Journal of Clinical and Cellular Immunology
ISSN: 2155-9899
OPEN ACCESS Freely available online
Mini Review

Puzzling Presentation of Inborn Errors of Immunity (IEIs) with Predominant Neuropsychiatric Symptoms-Experience in the Pediatric Allergy/Immunology Clinic

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ABSTRACT

Due to close interactions between the nervous system and the immune system, patients with Inborn Errors of Immunity (IEIs) can present clinical features of common neuropsychiatric and neurodevelopmental conditions. These include high anxiety, mood swing, developmental issues and dysautonomic symptoms, consistent with Postural Orthostatic Tachycardia Syndrome (POTS). These neuropsychiatric symptoms may be predominant clinical features in certain cases, making it further confusing for practicing physicians for diagnosing IEIs. This mini review focuses on the importance of these puzzling neuropsychiatric symptoms in patients with IEIs, by presenting clinical cases experienced in our clinic.

Key words: Inborn Errors of Immunity (IEIs); Neuroimmune network; Neuroinflammation; Dysautonomia

ABBREVIATIONS

AE: Autoimmune Encephalitis; Ag: Antigen; ASD: Autism Spectrum Disorder; COVID-19: Coronavirus Disease of 2019; FMF: Familial Mediterranean Fever; HD: High Dose; IEIs: Inborn Errors of Immunity; Ig: Immunoglobulin; IVIg: Intra Venous Immunoglobulin; JAK: Janus Kinase, KB: Kilo Base, LCR: Low Copy Repeats, OCD: Obsessive Compulsive Disorder, PANS: Pediatric Acute-onset Neuropsychiatric Syndrome, POTS: Postural Orthostatic Tachycardia Syndrome, SIBs: Self-Injurious Behaviors, SC: Sub Cutaneous

INTRODUCTION

The immune system closely interacts with the nervous system, which is often referred to as a neuroimmune network. Therefore, it is not surprising that many patients suffering from IEIs exhibit significant neuropsychiatric symptoms. These patients may be initially diagnosed with common neuropsychiatric conditions and/or developmental disorders prior to the diagnosis of IEIs. In that case, other features of IEIs may be overlooked that may cause delay in implementing gene-specific treatment measures appropriate for the identified IEI. This mini review addresses the importance of recognizing neuropsychiatric and developmental issues as clinical features of IEIs and what red flags can lead to diagnosis of the IEI, partly through presentation of representative IEI cases experienced in the pediatric allergy/immunology clinic at our institution.

IEIS ASSOCIATED WITH CHROMOSOMAL ABNORMALITIES AND CHROMOSOMAL REMODELING

22q11.2 microdeletion syndrome

One of the most common IEIs belonging to this category is 22q11.2 microdeletion syndrome or Di George syndrome (DGS), occurring approximately 1 in 3,000 to 6,000 [1]. This chromosomal region contains a cluster of low copy repeats (LCR) that regulate meiotic non-allelic homologous recombination between LCRs, rendering this region being uniquely susceptible to deletion/duplication. Typical DGS is reported to have microdeletion of 3.2 Kilo Base (KB) which encodes over 90 genes including T-Box transcription factor 1 (TBX1). TBX1 codes T box protein 1 that exerts a crucial role for morphogenesis of the 3rd and 4th brachial arches. In addition, genes encoded in this region include those important for mitochondrial metabolisms crucial for controlling oxidative stress and subsequent neuroinflammation. This region also encodes genes crucial for neuronal plasticity and morphogenesis. As a result, DGS patients frequently present with predominant neuropsychiatric symptoms and impaired stress responses, in addition to DGS triad (cardiac anomaly, immunodeficiency and hypoparathyroidism). For example, DGS patients are known to have a higher frequency of Autism spectrum disorder (ASD) and some patients may be diagnosed

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Received: 03-Jan-2025, Manuscript No. JCCI-25-36722; **Editor assigned:** 06-Jan-2025, PreQC No. JCCI-25-36722 (PQ); **Reviewed:** 21-Jan-2025, QC No. JCCI-25-36722; **Revised:** 28-Jan-2025, Manuscript No. JCCI-25-36722 (R); **Published:** 04-Feb-2025, DOI:10.35248/2155-9899.24.16.747

Citation: Jyonouchi H (2025). Puzzling Presentation of Inborn Errors of Immunity (IEIs) With Predominant Neuropsychiatric Symptoms-Experience in the Pediatric Allergy/Immunology Clinic. J Clin Cell Immunol. 16:747.

with ASD first. Such a representative case experienced in our clinic is described below [2-6].

