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AJNR Am J Neuroradiol 1996, 17 (7) 1315-1322

<http://www.ajnr.org/content/17/7/1315>

This information is current as
of July 19, 2025.

Subcortical Heterotopia: A Distinct Clinicoradiologic Entity

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PURPOSE: To investigate the clinical syndrome and associated brain anomalies in a group of patients with subcortical heterotopia. **METHODS:** The seizure history, developmental history, family history, electroencephalographic results, imaging studies, and pathologic results (where available) of 13 patients with subcortical heterotopia were reviewed retrospectively. The patients ranged in age from 1 month to 39 years (mean, 11 years; median, 3 years) at the time of the most recent update of their records. **RESULTS:** Fifteen hemispheres were involved in 13 patients. The cerebral cortex overlying the heterotopia was thin with shallow sulci and the affected part of the hemisphere was small as compared with the contralateral hemisphere. The corpus callosum was hypogenetic or agenetic in nine patients and the basal nuclei were dysplastic or hypoplastic in 11 patients. Most patients were developmentally delayed as children, had mild hemiplegia or hemihypesthesia contralateral to the affected hemisphere(s), and had partial epilepsy, most commonly evidenced by partial motor seizures in the body half contralateral to the malformation. Age at seizure onset varied from infancy to the second decade. Electroencephalographic results showed slow wave background with spike and spike wave complexes in the affected hemisphere. **CONCLUSION:** Subcortical heterotopia seems to have characteristic clinical, electrophysiological, and imaging manifestations. These results suggest that affected patients may be conveniently grouped together to study treatment outcomes.

Index terms: Brain, abnormalities and anomalies; Migration anomalies

AJNR Am J Neuroradiol 17:1315-1322, August 1996

In the last decade, the improved ability to depict the structures of the brain by neuroimaging has resulted in the increased recognition and classification of a number of malformations of cortical development (1, 2). As a result, clinical outcomes, clinical patterns, and chromosomal anomalies associated with particular malformations, such as lissencephaly (3-5), band heterotopia (6, 7), subependymal heterotopia (8, 9), bilateral perisylvian polymicrogyria (10, 11), and focal cortical dysplasia (12), have been clarified. Subcortical heterotopias are irregularly lobulated masses of gray matter that are located primarily in the subcortical white matter of the cerebral hemispheres (9). These

malformations have a distinct imaging appearance and, from the limited information in the literature (9), may have characteristic clinical manifestations. In this article, we report the neurologic, electrophysiological, and neuroradiologic manifestations of 13 patients with subcortical heterotopia.

Materials and Methods

A review of records compiled at our institution from 1986 through 1994 revealed that neuroimaging studies and clinical reports were available for 13 patients with subcortical heterotopia. The patients ranged in age from 1 month to 39 years (mean, 11 years; median, 3 years) at the time of the most recent update of their records. The reasons for referral to our institution included new onset of seizures (five patients), worsening medical control of seizures (four patients), developmental delay (three patients), and recent trauma (one patient). The patients' records were searched for age of onset of seizures, type of seizure disorder (if more than one seizure type was present, the age of onset of each seizure type was recorded), developmental history (particularly regarding development of motor and language skills, if available), family history of neurologic disorders, and electroencephalo-

Received October 30, 1995; accepted after revision February 15, 1996.

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AJNR 17:1315-1322, Aug 1996 0195-6108/96/1707-1315

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graphic (EEG) results. Developmental history was well documented in only three of the nine patients who were beyond infancy. In the other six, history was obtained from the patient or other family members and, therefore, was incomplete or imprecise. Extracranial EEG examinations were performed using the International 10–20 system and recorded on 16-channel EEG machines. Recordings were obtained during both wakefulness and sleep.

