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ORIGINAL ARTICLE

The clinical and imaging features of gray matter heterotopia: a clinical analysis on 15 patients

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Abstract

Objective To investigate the clinical and imaging features of gray matter heterotopia (GMH) and improve the clinicians' understanding of the disease.

Methods A retrospective study was performed on 15 patients with GMH diagnosed at The Affiliated Hospital of Xuzhou Medical University from November 2014 to November 2016. Their clinical and imaging features are also summarized.

Results The proportion of male and female patients was 2:1. The age of onset was 2~45 years and the average age was 19.1 years. There were 13 patients with epilepsy who also had cognitive decline (5 cases) and neurological deficit (3 cases). There were 2 patients with headache or dizziness. The imaging findings of GMH are unilateral or multiple spots in the periventricular or subependymal, subcortical, and centrum semiovale and are often accompanied by other cerebral malformations. We found that 10 patients had the subcortical type of GMH and 5 patients had the subependymal type or periventricular nodular heterotopia type. There were 8 cases of ventricular compression, 5 cases of ventriculomegaly, 5 cases of cerebral fissure malformation, 3 cases of pachygyria, 1 case of callosal agenesis, and 1 case of undeveloped septum pellucidum. All the patients were given symptomatic and supportive therapies and 3 patients were treated with antiepileptic drugs. Seizures were, however, poorly controlled.

Conclusion GMH should also be suspected in patients with juvenile onset of seizures, cognitive decline, and neurological deficits. Magnetic resonance scans may show lesions in the white matter of the brain with signals similar to the normal gray matter.

Keywords Gray matter heterotopia · Subcortical heterotopia · Periventricular nodular heterotopia · Ventriculomegaly · Magnetic resonance imaging · Epilepsy

Gray matter heterotopia (GMH) is a congenital developmental abnormality of the nervous system. While it can exist alone, it often coexists with other malformations of the central nervous system such as cerebral fissure deformity, ventriculomegaly, pachygyria, and callosal agenesis. Its main clinical features include epileptic seizure, cognitive decline, and neurological impairment [1]. This disease is relatively rare as there are very few reported cases in the literature. GMH tends to be missed and misdiagnosed, especially in cases of small lesions and atypical symptoms. We retrospectively analyzed the clinical data of 15 patients with GMH who were diagnosed at our hospital and discussed their clinical and imaging features to improve the physicians' understanding of the disease.

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Materials and methods

General information Fifteen patients with GMH admitted into the Neurology Department of The Affiliated Hospital of Xuzhou Medical University from November 2014 to

November 2016 were enrolled in this study. All the patients were diagnosed with the help of head magnetic resonance (MR) scans. Out of the 15 patients, 10 were males and 5 were females. The age of the enrolled patients ranged from 2 to 49 years old, and their age of onset ranged from 2 to 45 years old (average age of onset, 19.1 years). They all denied any positive family history of GMH. Their parents' marriages were not consanguineous.

Clinical features Thirteen patients had epileptic seizures as the main symptoms which were also associated with cognitive decline (5 cases) and speech disturbance (1 case). The other 2 patients mainly suffered from a paroxysmal headache and dizziness (see Table 1).

Medical imaging All 15 patients undertook head computed tomography (CT) scans and 3.0-T MR scans, including T1-weighted image (T1WI), T2-weighted image (T2WI), fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted image (DWI). Nine patients additionally undertook contrast-enhanced MR scans. MR scans in all the patients showed single or multiple slices of slightly longer T1 and slightly longer T2 signals in the subcortex around the subependymal zone which were similar to the normal gray matter signal. Subcortical heterotopia (SCH) was diagnosed in 10 patients which mainly involved fronto-temporal lobe while periventricular nodular heterotopia (PNH) was diagnosed in other 5 patients (Figs. 1 and 2). Other complications, including ventricular compression (8 cases), ventricular enlargement (5 cases), schizencephaly (5 cases), pachygyria (3 cases), dysplasia of corpus callosum (1 case), and undeveloped septum pellucidum (1 case), were also observed. Smaller subcortical lesions were observed in 2 patients. The brain CT scans did not show any abnormality. The contrast-enhanced MR scans undertaken by 9 patients did not reveal any abnormality (see Table 1).

