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The Immunologic Features of Patients with Early-Onset and Polyautoimmunity

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Abstract

Inflammatory conditions are increasingly described in patients with primary immunodeficiencies; however, little is known about the prevalence of immune defects in patients who present first with autoimmunity. We describe the immunologic features of children with early-onset/polyautoimmunity followed in the Multiple Autoimmunity and Immunodeficiency (MAID) Clinic, where patients are co-managed by rheumatologists and immunologists. The most common autoimmune manifestations were cytopenias, lymphoproliferation, and colitis. Recurrent infections were noted in 65% of patients. Abnormalities in lymphocyte subsets and immunoglobulins were common. A pathogenic variant was identified in 19% of patients, and 2 novel inherited disorders were discovered. Additionally, 42% of patients had treatment changes implemented in the MAID clinic. By evaluating this unique cohort of patients, we report on the immunologic underpinning of early-onset/polyautoimmunity. The high rate of genetic diagnoses and treatment interventions in this population highlights the value of collaboration between rheumatologists and immunologists in the care of these complex patients.

Keywords

Immune Dysregulation; Autoimmunity; Primary Immunodeficiency

1.0 Introduction

Patients with primary immunodeficiencies (PIDs) commonly present in childhood with recurrent and difficult to treat infections. Classically, it was thought that PID was on one end of the spectrum with an "overactive" immune system or autoimmunity (AI) on the other end. It is now increasingly appreciated that PIDs and AI co-exist in immune dysregulatory syndromes [1–5]. This may be due in part to the improved care of patients with PIDs and their longer lifespan, as time is typically needed for autoimmune phenomena to develop. In

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addition, better dissemination of information amongst immunologists and rheumatologists has allowed for the recognition of many monogenic immune dysregulatory syndromes over the past decade.

Autoimmune manifestations are frequently reported in patients diagnosed with monogenic PID [1–3]. Interrogation of different PID registries has provided estimates of the percentage of patients with PID who also have co-existing autoimmune disease. In 2014, Maggadottir and Sullivan queried the United States Immunodeficiency Network (USIDNET) records and estimated that between 1 and 11 percent of PID patients had a diagnosed autoimmune condition [4]. A recent large study of the French national PID registry found that 26.2% of PID patients developed autoimmune or inflammatory complications over their lifetime [5]. This increased risk of developing autoimmune/inflammatory complications was also present regardless of the type of PID, but patients with common variable immunodeficiency (CVID) and T cell deficient PIDs were most commonly affected [5]. CVID is the most commonly diagnosed PID after selective IgA deficiency, and autoimmune manifestations are estimated to occur in 27–48% of patients [6–8].

Fewer studies have examined the prevalence of PID in patients with autoimmune diagnoses. Barsalou *et al.* reviewed the records for patients referred to a single rheumatology clinic in Canada over 18 months. Patients diagnosed with autoimmune conditions aside from juvenile idiopathic arthritis (JIA) were included. Fifteen percent of their patients fulfilled criteria for a PID, and another 15% had abnormalities on their immune evaluation [9].

The Multiple Autoimmunity and Immunodeficiency (MAID) clinic at Boston Children's Hospital (BCH) was founded by Drs. Notarangelo and Hazen in 2009 with a focus on caring for patients with polyautoimmunity and/or co-existing AI and PID. The clinic was launched to facilitate better collaboration between immunologists and rheumatologists caring for affected patients and also to promote the use of cutting-edge molecular diagnostics. In addition to better characterizing each patient's disease, it was thought that a thorough immune evaluation would be helpful in choosing a targeted treatment plan. Since its inception, the MAID clinic has seen 144 unique patients and identified 28 patients with monogenic immune dysregulatory syndromes. The majority of these patients were referred from rheumatology, immunology, hematology, and gastroenterology clinics.