Magnetic resonance (MR) images were available for all patients. The MR studies were performed on a variety of scanners, as many of the patients were referred to our institution from outlying hospitals. Six studies were performed at 1.5 T, four at 0.5 T, one at 1.0 T, one at 0.35 T, and one at 0.30 T. Axial T1-weighted and T2-weighted images and sagittal T1-weighted images were obtained in all patients. Coronal T1-weighted images were obtained in nine patients and coronal T2-weighted images in six. Section thickness varied with the protocol at the institution at which imaging was performed and with the sophistication of the scanner, ranging from 3 to 7 mm, with intersection gaps ranging from 1 to 2.5 mm. The number of phase-encoding iterations varied from 128 to 256.

Computed tomographic (CT) scans were available for three patients. All CT studies were acquired in the axial plane with a section thickness of 5 mm. In two patients, the CT studies were obtained before and after intravenous administration of iodinated contrast material; in the third, the study was obtained without contrast material.

The CT scans and MR images were analyzed for the location and size of the heterotopia, the gyration and thickness of the overlying cortex, the size of the affected hemisphere, the configuration of the basal ganglia, and the presence or absence of associated brain abnormalities. The basal ganglia were considered dysplastic if discrete caudate nuclei and lentiform nuclei, of normal configuration and shape, could not be identified.

Pathologic results were available for two of the patients, one of whom (patient 5) had surgical resection of the heterotopia for seizure control. The other (patient 3) had a biopsy of the tissue for diagnostic purposes.

Results

Imaging Findings

Subcortical heterotopias were present in the right hemisphere in five patients, in the left hemisphere in six patients, and bilaterally in two patients, for a total of 15 involved hemispheres in 13 patients (Table). In all affected patients, the heterotopia was an irregularly lobulated mass of gray matter that extended from the ventricular surface into the hemispheric white matter (Figs 1–4) and, in some cases, to the cerebral cortex (Fig 3). In nine of the affected hemispheres, the heterotopia extended from the frontal lobe back to the parietooccipital region and was considered diffuse (Figs 1 and 2). In

three hemispheres, the heterotopia was confined to the frontal lobe (Fig 3) and in the final three, the occipital lobes were primarily involved (Fig 4).

The cortex overlying the heterotopia was abnormal in all patients in this study. In most patients, the cortex appeared thin with abnormally shallow sulci (Figs 1–4). However, in one patient with bilateral heterotopia, abnormally small gyri were identified, prompting a diagnosis of polymicrogyria (Fig 4). In 10 patients, the hemisphere was diminished in size in the region of the heterotopia (Figs 1 and 3). This diminution of size appeared to result from a combination of diminished volume of white matter, diminished ventricular size, and small, dysplastic basal ganglia in the affected region of brain. The basal ganglia were either dysplastic or unidentifiable in 11 patients (Figs 1, 3, and 4). When dysplastic, they typically had the appearance of globular masses of gray matter that did not have the normal shape of caudate and lentiform nuclei and were not separated by the presence of a discrete internal capsule.

The corpus callosum was hypogenetic in three patients and completely absent in six patients (Figs 1, 2, and 4). In three of the patients with callosal anomalies, an interhemispheric cyst was present (Fig 2). Other brain anomalies included hippocampal dysplasia in the patients with callosal anomalies, a repaired frontonasal encephalocele in one patient, thalamic fusion in one patient, and thalamic hypoplasia in one patient.

A comparison of the CT and MR studies revealed that CT was less sensitive in the detection of callosal hypogenesis, did not show the abnormalities (shallow sulci, small gyri, and thinning) of the overlying cortex, and, because of the decreased contrast sensitivity, did not show the abnormalities of the basal ganglia or the full spectrum of characteristics of the heterotopia itself. The presence of the heterotopia and the diminished size of the affected hemisphere were well illustrated by CT.

