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Case Report

A Rare Cause of Multisystem Vasculopathy in Children: Expanding Clinical Spectrum of DOCK8 Gene Mutation, A Case Report

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Abstract

A twelve-year-old girl with history of recurrent infections, severe eczema and failure to thrive with a diagnosis of hyper IgE syndrome presented to our hospital with recent onset of right hemiparesis. She had history of similar focal neurological deficits two years back. The magnetic resonance imaging (MRI) of brain showed subacute hemorrhagic infarct with atrophic changes suggestive of old infarcts. The Magnetic resonance angiography revealed left middle cerebral artery occlusion. Incidentally, CT abdomen with contrast showed sclerosing cholangitis. Her genetic work up showed DOCK 8 gene (Dedicator of cytokinesis 8) mutation. Hyper IgE (immunoglobulin E) syndrome with DOK8 mutation (an autosomal recessive form of Hyper Ig E syndrome), can have multisystem involvement with predominant vascular manifestations. There has been similar cases described in literature, although very rare. We report this case to exemplify the rarer presentation of a complex disease. This underlines the needs for accurate genetic diagnosis, which helps in early recognition of the associated complications.

Keywords: *DOCK8 Mutation; Vasculitis; Sclerosing Cholangitis*

Introduction

Hyper immunoglobulin E syndrome (HIES) is a rare primary immunodeficiency characterized by recurrent staphylococcal infections of skin and lungs with elevated levels of IgE, found mainly in consanguineous families. Autosomal recessive, autosomal dominant and the sporadic forms of hyper immunoglobulin E syndrome (HIES) have been identified recently. Increased recognition of these primary immunodeficiency disorders (PIDs) through advancements in genetic screening and diagnosis of these disorders has revealed surprisingly broad clinical spectra with which they may present [1].

The autosomal-dominant (AD) form of the hyperimmunoglobulin E syndrome (HIES) has been described as a multisystem disorder including immune, skeletal and dental abnormalities. The autosomal dominant form of this syndrome (AD-HIES) is caused by signal transducer and activator of transcription 3 (STAT3) mutations [1]. Recently, the evaluation of patients from families in which HIES was inherited in a manner more consistent with autosomal-recessive (AR) inheritance, showed that AR-HIES is a clinically distinct disease entity. In addition to classical immunologic findings of AD-HIES, the AR form presents with severe recurrent fungal and viral infections with herpes zoster, herpes simplex and characteristic mollusca contagiosa. Furthermore, cerebral vascular sequelae, including vasculitis, infarction and haemorrhage were also noted [2].

DOCK8 deficiency was identified as the underlying abnormality in the majority of patients with autosomal recessive Hyper IgE Syndrome (AR-HIES). Deficiency of DOCK8 is a newly described combined primary immunodeficiency disease (CID). The molecular basis of the disease was defined in 2009. CID due DOCK8 deficiency is caused by homozygous or compound heterozygous deletions and point mutations in the DOCK8 gene (9p24), which leads to an absence of DOCK8 protein in lymphocytes, resulting in low absolute T and B lymphocyte counts, mild-to-moderate eosinophilia and very high levels of serum IgE [3]. The mechanism by which DOCK8 deficiency, in particular, affects patients appears to be related to underlying autoimmunity caused by partial T cell deficiency, resulting in dysregulation and leading to elevated risks of developing both systemic and central nervous system (CNS) vasculitis [4]. Some authors also suggested that the bacterial infections that are typical of HIES might be the etiological factor for the vasculitis process. Bacteria may cause damage to vessel walls by activating coagulation and platelet aggregation, acting as antigens in immune complexes or as toxins directly damaging the endothelial cells [5]. Despite this association, cases of vasculitis and CNS involvement associated with DOCK8 mutations have been rarely reported in the literature.

Case Presentation

12 years old, girl of Asian origin, born to consanguineous parents, presented to our facility with history of, severe eczema, failure to thrive, recurrent chest infections and skin infections. She was diagnosed to have Hyper IGE syndrome based on the clinical features and investigation from the country of origin. She had been on prophylactic antibiotics, antifungals and regular monthly doses of Intravenous immunoglobulins since the age of five years. The child presented to our hospital with recent onset of right sided weakness and UMN facial paresis. There was history of similar weakness two years ago which partly recovered with physiotherapy.

On examination, she was febrile, vitally stable and had severe eczema. Neurologically she was conscious and oriented. Cranial nerves examination showed right upper motor neuron facial weakness. There was right hemiparesis with exaggerated deep tendon reflexes. Plantar was extensor on the right side. Left side examination was normal.