2.0 Material and Methods

2.1 Study Setting and Ethical Approval

This retrospective cohort study was conducted in the Immunology Division at BCH. Referrals to the MAID clinic are encouraged for patients with early-onset, atypical, or multiple autoimmunity. Patients are referred to the MAID clinic predominantly by physicians locally at BCH, but some are also referred at the national level. The physicians in the MAID clinic perform educational outreach to other pediatric specialties at BCH through emails, presentations at clinical conferences, and personal contacts. In clinic, patients are seen by both a rheumatologist and immunologist who work collaboratively to implement the diagnostic evaluation and therapeutic plan. IRB approved protocols are in place to allow whole exome sequencing and functional immune testing on a research basis in select

patients. The study was approved by the Institutional Review Board at BCH (Protocols P00024973, P00005723).

2.2 Data Source

A chart review for patients seen by a MAID clinic attending with 1 visits between March 2009 and May 2018 was conducted. Medical records were reviewed by a MAID physician for comprehensive information including: demographics, AI manifestations, infections, malignancies, laboratory testing, treatment history, and genetic findings. Data was entered into a RedCap database (Vanderbilt University, 2018) by a MAID physician.

2.3 Variable Definitions

Evan's Syndrome was defined as cytopenias in at least 2 different cell lines. Lymphoproliferation was characterized by the presence of hepatomegaly and/or splenomegaly, peripheral lymphadenopathy, or both. Atypical viral infections were defined as recurrent varicella infections or severe CMV, EBV, or other viral infections that required hospitalization and/or antiviral treatment. Laboratory values were standardized to units reported by the central BCH laboratory, which are normalized for age. Identified genetic diagnoses were confirmed by CLIA certified laboratories.

2.4 Statistical Analysis

To describe the population, values were expressed as frequency (number and percentage) and median $\pm$ IQR, as appropriate. Each of the autoimmune manifestation, infection, and immune system abnormality categories identified were considered independent dichotomous variables. Differences between subjects with an identified genetic diagnosis and those without were assessed with Fisher's exact probability tests using a significance threshold of $p=0.05$. Odds ratios (OR) and 95% confidence intervals (95% CI) are reported for significant findings. All data manipulation and analysis were conducted using SAS software package, version 9.4 (SAS Institute, Cary, NC).

3.0 Results

3.1 Patient Characteristics

From its inception in 2009 to 2018, 144 patients were seen in the MAID clinic (Table 1). Slightly more females (52%) were followed than males. Most individuals first presented to the MAID clinic before the second decade of life (average age 12 years, range 0.1–62 years) (Fig 1). A majority of the patients were Caucasian, reflecting the demographics of the local population in the Boston area. BCH is a major referral center for several countries in the Middle East, and 4% of patients seen in the MAID clinic were from this region. Since many PIDs are inherited in an autosomal recessive pattern, a high rate of consanguinity in a population increases the frequency and in some cases the severity of these disorders [10]. In this cohort, 4 patients were noted to be from consanguineous marriages.

3.2 Autoimmunity

As expected based on the mission of the MAID clinic, all patients had at least one autoimmune manifestation (Fig 2a). Cytopenias (defined by reduced platelet, absolute neutrophil, and absolute lymphocyte counts on a complete blood cell count (CBC)) were most frequently reported, and 45 patients (31%) presented with at least one affected cell lineage (Fig 2b). Thrombocytopenia (n=34) and anemia (n=29) were most commonly observed. Evan's Syndrome was documented in 29 patients. Often, the cytopenias were severe, and 18 patients required transfusions of either platelets or packed red blood cells. Lymphoproliferation was the second most common autoimmune manifestation and was noted in 33 patients (23%) (Fig 2c). All 33 patients with lymphoproliferation had peripheral lymphadenopathy, and 19 patients also had hepatomegaly and/or splenomegaly. Interestingly, a majority of patients with cytopenias did not have concurrent lymphoproliferation (18 patients with cytopenias also had lymphoproliferation). GI involvement was reported in close to a quarter (n=33) of MAID patients (Fig 2d). Autoimmune enteropathy (n=9), ulcerative colitis (n=8), Crohn's disease (n=4), and protein-losing enteropathy (n=2) were the most common forms of intestinal disease observed. Other prevalent autoimmune diseases included hypothyroidism, central nervous system (CNS) involvement, hepatitis, arthritis, and lung disease (Fig 2a). Autoantibodies were documented in close to 62% of patients (average 1 autoantibody, range 0–4) with anti-nuclear antibodies (ANA) and anti-thyroid antibodies being most common (Fig 2e).