Neurologic and Developmental Examinations

Results of neurologic examinations were normal in five patients. Of these, one was only 3 months old, making neurologic examination difficult. Patients 2, 8, and 9 all had severe gross motor delay, and patients 2 and 9 (both 3 years old) had significant cognitive delay with abnor-

Clinical and imaging findings in 13 patients with subcortical heterotopia

Patient	Sex/Age	Region of Involvement	Associated Malformations	Abnormal Neurologic Findings	Age at Seizure	Onset Seizure History
1	M/11 y	R hemisphere	Small hemisphere, absent ipsilateral ventricle, ACC, absent BG, thin cortex/shallow sulci	L hemiparesis, low-normal intelligence	5 y	L partial motor seizures with secondary generalization—new
2	F/3 y	R hemisphere	Small hemisphere, thin cortex/shallow sulci, small, dysplastic BG	Low-normal intelligence, gross/fine motor delay at 4 y, abnormal visual perception/visual motor skills	. . .	None
3	F/5 y	L hemisphere	Small hemisphere, thin cortex/shallow sulci, small, dysplastic BG	R hemiparesis	5 y	R partial motor seizures
4	M/39 y	L hemisphere	Small hemisphere, thin cortex/shallow sulci, absent ventricle, small, dysplastic BG	R hemihypesthesia	15 y	Partial seizures with secondary generalization for 20 y
5	M/23 y	L frontal lobe	Small frontal lobe, thin cortex/shallow sulci	R arm wasting	12 y	Partial motor seizures with secondary generalization for 10 y, partial complex seizures
6	M/37 y	R hemisphere	Small hemisphere, thin cortex/shallow sulci, small, dysplastic BG, ACC with IHC	Spastic L hemiparesis	9 y	Partial complex seizures with secondary generalization for 25 y, partial motor seizures L arm/leg
7	M/3 y	Bilateral	Thin cortex/shallow sulci, HCC with dorsal IHC, dysplastic BG, fused thalami	Severe developmental delay	7 mo	Generalized tonicoclonic seizures for 1 y
8	F/6 mo	L hemisphere	Small hemisphere, thin cortex/shallow sulci, small dysplastic BG, ACC	Developmental delay, mild R hemiparesis	5 mo	Partial motor seizures with secondary generalization
9	M/3 y	R frontal lobe	Small hemisphere, thin cortex/shallow sulci, small, dysplastic BG, ACC, dysplastic L hippocampus	Spastic L hemiparesis, slight craniofacial asymmetry, L dystonia, developmental delay (slight in motor skills, significant in language)	1 y	None
10	M/18 y	L hemisphere (small-moderate)	Slightly small hemisphere, slightly thin cortex/shallow sulci, slightly small BG, HCC, repaired frontonasal encephalocele	Mild R hemiparesis, low-normal intelligence	17 y	Partial motor seizures with secondary generalization
11	M/3 mo	L occipital lobe	Hydrocephalus, HCC with IHC, thin cortex/shallow sulci	Macrocephaly, developmental delay	. . .	None
12	M/1 mo	Bilateral, primarily posterior	ACC, polymicrogyria, dysplastic BG, thalami	Intractable seizures	2 wk	Head turning, eye rolling
13	M/1 mo	R frontal lobe	Small hemisphere, thin cortex/shallow sulci, small, dysplastic BG, ACC	L hemiplegia	2 wk	Partial motor seizures

Note.—ACC indicates agenesis of the corpus callosum; BG, basal ganglia; IHC, hemispheric cyst; and HCC, hypogenesis of the corpus callosum.