Treatment All the patients were given the conservative treatment. Of the 13 patients with epilepsy, 6 were treated with carbamazepine, 2 were treated with oxcarbazepine, and 2 were treated with a combination of oxcarbazepine and lamotrigine. Other 3 patients with SCH complicated by multiple deformities had refractory epilepsy and were treated with a combination of carbamazepine, sodium valproate, and lamotrigine. None of the patients had a good response to the treatment. Two patients with the headache and dizziness were given symptomatic treatment.

Discussion

GMH is a congenital disorder that leads to an abnormal neuronal migration. GMH can be seen anywhere from ependyma to piamater including the cerebral cortex and cerebellum. In the latest classification for malformation of cortical development, GMH was classified as a malformation due to an abnormal neuronal migration [2]. Its main clinical features are summarized as follows.

Pathogenesis GMH is the result of an abnormal migration of neurons to the cerebral cortex. Although the exact reason has not been fully elucidated, many pathogenic genes are believed to play an important role in the proliferation and differentiation of neural progenitor cells into radial glial cells. Most scholars believe that abnormal neural migration or the failure of apoptosis of neuroblasts in the periventricular stroma during third to fifth months of embryonic development results into the inability of subcortical neurons to migrate to the normal site so they are abnormally accumulated in the white matter [3, 4]. However, more and more evidence has proved that genetic factors also affect the proliferation and differentiation of cortical neural progenitor cells [5]. At present, GMH has been divided into four types according to the site of occurrence; PNH, SCH, subcortical band heterotopia (SBH), and mixed type [6].

Clinical features Main clinical features in GMH are frequent seizures, mental retardation, and neurological dysfunction. Epileptic seizures are the most common clinical manifestation in GMH. In our study, 13 patients had epileptic seizures with an incidence of 86.7% which is consistent with previous studies [7]. Barkovich et al. [8] reported 20 cases of GMH and observed that the larger the gray matter lesion, the earlier is the onset of epilepsy, the more serious are the symptoms, the greater is the damage to brain tissues, and the patient is more likely to develop mental retardation and speech disorder. The patients with the adult-onset GMH only suffer from a mild cognitive decline. Most of the patients have a normal or slightly poor computation power. In our study, there were 5 patients with cognitive decline (33.3%) and 3 patients with neurological deficit (20%). Out of those 3 patients, 2 patients had unilateral hemiplegia and 1 patient had a speech dysfunction. In our study, the most common type of GMH was SCH (66.7%) followed by PNH (33.3%) while Zajac et al. [1] had reported that PNH is the most common type of GMH. Huppertz et al. [9] found that most patients with PNH had normal cognitive and motor functions and 82% of the patients

