

## Gray Matter Heterotopia: Value of MRI

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### Abstract

**Background:** Gray matter heterotopia is defined as abnormally positioned but otherwise normal neurons. These cells are found anywhere along their normal migration path along radial glial fibers from ependyma to cortex. Gray matter heterotopia has been divided into three groups based on clinical and imaging characteristics; subependymal, subcortical, and band heterotopia.

**Objective:** The Purpose of this study is to evaluate MRI features of different types of gray matter heterotopia.

**Methodology:** A prospective study was conducted between June 2004 and December 2006, Department of Radiology, King Faisal University, Dammam, KSA. The medical records and MRI studies of patients with gray matter heterotopia were reviewed. The MRI morphologic findings of the heterotopia were recorded along with presence and type of associated cranial malformations. Available clinical and electrophysiological data were recorded as well.

**Results:** Twenty patients were included in the study. Their ages ranged from 9 months to 39 years with a mean age of 15 years. All patients suffered from epileptic seizures. According to the location of heterotopia, patients were classified into three groups; subependymal (12), subcortical (5) and band (3).

**Conclusion:** MRI was found to be accurate in diagnosis and differentiation between various types of gray matter heterotopia. Severity of clinical manifestations of heterotopia was related to the location and pattern of heterotopia. Determination of the heterotopia type and its extent is useful to direct the management plan and predict the prognosis.

**Keywords:** Heterotopia, MRI, Gray Matter

### Introduction

Gray matter heterotopia is a relatively common form of neuronal migration disorder in which collections of cortical neurons are found in an abnormal location. It results from an in utero arrest of radial migration of neurons from the germinal matrix in the wall of the lateral ventricle to the developing cerebral cortex between 6 and 16 weeks of gestation<sup>(1,2)</sup>. It is usually discovered during the evaluation of children or young adults with epilepsy, children with neurodevelopmental abnormalities, or as incidental findings<sup>(3-5)</sup>.

The pathogenic mechanisms of gray matter heterotopia are not fully understood, but they lead to distinct clinicoradiological syndromes. Pathological classification of heterotopia includes nodular, laminar, and leptomeningeal (double cortex or band heterotopia)<sup>(1,3,6)</sup>. This classification is not particularly useful from a clinical perspective<sup>(1)</sup>.

Neuroradiologists, basing their ideas on magnetic resonance imaging (MRI) appearances, have classified heterotopia into subependymal,

subcortical, and band heterotopia<sup>(3,7-9)</sup>. The three forms of heterotopia were classified on the basis of the location and configuration of the ectopic gray matter tissue. Subependymal heterotopia consists of small foci of gray matter that are located in a subependymal location in close proximity to the ventricular wall. Subcortical heterotopia occurs as masses of gray matter within the deep and subcortical white matter. Band heterotopia was described as a symmetrical thick band of gray matter with smooth inner and outer margins that lies between layers of white matter<sup>(10-13)</sup>. The purpose of this study is to evaluate MRI features of different types of gray matter heterotopia.

### Patients and Methods

A prospective study was conducted between June 2004 and December 2006 in department of Radiology, King Faisal University, Dammam, KSA. Consecutive series of patients with gray matter heterotopia were studied. Medical records and MRI studies of all patients were reviewed. MRI morphologic findings of the heterotopia were recorded along with presence and type

of associated cranial malformations. Available clinical and electrophysiological data were recorded as well. All patients presented with history of seizures, their clinical histories were reviewed with specific attention to the following; type of seizures, age at seizure onset, response to antiepileptic medications, associated cognitive or motor deficits; antenatal and perinatal history, developmental milestones, school performance and family history. Full systemic and neurologic examinations were performed during the visits to the neurology clinic. Electroencephalography (EEG) was done for each patient using the international 10-20 system. Head CT scans were available for 12 patients. Cranial MR imaging studies were performed using 1.5-T scanner (Symphony, Siemens Medical Systems, Erlangen, Germany). The following series of images were acquired:

1. Sagittal, and axial T1WI: TR: 500-600 msec, TE: 14-20 msec.
2. Axial and coronal T2WI: TR: 2500-4000 msec, TE: 80-120 msec.
3. Axial FLAIR (Fluid-attenuated inversion recovery): TR: 7000-9000 msec, TE: 90-140 msec, TI: 2500 msec.
4. Axial and coronal inversion-recovery (IR): TR/TI/TE (7000/400/70 msec).