Her lab investigations revealed elevated IgE and low IgM (Ig A-139, IgG-966 Ig M-<15.8 Ig E-2500) suggesting Hyper IgE syndrome. The routine workup for stroke including echocardiography, hematology work up including Protein C/protein S, Factor 5 Leiden, Antithrombin 3 were normal. Antinuclear (ANA) antibodies, anti-neutrophil cytoplasmic antibodies (ANCA), P-ANCA, Anti-double- stranded DNA Anti Ro, Anti la, Anti-Jo-1 Antibodies, RNP, Scl70, Anti-Smith antibody and Rheumatoid factor were normal. Flow cytometry from bone marrow revealed 2 %immature cells (myeloid cells). MRI brain was done suggestive of left middle cerebral artery occlusion, subacute hemorrhagic infarct in Middle cerebral artery, left cerebellar old hemorrhagic infarct, multiple bilateral cerebral changes. MRA done was suggestive of left middle cerebral artery occlusion either thrombosis or occlusion with collaterals. Rest arteries were normal and no aneurysms noted. Color Doppler study of bilateral carotid arteries and vertebral arteries were normal.

Based on her clinical presentation and MRI findings she was evaluated for DOCK8 gene deletion. Whole exome sequencing, using next generation sequencing, revealed homozygous deletion of exons 2-9, in Dock 8 gene. Both the parents were heterozygous carriers of the above variant.

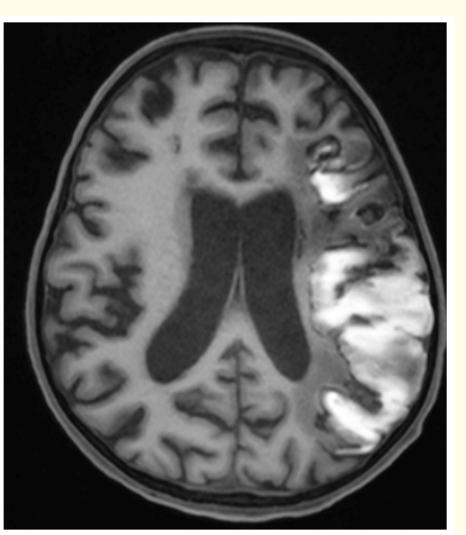

Figure 1: MRI brain axial section showing left MCA territory hemorrhagic infarct.

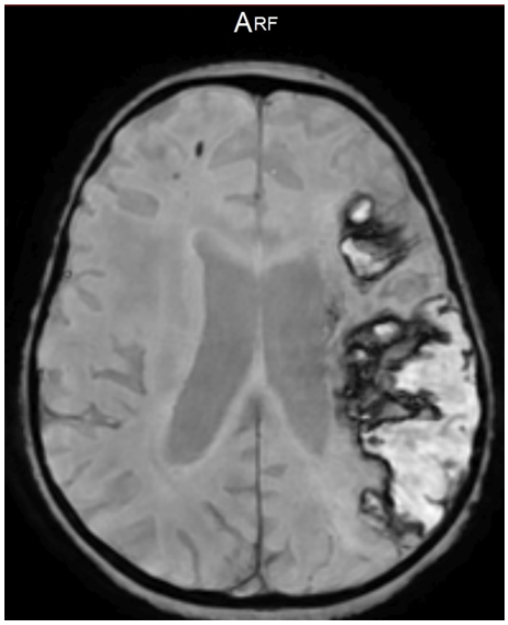

Figure 2: SWI Image of brain shows blooming suggestive of hemorrhage infarct.

