Posterior Cranial Structural Abnormality (Arnold Chiari Malformation) & Combined Immune Deficiency with Elevated IgM associated with PIK3R1 Mutation

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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 [1]. 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. 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 year 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 with found to have PIK3R1 gain of function gene mutation.

Figure 4. Physical features demonstrated by patient: Short stature, triangular facies, flattened facial features

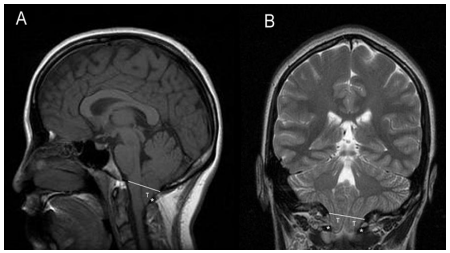

Figure 1. Coronal & Sagittal Views of Type I Arnold Chiari Malformation. Cerebellar Tonsillar Herniation depicted. Descent of cerebellar tonsils below level of foramen magnum demonstrated by the white line. Note: Patient images not available as per radiology (Reference Medscape)

Standard Quest Diagnostics Humoral Panel drawn including immunoglobulin levels IgG, IgA, IgM, IgG subclasses, pneumococcal titers, CBC with differential, Tetanus anti-toxoid

Genetics: Blood draw required for genetic testing for primary immune deficiency evaluation. Invitae immunodeficiency panel analyzes 207 genes associated with inherited disorders of immun system. Sequence analysis covers clinically relevant gene portion., coding exons, and 10 base pairs of adjacent intron sequence. Genetic testing may help in guiding management and treatment decisions.

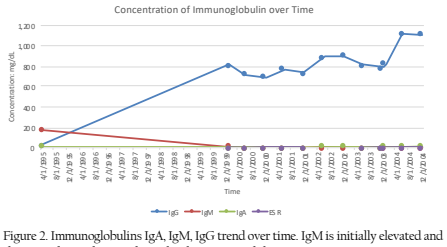

Figure 2. Immunoglobulins IgA, IgM, IgG trend over time. IgM is initially elevated and shown to diminish to an absent level over time while patient is on intravenous immune globulin replacement. Elevated IgM with immune globulin replacement is expected to reach a normal level.

Test	Result	Units	Reference Range
CD3 Absolute	0.861	X 10 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 3. 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.

Genes tested

ACD, ACP5, ACTB, ADA, ADA2, ADAM17, ADAR, AICDA, AIRE, AK2, AP3B1, ATM, B2M, BCL10, BLNK, BLOC1S6, BTK, CARD11, CARD14, CARD9, CASP10, CASP8, CD247, CD27, CD3D, CD3E, CD3G, CD40LG, CD79A, CD79B, CDA, CEBPE, CHD7, CIITA, CLPB, COPA, CORO1A, CR2, CSF2RA, CSF3R, CTC1, CTLA4, CTPS1, CTSC, CXCR4, CYBA, CYBB, DCLRE1B, DCLRE1C, DKC1, DNMT3B, DOCK2, DOCK8, ELANE, EPG5, FADD, FAS, FASLG, FERMT3, FOXN1, FOXP3, FPR1, G6PC3, GATA2, GFI1, HAX1, ICOS, IFIH1, IFNGR1, IFNGR2, IGLL1, IKBKB, IL10, IL10RA, IL10RB, IL12B, IL12RB1, IL17F, IL17RA, IL17RC, IL1RN, IL21, IL21R, IL2RA, IL2RG, IL36RN, IL7R, IRAK4, IRF7, IRF8, ISG15, ITCH, ITGB2, ITK, JAGN1, JAK3, LAMTOR2, LCK, LIG4, LPIN2, LRBA, LYST, MAGT1, MALT1, MAP3K14, MEFV, MOGS, MVK, MYD88, NBN, NCF2, NCF4, NFAT5, NFKB2, NFKBIA, NHEJ1, NHP2, NLRC4, NLRP12, NLRP3, NOD2, NOP10, ORAI1, PARN, PGM3, PIK3CD, PIK3R1, PLCG2, PMM2, PNP, POLE, PRF1, PRKCD, PRKDC, PSMB8, PSTPIP1, PTPRC, RAB27A, RAC2, RAG1, RAG2, RBCK1, RFX5, RFXANK, RFXAP, RHOH, RMRP, RNASEH2A, RNASEH2B, RNASEH2C, RORC, RTEL1, SAMHD1, SEMA3E, SH2D1A, SH3BP2, SLC29A3, SLC35C1, SLC37A4, SLC7A7, SMARCAL1, SP110, SPINK5, STAT1, STAT2, STAT3, STAT5B, STIM1, STK4, STX11, STXBP2, TAP1, TAP2, TAPBP, TAZ, TBX1, TCN2, TERC, TERT, TICAM1, TINF2, TLR3, TMC6, TMC8, TMEM173, TNFRSF13B, TNFRSF13C, TNFRSF1A, TNFRSF4, TNFSF12, TPP2, TRAF3, TRAF3IP2, TREX1, TRNT1, TTC7A, TYK2, UNC13D, UNC93B1, UNG, VPS13B, VPS45, WAS, WIPF1, XIAP, ZAP70, ZBTB24

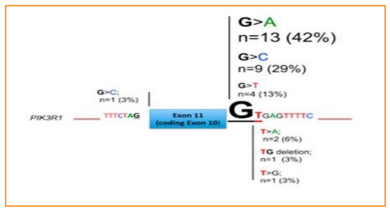

Figure 3. PIK3R1 gene permutations exemplified. Place exact mutation in Figure

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DISCUSSION

Primary immunodeficiency caused by mutation in PIK3R1 gene can potentially lead to hyper-activation of the enzyme phosphoionositidie-3 kinase.

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 [1,2]. The aberrant facial patterns are triangular facies, lipodystrophy, and hypoplastic nasal alae [1].

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 [3].

CONCLUSION

- PIK3R1 mutations are associated with posterior cranial malformation
- Combined Immune Deficiency may be linked to PIK3R1 mutation
- Hyper IgM syndrome may not be the initial presentation in a combined immune deficiency linked with PIK3R1 mutation