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Case Report

Grey matter hypertropia in a child with recurrent seizure: A case report ☆,☆☆

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ABSTRACT

Heterotopia is a common anomaly of cortical development often associated with early-onset and familial epilepsy. Grey matter heterotopias are macroscopically classified into nodular and diffuse types and clinically categorized as subependymal, subcortical, or band heterotopia. They are frequently associated with other neurological conditions, such as corpus callosum agenesis, pachygyria, schizencephaly, polymicrogyria, Chiari II malformation, and basilar cephalocele. The clinical presentation varies depending on the thickness of the arrested neuronal band, ranging from partial complex and atypical absence epilepsy to normal cognitive function, developmental delay, or severe intellectual disability. Magnetic resonance imaging (MRI) is the preferred diagnostic modality, as it reveals the abnormally located heterotopic grey matter within the white matter. Carbamazepine is the most commonly prescribed antiepileptic drug, but its use depends on patient-specific factors such as tolerance, side effects, and efficacy. Here, we report the case of a 7-year-old male with a history of three seizure episodes over the past three years, initially diagnosed as febrile seizures with atypical focal features.

Introduction

Gray matter heterotopia also called neuronal heterotopia is an occasionally observed disorder of neuronal migration with clusters of cortical neurons in an unusual anatomical location. It is the outcome of radial migration arrest of neurons in-utero between 6 and 16 weeks of gestation from the lateral ventricle wall germinal matrix to the developing cerebral cortex [1]. Anatomically they are classified as nodular and laminar forms. Nodular forms are often localized at the corners of the lateral ventricles as subependymal masses of gray matter forming rounded nodules clusters distinctly separated from the cortex by white matter which are myelinated. Thick layers of white matter separate the laminar structure from the cortex and ventricle walls [2].

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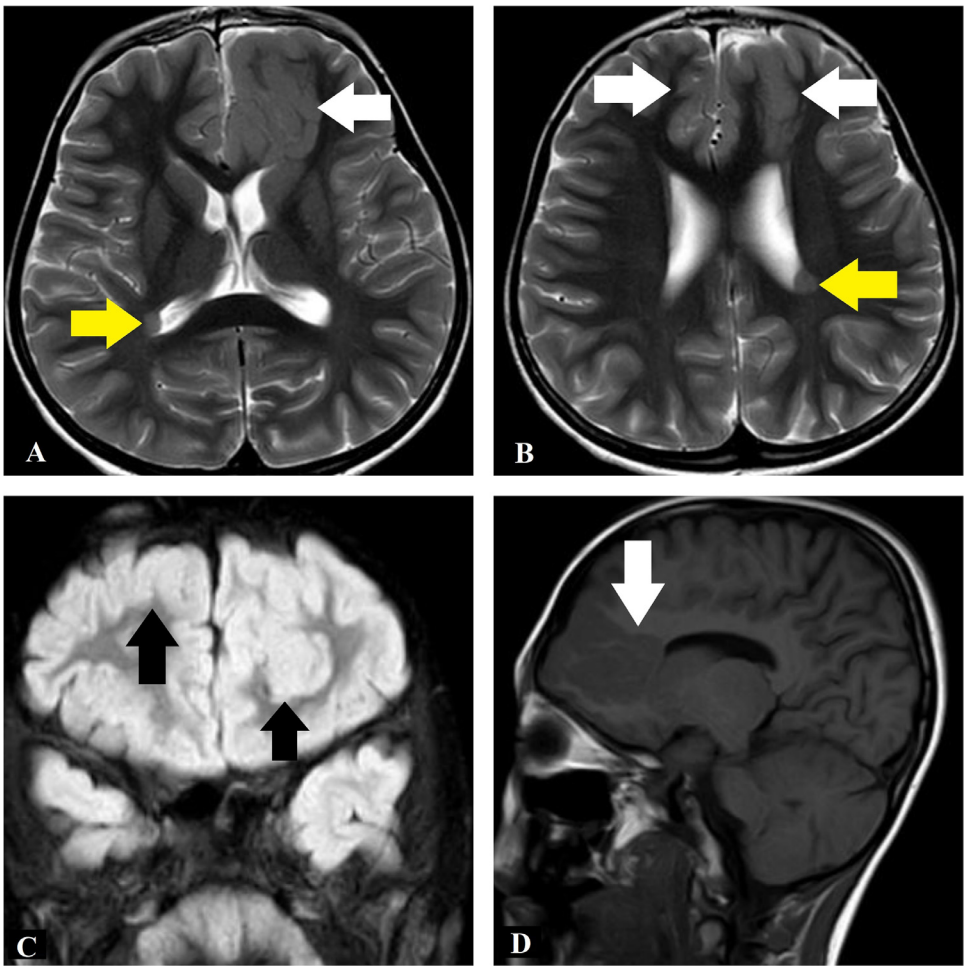