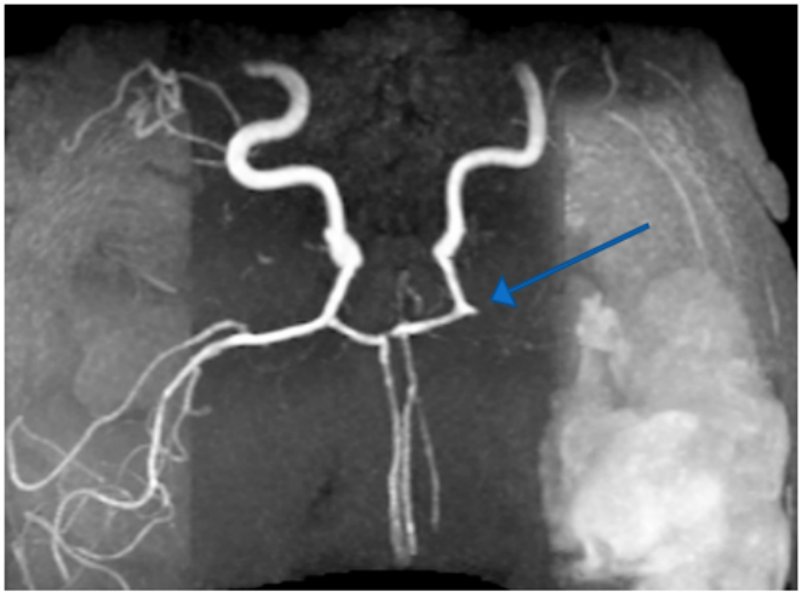

Figure 3: Magnetic resonance angiography brain shows total occlusion of M1 segment of left middle cerebral artery (arrow).

Discussion

DOCK 8 mutation is a rare autosomal recessive primary immunodeficiency seen predominantly in consanguineous populations. First reported in 2009, DOCK8 deficiency was identified as the underlying abnormality in the majority of patients with autosomal recessive HyperIgE Syndrome. Its exact prevalence, although is unknown [1].

Loss-of-function mutations in the DOCK8 gene are responsible for most forms of autosomal recessive HIES [7]. Dock8 protein was found to play an essential role in humoral immune responses and to be important in the proper formation of the B-cell immunological synapse [8]. Dock8 protein itself is highly expressed within the immune system. Thus, not surprisingly, patients with DOCK8 gene deficiency present with multiple abnormalities of the immune system, including defective CD8 T, Natural Killer T cell and natural killer (NK) cell survival and function, impaired generation of Th17 cells, impaired production of antiviral cytokines, and impaired production of antigen-specific antibodies [9].

Various vascular anomalies have been reported in hyper IGE syndrome patients, including aneurysms, vascular ectasia, and vascular thrombotic events [4]. However, CNS involvement like cerebral vasculopathy, vasculitis and moya moya are most frequently encountered in patients with DOCK8 deficiency [9]. Brain abnormalities have been frequently reported in these patients and manifest as MRI hyper intensities. These hyper intensities were observed in our patient and were attributed to old infarcts.

Till now, in literature very few cases have been reported with sclerosing cholangitis in DOCK8 mutation patients [10]. Although its rare, the possibility of sclerosing cholangitis should be kept in mind, even in asymptomatic patients with DOCK 8 deficiency. Our patient also showed evidence of sclerosing cholangitis in Computed Tomography scan of abdomen.

DOCK8 deficiency is associated with high morbidity and mortality. A recent large retrospective review showed a decline in overall probability of survival from 87% to 37% at 10 and 30 years, respectively. Cumulative incidence of life-threatening infections, cerebral events and malignancies was 88%, 32% and 48% at 30 years of age. Death in patients with DOCK8 deficiency has been reported to occur from infection, malignancies and less commonly vasculitis [11].

Management of DOCK8 deficiency includes evaluation and treatment of complications, administration of immunoprophylaxis and definitive therapy with hematopoietic stem cell transplantation. Patients should be also evaluated for indolent infections as well as malignancies. The literature lacks sufficient reports on CNS vasculitis associated with immunodeficiency disorders. Additionally, there is no definitive treatment protocol for such patients. Managing patients with CNS vasculitis in the context of a defective immune system is extremely challenging. Clinicians are confronted by the need to aggressively immunosuppress such patients. However, this approach may result in further suppression of an already weakened immune system. Therefore, careful consideration is necessary when selecting an immune suppressant [4].

Conclusion

DOCK8 deficiency is one of the rare primary immunodeficiency syndromes with multisystem involvement. Central nervous system vasculopathy and sclerosing cholangitis are unique for this mutation. The objective of this case report is to increase awareness about the rare comorbidities associated with DOCK 8 mutation. It also emphasizes the need of early genetic screening for the disease as well as screening for its associated comorbidities like vasculitis, to prevent catastrophic consequences. There is a clear lack of awareness and consensus regarding the treatment of vasculitis in children with immunodeficiency syndromes. Identifying DOCK 8 mutation as a unique disease entity, will pave way to early recognition of associated comorbidities and formulating an effective treatment strategy.

Consent

Written informed consent was obtained from the patient's legal parents for this case report and any accompanying images.

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