A Rare Presentation of Bilateral Periventricular Nodular Heterotopia with Intra-axial Pontine Lesion: A Case Report and Treatment Approach

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A rare presentation of bilateral periventricular nodular heterotopia with intra-axial pontine Lesion: A case report and treatment approach

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ABSTRACT

This report presents a rare case of a 19-year-old male with bilateral periventricular nodular heterotopia (PVNH), a congenital brain abnormality resulting from failed neural cell migration, along with an intra-axial pontine lesion of unknown pathology.

The differential diagnosis of childhood brainstem tumors in such cases commonly includes diffuse midline glioma (DMG), which is associated with a dismal prognosis due to H3 K27 gene mutation. However, this case exhibits a unique focal dorsal exophytic brainstem glioma variant, accounting for only a small percentage (approximately 10 %) of pontine tumors and carrying a more favorable prognosis. The lesion is suspected to be a pilocytic astrocytoma, presenting distinct neurological symptoms. In this case, the patient presented with symptoms include mainly occasional tonic-clonic seizures, right side mild spasticity with ataxic gait and right eye blurring of vision along with right side facial palsy. The patient's clinical evaluation, in conjunction with various medical diagnostic tests and MRI with and without contrast, led to the final diagnosis. Management began with anti-epileptic medication, with a plan for further treatment and follow-up.

1. 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]. This condition is caused by mutations in the filamin A gene (FLNA) located on the Xq28 chromosomal locus. FLNA is a crucial cross-linking protein found in non-muscle cells, playing a significant role in signaling and cell migration [2]. Mutations in the FLNA gene have been associated with a wide range of disorders, including cerebral periventricular nodular heterotopia (PVNH) [3]. This rare disease can have substantial impacts on morbidity and mortality rates worldwide [4].

Individuals with PVNH are predominantly female and often present with epilepsy as their sole comorbid condition. Although less common in males, the condition tends to affect them more severely, leading to a broader array of symptoms, such as epilepsy, intellectual disability, and various other neurological manifestations.

2. Patient informations

A 19-year-old male patient from Syria visited our clinic with episodic tonic-clonic seizures, right-side facial palsy associated with numbness, dysarthria, general fatigue, and ataxic gait. His medical history was unremarkable, with no chronic illnesses, prior surgical interventions, or relevant psycho-social history reported.

The onset of neurological symptoms was recorded as 15/4/2023, marked by the development of mild right-side upper limb spasticity, which was more pronounced than in the lower limbs and predominantly affecting the right side. Over subsequent weeks, the patient's condition

Abbreviations: CLE, Congenital lobar emphysema, MRI, magnetic resonance imaging; FLNA, Filamin A; PVNH, Periventricular nodular heterotopia, DMG (diffuse midline glioma.

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worsened, leading to dysarthria, blurred vision in the right eye, and increasing difficulty maintaining balance while walking.

3. Clinical findings

3.1. Careful clinical neurological examination was done

- The motor power was intact, with hypertonia and hyperreflexia in the upper and lower limbs, more pronounced in the right leg than in the left. Loss of balance while walking, along with an ataxic gait, was noted.
- The sensation was intact without any neurological deficits.
- Cranial nerves examination showed moderate hearing loss in the right ear, with blurry vision in the right eye.

4. Signs

- The patient exhibits intentional tremors in both hands when asked to use them, with the tremors being more pronounced in the right arm.
- An abnormal finger-to-nose test was observed.
- Moderate hearing loss in the right ear was noted.
- He described a significant increase in appetite lately, which correlates with the beginning of his symptoms.
- A right-side facial weakness was observed, with an inability to raise his right eyebrow.

5. Diagnostic tests

5.1. Blood tests

Medical laboratory tests were conducted at the time of presenting symptoms in Syria and were repeated during the second visit in Egypt.

All labs were within the normal range (Fig. 1) except for Vitamin D deficiency, which showed improvement later. When inquiring about the patient's sun exposure and dietary habits, the parents mentioned that the patient didn't have proper sun exposure during childhood and had poor dietary habits. Consequently, a parathyroid hormone profile was later ordered, and the results were found to be within the normal range. As a result, the patient was prescribed Vitamin D supplements.

All results will be summarized in the table below, indicating the dates of visits and the corresponding reference ranges:

6. Radiologic diagnostics

Patients underwent a diagnostic MRI with and without contrast to assess radiological changes and identify any brain abnormalities (Figs. 2, 3, 4, and 5).