Fig. 1 – (A) T2 axial image at thalami level shows a T2 hypointense lesion in the left frontal lobe extending to the frontal horn (white arrow) and a nodular lesion in the right ventricle atrium (yellow arrow). (B) T2 axial image at the parietal level shows mild cortical thickening in both frontal lobes (white arrows) and a left periventricular nodular lesion (yellow arrow). (C) Fluid attenuation inversion recovery (FLAIR) coronal image shows a lesion with signal intensity similar to the cerebral cortex in left frontal white matter with cortical thickening in both frontal lobes (black arrows). (D) Sagittal image shows a well-defined cortical-like lesion in the left frontal lobe extending to the frontal horn. Diagnosis of grey matter heterotopia in left frontal lobe, focal cortical dysplasia in bilateral frontal lobes and bilateral subependymal heterotopia was made.

Clinically they are classified as subependymal, subcortical, and band heterotropia. Women affected by subependymal heterotopia develop partial seizure in the second decade of life. At the same time, males are symptomatic depending upon the presence of X-linked which is associated with CNS and visceral anomalies or autosomal variants similar in course to symptomatic women. The subcortical heterotopia is linked to severe developmental delay while band heterotopia is usually observed in women; men with XLIS or DCX mutation generally die in utero or have severe brain malformations [3]. Diagnosis of GMH demands highly specialized expertise and MRI is the diagnostic tool of choice. The treatment strategies depend on the nodules' distribution, location, and number [4].

The index case is a seven-year-old boy presenting with a history of recurrent febrile seizures. Imaging revealed features of neuronal migration abnormality with band heterotopia in the left frontal lobe, nodular heterotopia in bilateral periventricular white matter, and focal cortical dysplasia in the right frontal lobe. This case highlights the need to consider the possibility of GMH in children presenting with recurrent seizures.

Case presentation

A seven-year-old male child presented to the OPD, with abnormal involuntary jerky movements involving his right side of the body; face, and upper and lower limbs lasting for a few minutes. It was not associated with loss of consciousness, confusion, frothing, ataxia, or incontinence. He has a history of 3 episodes of seizures in the past 3 years and has been diagnosed with febrile seizures. He was delivered at full term through normal vaginal birth at the hospital and cried immediately after birth. Development milestones are appropriate for his age with immunization as per national immunization schedule, details unknown. Physical examination displayed no abnormalities.

