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Neuronal Migration Disorder; A Case Report of Subcortical Band Heterotopia Associated with Corpus Callosum Agenesis

Subcortical band heterotopia (SBH) or 'double cortex' is a congenital brain abnormality that results from aberrant migration of neurons during development of the cortex. MRI shows a continuous band of heterotopic gray matter located between the cortex and ventricular walls, separated from them by a thin layer of white matter. The condition is quite rare, found predominantly in females, and is occasionally familial with an X-linked dominant inheritance. Corpus callosum agenesis is another brain abnormality, more common than SBH, diagnosed during neurological examinations for developmental delay.

We report a 6-month-old boy with SBH and corpus callosum agenesis associated with uncommon clinical and radiological findings such as polymicrogyria and periventricular cystic area.

Keywords: Subcortical Band Heterotopia, Corpus Callosum Agenesis, Neuronal Migration Disorder, Seizure, Child

Introduction

Disturbances of neuroblast migration are a prominent cause of epilepsy and abnormal neurological development. Among these disorders subcortical band heterotopia (SBH), also known as double cortex syndrome, is a cortical malformation characterized by the presence of symmetrical and bilateral bands of the heterotopic gray matter located between the ventricular wall and the cortical mantle, and clearly separated from both.^{1,2} Most cases with SBH are sporadic and females are affected more often.^{1,3}

Isolated corpus callosum agenesis is characterized by the absence of the principal interhemispheric commissure. This malformation is usually diagnosed in children undergoing examination for epilepsy or neuro-developmental delay. Epidemiologic studies show the prevalence of 0.05-0.7% in the general population and 2.3% among children with developmental disabilities. The prevalence of asymptomatic corpus callosum agenesis is unknown, but based on autopsy series or CT studies; it can be estimated to be 0.5/10,000 or 0.13-0.7%, respectively.^{4,5}

To our best knowledge, this is the first report of SBH associated with corpus callosum agenesis and periventricular cystic area.

Case Presentation

A 41-day-old male infant was referred to our outpatient department for evaluation of macrocephaly. He was the first child of consanguineous parents delivered by elective caesarean section. The birth weight and birth head circumference were 3600 grams and 38 cm, respectively. Family history was unremarkable for any neurological problems. The child's weight and head circumference at the

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first visit were 5100 grams and 42.5 cm, respectively. Except for mild hypotonia no other physical or neurological abnormality was found. There was no history of seizure. Brain sonography showed enlarged lateral ventricles suggesting hydrocephaly. No abnormality in blood cell count indexes, electrolyte levels, blood and urine amino-acid chromatography, lactate, and pyruvate and ammonia levels was detected.

In the second visit at the fifth month, his parents complained of occasional myoclonic jerks of the extremities but no definite seizure episode was reported. His weight and head circumference were 7100 grams and 45.5 cm, respectively. Incomplete head holding, mild head lag on a pull-to-sit maneuver, and no weight bearing were observed. Electroencephalography showed a few multifocal sharp waves in the tracing. No antiepileptic drug was administered for the patient. The patient was referred for rehabilitation. The patient was followed for developmental milestones and occurrence of seizure disorders. The patient's clinical and paraclinical characteristics are summarized in Table 1.

Brain MRI revealed several gross structural abnormalities.

Diffuse subcortical band heterotopia was suggested by the diffuse homogenous band of gray matter, situated between lateral ventricles and the cerebral cortex (Fig. 1A). The band thickness was medium to thick, thicker in the anterior part than the posterior. It was distributed from the anterior frontal to the occipital lobe with involvement of the periventricular temporal lobe.

Medial hemispheric sulci radiation into the third ventricle due to lack of inversion of the cingulate gyrus in the median sagittal section, quasi parallel

lateral ventricle in the axial plane, and characteristic lateral convexity of the frontal horns in the coronal plane suggested agenesis of the corpus callosum (Fig. 1B). The overlying cortex had shallow sulci more remarkably seen in the frontal area in concordance with the simplified gyral pattern. A periventricular cystic area, isosignal with CSF was observed close to the right frontal horn (Fig. 1C). Mild ventriculomegaly and a pattern of polymicrogyria or pachygyria were also present.