IR images were performed for 8 patients. Intravenous Gadolinium-DTPA (0.1 mmol/kg) T1WI in three planes were obtained for 9 patients whom there plain MRI suspected a space occupying mass. In all series the thickness/gap was 5/1 mm, the matrix was 256x256 and the field of view (FOV) was 23 cm. According to Barkovich (1), heterotopia was classified into three groups; subependymal, subcortical and band heterotopia.

## Results

During the study period, there were 20 patients with MRI diagnosis of gray matter heterotopia. Mean age ( $\pm$  SD) was 14.6 ( $\pm$  2.17) years, with a range from 9 months to 39 years. Fourteen patients were females and 6 were males. All patients had history of epileptic seizures. Patients were classified into three groups (Tables I-III).

**Subependymal heterotopia (SEH):** This group included 12 patients (8 females and 4 males), their ages ranged from 8 to 39 years with the mean age ( $\pm$  SD) was 17.9 ( $\pm$  2.66) years. Detailed data of the clinical, EEG and MRI findings for the patients with SEH are shown in Table I. SEH had the MRI appearance of round to ovoid subependymal nodules, located just beneath and abutted the ependymal lining of the lateral ventricles and protruding slightly into its lumen resulting in an irregular ventricular outline. The number and size of heterotopia varied widely, from small nodules to thick layer of coalescent nodules of gray matter lining the lateral ventricles. The nodules were isointense to the cortical gray

matter on all MRI sequences (Figs.1-3). Contrast-enhanced T1WI studies were obtained in 4 patients, where the nodules showed no enhancement. The nodules were bilateral in 8 patients and unilateral in 4 patients. The trigone and occipital horns of lateral ventricles were the commonest location of subependymal nodules followed by the body and frontal of the lateral ventricle. Associated brain anomalies were detected in only two patients, one had ventricular dilation and the other had Dandy Walker cyst.

**Subcortical heterotopia (SCH):** This group included 5 patients (3 females and 2 males), their ages ranged from 1 year to 27 years with the mean age mean age ( $\pm$  SD) was 11.8 ( $\pm$  4.4) years. Detailed data of the clinical, EEG and MRI findings for the patients with SCH are shown in Table II. SCH appeared on MRI as regions of gray matter signal intensity within the cerebral hemispheric white matter. Their sizes varied from few centimeters to large focal lesion that appeared as a mass with distortion of the adjacent ventricle but no enhancement after contrast. Three patients were diagnosed to have purely nodular SC heterotopia as there was no definite contiguity of the heterotopia with the cerebral cortex (Fig. 4). The affected part of the cerebral hemisphere was reduced in size compared with the normal contralateral hemisphere. One patient had curvilinear SCH (Fig. 5) as the heterotopic tissue had the appearance of enfolded cortex and showed contiguity with the cortex. One patient had mixed regions of both nodular and curvilinear SCH (Fig. 6) as the gray matter nodules were seen in deep portions within the cerebral hemispheric white matter and the curvilinear portions were seen in superficial portion and shows contiguity with the cortex. Three patients had associated brain abnormalities; two patients had agenesis of the corpus callosum and the third had ventricular distortion.

**Band heterotopia (BH):** This group included 3 patients, all of them were females; their ages ranged from 9 months to 13 years with the mean age ( $\pm$  SD) was 5.9 ( $\pm$  3.6) years. Detailed data of the clinical, EEG and MRI findings for the patients with BH are shown in Table III. Band heterotopia appeared as smooth, bilateral and symmetric ribbons of gray matter found in the central white matter between the cerebral cortex and the ventricular surface and separated from the cortex by normally myelinated white matter. BH was present in both cerebral hemispheres and had the same MRI signal intensity as the cortical gray matter on all MRI sequences (Figs. 7 and 8). Two patients had associated pachygyria and one patient had lissencephaly. All patients in this group were developmentally delayed.

