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Case Report

# Unveiling the intriguing puzzle: Nodular heterotopia and Mega Cisterna Magna in an adult female ☆

*Priyal Shrivastava, MBBS*[a,*], *Anand Hatgaonkar, MD*[a], *Meet Jobanputra, MBBS*[b], *Shivali Kashikar, MD*[a], *Pratapsingh Parihar, MD*[a]

[a] *Department of Radio-Diagnosis, Jawaharlal Nehru Medical College Wardha, Datta Meghe Institute of Higher Education and Research (DU), Sawangi (Meghe), Wardha, Maharashtra, India*

[b] *Department of Radio-Diagnosis, Datta Meghe Medical College Nagpur, Datta Meghe Institute of Higher Education and Research (DU), Sawangi (Meghe), Wardha, Maharashtra, India*

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ABSTRACT

The co-occurrence of Mega Cisterna Magna and Periventricular Nodular Heterotopia in an adult female patient is an uncommon and intriguing observation. Most instances are X-linked, typically with the Xq28-localized filamin A gene FLNA as the culprit. In this case study, we present a 52-year-old female patient who sought medical care for recurring headaches and epilepsy. The present case emphasizes the necessity for ongoing study and exploration into the clinical trajectory and imaging of uncommon correlations between nodular heterotopia and mega cisterna magna.



## Introduction

The term "heterotopia" in medical terminology describes the presence of incorrectly situated neuronal accumulations. These neurons can either be found near the cerebral ventricles or within the cerebral white matter when their migration to the cerebral cortex is interrupted prematurely. Alternatively, heterotopia can also describe neurons that have migrated excessively and are in the subpial space [1]. Based on the extent of migration, 3 distinct categories can be identified: periventricular (subependymal), subcortical, and banded which is also called double cortical heterotopia [2]. The most observed heterotopia in clinical practice is periventricular nodular heterotopia, representing approximately 15%-20% of all cases in cortical dysgenesis series [3].

The cause of periventricular nodular heterotopia is a problem with the neural progenitors lining the lateral ventricles.

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* Corresponding author.
E-mail address: priyalispriyal@gmail.com (P. Shrivastava).

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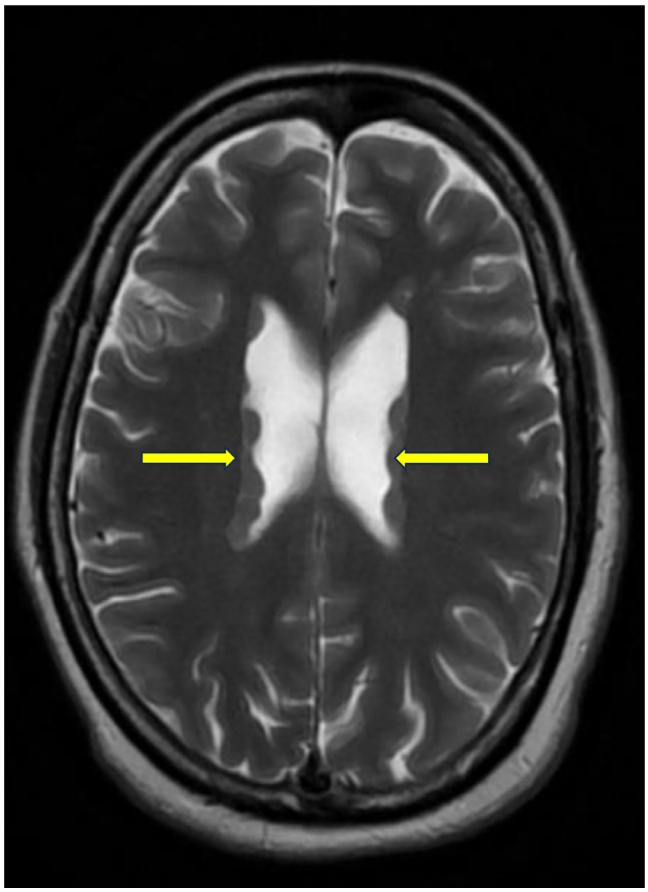

**Fig. 1 – Axial MRI T2WI: multiple nodular periventricular subependymal altered signal intensity lesions diffusely along the body of both lateral ventricles following gray matter signal intensity (yellow arrows).**

A rising body of evidence clearly shows that cortical malformation is largely caused by mutations in the filamin A gene (FLNA). Through the activation of ADP-ribosylation factors (ARFs), these mutations influence actin dynamics and regulate vesicle formation and transit [4]. Periventricular nodular heterotopia may be incidentally detected in asymptomatic individuals, but more commonly, they come to attention during the evaluation of delayed developmental milestones or epilepsy [5]. Magnetic resonance imaging (MRI) serves as the primary diagnostic modality, revealing clusters in the cortex that appear isointense and do not enhance following gadolinium injection [2].