7. Discussion

Filamin A is a pivotal protein that plays a critical role in cellular function by facilitating the connection between actin filaments and exerting precise control over the shape and motility of various cell types,

LABS	20/04/2023	7/29/2023	Unite	Reference Range
Hemoglobin	14	14.7	g/dl	F 12-16 M 13-17
MCV	82	80	FL	78-100
Neutrophils	3	2	%	1-8%
Basophils	0	0	%	0-1
Amylase	33	30	U/L	Less than 90U/L
Creatinine	1.1	1	mg/dl	M 0.9-1.5 F 0.7-1.3
Urea	3.2	5.6	mmol/L	2.5-10.7
INR	1	1.1		M 0.90-1.15 F 0.89-1.16
PT	13	13	sec	10-13.
PTT	29	32	sec	25-36
AST	20	33	U/L	Up to 50
ALT	27	45	U/L	Up to 50
Platelets	230	250	x10*3	150-500
R blood sugar	143	123	mg/dl	up to 160
Lymphocytes	10	12	%	20-45
RBCs	4.5	5.1	x10*6	F 4.1-5.4 M 4.5-6.0
CRP	Negative	Negative		Negative <6
NA	137	135	mmol/L	135-145
K	4.6	3.7	mmol/L	3.5-5
TSH	2.37	2.55	ulU/mL	0.55-4.78
FREE T3	4	3.88	pg/ml	2.3-4.2
FREE T4	1.3	1.7	ng/dL	0.8-1.8
25 OH VIT D (total)	12.15	14.6	ng/mL	Deficient <20

Fig. 1.

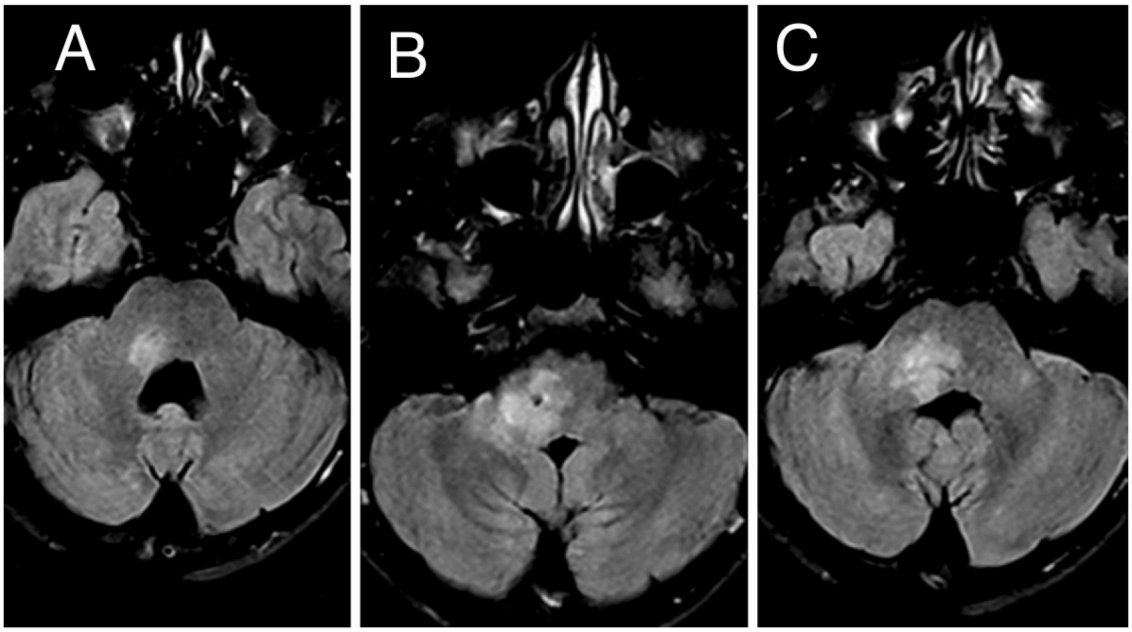

Fig. 2. A, B, & C: Axial MRI of the patient revealed an infiltrative intra-axial pontine lesion, measuring 4–15 mm in the right cerebellar peduncle and pons. The lesion appeared non-homogeneously hyperintense on T1 FLAIR/S.

