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CASE REPORT

Post-MMR vaccine vasculitis, encephalopathy and mortality in 2 siblings to an infant with heterozygous mutation in interferon alpha/beta receptor alpha chain (IFNAR1) gene

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KEYWORDS

viral infection,
MMR,
vasculitis,
immunodeficiency,
interferon

Abstract

A six-week-old boy presented to the immunology clinic for screening as he has previous 2 sibling deaths. He is the only living child for his 2nd degree consanguineous parents. The elder girl has died 3 days after the measles-German measles-mumps (MMR) vaccine due to unexplained peripheral febrile vasculitis. The other brother developed vasculitis, meningitis and recurrent infections few days after MMR vaccine, and he died after a serious gastroenteritis at age of 3 years. Screening for the only living infant using whole exome sequencing revealed a heterozygous likely pathogenic mutation in IFNAR1 gene.

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Introduction

Inborn errors of immunity (IEI) commonly present during childhood. Immune dysregulation, autoinflammation, allergic reactions and recurrent serious infections are different representations of IEI. Vaccinations seldomly work as triggers of IEI clinical expression.

Case presentation

The 1st cousin parents of 3 children presented to the immunology clinic for counseling. They have a

one living healthy infant aged 6 weeks. The elder siblings (a girl and a boy) died without clear diagnosis. Their first child was a girl. At age of 1 year, she received the measles-German measles-mumps (MMR) vaccine according to the national schedule of immunization. One day later, vasculitic eruptions appeared on her feet, legs and arms, followed by high grade fever. The next day, fever progressed, vasculitis involved wider body areas and became more palpable and painful and an underground of morbilliform rash appeared. A throat bio-fire revealed the presence of measles virus. The girl died at the third day.

The second child was born healthy. After MMR vaccine, he got the same febrile vasculitic eruptions in his extremities and trunk, however, in the 2nd day, his conscious level disturbed and he developed multiple seizures. Cerebrospinal fluid examination and brain MRI, among other investigations, suggested the possibility of viral encephalitis despite the inability to identify the virus. After 10 days in the pediatric intensive care unit (PICU), encephalitis was complicated with persistent increase in intracranial tension and hydrocephalus. Ventriculo-peritoneal shunt insertion was done and the boy had mild motor defect affected as a sequel. Along with physiotherapy, recurrent upper respiratory tract infections were common, delaying the response to physiotherapy. Although testing for immunoglobulins and flow cytometry for T and B cells was normal for age, the child was kept on monthly doses of intravenous immunoglobulins on dose of 0.5 g/kg to reduce the frequency of infections. At age of 3 years, he got an acute gastroenteritis, excessive watery diarrhea, severe dehydration and he died within 2 days. Therefore, the parents were anxious about their 3rd child and had inquiries about the real role of MMR vaccine in their children's mortalities. Whole exome sequencing revealed the presence of a heterozygous likely pathogenic mutation in IFNAR1 gene [NM_000629.3(IFNAR1):c.117dup (p.Thr392AsnfsTer4)]. This variant in IFNAR1 gene is a frameshift variant that results in truncal non-functioning protein. This variant is not present in the genomAD database (figure 1).

Discussion

Interferon alpha/beta receptor alpha chain (IFNAR1) deficiency can cause a unique form of inborn errors of immunity (IEI) known as immunodeficiency 106 (IMD106) associated with increased susceptibility to viral infections. It is an autosomal recessive disorder that requires homozygous or compound heterozygous mutation in IFNAR1 gene in order to be expressed phenotypically.¹ The main role of type I interferons (IFN-Is) is to fight viral infections as they have the ability to early recognize the microbial particles, especially viral nucleic acids through the innate immune receptors. IFNs bind to 2 types of heterodimeric receptors: alpha and beta subunits 1 and 2 (IFNAR1, IFNAR2). IFNs accomplish their anti-viral combating through activating the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway. Therefore, loss of function mutations in the IFN- α/β receptors or the JAK-STAT pathway are associated with profound viral infections and increased mortality rates.² IMD106 usually manifests during infancy or early childhood in the form of recurrent viral upper respiratory tract infections or viral gastroenteritis. Live attenuated viral vaccines were reported to be the initiator of the symptoms, specifically, MMR

and yellow fever.³ Another reported observation regarding IMD106 patients is that they can develop post-MMR vaccine hyperinflammatory reaction, encephalopathy and multiorgan failure.⁴ The risk of severity and complications of Sars-Cov-2 and herpes simplex 1 viruses is augmented in those patients.⁵⁻⁸ Revising our patients, gene studying of the affected children was not possible, however, the presence of heterozygous mutation of IFNAR1 gene in the living infant rises the possibility that his siblings carried the same mutation. It was not reported that heterozygous IFNAR1 mutation can manifest clinically,⁹ however, our recommendation was to avoid live attenuated viral vaccines particularly MMR vaccine in the living infant. Although immune dysregulation and vasculitis was not reported as a manifestation of IMD106, the 2 siblings developed post-MMR persistent vasculitis. The cause of death in the 2 children was exaggerated severity of viral infections, measles in the first child and viral gastroenteritis in the second one. Encephalopathy was clear in the second child with inability to isolate or define a pathogenic etiology. Moreover, encephalopathy in that child had a relatively severe pattern, ending with hydrocephalus and residual motor defect. The severity of the condition in the older siblings, their mortality and the absence of genetic testing to clarify if they had a homozygous or heterozygous IFNAR1 mutation encouraged us to be very cautious about the 3rd child and to recommend skipping live attenuated viral vaccines and to postpone the daycare attendance in order to minimize the exposure to viral infections.

Conclusion

An asymptomatic infant with heterozygous IFNAR1 mutation is a brother to 2 siblings who developed post-MMR serious complications in the form of vasculitis, encephalopathy and recurrent viral infections, ended with their death. It is impossible to know if the died siblings had heterozygous or homozygous mutations in IFNAR1, considering that the parents are first cousins. Avoiding live attenuated viral vaccines and reducing exposure to viral infections are the only available recommendations for the child. Whole exome sequencing for the parents is also recommended.

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IMMUNODEFICIENCY 106, SUSCEPTIBILITY TO VIRAL INFECTIONS; IMD106

Alternative titles; symbols

IFNAR1 DEFICIENCY

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
21q22.11	Immunodeficiency 106, susceptibility to viral infections	619935	AR	3	IFNAR1	107450

Figure 1. OMIM data for the IFNAR1 gene.

Abbreviations:

IEI: inborn errors of immunity
IFNAR1: interferon alpha/beta receptor alpha chain
IMD106: immunodeficiency 106
OMIM: online Mendelian inheritance in man
WES: whole exome sequencing