**Table (I): Data of 12 patients with subependymal heterotopia (SEH)**

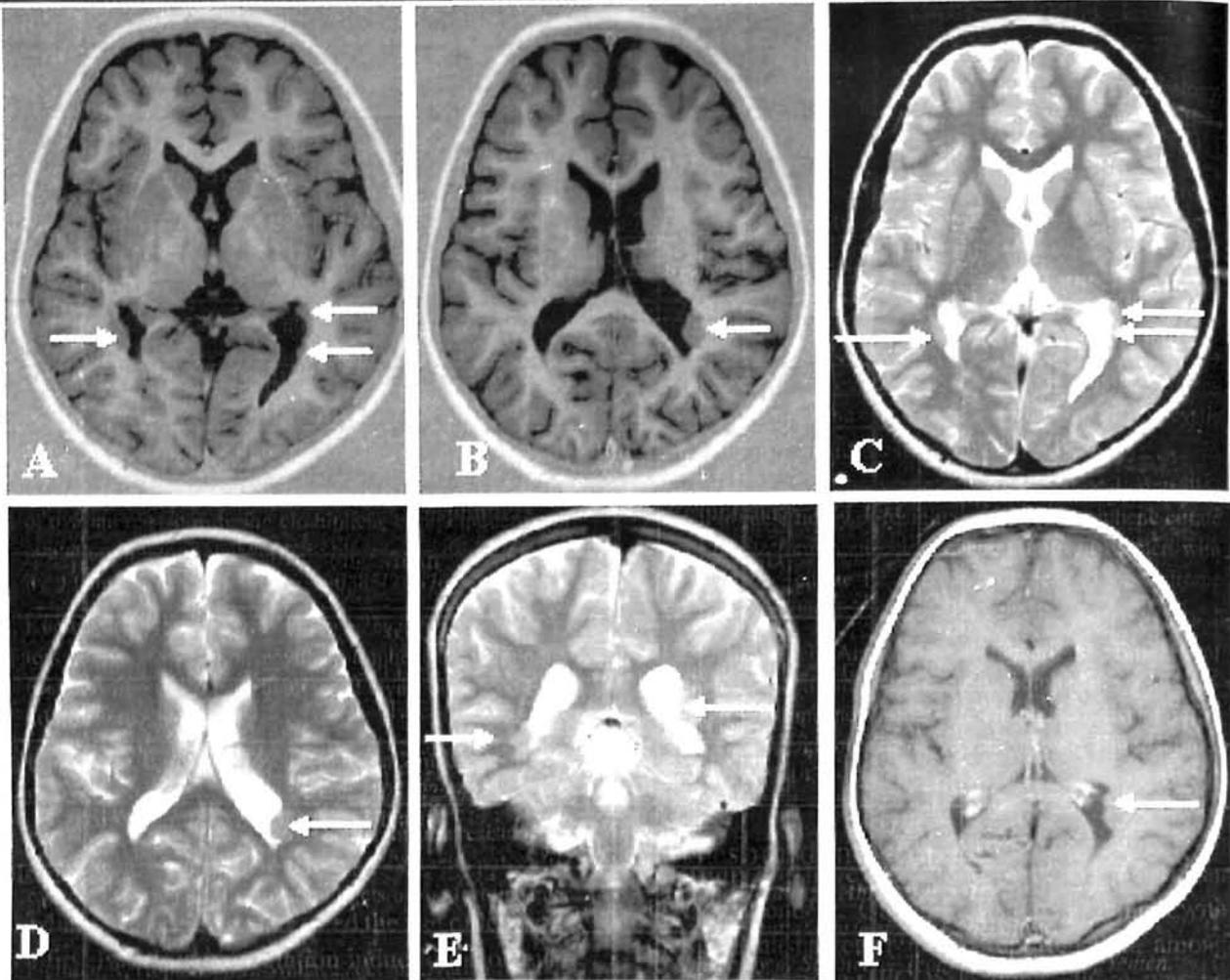
Patient/sex/Age	Seizure type	Developmental Milestones	Neurological Examination	EEG findings	MRI characteristics of heterotopia
1/F/8Y	Simple partial motor	Normal	Normal	Focal spikes	Unilateral nodule affecting frontal horn of right lateral ventricle.
2/F/15Y	Complex partial	Delayed speech	Mild spasticity	Focal spikes	Bilateral nodules affecting both trigones
3/F/22Y	Tonic-clonic	Delayed walking	Spasticity	Generalized spike-wave	Bilateral nodules affecting body of both lateral ventricles
4/F/14Y	Mixed	Learning disability	Hyperactivity, spasticity	Generalized slow wave	Bilateral nodules affecting body of right lateral ventricle
5/M/12Y	Complex partial	Delayed speech	Spasticity	Focal spikes	Unilateral coalescent nodules affecting frontal horn of left lateral ventricle
6/F/10Y	Simple partial motor	Normal	Normal	Focal spikes	Bilateral nodules affecting trigone and occipital horns
7/M/39Y	Complex partial	Delayed walking	Hyperactive stretch reflexes	Focal spikes	Bilateral nodules affecting trigone and occipital horns
8/F/26Y	Simple partial motor	Normal	Ataxia	Focal spikes	Unilateral nodules affecting trigone of right lateral ventricle, Dandy Walker cyst
9/F/18Y	Simple partial motor	Normal	Spasticity	Focal spikes	Unilateral nodules affecting body of left lateral ventricle.
10/M/13Y	Tonic-clonic	Delayed speech	Normal	Generalized slow wave	Bilateral nodules affecting body of both lateral ventricles
11/F/28Y	Clonic	Learning disability	Hyperactivity	Slow wave abnormality	Bilateral nodules affecting trigone and occipital horns & ventricular dilatation
12/M/10Y	Tonic-clonic	Normal	Normal	Generalized spike-wave	Bilateral nodules affecting trigone and occipital horns

