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Case Report

A Novel mutation in interferon binding protein Heterogenous c.23g >A p.Arg8Gln

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Abstract

This article dig into the spectrum of inherited disorders known as Mendelian Susceptibility to Mycobacterial Disease (MSMD). MSMD characterized by risk of localized or disseminated infections caused by viral and atypical mycobacteria autosomal dominant and Autosomal recessive Mutations in the genes encoding interferon and binding protein [1].

The first instance of genetic defects in MSMD patients was documented in 1996, involving four Maltese children exhibiting fever, weight loss, hepatosplenomegaly, bone lesions, and an intense acute-phase response, attributed to disseminated Nontuberculous Mycobacteria (NTM) infection resulting from a mutation in interferon-g receptor [1].

In this article, we identify a mutation in the Interferon Regulatory Factor 8 (IRF8) gene, also referred to as interferon consensus sequence-binding protein (ICSBP), which is one of nine members of the IRF family participating in the development and regulation of the immune system [2].

Keywords: Primary immunodeficiency; Interferon binding protein; Pediatrics

Abbreviations: Mendelian Susceptibility to Mycobacterial Disease (MSMD); Nontuberculous Mycobacteria (NTM); Interferon Regulatory Factor 8 (IRF8); interferon consensus sequence-binding protein (ICSBP); primary immunodeficiency (PID)

Introduction

Since the initial report of primary immunodeficiency (PID) in 1952, there has been a surge in knowledge, with over 400 recognized genetic defects linked to various PID phenotypes [3]. PID may manifest mildly and go undetected until adulthood or present issues in infancy and become apparent soon after birth [3]. A survey of 10,000 American households revealed a prevalence of diagnosed primary immunodeficiency approaching 1 in 1200 [4]. Milder forms, such as selective immunoglobulin A deficiency, are relatively common, while other disorders exhibit lower incidences between 1:100,000 and 1:2,000,000 [2].

The estimated prevalence of PID in Oman is 4.5 cases per 100,000, higher than that in European countries, with phagocytic disorders, mainly chronic granulomatous disease (CGD), being predominant. Consanguinity and a history of infant/child death were significant factors [5]. Iran was the second country in Asia to report the national PID [3]. The genetic diagnosis was identified in 152 patients (30.2%) from a cohort study was held in Saudi arabia in which consanguinity was observed in 75% [3].

(MSMD) is a rare congenital condition within the PID spectrum, characterized by a selective predisposition to infections caused by weakly virulent mycobacteria and other intra-macrophagic pathogens [6]. The 16 genes associated with MSMD display allelic heterogeneity, resulting in 31 distinct disorders with diverse clinical presentations and prognosis [6]. Genetic analysis has highlighted

the role of specific cell populations and molecular pathways in host defense.

In this article, we describe the case of a school aged boy with a history of recurrent cytopenia and infections since birth. Genetic testing revealed a novel mutation in the complete IRF8 gene.

Case Report

This is a report on an 11-year-old male patient who was born in a governmental hospital and didn't require NICU admission. The pregnancy was uneventful, and the patient's birth weight was 2800 grams. Although there is no history of consanguinity in the family, the patient did experience jaundice at one week of age. He was later diagnosed with anemia, with hemoglobin levels lower than 7, which necessitated a blood transfusion. He then required regular blood transfusions every two weeks until he reached four months old.

Afterward, the patient was transferred to our hospital for further evaluation. He was admitted at three months old for anemia investigation and was found to have hepatomegaly and pallor, but no changes in the color of urine or skin rash. The first CBC test showed that the patient's Hb was 8 g\dl, WBC was 17 *10*3 neutrophils 31%, platelets 607*10*3, MCH 25 pg., MCV 81um*3, and retics 1.4%. Tests were negative for G6PD deficiency and negative direct Coombs, as well as normal metabolic workup and negative viral serology.

At the age of 4 months, the patient underwent a bone marrow biopsy which revealed blast 5%, leading to suspicion of myelodysplastic disorder. The patient had four instances of pneumonia requiring hospitalization, at the ages of 5, 6, 7, and 13 months. The treatment included antibiotics administered for a period of 10-14 days. One of these admissions followed a period of persistent vomiting and diarrhea, which led to a suspicion of Pearson marrow pancreas syndrome (PMPS) based on the patient's clinical presentation.

At 17 months old, the patient developed oral ulcers and fever, and was diagnosed with herpetic mucositis. They were treated for two weeks with a combination of imipenem, vancomycin, acyclovir, gentamicin, and steroids. Later, at 18 months old, they were admitted to the Pediatric Intensive Care Unit with pneumonia infection. Gastric aspirates came back positive for Pseudomonas aeruginosa, as did sputum culture. The patient also had multiple admissions due to diarrhea, but stool analysis showed no issues. They were treated as a cystic fibrosis patient even though the sweat chloride test came back negative twice.