## Case presentation

A 52-year-old woman who had been diagnosed with epilepsy at 15 years of age arrived at the hospital complaining of headaches she had been experiencing for the preceding six months. She had taken antiepileptics for a few years and stopped medication against the treating physician's advice. She had no complaints of vomiting, fever, or weight loss. Her prior surgical history was unremarkable in terms of any substantial procedures or hospital stays. She had neither diabetes nor hypertension. Her blood tests turned out within normal limits. Except for the noted seizures, no cutaneous lesions or neurological signs were detected. She had to discontinue junior high school due to socioeconomic limitations but successfully completed it. Her cognitive function falls within the normal range. For further evaluation, a non-contrast MRI scan of the brain was performed (Figs. 1-4).

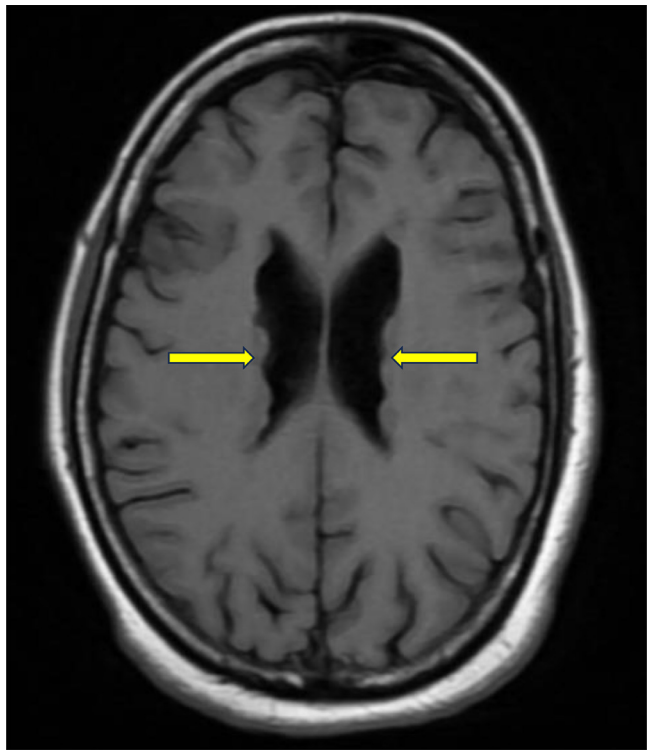

**Fig. 2 – Axial MRI T1WI: multiple nodular periventricular subependymal altered signal intensity lesions diffusely along the body of both lateral ventricles following gray matter signal intensity (yellow arrows).**

## Treatment and outcome

In managing this patient, a conservative approach involving antiepileptic medication and symptom management was deemed appropriate, given the relatively mild symptoms and uncertain clinical significance of Mega Cisterna Magna. Surgical intervention was not considered at this stage, emphasizing the importance of carefully weighing the risks and benefits in such a unique case.

## Discussion

The co-occurrence of Nodular Heterotopia and Mega Cisterna Magna in an adult female patient is a rare and interesting finding.