**Table (II): Data of 5 patients with subcortical heterotopia (SCH)**

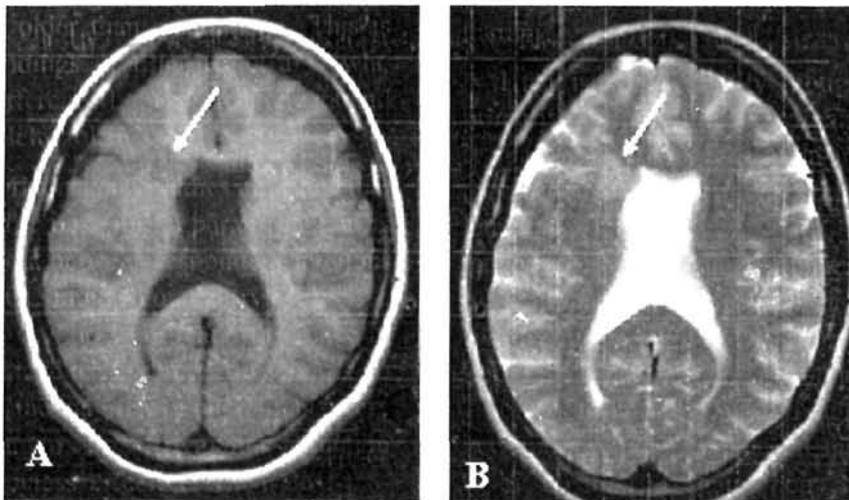
Patient/sex/age	Seizure type	Developmental Milestones	Neurological Examination	EEG findings	MRI characteristics of heterotopia
1/M/27Y	Complex partial	Delayed motor	Left hemiparesis	Focal spikes, slow wave	Large, nodular mass at right fronto-parietal lobes, extends across midline and ACC
2/F/15Y	Mixed	Delayed walking	spasticity	Focal spikes, slow waves	Small, multiple nodular, right frontal and parietal lobes
3/F/9Y	Generalized tonic-clonic	Delayed speech & motor	Right hemiparesis	Spike-wave	Small, multiple, nodular, left parietal and ACC
4/F/7Y	Generalized tonic-clonic	Delayed speech & motor	Attention deficit, hyperactivity, bilateral spasticity	Generalized spike-wave	Bilateral curvilinear
5/M/1Y	Mixed	Delayed walking	Hyperactive reflexes	Generalized, slow wave	Mixed nodular & curvilinear and distorted ventricles

**Table (III): Data of 3 patients with band heterotopia (BH)**

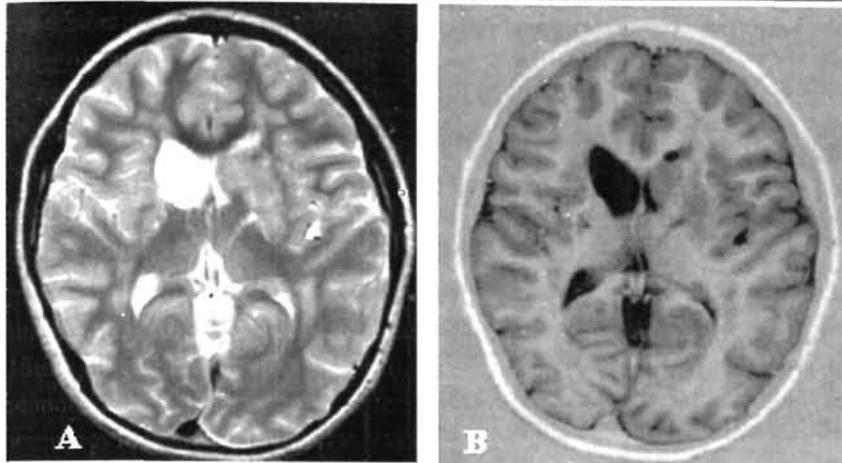
Patient/sex/age	Seizure type	Developmental Milestones	Neurological Examination	EEG findings	MRI characteristics of heterotopia
1/F/13Y	Mixed	Delayed speech, motor	Nystagmus, Dysarthria, spasticity	Generalized spike-wave	Bilateral diffuse thick bands at fronto-parietal lobes and pachygyria
2/F/4Y	Tonic-clonic, myoclonic	Delayed motor	Microcephaly, Bilateral spasticity	Generalized slow waves, polyphasic waves	Bilateral diffuse thick bands at both occipital lobes and pachygyria
3.F.9Month	Infantile spasms	Delayed speech, motor	Spasticity, hyperactive reflexes	hypsarhythmia	Bilateral diffuse thick bands at both fronto-parietal lobes and lissencephaly