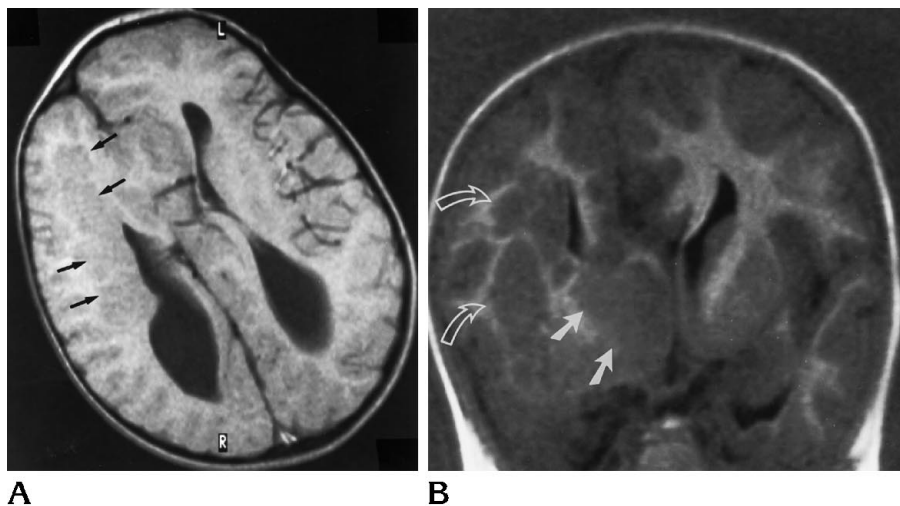


Fig 1. Patient 9. Hemispheric heterotopia with callosal agenesis and dysplastic basal ganglia.

A, Axial T1-weighted spin-echo image shows a large mass of heterotopic gray matter (arrows) in the right frontal lobe. Note that the right hemisphere is smaller than the left and the sulci in the right frontal region are shallow. The corpus callosum is agenetic.

B, Coronal T1-weighted inversion recovery image shows a mass of dysplastic gray matter (solid arrows), representing dysplastic basal nuclei, in the medial hemisphere. The heterotopia is marked by the open curved arrows.

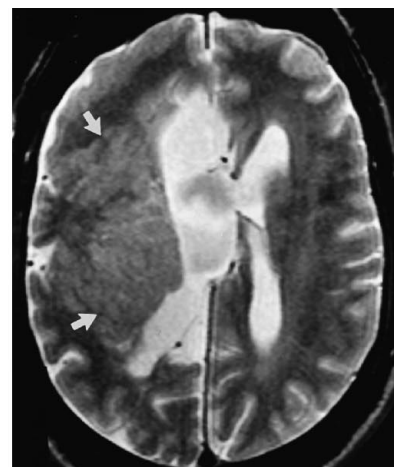


Fig 2. Patient 6. Hemispheric heterotopia with callosal agenesis and interhemispheric cyst. Axial T2-weighted image shows large hemispheric subcortical heterotopia (arrows) and agenesis of the corpus callosum. The cortex overlying the heterotopia is thin with shallow sulci. The hemispheres appear equal in size, probably because of the mass effect from the associated interhemispheric cyst.

mal visual perception and visual motor skills. The fifth patient with relatively limited involvement of the left frontal lobe (patient 5) had wasting of the right arm, which was 2 to 3 cm smaller than his left, but normal strength and reflexes in the arm.

Of the other eight patients, six had hemiparesis involving the side of the body contralateral to the involved hemisphere and one had hemihypesthesia contralateral to the involved hemisphere. The remaining patient, 1 month of age, had intractable epilepsy and it was difficult to be certain whether abnormalities detected on examination were the result of the epilepsy, underlying neurologic deficits, or both. Of the five patients in this group who were old enough to have their level of intelligence assessed accurately, all had low-normal intelligence; the two adults (patients 4 and 6) were functioning in low-level jobs.

Head circumference was normal to low-normal in all patients. None had a head circumference more than 2 standard deviations below normal.

A history of relatives with neurologic disorders was obtained in two of the patients; pre-

cisely which relatives and the exact disorders were not specified in the available records.

EEG

EEG results were available for eight patients. All eight showed abundant generalized interictal theta activity in the affected hemisphere. Focal and diffuse spikes were reported in the affected hemisphere in six patients. Delta waves were present in the affected hemisphere in one.