Case 1: This case was diagnosed with severely affected ASD (level III) around 2 years of age and remained non-verbal. The individual was also noted to have recurrent respiratory infections, which were difficult to clear using first-line antibiotics, requiring the use of multiple antibiotics. Moreover, respiratory infections caused worsening anxiety symptoms, including Obsessive compulsive disorders (OCD) and Self-Injurious Behaviors (SIBs). These symptoms were difficult to control with neurotropic medications. Initially, the individual was evaluated for pediatric acute-onset neuropsychiatric syndrome (PANS) in the neurology clinic. Microarray analysis was performed due to the ASD diagnosis, revealing classical 22q11.2 deletions. Subsequently, the individual was referred to the allergy/immunology clinic, where further immune workup revealed impaired antibody production against encapsulated organisms along with borderline low immunoglobulins (IgG and IgA). However, the numbers of T cell subsets were within normal range. Initially, a few doses of intra venous immunoglobulin (IVIg) were required to stabilize the recurrent infections. Prophylactic antibiotics have been used for over 10 years. However, after entering puberty, tonic convulsive seizures developed, which became under control with the use of anti-seizure medications (clobazam and oxcarbazepine). After the recurrent respiratory infections were better controlled, behavioral symptoms became substantially easier to manage. Retrospectively, neuropsychiatric symptoms were further aggravated by pain and discomfort associated with recurrent infections. Improved infectious control may have also reduced mitochondrial stress, as the individual is likely more susceptible to oxidative stress due to DGS, as described above.

Kabuki Syndrome (KS): KS is first described as a complex disorder affecting both the immune and nervous systems. Patients typically present with predominant neurodevelopmental issues, but also with recurrent respiratory infection with overlapping features of DGS. KS is reported to occur approximately at 1 in 32,000. However, its real frequency is likely higher, given the fact that several children's hospital in the United States have already developed clinics specialized in treating KS patients. Its pathogenesis is implicated in impaired chromatin remodeling due to defects of enzymatic modification of histone caused by pathogenic variants of lysine methyl transferase 2D (KMT2D) (75%) and lysine demethylase 6A KDM6A (5%). Most KS patients reveal impaired antibody production against encapsulated organisms and often require IVIg treatment by 4-5 years of age. However, their clinical manifestations vary considerably. Undertreatment of immunodeficiency components may further worsen neuropsychiatric symptoms in KS patients. We experienced such a case, as follows [7-10].

Case 2: A 14-year-old boy initially presented to the clinic for management of the immunological components of KS. Born with a left dysplastic multicystic kidney, significant developmental delay became apparent during infancy. By 2 years of age, the individual was diagnosed with ASD (level III) and remained non-verbal. Clinical seizures (tonic convulsive) developed at 13 years of age. Neuropsychiatric symptoms were often aggravated by recurrent respiratory infections, which the individual had suffered from frequently since early infancy. Due to facial dysmorphism, the parents raised concerns about the possibility of KS, and subsequent genetic analysis identified the pathogenic variant of KMT2D, confirming the diagnosis of KS. High dose (HD) IVIg was trialed for seizure control, but it caused severe adverse reactions resembling aseptic meningitis. After referral to the clinic, immune workup revealed typical immune abnormalities expected in KS patients, including slightly low Ig levels (low IgA), low antibody titers against encapsulated organisms, low percentage of cytotoxic T cells, and higher memory T-helper cells (70%), indicating oligoclonal expansion of T cells. Due to frequent infections and unresponsiveness to prophylactic antibiotics, the individual was started on supplemental Ig through weekly subcutaneous immunoglobulin (SCIg) infusions. The subcutaneous route was chosen because of the individual's kidney condition (the left kidney is non-functional). The SCIg infusion was well tolerated without adverse reactions, resulting in much better control of recurrent infections and seizures: Microbial infections were a major trigger for the seizures. Better control of microbial infections led to an improvement in behavioral symptoms. Unfortunately, the individual suffered from severe COVID-19 and resultant long COVID, which was dominated by severe fatigue and chronic respiratory symptoms, continuing to require O2 supplementation through a nasal cannula. This case illustrates the importance of proper management of immunodeficiency associated with KS. In this case, it was deemed best not to attempt HD IVIg due to the high risk of impairing renal functions in the presence of a non-functional left kidney, as well as the risk of severe adverse reactions given the expected microbial load in immunocompromised patients.

Antibody deficiency syndrome

Inadequate production of antibodies against pathogens, i.e., antibody deficiency, is the most common clinical manifestation of IEIs and well known to the physicians who manage patients with IEIs. However, these patients can also present with predominant neuropsychiatric symptoms affected by underlying genetic mutations. Such cases are presented below.