3.3 Infections

The majority of patients (n=94, 65%) self-reported a history of atypical or recurrent infections, although some patients (47/144 or 33% of the cohort) developed these infections while on immunosuppression to treat autoimmune disease (Fig 3a, 4). Sinopulmonary infections were by far the most common infectious manifestation of patients seen in the MAID clinic (n=73, 51%). Of these 73 patients, 40 had recurrent otitis media, 31 reported more than one pneumonia, and 28 had recurrent sinusitis (Fig 3b). Mucocutaneous infections were ranked as the second most frequent type of infection in this cohort (Fig 3c). Twenty-four patients (17%) reported mucocutaneous infections, including 16 with recurrent bacterial soft tissue infections, 10 with mucocutaneous viral infections such as molluscum or herpes simplex virus (HSV), and 9 with fungal infections affecting the skin, nails, or mouth. Atypical infections included uveitis (n=1), pericarditis (n=1), CNS abscess (n=1), meningitis (n=4), osteomyelitis (n=1), septic arthritis (n=1), sepsis (n=11), and candida esophagitis (n=1) (Fig 3a).

3.4 Atopy

Asthma and allergic diseases were reported less frequently in the MAID clinic cohort than infections and autoimmunity, which may represent referral bias. Fifty patients (35%) had at least one atopic manifestation. Twenty-six patients (18%) reported allergies to either medications (n=7), foods (n=13), or environmental allergens (n=11). One patient had idiopathic anaphylaxis. After allergies, asthma was the second most frequent atopic disease, affecting 23 patients (16%). Atopic dermatitis was observed in 12% of patients.

3.5 Immune Evaluation

Most patients seen in the MAID clinic underwent an immunologic evaluation to determine if an underlying immunodeficiency was driving immune dysregulation and autoimmunity. Immune system abnormalities were frequently observed in this patient population. While only 10% of patients were found to have absolute lymphopenia on a CBC, 45% (65 patients) had low absolute numbers of T, B, and/or NK cells (Fig 5a), making this the most common immunologic abnormality in our cohort. Interestingly, low switched or unswitched memory B cells were the second most commonly noted immunologic abnormality (43 patients, 30%) (Fig 5a). By contrast, increased percentages of memory CD4 and CD8 T cells were frequently noted (32 patients, 22%). To exclude infection as the cause of the increased memory CD4 and CD8 T cells, 22 of these 32 patients underwent testing for chronic viral infections such as CMV, EBV, and HIV. Only 3 patients were found to have an active infection (2 with positive EBV PCR tests in the blood and 1 with norovirus detected in the stool); therefore, the elevated memory T cell frequencies were likely secondary to immune activation from autoimmunity (Fig 5a). Many autoimmune conditions present with hypergammaglobulinemia; yet, patients seen in the MAID clinic were often found to have low immunoglobulins: 28 patients (19%) had low IgA, 26 (18%) had low IgG, and 12 (8%) had low IgM levels (Fig 5b). Two patients met criteria for CVID. Other observed abnormalities included 17 patients (12%) with elevated double negative T cells, 13 patients (9%) with high IgE levels, 12 patients (8%) with increased gamma delta T cells, 8 patients (6%) with increased CD21^{lo} B cells, and 6 patients (4%) with low regulatory T cells (Fig 5c).

One-third of patients in this cohort were on at least one immunosuppressive medication at the time of the immunologic evaluation, which may have altered testing results in a subpopulation of patients (Fig 4). Accordingly, the 97 individuals who were not taking immunosuppressive medications were analyzed separately. When compared to the entire MAID clinic cohort, patients off immunosuppression were found to have comparable immunologic parameters (Fig S1). For example, 38% of these patients had low numbers of absolute T, B, or NK cells (while 45% of the entire cohort was noted to have this finding).