Seizure History

Ten patients had epilepsy. The age at the time of first seizure ranged from 2 weeks to 17 years (mean and median, 5 years). Seven patients had simple partial motor seizures, including four who had secondary generalization. One patient had partial sensory seizures with subsequent impairment of consciousness and, sometimes, secondary generalization. This patient and one of the patients with simple partial motor seizures also had complex partial seizures with impairment of consciousness at onset of the seizure. One boy (patient 7) had generalized tonicoclonic seizures. The final patient, aged 2

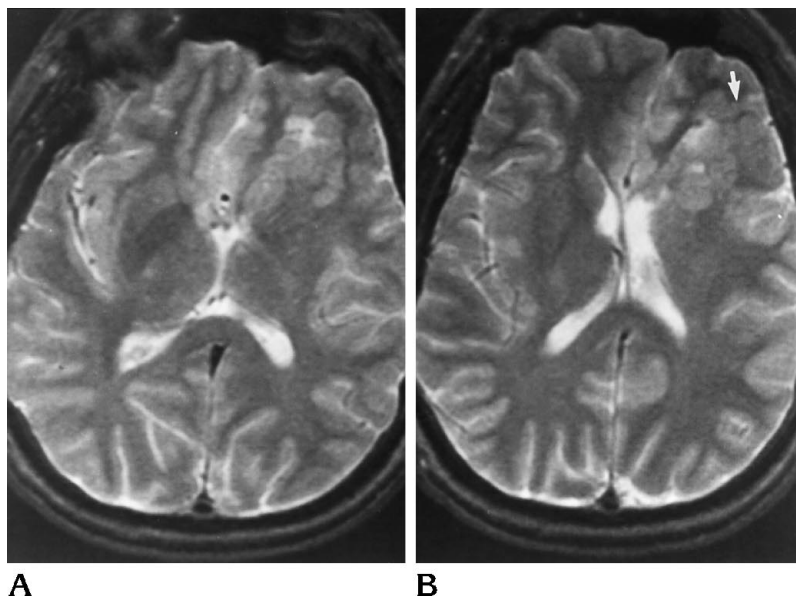


Fig 3. Patient 5. Focal heterotopia. Axial T2-weighted images show a small left frontal lobe with abnormal gyral pattern and subcortical heterotopia. The diminished size of the lobe and abnormal gyral pattern are restricted to the region of the heterotopia. In one focus, the heterotopia is continuous (*arrow*) with the overlying cortex. Note that the left thalamus and basal ganglia are small or dysplastic.

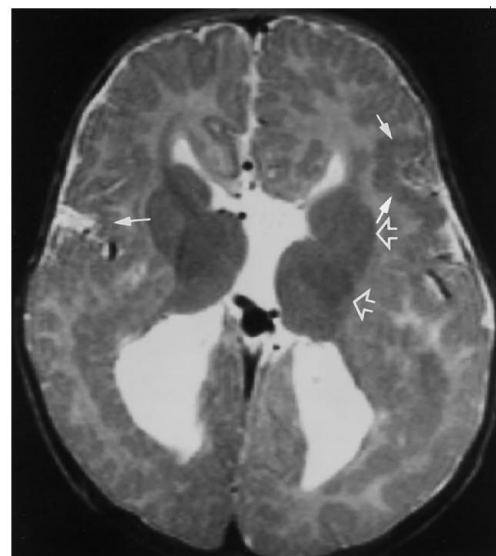


Fig 4. Patient 12. Polymicrogyria and bilateral heterotopia. Axial T2-weighted image shows bilateral heterotopia more extensive in the left hemisphere than the right, extending from the ventricular surface into the hemispheric white matter. The basal ganglia are dysplastic, especially on the left (*open arrows*). Several areas of polymicrogyria (*solid arrows*) are present. The corpus callosum is agenetic.

weeks, had unclassifiable stereotypical movements with head turning and eye rolling.

Neuropathology

Pathologic reports were available for two patients who had resection (patient 5) or biopsy (patient 3) of the heterotopia. Both reports revealed the presence of gray and white matter with no specific pathologic abnormality, moderate reactive astrocytosis, and thickened vessels.