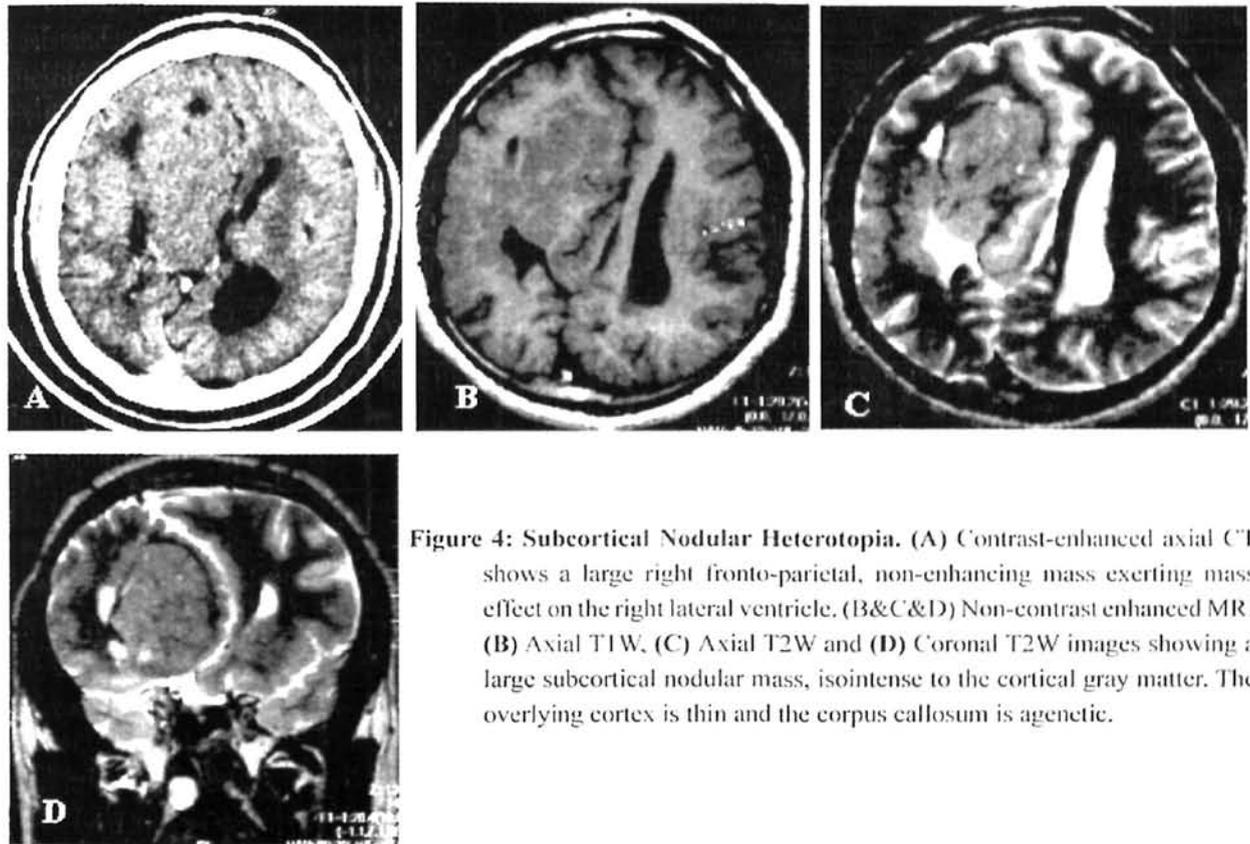
**Figure 1: Subependymal heterotopia:** (A& B) Axial inversion-recovery MR images, (C&D) Axial and (E) coronal T2 W images showing multiple bilateral subependymal gray matter heterotopic nodules protruding into and indenting trigone of the lateral ventricles and the left occipital horn (arrows). The nodules are isointense to cortical gray matter. (F) Axial contrast-enhanced T1WI shows no enhancement of the nodules.