Between the ages of 21 and 24 months, the patient experienced two simple febrile seizures but did not receive antiepileptic treatment. At the age of 28 months, a bone marrow test was repeated in December 2012, which showed normal trilineage with maturation. Between the ages of 31 and 36 months, the patient was admitted multiple times due to recurrent infections, including follicular tonsillitis and enterovirus-positive meningitis. After presenting with multiple episodes of fever and abdominal pain, a common mutation test for FMF by PCR was negative. Colonoscopic biopsy results were normal, and the celiac workup was negative.

In the same year, the patient had a positive stool culture for cryptosporidium after experiencing a severe episode of diarrhea. The patient continues to have multiple types of infections, including septic infections, multiple dental abscesses, and otitis media with a positive MRSA culture.

At the age of 7, the patient underwent a colonoscopy to rule out IBD, which was normal for the second time. The bone marrow was unremarkable, and flow cytometry, immunoglobulin, and complement levels were normal.

After reviewing his medical history and disease manifestation we gain crucial insights into their condition and can provide more effective treatment. The patient started receiving IVIG treatment at the age of 8, their symptoms have become less frequent and less severe. They no longer require hospitalization for cytopenia infection and are now admitted regularly every four weeks for an IVIG infusion of 500mg/kg.

It is crucial to quickly diagnose genetic defects related to interferon, just like with other types of interferon. This helps in planning and managing clinical treatments. However, to identify the exact molecular cause of the disease in each patient, specialized assays are required [8].

An immunological investigation was conducted, which revealed a Heterogenous nonsense mutation in the IRF8 - interferon consensus sequence-binding protein (ICSBP) gene. This particular patient was found to have a novel variant c.23g >A p.Arg8Gin which has not been documented in the literature before. This demonstrates that IRF8 mutations can manifest as common respiratory symptoms and recurrent severe infections in early childhood.

Discussion

We present a case study of an 11-year-old boy who suffered from recurrent infections. Subsequently, we identified and described a primary immunodeficiency, caused by a unique heterozygous nonsense mutation in the IRF8 gene.

This mutation can be inherited as an autosomal recessive or an autosomal dominant trait [6]. The autosomal recessive complete deficiency is the rarest but most severe disease form [8]. In comparison to other reported cases, our patient presented early after birth with two autoimmune hematological problems: hemolytic anemia and thrombocytopenia. This combination has not been described in other cases.

We came across a study reporting a case of interferon-related immunodeficiency. The study found that the patient suffered from recurrent diarrhea caused by cryptosporidium infection [9]. It was associated with a deficiency of Interferon γ. The patient did not respond to antibiotics but showed significant improvement when treated with interferon [9]. In our patient's case, we administered IVIG treatment which resulted in a good response.

Our findings indicate that there were no instances of pneumonia that were confirmed by positive bacterial culture of sputum for Pseudomonas aeruginosa. Similarly, we found no evidence of cases that presented with recurrent mastoiditis with positive cultures for MRSA.

It has been reported that patients with complete deficiency of IFNγR1 or IFNγR2 are susceptible to other rapidly growing mycobacterial species, such as M. fortuitum, M. avium, Salmonella, and Listeria monocyte gene infections [5]. Our patient did not experience any of this infection but he is at high risk for.

Two children have been diagnosed with severe diseases caused by viruses, such as CMV and HSV. Our patient also had a similar episode of HSV infection that manifested as severe herpetic mucositis, which matches the symptoms described in the other cases [10].

Similar to other cases of PID and specifically interferon binding protein pur patient had 2 episodes of viral meningitis (enterovirus meningitis) complicated with seizures [10].

In recent years, multiple experiments have provided evidence that IVIG can be beneficial in treating immunodeficiencies and autoimmune disorders. The antibodies present in IVIG play an essential role in the immune system by neutralizing bacteria and viruses, as well as enhancing their phagocytosis and destruction [7].

To the best of our knowledge, this is the first case of interferon-related immunodeficiency that was treated with regular IVIG infusion to relieve the symptoms. our patient was started on regular, monthly IVIG infusion 500mg /kg.

Conclusion

This case highlights the significance of exploring primary immune deficiencies when there is a clinical suspicion. Early diagnosis can save expenses related to repeated hospitalizations, prompt management as seen in our patient with IVIG, should be given careful attention. This case also adds to the growing comprehension of the IRF8 protein defect in primary immunodeficiency.

Acknowledgement

None.

Conflict of interest

None.

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