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Bilateral Periventricular Nodular Heterotopia due to Disruption of MAP1B and MYH2 Genes: A Rare Case Report

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Abstract

We report a rare case of bilateral periventricular nodular heterotopia (PVNH), a congenital brain abnormality resulting from failed neural cell migration associated with disruption of MAP1B and MYH2 genes which are involved in microtubule assembly in neurogenesis.

A 1.2 years old girl presented with symptoms of focal seizure since 9 months of age. The patient's clinical evaluation, in conjunction with CT, MRI brain without contrast and genetic testing, led to the final diagnosis.

Keywords : *Epilepsy, PVNH, Congenital anomaly, genes.*

Introduction

Periventricular nodular heterotopia (PVNH), also known as subependymal gray matter heterotopia, is a congenital brain malformation that arises during early cortical development, resulting in abnormal clumping of grey matter around the ventricles[1]. It is a disorder of neuronal migration in which neurons fail to migrate appropriately from the ventricular zone to the cortex during development, resulting in the formation of nodular brain tissue lining the ventricles.

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The microtubule-associated protein 1B (*MAP1B*) gene serves an important role in axonal growth and brain development. Disruption of the gene due to pathogenic dominant variants are found to be associated with periventricular nodular heterotopias[3].

The Myosin heavy chain 2 (MYH2) gene encodes a member of the class II or conventional myosin heavy chains and functions in skeletal muscle contraction. Disruption of the gene due to dominant or recessive variants are found to be associated with congenital myopathy 6 with opthalmoplegia, is a muscle disorder which is characterized by variable clinical presentation such as hypotonia, neck muscle weakness, upper and lower limbs weakness, generalized muscle weakness and joint hypermobility[5].

Clinical informations

A 1.2 years old girl born to healthy nonconsanguineous parents, came to our Radiology and Imaging department for plain MRI of brain with symptoms of microcephaly, failure to thrive, epilepsy, global developmental delay, hypotonia and joint laxity.

Diagnostic tests

A. Radiologic diagnostics

Patient underwent a diagnostic CT scan and MRI without contrast to assess radiological changes and identify any brain abnormalities (Fig.-1 and Fig.-2)

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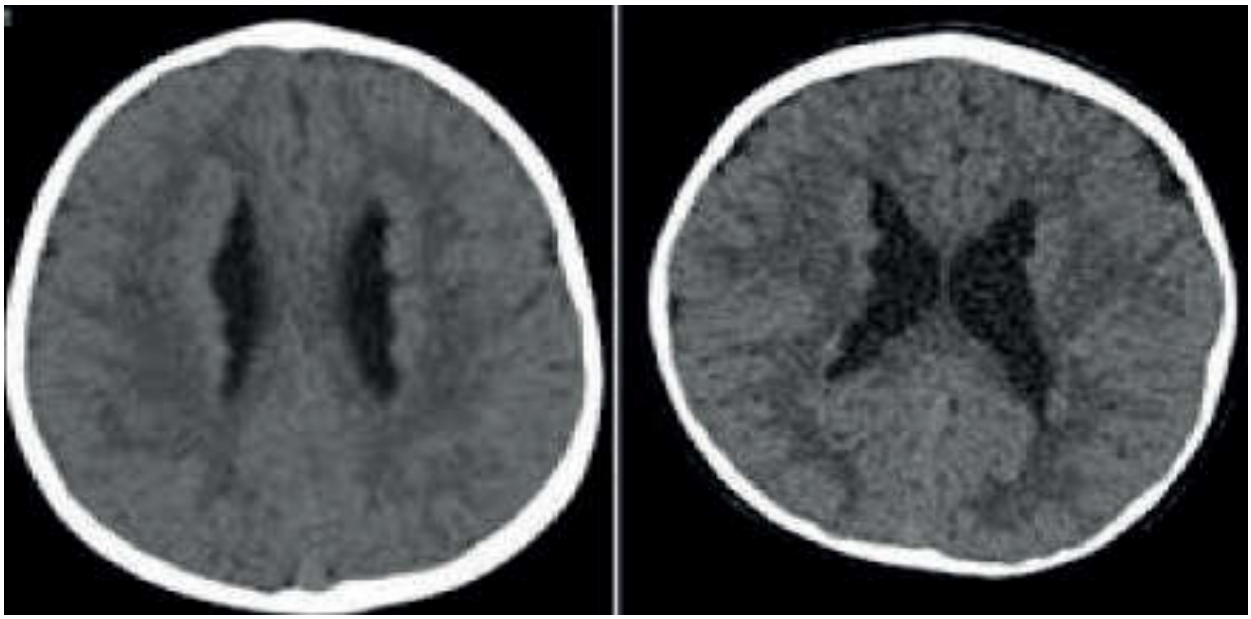

Figure 1: *Brain CT scan revealing the nodular heterotopic grey matter along the lateral ventricles giving them a ragged appearance.*