Table 1 Clinical features and imaging data of 15 patients with GMH

Type of GMH	Case No.	Age (years)/ sex	Age of onset (years)	Clinical features	Imaging features					
					Lesion location		Examinations (lesion visibility)			Associated abnormalities
					Right/left side of the brain	Brain structure	CT	Plain MRI	Contrast-enhanced MRI	
SCH	1	15/M	12	Seizures and mental retardation	Right	Parietal lobe	Yes	Yes	No	Schizencephaly, pachygyria, ventriculomegaly, and undeveloped septum pellucidum
	2	32/F	20	Seizures	Left	Temporal lobe	Yes	Yes	No	Schizencephaly, ventriculomegaly, and ventricular compression
	3	27/M	15	Seizures and mental retardation	Both	Frontal and parietal lobes	Yes	Yes	No	Schizencephaly and pachygyria
	4	29/M	21	Seizures	Right	Frontal lobe	Yes	Yes	No	Ventriculomegaly, ventricular compression, widened sulci, and callosal agenesis
	5	30/F	26	Seizures	Right	Frontal lobe	No	Yes	No	No
	6	2/M	2	Seizures and intellectual disability	Right	Centrum semiovale	No	Yes	Not performed	No
	7	29/M	14	Seizure, intellectual disability, and dysphasia	Left	Frontal lobe	Yes	Yes	Not performed	Schizencephaly, pachygyria, ventriculomegaly, and ventricular compression
	8	35/M	35	Headache	Both	Frontal lobe	Yes	Yes	No	Schizencephaly, widened sulci, and ventricular compression
	9	20/F	10	Seizures and intellectual disability	Right	Frontal and parietal lobes	Yes	Yes	Not performed	Schizencephaly, pachygyria, and ventriculomegaly
	10	34/M	30	Seizures	Right	Centrum semiovale	Yes	Yes	No	No
PNH	11	18/F	2	Seizures	Both	Periventricular	Yes	Yes	No	Ventricular compression
	12	49/F	30	Seizures	Both	Subependymal region	Yes	Yes	Not performed	Ventricular compression
	13	15/M	15	Seizures	Both	Subependymal region	Yes	Yes	Not performed	Ventricular enlargement and enlarged cisterna magna
	14	45/M	45	Dizziness	Right	Subependymal region	Yes	Yes	Not performed	Ventricular compression
	15	18/M	10	Seizures	Both	Subependymal region	Yes	Yes	No	Ventricular compression

CT computed tomography, *F* female, *GMH* gray matter heterotopia, *M* male, *MRI* magnetic resonance imaging, *PNH* periventricular nodular heterotopia, *SCH* subcortical heterotopia