**Figure 2: Subependymal Heterotopia:** (A&B) Axial T1W and T2W MR images revealing unilateral focal subependymal gray matter nodule (arrow) protruding into and indenting the frontal horn of right lateral ventricle. The nodule is isointense to the cortical gray matter. Mild ventricular dilatation is noted with absent septum pelucidum.

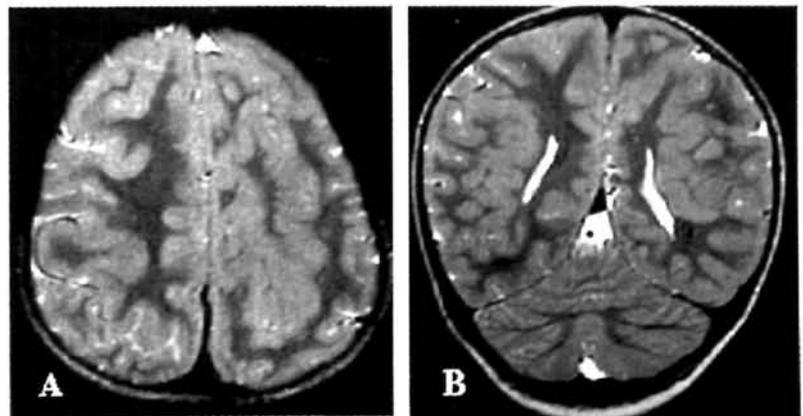


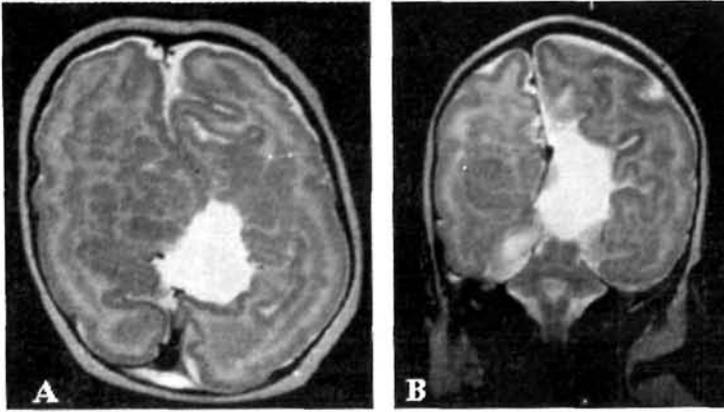
**Figure 3: Subependymal Heterotopia:** (A&B) Axial T2 WI and inversion-recovery MR image showing a unilateral, large subependymal heterotopic gray matter mass projecting into the frontal horn of the left lateral ventricle. The mass is isointense to the cortical gray matter.



**Figure 4: Subcortical Nodular Heterotopia.** (A) Contrast-enhanced axial CT shows a large right fronto-parietal, non-enhancing mass exerting mass effect on the right lateral ventricle. (B&C&D) Non-contrast enhanced MRI (B) Axial T1W, (C) Axial T2W and (D) Coronal T2W images showing a large subcortical nodular mass, isointense to the cortical gray matter. The overlying cortex is thin and the corpus callosum is agenetic.

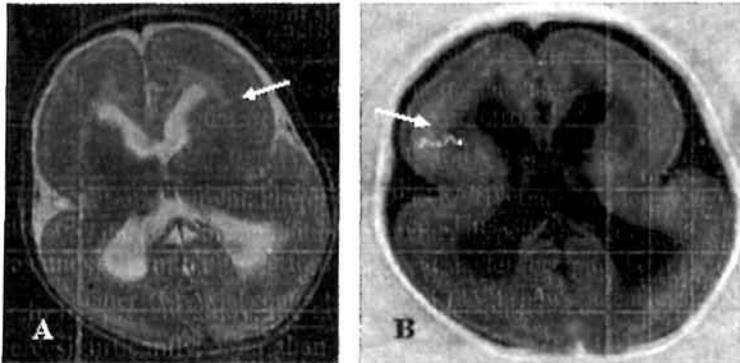
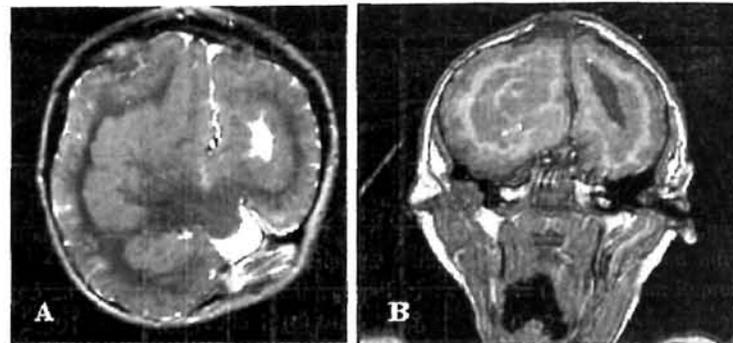
**Figure 5: Subcortical Curvilinear Heterotopia:** (A&B) Axial T2W and coronal T2W images showing bilateral curvilinear heterotopia within the white matter. The heterotopic tissue is convoluted and contiguous with the overlying cortex. Linear and punctuate CSF signal are seen within the heterotopic tissue. The cerebral cortex shows pachygyria.