3.6 Genetic Diagnoses in the MAID Clinic

Close to 20% (n=27) of patients in the MAID clinic had a genetic mutation identified as the cause of their presentation (Table S1). Of these 27 patients, 8 came to the MAID clinic for management of a known molecular diagnosis, and 1 patient was found to have a genetic diagnosis after transfer from the MAID clinic to the National Institutes of Health. The remaining 18 patients had a causative genetic mutation identified during the diagnostic evaluation in the MAID clinic. In keeping with the prominent autoimmunity in this cohort, pathogenic variants involving the regulatory T (Treg) pathway were the most commonly identified immune defect (*FOXP3*, 2 patients; *CTLA4*, 4 patients). Gain of function mutations in *STAT1* (n=3) and *STAT3* (n=1), which are known to cause early-onset autoimmunity, were also found. Three patients with features of hypomorphic hemophagocytic lymphohistiocytosis (HLH) were found to have mutations in known familial HLH (FHL) genes. One patient had homozygous mutations in *UNC13D*. The other two individuals had low NK cell function and pathogenic mutations that were heterozygous

in the perforin gene, consistent with other reports of HLH in carriers of FHL genes [11–13]. Monogenic autoinflammatory disorders were identified in 2 patients (*NLRP12*, 1 patient; *NLRP4*, 1 patient). One young man was found to have compound heterozygous mutations in *AIRE*. Three individuals had heterozygous variants of unknown significance in two immune-related genes, which were thought to be contributing to the patient's phenotype: 1) heterozygous *PRF1* and *FAS* mutations, 2) heterozygous *ZAP70* and *CD274* (PDL1) mutations, and 3) heterozygous *CARD9* and *TLR3* mutations.

We endeavored to determine if patients with a genetic diagnosis displayed different clinical features compared to patients without a known molecular diagnosis. While autoimmune colitis ($p=0.07$) and recurrent infections (sinopulmonary, $p=0.09$) were observed at much higher frequencies in patients with a known genetic defect, this did not reach statistical significance. There was also no statistical difference in age at presentation to the MAID clinic, number of autoimmune manifestations, number or type of autoantibodies, or prevalence of atopy. Patients with an identified genetic mutation were significantly more likely to have low absolute number of T, B, or NK cells (OR=0.4, 95% CI=0.2–0.9, $p=0.05$) and IgA (OR=4.0, 95% CI=1.6–10.2, $p=0.005$). Interestingly, genetic diagnoses were made at an increasing rate over time. In the 2009, only 7% of new patients in the MAID clinic were given a molecular diagnosis while in 2018 this had increased to 17%.

3.7 Identification of Novel Monogenic Immune Dysregulatory Syndromes

Patients followed in the MAID clinic are enrolled in research-based protocols that include whole exome sequencing (WES) paired with immune profiling and functional assays to validate variants of unknown significance (VUS) found through gene sequencing. To date, 2 new inherited disorders have been discovered in MAID clinic patients. As described by Boisson *et al*, biallelic mutations in *HOIP* were identified by WES and then Sanger sequencing in a young woman who presented with combined immunodeficiency (CID), autoinflammatory features, amylopectinosis, and lymphangiectasia [14]. The *HOIP* gene encodes for a protein in the linear ubiquitination chain assembly complex (LUBAC), which ubiquitinates targets such as NF-kappa-B essential modulator (NEMO). The resulting CID is due to defects in NF-kappa B signaling while the autoinflammatory features of this disease are secondary to hyper-responsiveness of monocytes to IL-1 β . The second gene defect was identified in a 4-year-old girl who presented to the MAID clinic with CID, autoimmune enteropathy, juvenile idiopathic arthritis (JIA), vasculitis, developmental delay, strokes, dysmorphic features, and strabismus. WES revealed pathogenic, homozygous variants in the *MAN2B2* gene resulting in abnormal glycosylation and lysosomal processing consistent with a congenital disorder of glycosylation (CGD)[15].