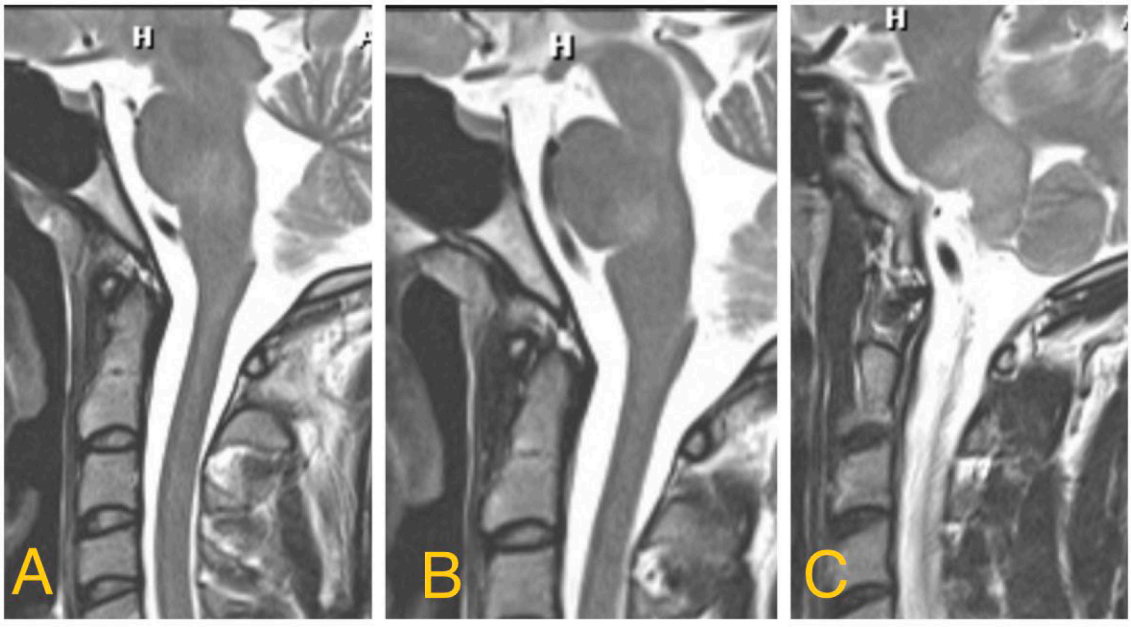

Fig. 3. A & B: Sagittal T2 MRI shows a hyperintense pontine infiltrative lesion that extends into the cerebellum, with no mass effect on the surrounding structures. C: The image reveals significant infiltration extending from the pons to the right cerebellar peduncle. H*: Hypothalamus.

including neurons, blood vessels, and skin cells [2]. Null mutations in the FLNA gene have been found to lead to significant impairments in neuronal migration, vascular function, and the structural integrity of connective tissues. Conversely, gain-of-function missense mutations in the same gene have been associated with a spectrum of abnormalities affecting multiple organ systems, with a notable impact on skeletal development [5]. One neurological abnormality observed in the (CNS) associated with FLNA mutations is (PVNH). This condition leads to the formation of nodules or clusters of neurons situated outside their usual location near the ventricles[6].

PVNH can be associated with various neurological symptoms depending on its location and extent [7]. In this case, the presence of PVNH nodules in the cerebral ventricles may contribute to the patient's motor abnormalities, which appeared in the clinical examination as hypertonia and spasticity.

The patient's clinical presentation also includes sensorineural hearing loss and visual impairments. These findings may be attributed to the involvement of cranial nerves associated with these functions. The decreased hearing sensation in the right ear and decreased visual acuity in the right eye could be related to compression or infiltration of these cranial nerves by the pontine lesion or PVNH nodules [8].

The manifestation of intentional tremors in both hands and abnormal performance in the finger-to-nose test are indicative of cerebellar dysfunction. The cerebellum is known to have a pivotal role in the