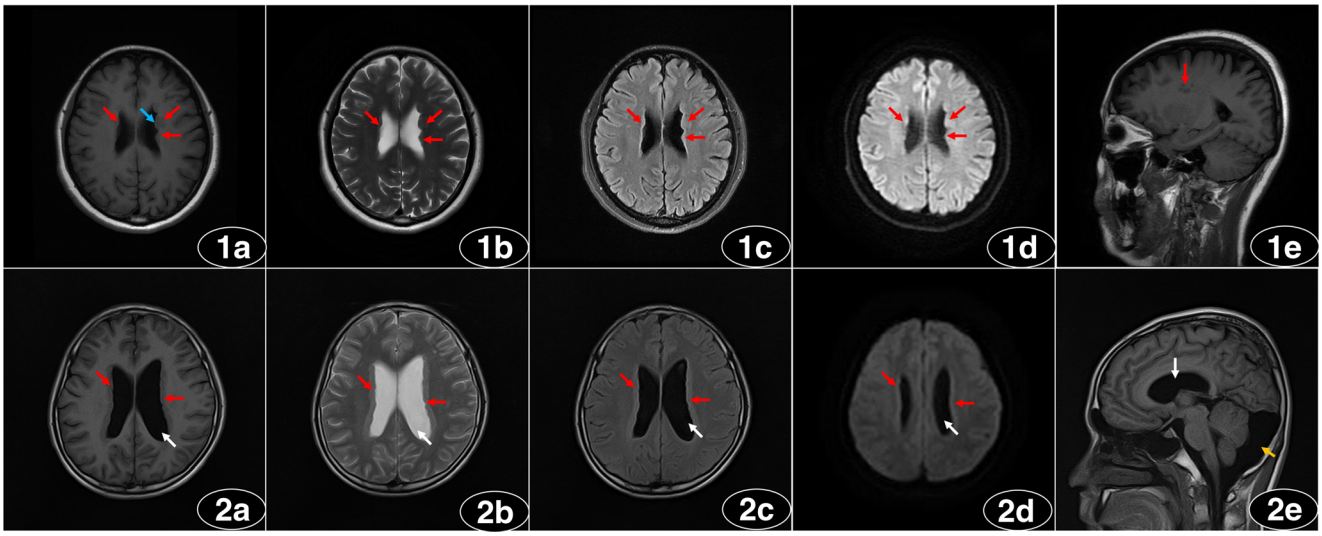

Fig. 1 Imaging findings in patients with GMH (PNH type). (1A–1E) (typical PNH type) Head magnetic resonance (MR) scans show multiple nodules around bilateral periventricular and subependymal regions with slightly long T1, slightly long T2, and high diffusion-weighted imaging (DWI) signals. The signals are similar to normal gray matter signals. A slight ventricular compression is also evident. (2A–2E) (PNH type) Head MR scans show multiple nodular abnormal signals around bilateral periventricular and subependymal regions with slightly long T1, slightly long T2, and high DWI signals. The signal is similar to normal gray matter signal. Ventriculomegaly and enlarged cisterna magna are also evident

had seizures with the average age of onset in the teens. In our study, all 5 patients with PNH had normal cognitive and motor functions and 80% of those had seizures. Our results are consistent with the abovementioned study. In short, most patients with SCH are presented with seizures accompanied by varying degrees of motor and mental retardation. In our study, out of 10 patients with SCH, 9 patients presented with seizures and 5 patients had decreased cognitive and motor functions.

Imaging features The recent advancements in imaging technologies have provided high-resolution images of gray matter and white matter, which, in turn, have improved the diagnostic rate of GMH. The typical changes in GMH are a single or multiple slices of high T1 and high T2 signals around the lateral ventricle or in the subependymal zone which are similar to the true gray matter signal from other parts of the cerebrum. These lesions are usually accompanied by other intracranial malformations