**Figure 6: Mixed nodular and curvilinear subcortical heterotopia: (A&B)** Axial T2W and coronal T2W images showing multiple nodular and curvilinear heterotopia within the white matter bilaterally. The overlying cortex shows pachygyria. The right cerebral hemisphere is smaller compared to the left one. The corpus callosum is agenetic with distorted lateral ventricles.

**Figure 7: Band heterotopia: (A&B)** Axial T2W and coronal inversion-recovery images showing bilateral thick bands of heterotopia, isointense to cortical gray matter within the white matter. Noted pachygyria and small left cerebral hemisphere.



**Figure 8: Band Heterotopia: (A&B)** Axial T2W and inversion-recovery images showing bilateral, symmetric, continuous, smooth, thick bands of gray matter (arrow), outlined by thin layers of white matter and seems like a "double cortex". Noted very thin, smooth cerebral cortex with absent cortical sulci (lissencephaly).

## Discussion

Malformations of cortical development are more common than was recognized in the era before MRI, as on CT heterotopia may be difficult to visualize<sup>(1,14)</sup>. Heterotopia is the most frequently occurring anomaly affecting cortical development. It is considered to be one of the most common congenital disorders in familial and early onset epilepsy<sup>(14-18)</sup>. MRI classification of gray matter heterotopia into subependymal, subcortical, and band types has been considered useful because patients in these three groups have different clinicoradiologic presentations and different underlying genetic disorders<sup>(3,5,19)</sup>. This classification of heterotopia may be useful in predicting the patient outcome<sup>(2)</sup>.

Several authors<sup>(1,3,11,14)</sup> have reported that patients in all three groups of heterotopia are very likely to develop epilepsy and more common in females than males. In our study, all patients had history of seizures and female to male ratio was 14:6. In the current study, the three types of heterotopia were detected by MRI; SEH was the commonest type, followed by SCH, while BH was the least common type. On MRI; the heterotopic tissue was isointense with gray matter on all MR pulse sequences. The inversion recovery sequence was considered useful in the demonstration of the heterotopic gray matter and the assessment of cortical thickness as it provides a strong contrast between gray and white matter. A similar frequency and MRI appearance has been reported in the literature<sup>(1-5)</sup>.

SEH is characterized by periventricular nodules adjacent to the lateral ventricular walls just beneath and abutting the ependyma giving nodular ventricular wall, and not enhance after intravenous contrast administration. This allows distinguishing these nodules from the subependymal nodules of tuberous sclerosis that do not follow gray matter signal, and enhance after contrast administration<sup>(1,2,10-13)</sup>. SEH may be isolated or may develop in conjunction with other CNS malformations. It can be subdivided genetically into X-linked and non-X-linked inheritance patterns. They can be subdivided anatomically into unilateral focal, bilateral focal, and bilateral diffuse groups. Some patients with SEH are neurologically and developmentally normal<sup>(1,12,20)</sup>.

In this series, patients with SEH had a relatively late onset of seizures of different types. Simple partial seizure was the commonest type reported. Five patients had normal development and the rest had mild developmental delay. The most common EEG abnormality was focal spikes. These are in agreement with other studies<sup>(1,2,8,10,11,15)</sup>.