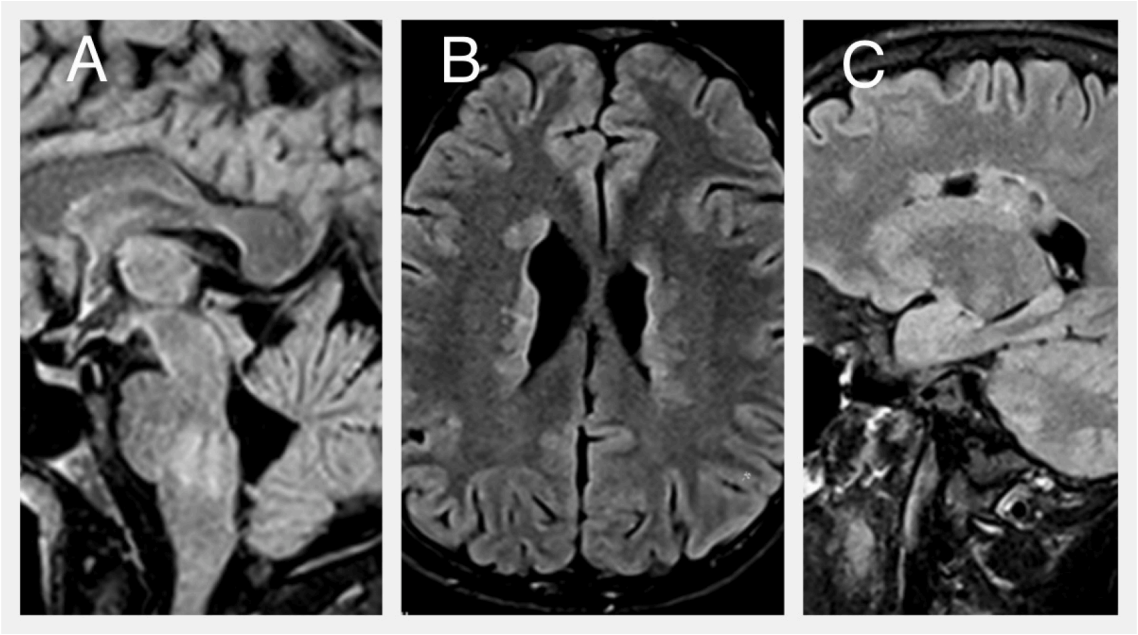

Fig. 4. Axial and sagittal MRI findings: A: The image shows a hypointense infiltrative cerebello-pontine lesion, which does not exert any pressure effect on the 4th ventricle. B: Bilateral hypointense multiple nodules (PVNH) are observed in both cerebral ventricles, with no midline shift. There is a mild decrease in the size of the right ventricle. C: The sagittal Flair MRI displays multiple hypointense nodules filling the cavity of the lateral ventricles. These nodules do not enhance with contrast.

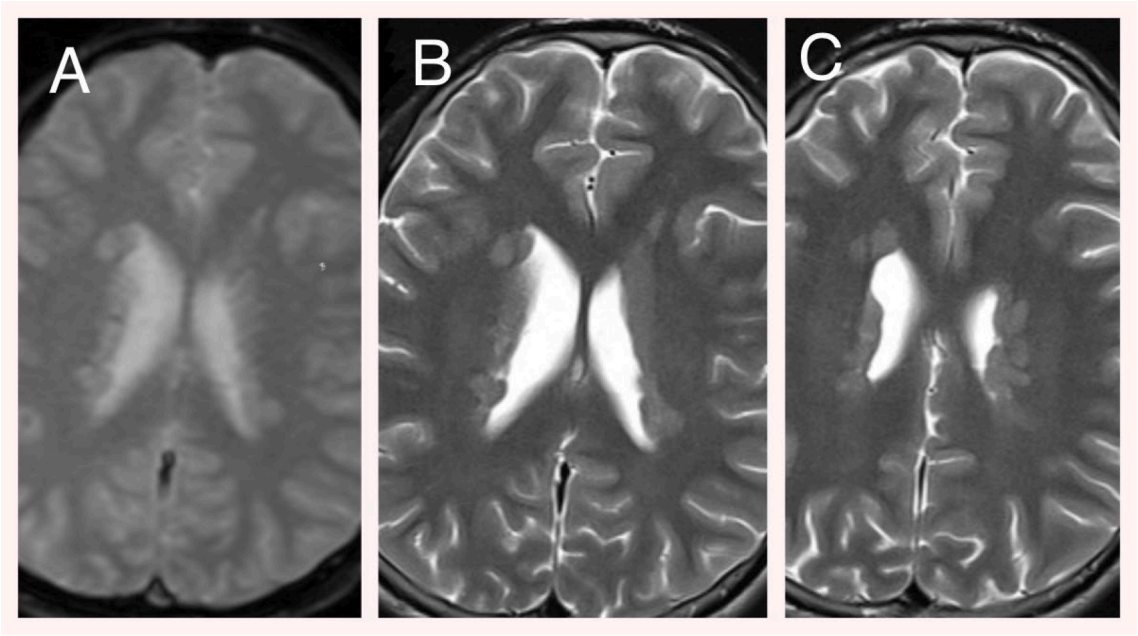

Fig. 5. PVNH in both lateral ventricles are shown in both ventricles more in the left side as shown in A,B&C.

coordination of voluntary movements and the maintenance of balance. The infiltrative nature of the pontine lesion extending into the cerebellum may disrupt its normal functioning, leading to ataxic gait and loss of balance observed in this patient.

The detection of Vitamin D deficiency during laboratory tests is considered an incidental finding, likely resulting from inadequate sun exposure. Although it may not directly contribute to the patient's neurological symptoms, addressing this deficiency is crucial as it can significantly impact overall health and well-being. Therefore, managing the deficiency becomes essential to promote better health outcomes.

