A PIK3R1 Mutation Associated with A Posterior Cranial Structural Abnormality (Arnold Chiari Malformation) with Elevated IgM Progressing to Absent IgM

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INTRODUCTION

The PIK3R1 mutation phenotype is associated with frontonasal cranial facial abnormalities. Partial lipodystrophy, triangular facies, ocular depression, and hypo-plastic nasal area are several phenotypic facial features associated with PIK3R1 gene mutation. Posterior cranial structural anomalies in association with the PIK3R1 gene have not been identified in the literature.

The patient started her infectious symptomology at 3 months of age which progressed into her adult life. These infections included recurrent otitis media, sinusitis, bronchitis, and pneumonia. On physical exam, the patient demonstrated prominent cervical lymphadenopathy. There was no apparent family history of recurrent infections. She was discovered to have elevated IgM with absence of IgG and IgA. The patient was started on intravenous immune globulin replacement. After years of intravenous immune globulin replacement, the patient is on intravenous immune globulin replacement. The patient started her infectious symptomology at 3 months of age which progressed into her adult life. These infections included recurrent otitis media, sinusitis, bronchitis, and pneumonia. On physical exam, the patient demonstrated prominent cervical lymphadenopathy. There was no apparent family history of recurrent infections. She was discovered to have elevated IgM with absence of IgG and IgA. The patient was started on intravenous immune globulin replacement. After years of intravenous immune globulin replacement, the patient is on intravenous immune globulin replacement.

CASE: CLINICAL AND LABORATORY RESULTS

Standard Quest Diagnostics Hemoplate Panel drawn including immunoglobulin levels IgG, IgA, IgM, IgG subclasses, pneumococcal titers, CBC with differential, Tetanus anti-toxoid were performed (Figure 3 & 4).

Genetics: Blood draw required for genetic testing for primary immune deficiency evaluation. Invitae immune deficiency panel analyzes 207 genes associated with inherited disorders of the immune system. Sequence analysis covers clinically relevant gene portions, coding exons, and 10 base pairs of adjacent intron sequence.

DISCUSSION

Primary immunodeficiency caused by mutation in PIK3R1 gene can potentially lead to hyper-activation of the enzyme phosphoinositide-3 kinase. This yields elevated IgM levels in up to 79% of cases. Our patient while initially presenting with a hyper IgM phenotype eventually lost her IgM levels.

Our patient demonstrates various clinical features associated with PIK3R1 mutation. The phenotypic clinical presentation of PIK3R1 mutations may include short stature, hyper-extensibility of joints, delayed tooth, and ocular abnormalities. Other PIK3R1 related phenotypes are lipodystrophy secondary to insulin resistance, and mild intrauterine growth restriction, as well as characteristic facial features. The aberrant facial patterns are triangular facies, lipodystrophy, and hypoplastic nasal alae.

Our observations of our patient and other patients in the literature demonstrate a propensity for anterior structural cranial defects associated with PIK3R1 mutation as opposed to posterior cranial defects. This can potentially be explained by embryogenesis. The anterior and posterior components of the skull are derived from separate embryonic structures. The anterior facial cartilage structures are derived from the first pharyngeal pouch and the anterior facial bone structures are formed from the neural crest mesenchyme. The posterior cranial structures are primarily derived from the paraxial mesoderm.

CONCLUSION

- PIK31 mutation is often associated with elevated IgM & anterior facial abnormalities.
- We describe the first case of PIK3R1 mutation beginning with a transient hyper IgM phenotype with progression to absent IgM.
- We describe the first case of a posterior cranial malformation in a PIK3R1 mutation.