
Periventricular heterotopia and epilepsy

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Article abstract—We report a family with nodular subependymal masses of heterotopic gray matter occurring in six members in four generations. Only female members of the family are affected, and there is a high rate of spontaneous abortion, consistent with X-linked dominant inheritance, and lack of viability in affected males. Both in this family and in sporadic cases of subependymal heterotopias there is a high frequency of convulsive disorders, suggesting that epilepsy may be the major clinical manifestation of this developmental defect.

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Neuronal migration in the embryonic CNS is a complex process of outward radial movement of neuronal and glial precursor cells from the periventricular proliferative zone to the cortical plate. This migration may be arrested at various stages, giving rise to heterotopias. Heterotopic gray matter may occur in subcortical regions, as in lissencephaly, where entire populations of neurons that normally form the upper cortical layers remain below the cortical plate. Less severe defects include laminar bands of heterotopia and islands of heterotopic neurons in the subcortical white matter.¹ Another form of heterotopic gray matter occurs in a periventricular location, in the region of the original germinal matrix. Periventricular (subependymal) heterotopias are nodular masses, up to 2 cm in size, that protrude into the ventricular lumen. They are a prominent component of the migratory disorder of tuberous sclerosis² but may occur as isolated defects in otherwise normal brains. Reports of the latter type were primarily as incidental autopsy findings³⁻⁵ or as abnormalities on imaging studies of the brain.⁶⁻⁸ There are few reports that address the clinical findings in such cases, and there is no information about genetic factors.

We studied a large family in which six members in four generations have nodular subependymal heterotopias, indicating that this developmental defect may be genetically determined.

Patient reports. The family was initially referred to the Tuberous Sclerosis (TSc) Clinic at the University of Chicago. A diagnosis of TSc had been made elsewhere. However, none of the affected family members had the skin, renal, or cardiac lesions of TSc. Four of six family members with subependymal heterotopias on brain imag-

ing studies had a history of prolonged tonic-clonic seizures that responded well to therapy with standard anticonvulsant agents. Cognitive impairments were absent or mild. Strokes have occurred in at least two and most likely three affected family members (patients 1, 3, and 5), including an apparent embolic stroke in a 19-year-old.

Only female members of the family are affected (figure 1). There is a high incidence of spontaneous abortion, with 11 miscarriages in five affected women. Affected women have nine live daughters and only two sons. The inheritance pattern is suggestive of X-linked dominant transmission with fetal death in affected males. The family is of Irish-Swedish origin.

In addition to this family, we studied one other patient with similar periventricular heterotopias on MRI who also presented with a seizure but whose family history is negative (patient 7).

Patient 1. This 71-year-old woman has a history of multiple strokes since age fifty. She has a mild right hemiparesis but otherwise is remarkably intact neurologically. Cerebral angiogram at age 69 showed left carotid artery occlusion. She subsequently had a left carotid endarterectomy. Imaging studies of the brain showed multiple, bilateral cortical and subcortical lesions consistent with infarcts. In addition, there were bilateral nodular subependymal gray matter heterotopias.

She has a history of Sydenham's chorea in childhood, negative for seizures. She has three daughters, including patients 2 and 3. She has also had three miscarriages.

Patient 2. This 48-year-old woman had onset of generalized tonic-clonic seizures at age eighteen. She at first had frequent recurrences, but has had complete seizure control since age 46 on carbamazepine monotherapy. Her neurologic examination was normal. MRI of the brain showed nodular periventricular heterotopias (figure 2). The patient has one daughter (patient 4). She has a history of three miscarriages.

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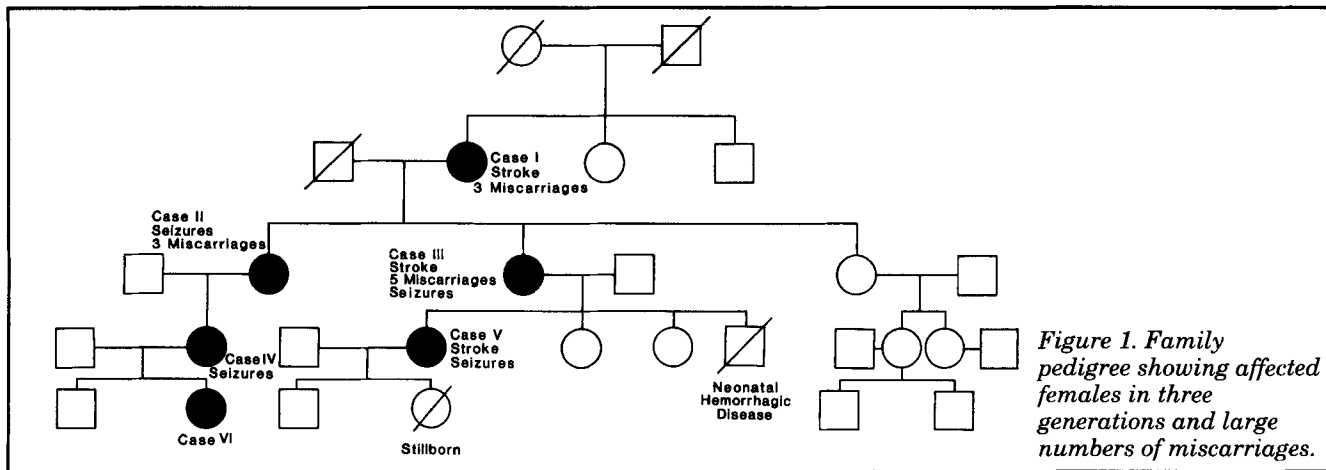


Figure 1. Family pedigree showing affected females in three generations and large numbers of miscarriages.