3.8 Clinical Course

On average, patients were seen at least 3 times in the MAID clinic (range 1–26) from 2009 to 2018. Individuals with a genetic diagnosis returned to the MAID clinic more frequently (average 5 visits) than patients without a known genetic mutation. Consultation in the MAID clinic resulted in treatment initiation or changes in 42% of patients. The most commonly started medications included non-biologic disease-modifying antirheumatic drugs (DMARDs) ($n=16$), intravenous immunoglobulin (IVIG) ($n=13$), biologic DMARDs ($n=7$),

glucocorticoids (n=6), and prophylactic antibiotics (n=3) (Fig 6). Of patients for whom a genetic diagnosis was made in the MAID clinic, 48% had a change in management as a direct result of the new diagnosis, including 3 patients who were referred to the hematopoietic stem cell transplant team (Table S1).

4.0 Discussion

As our understanding of the genetic basis of immune dysregulatory syndromes advances, our ability to recognize and manage these potentially dangerous conditions has also improved. The experience in the MAID clinic over the last decade highlights the importance of a multidisciplinary immunologically-minded approach to children with immune dysregulation. By studying this cohort of patients, we were able to characterize the features of pediatric-onset immune dysregulatory syndromes as well as the monogenic defects that drive these disorders.

Several studies have documented a high prevalence of autoimmunity in patients with PIDs, but there is sparse data on the rates of immune dysfunction in individuals who primarily present with autoimmune/inflammatory conditions [4,5]. Since the MAID clinic is a referral center for pediatric patients with early-onset and/or polyautoimmunity, our patient population provides an opportunity to evaluate this question. Overall, our cohort was characterized by autoimmunity but also increased susceptibility to infection, alterations in normal immune functioning, and high rates of monogenic PIDs. In terms of autoimmunity, cytopenias are a hallmark feature of the polyautoimmune phenotype observed in our clinic, followed by lymphoproliferation and gastrointestinal disorders. Interestingly, immune-mediated cytopenias were found to be the most common autoimmune manifestation in patients who were first identified as having an immunodeficiency [4,5]. Indeed, Fischer and collaborators reported that 31% of patients followed in a national PID registry had autoimmune cytopenias [5]. In particular, children with PIDs demonstrated high rates of immune-mediated cytopenias with an 830-fold increased risk compared to children in the general population [5]. Hematologists have also noted that pediatric patients with chronic and/or multi-lineage cytopenias have high rates of PIDs and lymphoproliferative syndromes [16]. Our results coupled with these previous reports confirm that refractory and/or severe cytopenias in a pediatric patient should trigger an immunologic evaluation. Similarly, gastrointestinal diseases are common in our population and have been reported in association with multiple PIDs [17–19]. There is a well-established enrichment of monogenic immune defects in children with very early-onset inflammatory bowel disease [18,19]. In total, the high prevalence of autoimmune cytopenias, lymphoproliferation, and gastrointestinal involvement observed in our patients with inflammatory conditions mirrors findings of individuals with monogenic PIDs. This strongly suggests that children with early-onset and/or multiple autoimmunity have a high rate of underlying immune dysfunction.

The connection between polyautoimmunity and immunodeficiency in our patient cohort is highlighted by the high rates of recurrent infections. Sixty-five percent of patients self-reported a history of problematic infections, most notably sinopulmonary infections. While some of these infections may be attributed to immunosuppressive medications, many

patients reported recurrent infections before initiation of such treatments. Furthermore, a large proportion of patients were found to have low absolute numbers of T, B, or NK cells (45%), a low proportion of memory B cells (30%), and low immunoglobulins (31%). These immunologic abnormalities were noted in the face of systemic inflammation when patients often display increased frequencies of memory lymphocytes and hypergammaglobulinemia [20]. In addition, patients with a monogenic cause of autoimmunity were statistically more likely to have low T, B, or NK cells and IgA levels, highlighting the importance of screening immune laboratory testing in these patients. If abnormal, a further immunologic evaluation should be undertaken to identify a potential genetic cause of the presentation.

Atopic diseases were noted less frequently in patients cared for in the MAID clinic than autoimmunity and susceptibility to infection. Although atopy may figure into a larger scheme of immune dysregulation, its under-representation in our patient population likely reflects referral bias. The MAID clinic is considered a referral center for patients with autoimmunity. In addition, allergists and immunologists, who are well equipped to care for patients with atopy, are likely less apt to refer patients for a multidisciplinary evaluation.