Common Variable Immuno Deficiency (CVID): CVID is the most common category of antibody deficiency syndrome occurring 1 in 20,000. The CVID diagnosis is made in the presence of low IgG with low IgA or IgM, along with proven defects of impaired responses to specific antigens. CVID patients are characterized by frequent respiratory infection which is usually successfully controlled by antibody replacement therapy with the use of IV or SC Ig. However, pathogenesis of CVID is heterogenous and many CVID patients manifest autoimmune, auto inflammatory and lymphoproliferative conditions associated with dysregulated activation of the immune system. Pathogenic variants of several genes are now identified to cause CVID with autoimmune and auto inflammatory conditions, including nuclear factor kappa B subunit 1 (*NFKB1*) and nuclear factor kappa B subunit 2 (*NFKB2*). Autosomal dominant, loss of function (LOF) variants of *NFKB1* and *NFKB2* are associated with various autoimmune and autoinflammatory complications and are often manifested in more than one member of the family. These two genes encode transcription factors that are essential to generate the mature forms of DNA binding NFκB1 and NFκB2 for normal signaling of Nuclear Factor-Kappa B (NF-κB) pathway. *NFKB1* deficiency may be manifested as typical CVID, but *NFKB2* mutation may be manifested with early-onset CVID, with atypical clinical features including neuropsychiatric manifestations. Such representative cares are shown below [11-14].

Cases 3 and 4: A six-year-old female presented to the clinic with acute onset of PANS-like neuropsychiatric symptoms following viral gastroenteritis, characterized by severe separation anxiety with OCD and later onset of facial tics. The throat swab at that time

was negative for Streptococcal antigen. By the time of presentation to the clinic, the symptoms had persisted for over a year and had not responded to antibiosis. The PANS-like behavioral symptoms flared up following viral syndromes, such as the flu. Immune workup revealed an IgG level around 500, low normal IgM and IgA levels, and a lack of response to PPV23. Further workup revealed a pathogenic variant of *NFKB2*, which was inherited from the father, who is known to suffer from chronic rhinosinusitis but with much less severe clinical manifestations. Supplemental IVIg infusion was started, and neuropsychiatric symptoms and recurrent viral syndromes gradually subsided over 6-8 months.

A brother of the six-year-old female (Case 3) presented to the clinic after the onset of PANS-like neuropsychiatric symptoms, predominantly high anxiety and OCD, at 14 years of age, following the sister's diagnosis of CVID. The neuropsychiatric symptoms were significant enough to require a two-week psychiatric admission. Immune workup by the neurologist revealed a low IgG level of 485, leading to a referral to the immunology service. The immune workup in the clinic revealed results similar to those of the sister (Case 3), and supplemental IVIg infusion was started. The brother responded well to supplemental IVIg, and neuropsychiatric symptoms resolved over 8-12 months.

The signaling of NF-ƙB pathway is closely associated with the phoshatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin pathway (PI-3K/Akt/mTOR pathway), affecting the neuroimmune network [14,15]. It is also reported that patients with *NFKB2* deficiency are reported to develop autoantibodies against type 1 interferons, which may make them more vulnerable to viral syndrome. Treatment resistant recurrent infection indicates the importance of screening for antibody deficiency syndrome and not be distracted by the predominant neuropsychiatric symptoms which may be greatly aggravated by infection induced immune action, as in the presented cases [16].

Auto inflammatory syndrome

In the field of IEIs, the area of monogenic auto inflammatory syndrome is rapidly expanding in the past two decades. Auto inflammatory syndrome is generally associated with impaired or dysregulated signaling of innate immune cells that serve as the 1st line immune defense. In general, the functions of T and B cells, major cells that execute adaptive immunity, are not affected. However, persistent chronic inflammation may affect adaptive immune responses indirectly. Since innate immune responses are closely associated with the neuroimmune network, these patients suffering from auto inflammatory syndromes often present with predominant neuropsychiatric symptoms. This may be particularly true in patients with interferonopathy and those with activation of inflammasome. We present representative such cases experienced in our clinic.

Interferonopathies: Type 1 IFNs are produced by many lineage cells and these cells exert the 1st line immune defense against viral pathogens [17]. Excessive production of type 1 IFNs or dysregulated signaling of type 1 IFN pathway can cause auto inflammatory syndrome, referred to as type 1 interferonopathies. Many of their clinical features are associated with neuroinflammation affecting many neuronal cells. Representative cases of 2 siblings of COPA syndrome, one of the interferonopathies, experienced in our clinic are briefly described below [18-21].