Discussion

Subcortical heterotopia has previously been described as a distinct malformation (9). In this study, we found a characteristic clinical syndrome in most of the patients and a high prevalence of characteristic associated anomalies in affected brains. Identification and recognition of specific clinicoradiologic syndromes are important, both to understand the disorders better and to help counsel the families of affected children. Use of clinicoradiologic criteria to help categorize patients into reasonably homogeneous

groups has ample precedent; such criteria have been used for cytomegalic inclusion disease (13), congenital bilateral perisylvian syndrome (10), and band heterotopias (6, 7). An analysis of clinicoradiologic groups may advance our understanding of pedigrees and give indications of modes of genetic transmission (14); this information is invaluable in genetic counseling. Although patients with similar neurologic signs and symptoms may have a wide range of underlying neuropathology, and although there is often some variation in the clinical presentation among patients with similar imaging findings (6, 10), the combining of clinical and imaging findings allows fairly specific categorization of patients. Once the patients are categorized, an analysis of their imaging studies may enable some degree of prognostication of outcome at an early age (6); this information is important in planning occupational and physical therapy.

Our patients appeared to manifest a fairly consistent clinical syndrome, which included paresis of the hemibody contralateral to the heterotopia, some developmental delay, ultimate low-normal intelligence, simple partial motor seizures that may develop at any time up to the

middle of the second decade of life, and characteristic imaging features of a small hemisphere with a thin cortex, shallow sulci, hypoplastic or dysplastic basal ganglia, and a large mass of gray matter in the periventricular and subcortical white matter of the affected hemisphere. The corpus callosum was frequently absent or hypoplastic. EEG results showed abundant generalized slow wave activity in the affected hemisphere with occasional focal and diffuse spikes and spike wave activity. Two of our patients had relatives with neurologic disorders, but precisely which relatives and the exact disorders were not specified in the available records. Unfortunately, these patients and their families were lost to follow-up so we were unable to pursue the family histories.

Associated malformations of the brain were common. The most frequent finding was diminution of the size of the ipsilateral hemisphere and thinning of the overlying cortex with shallow sulci (Figs 1–4). We presume that the small hemispheric size is related to the fact that most of the neurons destined for the cerebral cortex ceased their migration prematurely. Neurons that do not form synapses with other neurons during development die. Although rare axons, myelin sheaths, and synapses can be seen in masses of heterotopic gray matter (15), it is clear that the normal number of axonal and dendritic ramifications from heterotopic nodules to other regions of the cortex has not been established. In addition, the arrest of so many neurons en route to the cortex results in a diminished number of neurons in the cortex; thus, the normal intracortical and intercortical connections do not develop. Moreover, we found small, dysplastic, or even absent, basal ganglia in 11 patients and dysplastic thalami in two. Because many reciprocal axonal connections exist between the cortex and the basal ganglia, the absence of normal basal ganglia almost certainly contributes to the diminution in the volume of white matter in the affected hemisphere and, thus, to diminished hemispheric size.

Regarding the mechanism of development of the malformation, it seems quite clear that neuronal migration is interrupted along the course from the germinal zone to the developing cortex. Unlike the sharply demarcated inner and outer borders of the heterotopic neurons as seen in classical lissencephaly or band heterotopia, however, the heterotopia seen in our group displayed a multinodular, lobulated appearance.

Thus, it appears unlikely that mutation of a single gene coding for a molecule that facilitates neuronal migration along radial glial cells, as has been postulated for classical lissencephaly (4) or X-linked lissencephaly (5, 14), can be responsible for this malformation. Because the malformation is unilateral, chromosomal mosaicism—in which abnormal disjunction occurs at an early cleavage division of the zygote, resulting in two or more cell lines containing different chromosomal components (16)—would have to be invoked for this disorder to be the result of a mutated gene or group of genes on a single chromosome. The other major possibility as a cause of the malformation is injury, either ischemic or infectious, during the late first trimester or early second trimester, when the basal ganglia are forming and the initial wave of cortical neurons is migrating from the germinal zone to the cortex (17). If such an injury involved the midline, it could also explain the frequent association of callosal agenesis or hypogenesis. However, an early injury cannot explain the polymicrogyria seen in patient 12, since polymicrogyria, when acquired as a consequence of in utero injury, is believed to result most commonly from a late second trimester injury (15, 18, 19). Note, though, that polymicrogyria can be seen in a number of genetic disorders, such as Aicardi syndrome, Walker-Warburg syndrome, and Fukuyama congenital muscular dystrophy (15, 20, 21), and patient 12 was somewhat atypical in this series, in that he had bilateral heterotopia; thus, a genetic cause is certainly a possibility.

