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Filamin A associated Periventricular Nodular Heterotopia presenting with Mutism

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ICNC 2022
17th INTERNATIONAL CHILD NEUROLOGY CONGRESS
ANTALYA, TURKEY | OCTOBER 5-7, 2022

Introduction

Periventricular nodular heterotopia PNH is a **congenital disorder of neuronal migration** in which cerebral neurons fail to migrate appropriately from the ventricular zone to the cortex resulting in the formation of grey matter nodular lesions lining the walls of the lateral cerebral ventricles.

The etiology of PNH is heterogeneous, with **X-linked dominant mutations within the Filamin A (FLNA) gene in Xq28** the most common cause.

We report the clinical and mutation spectrum of Filamin A associated PNH in a young female who presented with mutism.

Case Report

An **11-year-old previously well female** presented with a three month history of **total mutism**. There were no preceding triggers, stressors, mood disturbances, seizures or significant life events. Psychomotor development had been normal, and she was a good student.. Her birth and developmental history and family history were unremarkable. She has an elder 12-year-old sister who is well.

Physical Examination revealed an alert female with unremarkable body proportions who was mute but able to comprehend. She would answer questions by signaling or gesturing / writing or not responding at all. If she needed a form signed, or other request, she would write to communicate the message. She had intermittent eye contact with prompting. She held her head tilted to the right and downwards. Slight mouth puckering movements were noted but no other dyskinesia was evident. The rest of the neurological examination including fundoscopy, visual field, cranial nerves, power, sensation, reflexes, coordination, plantar responses was normal. She walked with a stooped posture and a slightly reduced arm swing. Tandem gait was normal, there was no ataxia. Blood pressure was normal, as was examination of the cardiovascular system, pulmonary system, skeletal system and abdomen.

She was commenced on **speech and language therapy, psychotherapy and fluoxetine** with subsequent improvement.

Investigations included normal metabolic studies (Plasma amino acids, CSF amino acids, plasma acylcarnitine, Urine organic acid) and a negative blood NMDAR antibody.

Two EEGs revealed normal recordings.

Her cranial MRI scan revealed periventricular grey matter heterotopia and a prominent CSF space in the posterior fossa due to mega cisterna magna. (Figure 1)

Sequencing of her **FLNA gene** revealed a likely pathogenic splice site variant (c.622+1G>A). Her mother's sequencing revealed a similar FLNA mutation.

Discussion

Mutations within the Filamin A (FLNA) gene in Xq28 are the most common cause of PNH. The FLNA gene encodes an **actin-crosslinking phosphoprotein** of diverse functions including initiation of cell migration, coagulation and aspects of vessel wall integrity.

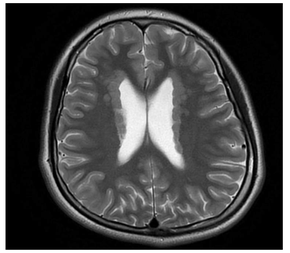

Figure 1: Axial T2 weighted brain magnetic resonance imaging showing grey matter nodules along the surface of the lateral ventricles.

A variety of **neurological and non-neurological manifestations** has been described including mega cisterna magna, corpus callosum hypoplasia, defects of the cardiovascular system, such as persistent ductus arteriosus, bicuspid aortic valve, as well as a spectrum of connective tissue disorders such as scoliosis, pectum excavatum and the oto-palato-digital syndrome (ref 1). There are occasional reports of PNH in patients with a range of neuropsychiatric disorders including depression, anxiety, and autism (ref 2).

The **phenotype** is very variable. Intelligence is normal to borderline. **Epileptic seizures** are the core clinical finding in the majority of patients. Max Lange et al (ref 3) reported 47 patients with FLNA associated periventricular nodular heterotopia. In 13 patients, the first seizure occurred at a mean age of 15.5 years. Seven had their first seizure beyond the age of 20 years, mean 27.4. Ten patients had not experienced any seizure at a mean age of 19.7 years. All these ten patients were neurologically normal. Cardiac disease was recognized in almost half of the cohort of 47 patients.

Conclusion

- We have highlighted **mutism as a potential consequence of FLNA-related PNH**. Clinicians need to be alert to the possibility of patients with PNH presenting with psychiatric disorders, behavioral issues and mutism. The actual relationship remains uncertain.
- Early mutation detection is important for **extended medical surveillance** in particular for cardiovascular disease.
- Our patient will require extended medical surveillance for both cerebral and extracerebral manifestations including **seizures, psychomotor development and cognition, skeletal, cardiovascular and gastrointestinal function.**

References

1 Reinstein E et al. **Vascular and Connective tissue anomalies associated with X-liked Periventricular Heterotopia due to Mutations in Filamin A**. Europ J Human Genet 21:494-502, 2013.

2 Andrew E Fry et al **Neuropsychiatric Disease in Patients With Periventricular Heterotopia** Jou of Psychiatry and Clinical Neurosciences 2013; 25:26–31.

3 Max Lange et al. **47 patients with FLNA associated Periventricular Nodular Heterotopia**. Orphanet Journal of Rare Diseases 15 Oct 2015