Discussion

Subcortical band heterotopia is now classified in the agyria-pachygyria-band spectrum.⁶ In SBH the normal gyral pattern is seen, but beneath the cortical ribbon, a thin band of white matter separates the cortex from a heterotopic band of gray matter. Differences in thickness and extension are used for grouping the abnormality: (1) thin partial frontal SBH with no involvement of the posterior regions; (2) thin partial posterior SBH with no involvement of the frontal regions; (3) medium or thick intermediate SBH that is always more prominent posteriorly; (4) diffuse thin SBH; (5) diffuse medium or thick SBH; and (6) anterior pachygyria that merges into posterior SBH.⁷

Two genes are involved in the etiology of SBH: first, DCX located on chromosome X,^{1,8} and second, LIS1 on chromosome 17.^{9,10} Mutations of these genes represent a malformative spectrum from lissencephaly-pachygyria to SBH.¹¹ Missense mutations in DCX in males cause anteriorly predominant SBH, while missense or mosaic LIS1 mutations predominate posteriorly.^{12,13}

Individuals affected by SBH commonly present epi-

Table 1. Clinical and Paraclinical Characteristics of the Patient

Finding	5 months
Seizure type	None
Main EEG finding	Multifocal spikes
Neurological and physical examination	Mild hypotonia and macrocephaly
Response to therapy	Good
Dysmorphic features	None
Band heterotopia	Type 5, thick & diffuse in three lobes, anterior > posterior
Other brain anomalies	Simplified gyral pattern, enlarged ventricles, periventricular cystic area and corpus callosum agenesis
Laboratory data	Normal

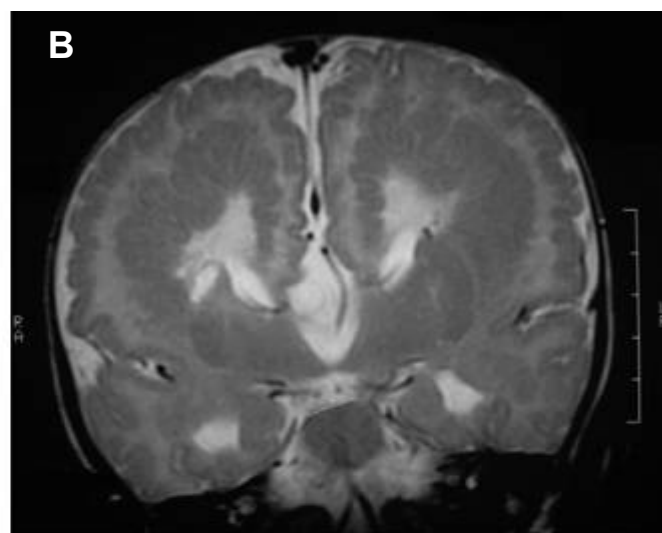
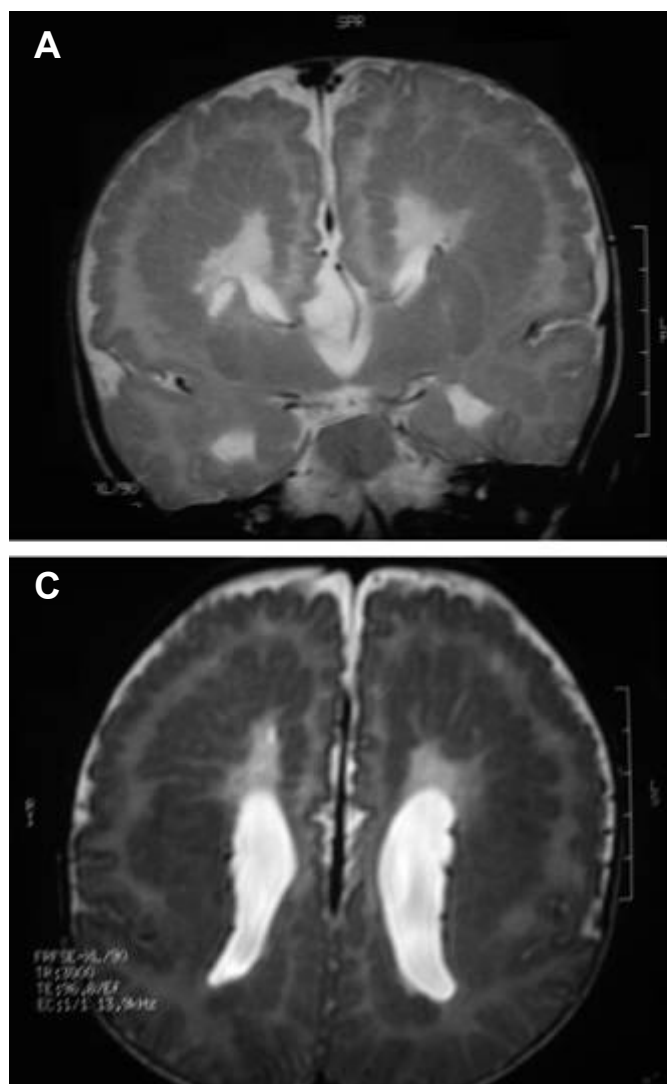