Genetic causes of immune dysregulation were found in 27 patients (19%). Historically, rheumatologic conditions were thought to be driven by polygenic susceptibility to disease coupled with environmental triggers. Yet, increasingly, monogenic causes of rheumatic diseases have been identified in patients with conditions such as systemic lupus erythematosus and autoinflammatory diseases suggesting that single gene defects may play a more important role in polymorphous autoimmune disease than previously understood [21–23]. In a prior report of non-JIA patients presenting to a general pediatric rheumatology clinic, 15% were found to meet criteria for a PID such as CVID or complement deficiency, although these patients were not evaluated for gene defects [9]. The rates of immune abnormalities and molecular diagnoses were higher in our patient population, likely in part because these patients were preselected to have severe autoimmunity based solely on referral to the MAID clinic. In addition, our systematic approach to the diagnostic evaluation of patients, which includes obtaining an immunologic evaluation and genetic sequencing on a vast majority of patients, also contributed to the high diagnostic yield. Two novel genetic conditions were identified in this population of only 144 individuals, further highlighting the enrichment of monogenic defects in the pediatric population with early-onset, atypical, or multiple autoimmunity.

The genetic disorders recognized in our cohort of patients can be predominantly classified as immune dysregulatory syndromes, which have features of both immunodeficiency and autoimmunity. Several patients had mutations in genes (*FOXP3* and *CTLA4*) important for Treg cell development or function. IPEX, which is caused by hemizygous mutations in *FOXP3*, was originally thought to present exclusively within the first months of life with a classic triad of enteropathy, endocrinopathy and skin disease [24,25]. However, an estimated 10% of patients will manifest their first symptoms outside of the neonatal period, usually with a more varied phenotype as observed in our cohort [26]. Pathogenic mutations in co-stimulatory molecule *CTLA4* produce a phenotype with shared attributes with *FOXP3* deficiency. In a recently described cohort of 133 patients with *CTLA4* haploinsufficiency, hypogammaglobulinemia and recurrent respiratory tract infections were observed in more

than half of patients, while lymphoproliferation, cytopenias, and gastrointestinal involvement were the most common autoimmune features [27]. Our MAID cohort of CTLA4 haploinsufficient patients had a similar broad spectrum of presenting phenotypes. Gain of function (GOF) mutations in *STAT1* and *STAT3* were also frequent in our patients and are known to be associated with immune dysregulation. About a third of *STAT1* GOF patients manifest inflammatory features, and patients with *STAT3* GOF mutations display prominent lymphoproliferation and early-onset autoimmunity [28,29].

None of our patients had severe combined immunodeficiencies (SCID), possibly because affected individuals often present with increased susceptibility to infections and are more likely to be referred to immunology. CVID is commonly associated with autoimmunity; yet, none of our patients were found to have mutations in genes known to cause this disease. Further, only 2 patients met clinical criteria for CVID. This observation may be explained by our pediatric referral base and the inability to diagnose CVID before 4 years of age. In addition, autoimmunity tends to present later in B-cell PIDs than T-cell and innate driven immune defects and may not yet be observed in the age group followed in the MAID clinic [5].

Over time, our “hit rate” for genetic diagnoses has improved. This is in part explained by improvements in technology that have reduced barriers to genetic testing, including the advent of high throughput sequencing that has dramatically reduced the costs of sequencing panels of genes or performing WES [30]. While gene sequencing was initially done on a research basis for most of our MAID clinic patients, the use of CLIA certified gene panels and WES has increased over the last 1–2 years. In addition, our ability to identify gene defects has been greatly augmented by the exponential increase in known monogenic PIDs. As new syndromes are identified, our ability to recognize certain patterns and fit them into known categories has improved our yield.