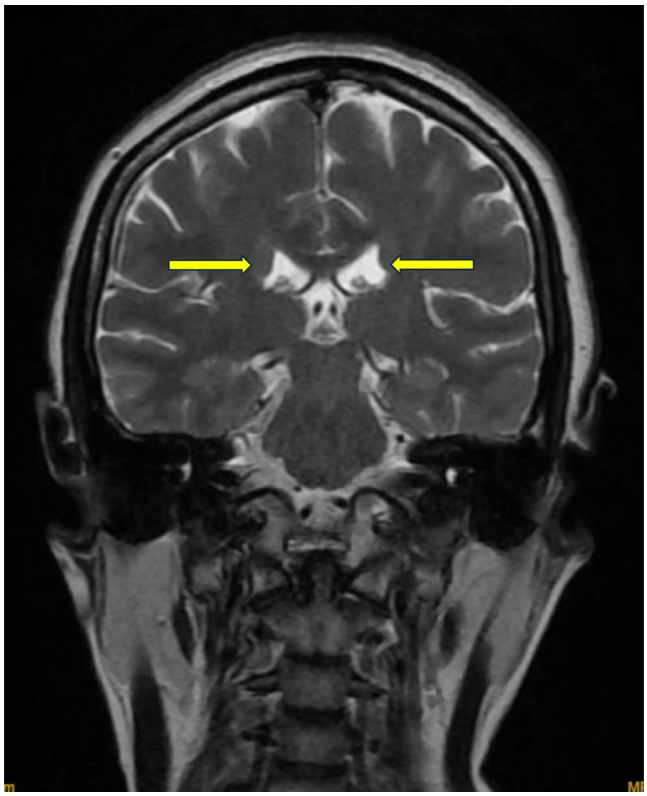

**Fig. 3 – Coronal MRI T2WI: multiple nodular periventricular subependymal altered signal intensity lesions diffusely along the body of both lateral ventricles following gray matter signal intensity (yellow arrows).**

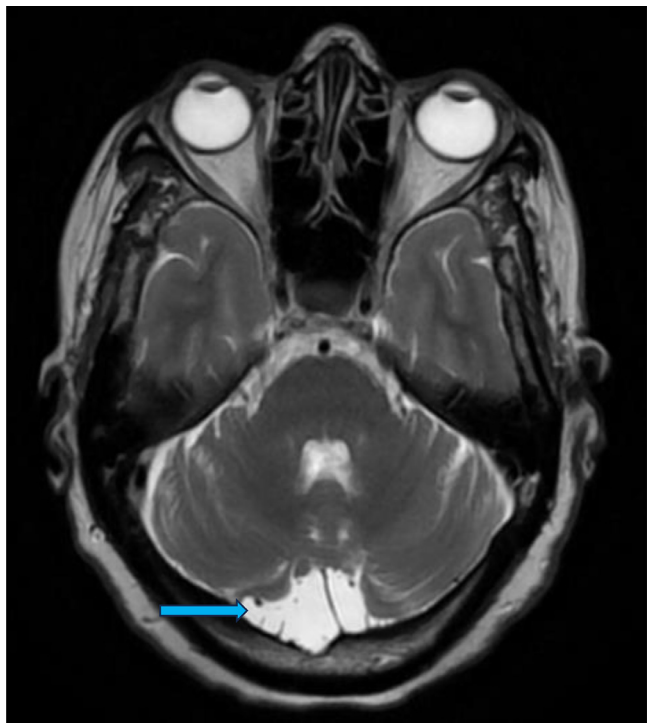

**Fig. 4 – Axial MRI T2WI: large retro-cerebellar fluid-filled space following CSF intensity on all sequences with normal cerebellar vermis suggestive of Mega Cisterna Magna (blue arrow).**

The interruption of regular neuronal migration along radial glial cells can lead to the formation of visibly abnormal clusters of "heterotopic" gray matter. These accumulations can be located anywhere within the space between the ventricles and the pia mater. They may occur as single or multiple masses and can either manifest independently or coexist with other malformations. Based on the extent of migration, 3 distinct categories can be identified: periventricular (subependymal), subcortical, and banded which is also called double cortical heterotopia [2].

Periventricular Nodular Heterotopia comprises circular clusters of typical neurons and glial cells, lacking a layered structure. These clusters are situated in proximity to the periventricular germinal matrix, which is why they are referred to as periventricular or subependymal nodular heterotopia [6].

Patients can also be categorized into 5 periventricular nodular heterotopia groups based on imaging data: (1) bilateral and symmetrical; (2) bilateral single-noduled; (3) bilateral and asymmetrical; (4) unilateral; and (5) unilateral with extension to the neocortex [6].

This disorder has been linked to at least 20 genes, with the filamin A gene FLNA being the one that is most frequently altered. However, it is also advised to include ARF1 in diagnostic cortical malformation gene panels. Periventricular nodular heterotopia has a wide range of anatomical and clinical characteristics [4]. Pathogenic genes connected to subependymal heterotopia have been identified, and they can be separated into X-linked and non-X-linked inheritance patterns. Most instances are X-linked, typically with the Xq28-localized filamin A gene FLNA as the culprit [7]. In 1993, Oda et al. [8] reported the first documented case of familial nodular heterotopia with mega cisterna magna.