Fig.1 Five-month-old infant with a neuronal migration disorder.

A. T2 weighted MRI in the axial plane shows SBH and periventricular cystic area.

B. T2 weighted MRI in the sagittal plane shows medial hemispheric sulci radiation into the third ventricle characteristic of corpus callosus agenesis.

C. T2 weighted MRI in the coronal plane shows thick SBH plus polymicrogyric and pachygyric changes, lateral convexity of the frontal horns and upward extension of the third ventricle into the interhemispheric fissure.

lepsy and variable degrees of mental epilepsy and variable degrees of mental retardation. Seizures often start early and vary from partial to generalized attacks. Epilepsy is present in almost all cases of subcortical band heterotopia and is intractable in about 65% of cases.¹⁴ About 50% of epileptic patients have focal seizures and the remaining 50% have generalized epilepsy, which is often the Lennox-Gastaut syndrome.¹⁵ Electrophysiological studies on the band demonstrate that epileptiform activity can originate directly from the heterotopic neurons.¹⁶

Neurological examination may be normal, except for dysarthria, hypotonia, and poor fine motor control.^{17,18} Facial dysmorphism can occur following the ventricular dilation accompanying the malformation: hypertelorism, frontal bossing and/or macrocranium.

Corpus callosus agenesis can be isolated or accompanied with other brain abnormalities. It is associated

with different diseases such as malformation syndromes (e.g. Aicardi, orofacioidigital, Anderman, Shapiro, and XLAG), chromosomal abnormalities, metabolic diseases (e.g. pyruvate dehydrogenase deficiency, hyperglycinemia without ketosis and glutaric aciduria), viral embryopathy, intoxication (drugs, alcohol) or medication (valproate), forebrain malformation (holoprosencephaly, septo-optic dysplasia) and brain or somatic malformations (lissencephaly, posterior fossa malformations, such as Dandy-Walker cysts, interhemispheric cysts).^{19,20}

In this case SBH with an anteroposterior gradient was associated with corpus callosus agenesis. Band heterotopia is often accompanied by seizure and dysmorphic facial features which were not reported here. Although there are reports of SBH with mild or no seizure,²⁰ lack of seizure in this case can be justified by corpus callosus agenesis knowing that corpus

callosotomy is a treatment for intractable seizure.²¹ Ventriculomegaly commonly causes dysmorphic facial features; in this case ventriculomegaly was mild therefore no abnormality was observed.

Although temporal extension is not common in SBH or corpus callosum agenesis,²⁰ MRI findings included a diffuse subcortical band of gray matter which was thicker in the frontal area with extension to the temporal lobe. An abnormal unexplained periventricular cystic area isosignal with CSF was present close to the right frontal horn in all sequences, which is not a classic finding in corpus callosum agenesis or this type of migration abnormality. Anterior commissure was relatively prominent secondary to agenesis of the corpus callosum. SBH is classically accompanied by pachygyria, but fine irregularity or serration of the cortical gray matter and white matter junction in the anterior frontal lobe may suggest focal polymicrogyric changes in some areas and pachygyric changes in others.

Based on the MRI findings, the case is classified as type 5; diffuse SBH with substantial involvement of three or more lobes associated with corpus callosum agenesis.⁷

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