Patients with a genetic diagnosis in the MAID clinic were followed on average longer than those without such a finding, although we were unable to determine the exact date the genetic diagnosis was made in many patients. This increased frequency of follow-up may be in part due to the severity of the underlying disease, types of treatments recommended for such patients, family “buy-in” to the clinic, and insurance eligibility of patients with a molecular diagnosis to seek treatments or services. In part, patients followed for longer periods of time may also be more likely to gain a molecular diagnosis as more PIDs are identified. This highlights the importance of long-term follow-up in this patient population. Learning from this experience, we now bank biosamples and have permission to retrospectively study biologic material from enrolled patients, such that we may revisit clinical and research testing of patient materials as new information becomes available. In addition, we strongly encourage our patients to return on at least a yearly basis for re-evaluation.

The co-management of patients by physicians with expertise in both autoimmunity and immunodeficiency is essential in this complex patient population. Immunologists are often more familiar with genetic causes of immune dysfunction, and their knowledge greatly contributed to the completeness of the immunologic evaluation and identification of genetic

mutations in this cohort of patients. Immunologic expertise also facilitated the selection of antimicrobial prophylaxis regimens and IVIG supplementation. These patients also need careful selection of immunomodulators to control their autoimmune disease, made more complicated by inherent risk for infection [3,31]. Rheumatologists excel at the management of complex inflammatory conditions and contributed to the high rates of therapeutic interventions with non-biologic and biologic DMARDs. Interestingly, treatments were initiated in a near equal proportion of patients with and without a genetic diagnosis, likely reflecting the comfort of rheumatologists and immunologists in treating patients with inflammatory conditions and recurrent infections regardless of the underlying molecular diagnosis. Immunosuppression in an immunocompromised host can be a challenge from an infectious standpoint. As we accrue further patient numbers and years of follow-up, we hope to evaluate the outcomes of the selected treatment regimens to determine efficacy and safety in this patient population.

There are limitations to our study that need to be noted. First, this study represents our initial report of patients with early-onset and polyautoimmunity and ongoing characterization of the patient population under study is likely to yield additional relevant information. The results reported here must also be interpreted in the context of a retrospective medical record review. It is possible that relevant clinical data were not fully captured during the clinical encounter or recorded in the medical record. Several patients were lost to follow-up, limiting our ability to report on longitudinal outcomes. In addition, some information such as a previous history of recurrent infections was collected based on patient self-reporting, which may be susceptible to response bias. Further, close to 1/3 of the studied patients was on an immunosuppressive medication that may have increased the prevalence of infections and immune evaluation abnormalities in this cohort. In particular, glucocorticoids are known to cause lymphopenia and 30 individuals (20% of patients) were on this medication at the time of testing. By contrast, 8 individuals were treated with intravenous or subcutaneous Ig, which may have falsely elevated IgG levels in these patients. Fortunately, a majority of patients was not on such medications. In addition, measured immunologic parameters were similar in patients on and off immunosuppression. For these reasons, prospective studies of treatment naïve patients are needed to further and more accurately characterize this population. In addition, these results represent the experience at a single center and need to be replicated through multi-site collaborations.

5.0 Conclusions

Patients with early-onset inflammation and polyautoimmunity are characterized by a unique constellation of clinical features. These patients manifest certain forms of autoimmunity that are also common in individuals with PIDs, including cytopenias, lymphoproliferation, and GI disease. Immunologic dysfunction in the form of recurrent infections and an abnormal immunologic profile underscores the high rates of monogenic disease in this population. To improve outcomes, further research is needed to develop a diagnostic approach that will rapidly identify patients with gene defects. Therapeutic interventions aimed at controlling inflammation in the setting of immune dysregulation need to be studied rigorously for safety and efficacy. Until we better understand atypical autoimmunity, it is imperative that these

complex patients are managed collaboratively by a team of experts in both immunology and rheumatology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Age Distribution of Patients in the MAID Clinic.

The graph depicts the ages of patients at initial presentation to the MAID clinic. MAID, Multiple Autoimmunity and Immunodeficiency Clinic

Figure 2. Autoimmune Manifestations of Patients in the MAID Clinic.

A) The percentage of patients in the MAID clinic with each autoimmune manifestation is depicted in the graph. B) Forty-five patients had cytopenias, and the total number of patients with each affected cell line is depicted. C) Thirty-three patients had lymphoproliferation, and the number of patients with LAD and HSM is depicted. D) Thirty-three patients had GI involvement, and the number of patients with the most frequent types of GI manifestations is depicted. E) The percentage of patients in the MAID clinic with each autoantibody is depicted in the graph.