Case 5 and 6: Case 5 started to suffer from recurrent respiratory infections after 5 years of age, following an H1N1 influenza infection. The clinical courses were characterized by progressively worsening fatigue (mental and exertion intolerance), chronic encephalopathy (anxiety/OCD, brain fog, etc.), and myelopathy (chronic musculoskeletal pain and progressive loss of muscle mass), along with recurrent respiratory infections. Extensive immune workup revealed variants of COPA in the individual and a younger sibling. However, significant respiratory symptoms did not develop, and the positive autoantibodies typically reported in patients with COPA syndrome were not found. Treatment included various immunomodulating agents aimed at the type 1 IFN pathways. The individual responded best to the JAK1 inhibitor (Upadacitinib), which partially blocks the type 1 IFN signaling pathway, along with IVIg, which helped control recurrent infections. The lack of significant respiratory symptoms may be associated with the initiation of immunomodulating agents during the early years of life. [22].

Case 6, a 2-year-younger brother of Case 5, also began to develop profound fatigue, similar neuropsychiatric symptoms (anxiety, OCD, brain fog, etc.), and joint and muscle aches around 8 years of age, following a viral syndrome. Unlike Case 5, the individual was found to have low IgG1 and a lack of response to Pneumococcal Vaccines (PPV23). IVIg treatment was started around 11 years of age. IVIg helped control recurrent respiratory infections and neuropsychiatric symptoms. However, after suffering from COVID-19, the general condition progressively worsened, requiring the addition of other immunomodulating agents. As expected, the individual showed the best response to upadacitinib, a JAK1 inhibitor, as was observed in the brother. Interestingly, the individual was diagnosed with high-functioning ASD, with declining cognitive functioning and worsening behavioral symptoms around 10 years of age.

These 2 cases reveal profound neuropsychiatric symptoms and complex clinical manifestations encountered in patients with type 1 interferopathies.

Syndrome affecting inflammasome activation: Among the IEIs affecting inflammasome activation, Familial Mediterranean Fever (FMF) is the most well established and one of the most common auto inflammatory syndromes. In the endemic areas, pathogenic variants of Mediterranean Fever (*MEFV*) occurs 1 in 500 to 1,000. As opposed to classical presentations of periodic fever syndrome, FMF patients present highly variable clinical manifestations affected by genotypes and epigenetic regulations, often presented with concurrent autoimmune conditions [23-26].

Case 7: Case 7 was initially presented in the clinic for administration of HD IVIg as part of the treatment for autoimmune encephalitis (AE), which was attributed to a paraneoplastic syndrome caused by ovarian teratoma. However, resection of the ovarian teratoma did not resolve the AE symptoms, and repeated studies failed to detect any autoantibodies associated with AE or paraneoplastic syndrome. The individual only revealed temporary responses to HD IVIg, rituximab, and tocilizumab. The puzzling clinical features included significant joint and muscle aches that markedly aggravated the neuropsychiatric symptoms. Further workup revealed heterozygosity for a pathogenic variant of the *MEFV* gene. Daily colchicine (0.6 mg three times a day) and anakinra SQ injection were started. Anakinra was chosen as an IL-1ß blocker, with the hope that its better access to the brain by passing the intact blood brain barrier (BBB) would help improve the AE symptoms. Colchicine and anakinra helped control the AE symptoms better, although fluctuating neuropsychiatric symptoms continued, typically triggered by microbial infections. The individual was also treated with SQIg due to secondary hypogammaglobulinemia

caused by rituximab treatment. A bilateral oophorectomy was then performed due to the presence of another ovarian teratoma, which may have attenuated the AE symptoms. Most recently, a flare-up of AE symptoms occurred, apparently following a viral syndrome, which was controlled with the addition of a JAK1 inhibitor (Upadacitinib). [27].

CONCLUSION

In summary, we discussed the atypical clinical presentation of IEIs where neuropsychiatric symptoms predominate, often delaying referral to immunology services. The presented case highlights that treating the underlying IEIs can help manage these neuropsychiatric symptoms effectively. Recognizing the broad spectrum of neuropsychiatric symptoms in IEI patients is essential for timely diagnosis and early intervention. Early identification and targeted treatment of the underlying immune disorder can significantly improve clinical outcomes. Raising awareness among clinicians about the potential neuropsychiatric manifestations of IEIs can lead to more accurate and prompt diagnoses, ensuring better patient care and management.

ACKNOWLEDGEMENT

This work is partly supported by funding from the Jonty Foundation, St. Paul, MN, the Brain Foundation, Pleasanton, CA and the O'Sullivan Foundation, Princeton, NJ. These cases presented in this review were all involved in the IRB approved clinical studies and the signed consent forms were obtained at that time. The author is thankful for Dr. Lisa Huguenin for critically review this mini review.

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