The identification of an intra-axial pontine lesion on Axial MRI in this patient necessitates further investigation. The infiltrative nature of the lesion raises concerns about potential neoplastic or inflammatory processes. However, to ascertain the precise cause of the lesion, additional diagnostic procedures such as biopsy or cerebrospinal fluid analysis would be required. Unfortunately, due to the complexity of the lesion's location near the cerebral ventricles, these tests were not performed to avoid the risk of hemorrhage. Although cerebrospinal fluid analysis was planned, the patient returned to his home country before the procedure could be carried out. We advised the family to pursue the necessary diagnostic tests, including Para-thyroid profile tests, in their home country to aid in the proper diagnosis and management of the patient's condition.

In previous instances of (PVNH), patients have commonly presented

with refractory epilepsy, cognitive and developmental challenges, and an unfavorable prognosis (Broix et al., 2016). Nevertheless, in our patient's case, a positive response to anti-seizure medications was observed, and there were no notable signs of significant cognitive or developmental impairment. This observation suggests that there could be variations in the clinical manifestations and outcomes of PVNH among different individuals.

The existing literature supports the notion that a higher proportion of individuals with PVNH suffer from seizures[9]. This aligns with our case where the presence of seizures prompted further investigation, leading to the diagnosis of PVNH, which was subsequently confirmed through neuro-imaging. Regrettably, due to the urgency to stabilize the patient, a gene test could not be conducted before he returned to his home country. This genetic test would have been valuable in precisely determining whether there was an FLNA or other genetic mutation contributing to his condition.

The hyperphagia observed in our patient is consistent with a similar case reported by [10]. This finding contributes to the existing understanding of PVNH, which is currently hindered by the absence of genotype-phenotype correlations. While it is plausible that this hyperphagic behavior could be attributed to mutations in genes such as melanocortin 3 or 4 receptor, leptin, or leptin receptor, we cannot definitively exclude other monogenic causes.

The coexistence of PVNH and an intra-axial pontine lesion suggests a possible shared etiology or pathogenic mechanism. One hypothesis is that the pontine lesion could be a result of abnormal neuronal migration during embryonic development, similar to PVNH [11]. This could lead to aberrant positioning or clustering of neurons within the pons, resulting in an infiltrative lesion. Another possibility is that the pontine lesion represents a separate pathological entity that coincidentally coexists with PVNH. In this case, it would be important to investigate other potential causes for the pontine lesion, such as neoplastic or inflammatory processes. However the infiltrative lesions that do not exhibit aggressive behavior or neoplastic characteristics.

8. Treatment approach

- The first line of treatment focused on controlling seizures through the use of anti-epileptic medications. The management and medications employed in the treatment were as follows:
  Tegretol (Carbamazepine): The patient was prescribed Tegretol at a dose of 100 mg/kg, to be taken as a tablet every 12 h. The dosage was adjusted as necessary during the course of treatment.
  Teraterm (Levetiracetam): Another medication used was Teraterm (Levetiracetam) at a dose of 500 mg/kg, to be taken as a tablet every 12 h. Similar to Tegretol, the dosage of Levetiracetam was also adjusted as needed during the treatment period.
  Ketogenic Diet: In addition to the anti-epileptic medications, a ketogenic diet was recommended for the patient. The ketogenic diet was closely monitored by a specialized dietitian. This dietary intervention is particularly beneficial for some forms of epilepsy, especially cases that are resistant to conventional medications. Several studies have demonstrated the efficacy of the ketogenic diet in controlling seizures in such cases.
- Epilepsy surgery together with deep brain stimulation,responsive neurostimulation and vagal stimulation were all discussed with the family in case of resistance of medications to seizures.
- Multivitamins were prescribed as well as it has an important role especially that ketogenic diet may not provide the full range of vitamins the body needs.
- Careful treatment of vitamin D deficiency was advised with proper sun exposure and monthly vitD level follow-up.

9. Conclusion

This case report highlights a rare combination of periventricular nodular heterotopia (PVNH) with an intra-axial pontine lesion in a 19-year-old male. 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 together with infiltrative pontine lesions involving the right cerebellar peduncles. The differential diagnosis for these lesions includes diffuse glioma and pilocytic astrocytoma. Blood tests were ordered and showed normal laboratory values except for vitamin D deficiency, which was attributed to decreased sun exposure and poor dietary habits. The patient's condition was managed with anti-epileptic medications as the first line of treatment to control his episodic seizures. He was also advised to follow a ketogenic diet with a dietitian, as this has been shown to be helpful in patients with similar conditions. The patient will continue to be monitored with follow-up MRIs every 6 months and clinical evaluations.

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.

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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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