Of interest is the fact that 10 (77%) of the 13 patients in our group were male. Although the size of the group is small enough that this may well be a random variation, it may be significant that two other types of migration disorders, bilateral periventricular nodular heterotopia (8, 22, 23) and the “double cortex” or band heterotopia (6, 7), appear to be sex-linked in some cases, arising in female subjects in an overwhelming preponderance. A high frequency of pregnancy loss is documented in these families, and the ratio of sons to daughters in the surviving offspring is markedly skewed, suggesting that most of the miscarriages were male and, thus, that the mutation is likely lethal to males (6–8, 14, 22–25). X-linked inheritance is suggested in both these disorders on the basis of the high prevalence of mother-daughter transmission and the lack of any evidence of father-

son transmission. The predominance of male subjects in our series might also suggest X-linked inheritance if the mutation were not lethal in males and if female heterozygotes (those with one normal X chromosome and one abnormal X chromosome) were affected minimally or not at all. The three affected female subjects in this series could then be accounted for by any of the following: (a) the malformation is heterogeneous (has more than one cause), one cause being a mutation on the X-chromosome but the others being autosomal mutations or an in utero insult; (b) the normal X-chromosome may have been randomly inactivated; (c) the child may have been an offspring of a heterozygous, clinically normal mother and an affected father; or (d) the child may have been an offspring of an affected father with a new mutation in the maternal X-chromosome or an offspring of a heterozygous mother with a new mutation in the paternal X-chromosome.

Despite the severe imaging appearance of the malformations, most patients were judged to have low-normal intelligence and functioned at a surprisingly high level. Of the four adults in the group (age 18 and over), all had finished high school (one attended special classes) and one (patient 5) had graduated from college (he had a C+ grade average). Two of them currently hold steady jobs, one as a laborer and one as a clerk in an auto parts store. The younger patients were developmentally delayed to some degree but only one was considered severely retarded. We speculate that the relatively high level of performance is related to the fact that one hemisphere was normal in 11 of the 13 patients. The high degree of plasticity of the developing brain, therefore, presumably allows the normal hemisphere to take over the function of the dysplastic regions. Of the two patients with bilateral disease, one was severely retarded and the other, with intractable seizures at age 2 months, has a guarded prognosis.

It is reasonable to ask why five of the patients in this series did not have signs and symptoms identical to those of the eight patients with the "characteristic" clinical syndrome. The easiest explanation for this apparent inconsistency is that four of the five patients were still very young and the fifth had a small heterotopia in the prefrontal region. The four young patients all were developmentally delayed, which is often the first clinical sign of hemiparesis or mental retardation. It is likely that several of these

children will eventually manifest the characteristic syndrome displayed by the others in the series. The fifth atypical patient had a small heterotopia that was located in a silent region of the brain as far as neurologic signs and symptoms are concerned. All of the other patients in the series had involvement of the region of the motor strip on the involved side. It is possible that neuropsychological testing would have revealed some signs of frontal lobe dysfunction in this patient, but such testing was not performed.

To summarize, we have described the clinical, electrophysiological, and imaging findings of a group of patients with large masses of heterotopic gray matter and consequent changes in morphology of their affected hemispheres. The similarity of the clinical, electrophysiological, and imaging findings suggests that these patients may be conveniently grouped together to study treatment outcomes. The finding of relatively mild clinical manifestations relative to the severe imaging appearance is noted and may relate to the plasticity of the developing brain.

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