MAID, Multiple Autoimmunity and Immunodeficiency Clinic; GI, gastrointestinal; CNS, central nervous system; DM, diabetes mellitus; SLE, systemic lupus erythematosus; LAD,

lymphadenopathy; HSM, hepatosplenomegaly; AIE, autoimmune enteropathy; PLE, protein losing enteropathy; ANA, anti-nuclear antibodies; TPO, thyroid peroxidase antibodies; dsDNA, anti-double stranded DNA antibodies; ENA, extractable nuclear antigens; ANCA, anti-neutrophil cytoplasmic antibodies

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Figure 3. Infectious History of Patients in the MAID Clinic.

A) The percentage of patients in the MAID clinic with each type of infection is depicted in the graph. B) Seventy-three patients had recurrent sinopulmonary infections (self-reported by the patient), and the total number of patients with each type of sinopulmonary infections is depicted. C) Twenty-four patients had recurrent mucocutaneous infections (self-reported by the patient), and the type of pathogen that caused these infections is depicted. MAID, Multiple Autoimmunity and Immunodeficiency Clinic; GI, gastrointestinal; GU, genitourinary; CNS, central nervous system; RSV, respiratory syncytial virus

Figure 4. Immunomodulatory Medications at Initial MAID Clinic Evaluation.

The number of patients taking a given medication at the first MAID clinic visit is shown in the graph. Patients may be on more than one immunomodulatory medication simultaneously. MAID, Multiple Autoimmunity and Immunodeficiency Clinic; IVIG, intravenous immunoglobulin; SQIg, subcutaneous immunoglobulin; Aza, azathioprine; TNF, tumor necrosis factor; MMF, mycophenolate mofetil; HCQ, hydroxychloroquine; 6MP, 6-mercaptopurine; MTX, methotrexate; LEF, leflunomide; CsA, cyclosporine; ABT, abatacept

Figure 5. Immune Evaluation of Patients in MAID Clinic.

A) The percentage of patients in the MAID clinic with given immune system abnormality is depicted. Patients with low absolute numbers of B, T, and NK cells are included (124 of the 144 patients in the MAID cohort were screened for T/B/NK subsets). Patients with a low percentage of unswitched and/or switched B cells are included (97/144 patients screened). Patients with elevated CD4 and/or CD8 T cells are included (85/144 patients screened). B) The percentage of patients with the given low immunoglobulin is depicted (133/144 patients screened). C) The percentage of patients with the given immune system abnormality is depicted (42 patients were screened for DN T cells, 78 for IgE, 37 for γ T cells, 67 for CD21^{lo} B cells, and 51 for Treg cells). Normal values for all immune system parameters were determined based on age.

MAID, Multiple Autoimmunity and Immunodeficiency Clinic; DN double negative; Treg, regulatory T cells

Figure 6. Treatments Started in the MAID Clinic.

A) The number of patients in the MAID clinic who were started on the given treatment is depicted. B) Of the 16 patients started on non-biologic DMARDs, the proportion of patients started on each medication is depicted. C) Of the 7 patients started on biologic DMARDs, the proportion of patients started on each medication is depicted.

DMARDs; disease-modifying antirheumatic drug; IVIG, intravenous immunoglobulin; bio, biologic; TNF, tumor necrosis factor

Table 1.**Characteristics of Patients in the MAID Clinic**

Characteristic	
Female sex – No. (%)	75 (52.1)
Age (years) – median (IQR)	12 (5,16)
Race – No. (%)	
White	102 (70.8)
Black	7 (4.9)
Asian	4 (2.8)
American Indian	1 (0.7)
Other	10 (6.9)
Unknown	20 (13.9)
Ethnicity – No. (%)	
Hispanic/Latino	10 (6.9)
Non- Hispanic/Latino	113 (78.5)
Unknown	21 (14.6)

MAID, Multiple Autoimmunity and Immunodeficiency Clinic