Neuronal migratory anomalies have been linked to vascular abnormalities, genetic abnormalities like point mutations in the filamin A gene (FLNA), environmental abnormalities like methylmercury poisoning, and environmental abnormalities like radiation exposure. There are allegedly additional associations, including those with trisomy 13, fetal alcohol syndrome, and neurofibromatosis type I [2].

Subependymal heterotopia exhibited a robust correlation with additional structural abnormalities such as Chiari malformation, cerebral cortical malformations, and anomalies of the corpus callosum [7].

A mega cisterna magna (cisterna magna >10 mm) is the result of a defect in the posterior membranous area during embryogenesis [9].This condition is usually considered a benign anatomical variant rather than a pathological condition. It does not typically cause symptoms on its own and is often discovered incidentally during brain imaging for unrelated reasons.

Gonzalez et al. studied related abnormalities in research where they retrospectively reviewed MR images of 200 individuals who had previously been diagnosed with Periventricular nodular heterotopia. They discovered frequently related malformations including mega cisterna magna, brain stem

malformations, vermis malformations, cerebellar hemispheric malformations, and malformations involving the cerebral cortex. It is important to note that the study found that mega cisterna magna was one of the linked abnormalities in 12% of Periventricular nodular heterotopia patients. The patient in our study also had a mega cisterna magna incidental finding.

Bilateral and symmetrical periventricular nodular heterotopia occurs mostly in female subjects, also observed in our patient [5].

Periventricular nodular heterotopia is typically identified through seizures. The study by Battaglia et al. provides evidence supporting the notion that epilepsy in individuals with PNH is caused by irregular anatomical circuitry, which encompasses the heterotopic nodules along with neighboring archicortical and neocortical regions [6].The patient's recurrent headaches may be attributed to the epileptiform discharges associated with Nodular Heterotopia, although the exact mechanisms require further exploration.

These are frequently of the partial and drug-resistant type. With an average age of 14 years, these seizures often start between the ages of 2 and 14 [2]. Our patient also reported her first episode of seizure at 15 years of age.

In Max Lange's study [10], it was observed that a higher incidence of the condition occurred in females when it was linked to the X-linked FLNA gene. Studies by Gonzalez and Zianki also indicated a greater occurrence of the condition in females. This suggests a potential X-linked FLNA gene mutation in our patient. However, due to resource constraints, genetic testing was not conducted to confirm this hypothesis.

MRI is the modality of choice in assessing heterotopic gray matter. On all MRI sequences, heterotopic tissue follows gray matter. In contrast to the normal control subjects, general MR spectroscopy shows a decline in the NAA/Cr ratio in the heterotopic gray matter [11].

Fetal ultrasound is a safe method for diagnosing many fetal cerebral abnormalities, but its use is restricted to showing brain parenchyma and the side near the mother's spine. It is also susceptible to interference from the skull and gases, which makes it difficult to detect SEH in the early stages of pregnancy. Additionally, genetic testing is expensive and time-consuming in developing nations. A quick, repeatable, affordable, and reliable option for identifying and screening familial nodular heterotopia is the adult or fetal MRI [7].

Frequently, a conservative approach involving antiepileptic medication is employed. The deep position of PVNH and the eloquent cortex or white matter that lies above it imposes restrictions on resective surgery. Recently developed stereotactic MR-guided laser interstitial thermal treatment (MRgLITT) is now accessible [12].

## Conclusion

This case highlights the need for continued research and investigation into the clinical course and imaging of rare associations of Nodular Heterotopia with Mega Cisterna Magna. The clinical significance of this association raises intriguing questions about the evolution and management of these neurodevelopmental anomalies. It underscores the complexity of neurodevelopmental anomalies and their potential to present with diverse clinical phenotypes. Clinicians and researchers should remain vigilant in considering uncommon X-linked FLNA gene mutation.

## Patient consent

We confirm that the patient's informed consent has been acquired in a language comprehensible to them and in their own words for the study titled "Unveiling the intriguing puzzle: Nodular heterotopia and Mega Cisterna Magna in an adult female."

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