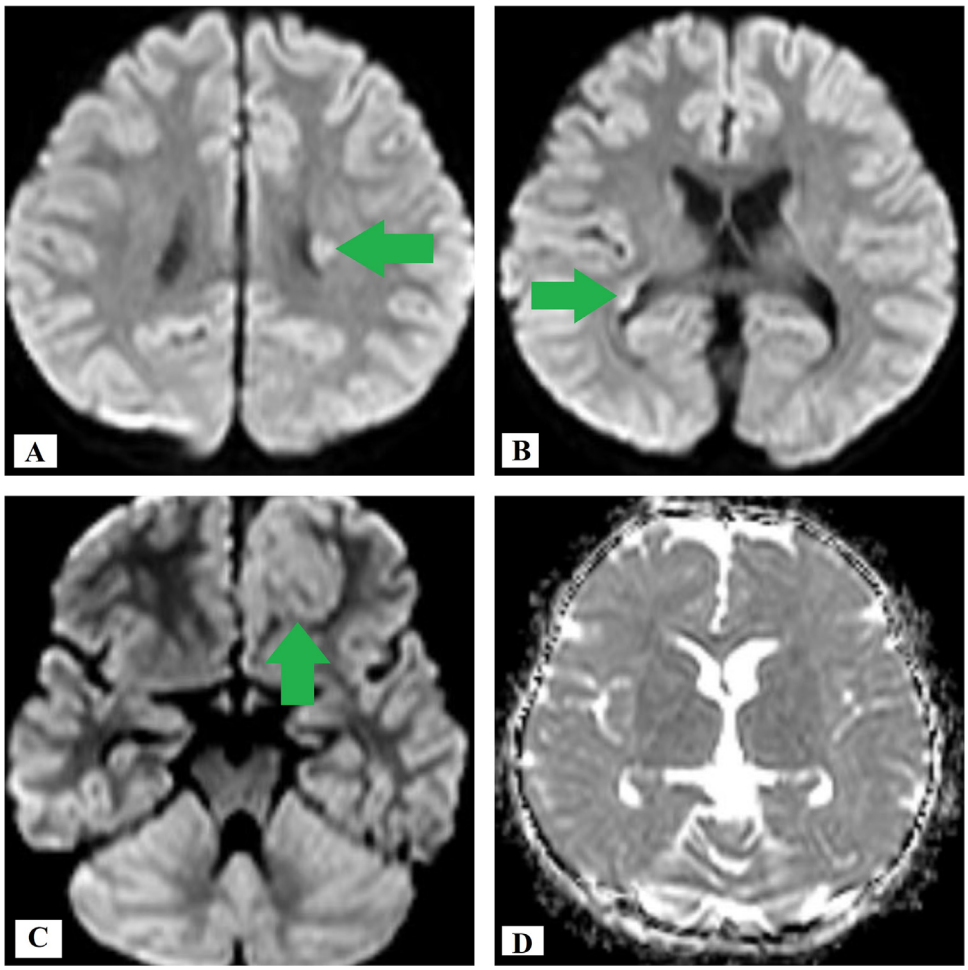

Fig. 2 – (A-C) Axial diffusion-weighted images at different brain levels show a mildly high signal in the grey matter heterotopia of the left frontal lobe and bilateral subependymal regions (green arrows). The lesions are isointense in the apparent diffusion coefficient images (D). No blooming is seen within the lesions on susceptibility-weighted images (not shown).

(1A) T2 axial image at thalami level shows a T2 hypointense lesion in the left frontal lobe extending to the frontal horn (white arrow) and a nodular lesion in the right ventricle atrium (yellow arrow). (1B) T2 axial image at the parietal level shows mild cortical thickening in both frontal lobes (white arrows) and a left periventricular nodular lesion (yellow arrow). (1C) Fluid attenuation inversion recovery (FLAIR) coronal image shows a lesion with signal intensity similar to the cerebral cortex in left frontal white matter with cortical thinning in both frontal lobes (black arrows). (1D) Sagittal image shows a well-defined cortical-like lesion in the left frontal lobe extending to the frontal horn. Diagnosis of grey matter heterotopia in left frontal lobe, focal cortical dysplasia in bilateral frontal lobes and bilateral subependymal heterotopia was made.

A magnetic resonance imaging of the brain revealed a T1/T2 hypointense area (signal intensity similar to grey matter) in the left frontal lobe, extending to the frontal horn (Fig. 1A,D). The area shows signal intensity similar to grey matter in fluid attenuation inversion recovery (FLAIR) image as well (Fig. 1C). A thickened cortex is also seen in this region. A thickened cortex is also seen in the right frontal lobe (Fig. 1B). Nodular lesions of grey matter signal intensity were noted in bilateral periventricular white matter adjacent to the bodies and atrium of lateral ventricles (Fig. 1A). The lesions show slightly high signal in diffusion weighted images (Fig. 2A, B and C). However, signal in apparent diffusion coefficient (ADC) is normal (Fig. 2D). Electroencephalogram (EEG) demonstrated abnormal discharge from the bilateral frontal lobe. His electrocardiogram, and routine laboratory examinations (including complete blood cell count, urinalysis, liver function, renal function, electrolytes, and thyroid function) were within normal limits. A team of pediatrician and neurologist's opinion was sought and he was started on carbamazepine. His seizures are now under control and now is followed up in the outpatient department regularly.

