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 frontal cranial facial abnormalities. Partial lipodystrophy, triangular facies, ocular depression, and hypo-plastic nasal alae 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 IgA and IgG. The patient was started on intravenous immunoglobulin replacement. After years of intravenous immune globulin replacement, the pt's IgM serum concentration became undetectable. Genetic analysis was performed (Invitae) and a heterozygous mutation with the c.1425+1G>A (with splice donor) variant. Typical facial features were noted at birth. At 8 years of age, the patient acutely developed numbness in her bilateral upper extremities, hands, bilateral lower extremities and feet and was unable to walk due to the symptoms. A diagnostic MRI demonstrated a herniation of the posterior cerebellar tonsils (Arnold Chiari Malformation type 1). A subsequent decompression was performed with resolution of neurological symptoms.

Anterior cranial structural abnormalities have been reported previously with a PIK3R1 mutation. There have been no reported cases highlighting the posterior cranial structural defects in this mutation. We describe a novel case of Arnold Chiari malformation in a young female discovered to have PIK3R1 gene mutation with a loss of all immunoglobulin isotypes after presenting as an hyper IgM phenotype.

CASE: CLINICAL AND LABORATORY RESULTS

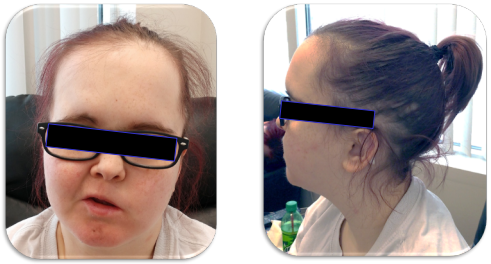

Figure 1. Physical features demonstrated by the patient: Short stature, triangular facies, flattened facial features

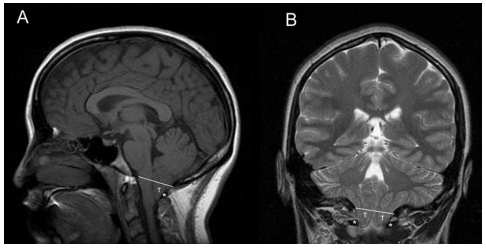

Figure 2. Coronal & Sagittal Views of Type 1 Arnold Chiari Malformation. Cerebellar Tonsillar Herniation depicted. Descent of cerebellar tonsils below level of foramen magnum demonstrated by the white line. Note: Patient images not available as per radiology (Reference: Medscape)

Standard Quest Diagnostics Humoral 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 immunodeficiency panel analyzes 207 genes associated with inherited disorders of immune system. Sequence analysis covers clinically relevant gene portions, coding exons, and 10 base pairs of adjacent intron sequence.

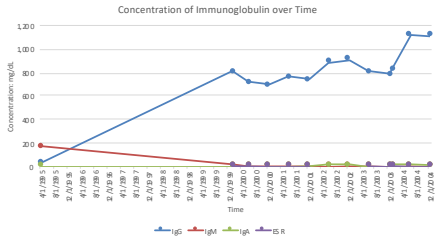

Figure 3. Immunoglobulins IgA, IgM, IgG trend over time. IgM is initially elevated (red) and shown to diminish to an absent level over time while patient is on intravenous immune globulin replacement.

Test	Result	Units	Reference Range
CD3 Absolute	0.861	X10 E9 / L	0.710-4.180
CD3+ CD4+ Absolute	0.295	X 10E9 / L	0.350-2.740
CD3+ CD8+ Absolute	0.529	X 10E9 / L	0.080-1.490
CD19 Absolute	0.000	X 10E9 / L	0.070-0.910
CD3 %	70	%	58-97
CD3+ CD4+ %	24	%	29-57
CD3+ CD8+ %	43	%	7-31
CD4/CD8 Ratio	0.56		1.00-3.50
CD3+CD4-CD8- %	3.00	%	0.00-4.00
CD45 %	100	%	
CD3- CD16+ CD56+ %	30	%	0-18
CD3- CD16+ CD56+ Absolute	0.369		0.000-0.860
CD19 %	0	%	6-19

Figure 4. Our patient demonstrates a decreased number of T cells with a markedly low CD4 T cell count highlighted by the inverse CD4/CD8 ratio. The B cells (CD19) are absent.

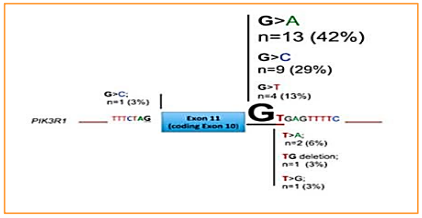

Figure 5. PIK3R1 gene permutations exemplified.

DISCUSSION

Primary immunodeficiency caused by mutation in PIK3R1 gene can potentially lead to hyper-activation of the enzyme phosphoionositidie-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.