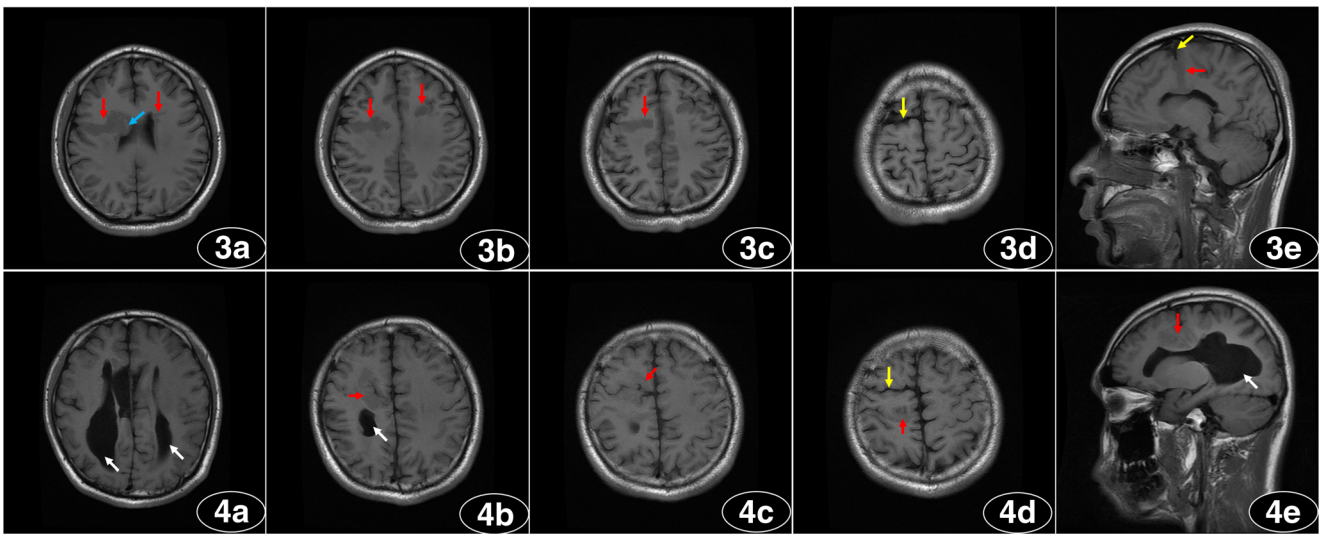

Fig. 2 Imaging findings in patients with GMH (SCH type). (3A–3E) (typical SCH type) Head MR scans, on T1-weighted image (T1WI), show widened sulci in the right frontal lobe and multiple irregular low-signal shadows in bilateral frontal lobes. The low-signal shadow is stretched into the white matter zone and a slight ventricular compression is also evident. (4A–4E) (SCH type) Head MR scans, on T1-weighted image (T1WI), show widened sulci and multiple irregular low-signal shadows in the right frontal lobes. The low-signal shadow is stretched into the white matter zone and right lateral ventricle. A slight ventricular compression is also evident

[1]. In our group of patients, GMH was accompanied by ventricular compression (8 cases), ventriculomegaly (5 cases), schizencephaly (5 cases), pachygyria (3 cases), callosal agenesis (1 case), and undeveloped septum pellucidum (1 case). Hung et al. [7] had suggested that different types of GMH are associated with different malformations. For example, PNH is mostly associated with ventriculomegaly followed by callosal agenesis, while SBH is mostly associated with pachygyria. In our study, all 5 patients with PNH had varying degrees of ventricular compression but none of them had ventriculomegaly. Only one patient with SCH had callosal agenesis. We observed that patients with SCH are more likely to have other intracranial malformations, such as a deformity or enlargement of brain fissures (70%). There are some discrepancies with other reports, perhaps due to the small sample size. Further studies with larger sample size are required to elucidate the relationship between GMH and other intracranial malformations. A CT scan is able to provide a clear diagnosis in case of typical GMH, but it has marked limitation in cases of atypical GMH or small lesions. An MR scan is the preferred method to diagnose anomalies related to the neuronal migration including GMH since it can display soft tissues with high resolution and better distinguish between gray matter signals and white matter signals [1]. All the patients in our study underwent routine head CT and MR scans. The CT scans did not show any abnormality in two cases, perhaps due to small lesions. Although conventional MR scan has an important diagnostic value in GMH, some small lesions can still be missed. Huppertz et al. [9] reported that some epileptic cases of GMH might remain unrecognized by conventional MR scans and the addition of 3D MR scans and other new techniques would provide more help for the diagnosis of GMH. The diagnostic rate of contrast-enhanced MR scan is better than that of plain MR scan. That difference in diagnostic rate is probably due to its multi-directional scanning including axial, coronal, and sagittal scans. Other imaging techniques such as functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), and positron emission tomography (PET) scans are of great importance to study the pathogenesis of GMH and epileptic foci [10–12].

Differential diagnosis GMH can be misdiagnosed when the heterotopic foci are small. Physicians need to identify and differentiate GMH from other lesions. SCH needs to be differentiated from neural hamartoma while PNH should be differentiated from tuberous sclerosis.

Treatment and prognosis Patients with GMH are generally given symptomatic treatments. The main goal is to control the epileptic seizures with medications or surgery. In patients with drug-refractory epilepsy, the resection of heterotopic gray matter plus bipolar coagulation of the cortex can achieve good results [13]. All the patients in this study were given a conservative treatment. There were 3 cases of SCH with multiple malformations who had refractory epilepsy. A combined therapy of carbamazepine, sodium valproate, and lamotrigine was given to them but the response was still poor. Some patients were advised to undergo surgery but they refused due to financial reasons.

In summary, GMH is a developmental brain abnormality with an unclear mechanism. Further research is required to elucidate its exact pathogenesis. With the application of new imaging techniques, new mechanisms are being proposed. In addition, due to its relatively rare incidence, GMH is easy to be missed and misdiagnosed which may delay the treatment and aggravate the clinical state of the patients. Therefore, the physicians need to be aware of this condition.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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