemia with immune thrombocytopenic purpura. The two autoimmune conditions can occur simultaneously or in sequence. In some cases, autoimmune neutropenia can also be present. The term “Evans syndrome” refers to cases in which another definite diagnosis has not been made. However, a search for underlying immune defects may reveal the presence of a monogenic disease in a significant proportion of cases, in particular among those associated with signs of lymphoproliferation, that may be due to immune dysregulation immunodeficiencies[96]. The diagnosis of autoimmune lymphoproliferative syndromes (ALPS), activated PI3Kδ syndromes, IPEX syndrome, and CTLA4 or LRBA deficiencies can pave the way to the administration of targeted therapies like sirolimus, PI3Kδ inhibitors, and abatacept. Of note, sirolimus has been proven effective also in subjects with idiopathic Evans syndrome, suggesting that the disease may share relevant pathogenic features with ALPS. Since autoimmune cytopenias may be the presenting clinical condition in subjects with a common variable immunodeficiency or in SLE, a study of immunoglobulins, antinuclear antibodies and lymphocyte subpopulations is warranted in all subjects with Evans syndrome. Specific cytometric analyses may also give significant hints for rare IEIs[7].

Dermatology and allergology

Refractory eczema: Eczema is a common complaint in young children. If not treated properly, an active eczema may favor the development of allergies and other immune disturbances, fueling a vicious circle of inflammation, scratch injuries and infection. In most cases the disease can be easily treated until it wanes and disappears with age. However, in some rare cases the eczematous dermatitis shows a severe course and a refractoriness to treatments from the first weeks of life. These cases are often associated with poor growth or failure to thrive and sometimes with a history of infections. Blood examinations are usually performed to rule out a severe combined immunodeficiency or a Wiskott Aldrich Syndrome. However, other immune dysregulations are not as easy to diagnose. Peripheral eosinophilia is a clue to diagnosis, but a genetic panel for primary immune defects may be worthwhile in all severe cases. A diagnostic algorithm for IEIs associated with atopic phenotypes has been recently proposed by the Immunology Task Force of the Italian Society of Pediatric Allergy and Immunology[97].

Alopecia, vitiligo: Autoimmune alopecia and vitiligo may present in children at any age. The presence of autoimmune disorders in relatives, like thyroiditis is also common. However, if these complaints present together with other autoimmune or inflammatory disorders or with laboratory abnormalities like eosinophilia or a positive inflammatory index, it may be reasonable to perform an immunological and genetic investigation. For example, when associated with panniculitis, alopecia can rise suspicion of an interferon related disease like CANDLE syndrome, which can benefit from JAK inhibitors; if associated with severe dermatitis it may make you think of an immune dysregulation, like IPEX or CTLA4 or LRBA deficiency. It is worth noting that tofacitinib and other JAK inhibitors, and to a lesser extent abatacept, have been successfully used in subjects with alopecia areata even in the absence of a known underlying immune defect[98-100].

OVERLAP SYNDROMES MAY HIDE MONOGENIC DISORDERS

As described in the paragraphs above, IEIs may present with simultaneous or sequential involvements of various organs and systems. Many cases actually present substantial clinical overlap between disorders pertaining to different medical specialties. Whilst overlap syndromes are not rare in adult rheumatology or gastroenterology, this kind of conditions are not frequently encountered in children. Thus, we propose that IEIs should be considered in every child with immunological complaints overlapping diagnoses that are not usually seen in combination at this age. Since not all cases appear
Table 2 Clinical and laboratory red flags

**Clinical red flags**

Early onset in childhood: The development of complex inflammatory disorders before puberty and particularly before early childhood rises suspicion of a congenital immune dysregulation.

Overlap of symptoms in distinct specialties: A clinical history of distinct rheumatologic and non-rheumatologic conditions is not common in pediatrics, addressing a monogenic disorder.

Lymphoproliferative manifestations: The presence of splenomegaly and/or lymphadenopathy in association with inflammatory or autoimmune diseases suggests an underlying inborn error of immunity.

Recurrent infections: The recurrence of severe or atypical infections (especially candidiasis) in association with inflammatory or autoimmune diseases is rarely a consequence of immunomodulatory therapies in children, but it does suggest an immunological defect.

Familiarity with autoimmunity: The clustering of autoimmune disorders in families acknowledges a likely monogenic cause.

**Laboratory red flags**

- Hypogammaglobulinemia
- Hypergammaglobulinemia
- Leukopenia
- Hypereosinophilia
- Wide positivity of autoantibodies
- Positive interferon signature

Figure 2 Some druggable inborn errors of immunities in areas of intersection between more common gnoseological entities: In red druggable inborn errors of immunities and in black common gnoseological entities. JIA: Juvenile idiopathic arthritis; BD: Bowel disease; A20: A20 haploinsufficiency; HPF: hereditary periodic fever; IBD: Inflammatory bowel disease; CTLA4: Cytotoxic T-Lymphocyte antigen 4; IPEX: Immunodysregulation polyendocrinopathy enteropathy X-linked; LRBA: Lipopolysaccharide-responsive and beige-like anchor protein; STAT1: Signal transducer and activator of transcription 1; SLE: Systemic lupus erythematosus.

severe at beginning, the correct diagnosis may be often delayed to adult age or even missed. However, to recognize the underpinning monogenic disorder, in particular for druggable ones, it is crucial to choose molecularly targeted therapies able to prevent the development of further damages.

In Figure 2, we propose a schematic view of some druggable IEIs in areas of intersection between more common gnoseological entities. In Table 2, we highlight some “red flags” that could help consider a druggable IEI when dealing with complex immune disorders in any medical specialty.
CONCLUSION

Monogenic immune disorders are very rare, especially in subjects with adolescent/adult-onset diseases. Monogenic causes are more likely in subjects with a very early onset than in older ages. We thus provide some hints on when to suspect a group of monogenic disorders, the natural history of which can be favorably influenced by the availability of effective treatments (Figure 3).

FOOTNOTES

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