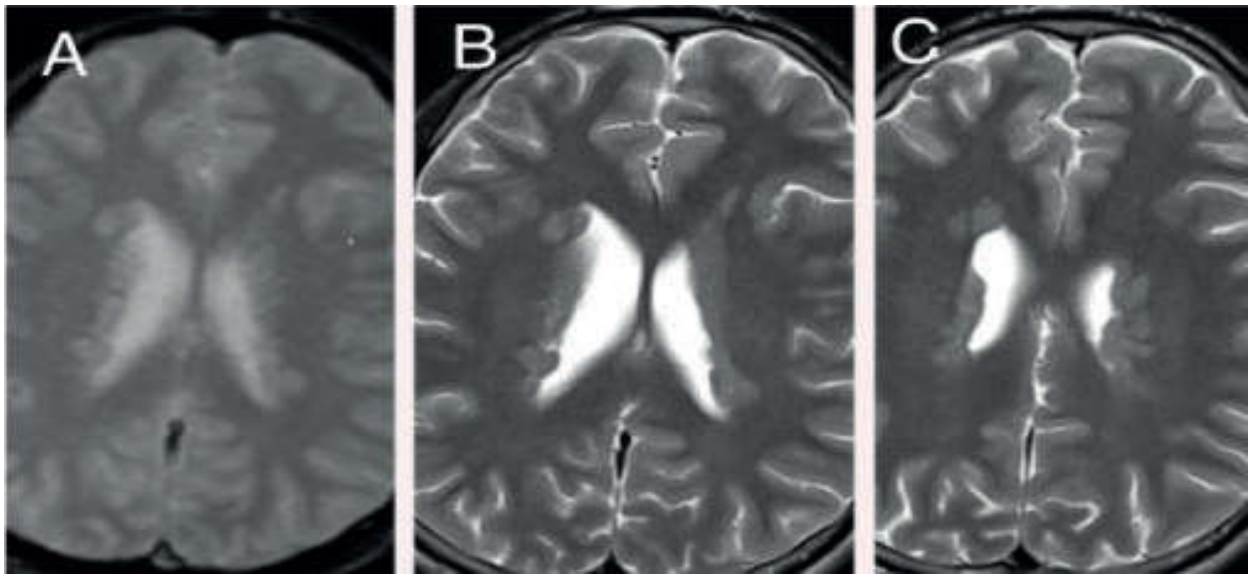

Figure 2: MRI of brain showing nodularity of the ependymal surface of the lateral ventricles giving it a 'lumpy bumpy' appearance as shown in A,B&C.

B. Genetic test

Protocol

Peripheral blood sample was collected from the patient in an EDTA vacutainer tube. Genomic DNA was isolated using Relia Prep TM Blood gDNA isolation kit (Promega USA) according to manufacture instructions. The concentration and quality of DNA was determined using NanoPhotometer C40. The quality of DNA was also checked by 0.8% agarose gel electrophoresis. The pathogenecity of the variant has been assigned following American College of Medical Genetic (ACMG) guidelines.

Limitations

Test results are interpreted in the context of clinical findings, family history and other laboratory data. Only variations in genes potentially related to the probands medical conditions are reported. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

Exome Sequencing Result

Primary Findings: Associated with disease phenotype

This molecular test was ordered to find out genetic abnormalities in the genes relevant to above mentioned phenotypes. After deliberate searching of sequence variations in 36.6 Mb human coding regions of the entire genome, the following variant were found.

Gene	Chr.	Transcript Id	Variant coordinate (GRCh38) dbSNP ID	Variant type Zygosity	Variant Information	Classification as per ACMG guideline
MAP	5	NM 005909	72199082	Frameshift	c.5727_5730del	Pathogenic
1B		Exon 5	Novel	deletion*	p.Arg1911Profs*48	(PVS1, PM2,
				Heterozygous		PM4, PP4)
MYH2	17	NM_017534	10529079	Missense**	c.3355G>A	VUS
		Exon 27	Novel	Heterozygous	p.Ala1119Thr	

Discussion

Periventricular nodular heterotopia, is the most common form of grey matter heterotopia and is characterized by nodules of grey matter located immediately beneath the ependyma of the lateral ventricles. It is thought to result from interruption of normal neuronal migration.[2] The nodules themselves consist of clusters of neurons and supporting glial cells. The disorder is characterized by variable clinical phenotypes such as microcephaly, poor overall growth, seizure, focal seizures, global developmental delays, language delay, impaired intellectual development, short stature, dysmorphic feature and abnormal gait.[4]

Mutations in the MAP1B gene are associated with periventricular nodular heterotopia (PVNH). MAP1B is a microtubule-associated protein. The MAP1B gene encodes a protein that belongs to the microtubule associated protein family which is involved in microtubules assembly in neurogenesis.[3] The product of this gene is a precursor polypeptide that presumably undergoes proteolytic processing to generate the final MAP1B heavy chain and LCI light chain. Gene knockout studies of the mouse microtubule associated protein 1B gene suggested an important role in development and function of the nervous system.

The Myosin heavy chain 2 (MYH2) gene encodes a member of the class II or conventional myosin heavy chains and functions in skeletal muscle contraction. Myosins are actin-based motor proteins that function in the generaion of mechanical force in eukaryotic cells. Muscle myosins are heterohexamers composed of 2 myosin heavy chains and 2 pairs of nonidentical myosin light chains.[5] Disruption of the gene due to dominant or recessive variants are found to be associated with congenital myopathy 6 with opthalmoplegia, is a muscle disorder which is characterized by variable clinical presentation such as hypotonia, neck muscle weakness, upper and lower limbs weakness, generalized muscle weakness and joint hypermobility.

Conclusion

This case report highlights a rare combination of periventricular nodular heterotopia (PVNH) due to disruption in MAP1B and MYH2 genes. PVNH is a brain malformation that is more prevalent in females, but it can have a more severe impact on males. This patient was presented to the hospital with a variety of neurological manifestations. Diagnostic imaging revealed bilateral PVNH and genetic testing revealed presence of MAP1B and MYH2 genes. Radiological imaging along with gene analysis plays a pivotal role in conclusive diagnosis of rare congenital brain abnormalities.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Statement of Ethics

Verbal informed consent was obtained from the patient for publication of this case report and any accompanying images.

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