The present study, like others<sup>(1,2,11,21-23)</sup> has demonstrated that MRI is excellent in detection and characterization of SEH nodules that is most likely to be bilateral and commonly at trigone and occipital horns of lateral ventricles. It was reported that SEH caused little or no distortion of the remaining brain, whereas focal SCH caused marked distortion of the ventricles and diminished hemisphere size. Also, surrounding white matter is normal in SEH, whereas most of the hemispheres containing SCH had qualitatively diminished white matter<sup>(1,3)</sup>. In our study, patients with SEH had associated brain anomalies in only (18%). Mitchell et al<sup>(12)</sup> reported that SEH was occasionally accompanied with mild ventricular dilation.

In the present study, MRI showed SCH in five patients. Three patients had purely nodular SCH, one patient had curvilinear SCH and another patient had mixed nodular and curvilinear SCH. Barkovich et al<sup>(3)</sup> reported that SCH usually consist of swirling, heterogeneous, nodular or curvilinear masses of gray matter containing blood vessels and CSF. It is reported that SCH extends through the white matter, from the ventricular surface to the cerebral

cortex. In the current study, the affected part of the hemisphere was reduced in size compared with the normal contralateral hemisphere in three patients. Three of the five patients with SCH had associated brain abnormalities. In the present study, and others<sup>(3,5)</sup>, patients with SCH had more prevalence of developmental delay and motor dysfunction compared to SEH group and have variable motor and intellectual disturbances, depending on the size of the lesion and the effect on the underlying cortex. There is no difference in clinical manifestations among different types of SCH.

Band heterotopia or double cortex syndrome occurs usually in females and very rarely in males. MRI shows the characteristics appearance of BH as a smoothly marginated layer of gray matter coursing parallel to the lateral ventricle, separated from the overlying cortex and underlying ventricle by layers of white matter. Bands are neither convoluted nor contiguous with the overlying cortex. They do not contain blood vessels or CSF. The thicker the band of heterotopic neurons; the worse the disability and had increased prevalence of developmental delay<sup>(4,9)</sup>. In present study, MRI showed band heterotopia in three females. Two patients had associated pachygyria and one had lissencephaly. All patients in this group had severe developmental delay.

In conclusion, MRI is an accurate diagnostic imaging modality in differentiation between various types of gray matter heterotopia. Severity of clinical manifestations of heterotopia is related to the location and pattern of heterotopia. Determination of the heterotopia type and its extent is useful to direct the management plan and predict the prognosis.

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## تغايير موضع المادة الرمادية: قيمة التصوير بالرنين المغناطيسي

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يعرف تغايير موضع المادة الرمادية بأنه ظهور بالموضع الغير طبيعي لكنه من جهة أخرى يعتبر خلايا عصبية طبيعية، فهذه الخلايا توجد في أي مكان خلال مسار انتقالها الطبيعي بطول الألياف العصبية من البطانة العصبية إلى القشرة، وقد تم تقسيم تغايير موضع المادة الرمادية إلى ثلاث مجموعات مبنية على خصائص التصوير والخصائص الإكلينيكية وهي ما دون البطانة وما دون القشرة وشريط تباين.

الغرض من هذه الدراسة هو تقييم خصائص التصوير بالرنين المغناطيسي في تغايير موضع المادة الرمادية المختلف الأنماط.

المرضى والطريقة المتبعة: تم مراجعة السجلات الطبية والفحوصات بالرنين المغناطيسي للمرضى ذوي تغايير موضع المادة الرمادية وذلك خلال الفترة ما بين يونيو ٢٠٠٤م حتى ديسمبر ٢٠٠٦م، وقد تم تسجيل نتائج التصوير بالرنين المغناطيسي الشكلية لحالات التغايير مع تسجيل وجود أي تشوهات مخية ونوعها، كما تم تسجيل البيانات الإكلينيكية والإلكتروفسيولوجي.

النتائج: شملت الدراسة ٢٠ مريضاً تراوحت أعمارهم بين ٩ شهور و ٣٩ سنة العمر المتوسط هو ١٥ سنة، جميع المرضى كانوا يعانون من نوبات صرع، وقد تم تقسيم المرضى لثلاث مجموعات طبقاً للمكان الذي يقع فيه التغايير وهذه المجموعات ضمت ما دون البطانة (١٢)، ما دون القشرة (٥) وشريط التباين (٣).

الخلاصة: لقد وجدنا أن التصوير بالرنين المغناطيسي دقيق في تشخيص التباين بين مختلف أنواع تغايير موضع المادة الرمادية، وأن شدة الظهور الإكلينيكي للتغايير كان له علاقة بمكان وشكل التغايير، وأن تحديد نوع التغايير وامتداده مفيد في توجيه الخطة العلاجية وفرض التكهنات.