Discussion

The grey matter heterotopias are a subset of cortical formation disorder characterized by normal neurons in abnormal

locations due to a defect in the migration of neurons to the overlying cortex from the ventricular zone between the 10th and 16th week of gestation. This condition has been associated with fever, radiation, toxins, or single gene mutations like doublecortin and filamin involved in radial neuronal migration and confirmed to be essential for normal radial neuronal migration [5,6].

Heterotopic cells can adopt a nodular or laminar form. Depending upon their positional shift, they are categorized into periventricular or subependymal, subcortical, and banded or double cortical heterotopic; Periventricular nodular type being the most common. These neurons have never begun migration, preserving their function stayed adjacent to the lateral ventricles with cerebral cortex normal macroscopically. These heterotopic nodules can produce white matter connections between themselves and the overlying cortex [7]. In our case, a thick band-like area displaying signal intensity similar to that of grey matter was noted in the left and right frontal lobes.

Many studies have reported that patients of all three heterotopia groups are very likely to develop epilepsy more commonly in females than males. Seizures and developmental delays are typically present in the first few years of life. Over time, seizures may become chronic and resistant to treatment. In some instances, neurological and physical examination can be normal; though hypotonia, poor fine motor, and dysarthria in certain cases, pyramidal symptoms can still develop [8]. The seizure can vary among patients from focal onset (partial seizures) to generalized onset seizures, with simple/complex partial seizures (68 %-69 %) being most common with drop attacks (26 %-30 %), absence seizures (23 %-29 %), and myoclonic seizures (14 %-16 %) may appear alone or in combination (43 %-60 %). Generalized tonic-clonic seizures are found in 19 %-57 % of cases [9]. They are commonly associated with other neurological conditions such as corpus callosum agenesis, pachygyria, schizencephaly, polymicrogyria, Chiari II malformation, and basilar cephalocele [6].

Accurate diagnosis of GMH relies on expert knowledge from highly specialized and multiple disciplines. MRI excels in detecting and characterization of GMH. A CT scan can detect sufficiently large grey matter heterotopias because due to their density, they can be distinguished from their surrounding white matter. SCH nodules are often bilateral and located at the lateral ventricles' occipital horns and trigone. It has been reported that SEH causes minimal brain distortion of the remaining but focal SCH causes a reduction in hemisphere size, qualitatively diminished white matter, and substantial distortion of the ventricles. Band heterotopia (double cortex syndrome) is more prevalent in females than males. MRI reveals the distinctive appearance of BH as a smooth, well-defined gray matter layer running parallel to the lateral ventricle, with layers of white matter separating the overlying cortex and underlying ventricle. Bands are neither convoluted nor contiguous with the overlying cortex lacking blood vessels or CSF. A thicker band of heterotopic neurons; corresponds to a more significant disability and an increased risk of developmental delay. In electroencephalogram, unilateral or bilateral temporal epileptic discharges may be seen [10].

The possible differential diagnoses considered are tuberous sclerosis, choroid plexus papilloma, ependymal seeding from malignant tumors, and other anatomic variants [11]. The most frequently used medication for grey matter heterotopia and patients suffering from focal seizures is carbamazepine, though factors like side effects, tolerance, and effectiveness guide the treatment of choice. Surgical intervention is required in case of seizures resistant to conventional drug treatments and involves excision of the heterotrophic nodules by stereotactic techniques [7].

Conclusion

Grey matter heterotopia which occurs due to the arrest of migration of primitive nerve cells (neuroblasts) in the developing fetal cerebrum has critical implications for the development and function of the brain cortex, including seizure with studies suggesting it contributes to causing up to 40 % of drug-resistant epilepsy. Utilizing advanced imaging technology, MRI allows for precise diagnosis of the problem and helps guide the neurologist/physician to devise a more tailored management plan for the patient.

CRediT authorship contribution statement

Natasha Dhakal: Software, Writing – original draft. **Prajwal Dahal:** Conceptualization, Writing – original draft, Supervision.

Patient consent

A written consent was obtained from the patient for publication of the case report and accompanying images. A copy of written consent will be available for review by the editor-in-chief of this journal if requested.

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