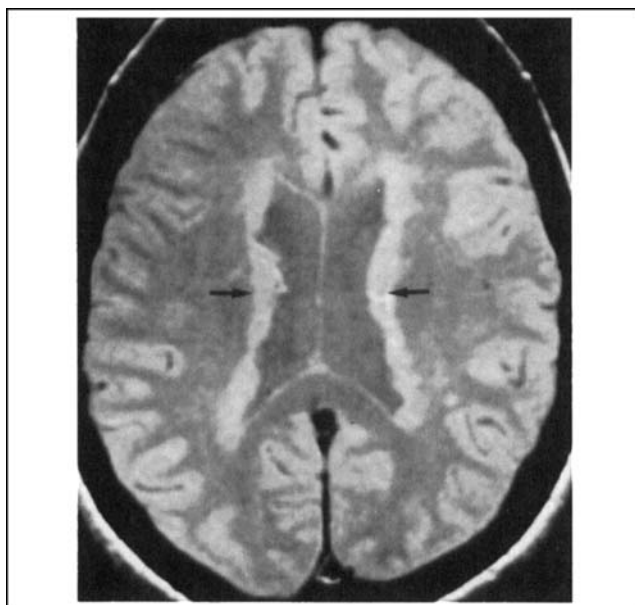


Figure 2. Brain MRI. T_1 -weighted image showing periventricular heterotopias in patient 2 (arrows).

Patient 3. This 45-year-old woman has had generalized tonic-clonic seizures since age four. The seizures have recurred as frequently as once per week, and some have been prolonged, including status epilepticus. Present therapy includes phenytoin and primidone. At age 41, she developed a right hemiparesis. Subsequent brain MRI showed a large area of encephalomalacia in the left temporal lobe as well as multiple small lesions in the subcortical white matter with increased signal on T_2 . The white matter lesions have been variously interpreted as strokes and areas of demyelination. In addition, the MRI showed extensive nodular periventricular heterotopias. An MRI of the spinal cord was normal, as were visual and somatosensory evoked potentials, spinal fluid examination including measurement of immunoglobulin G, and serum values for antigenic protein C, protein S, and antithrombin III. An EEG showed epileptiform discharges arising independently from both temporal regions, more marked on the left, as well as bipartite and frontal slowing of background rhythms.

The patient has three daughters, including patient 5. She had one son who died at age 7 days due to multiple systemic hemorrhages. Autopsy did not reveal any brain

lesions. The patient has also had five miscarriages.

Patient 4. This 26-year-old woman had a single generalized tonic-clonic seizure at age twenty-four. She is presently receiving phenytoin therapy, without seizure recurrence. Her medical history is unremarkable, except for migraine. A head CT showed multiple nodular periventricular heterotopias. She had a normal EEG.

The patient has two children. A 5-year-old son is clinically normal and had a normal brain MRI. A 2-year-old daughter (patient 6) has periventricular heterotopias on MRI.

Patient 5. This 21-year-old woman had a generalized tonic-clonic seizure at age 5 years. She had one recurrence at age 18, and has been seizure-free since then on phenobarbital therapy. At age 19 years, she had sudden onset of left hemiparesis. A cerebral angiogram showed a thrombus in the right middle cerebral artery (MCA). MRI of the brain showed a large infarct in the right MCA territory as well as extensive nodular periventricular gray matter heterotopias (figure 3). No source of an embolus was found. An EEG 3 days after the stroke showed a slow-wave focus in the right temporal and frontal regions but no epileptiform discharges. Serum antigenic protein C was deficient in the heterozygote range (52%; normal range, 80% to 120%).

At age 19, the patient had a still-born girl with a nuchal cord. She recently had a clinically normal boy who has not as yet had an imaging study of the brain.

Patient 6. This 2-year-old girl has a history of surgery for patent ductus arteriosus. She is developing normally and has not had seizures. Her head circumference is at the 25th percentile. At age 21 months she had an MRI of the brain as part of a family study. This showed an irregular contour of the lateral walls of the lateral ventricles due to small nodular masses that were isointense to the gray matter. The nodular gray matter heterotopias were somewhat less extensive than those found in other affected family members.

Patient 7. The patient is a 26-year-old man who is unrelated to the large family. He was well until age 25, when he had a single generalized tonic-clonic seizure. CT and MRI of the brain were obtained as part of a seizure workup. These showed extensive bilateral nodular periventricular heterotopias (figure 4). A diagnosis of TSC was considered, and the patient was referred to the TSC Clinic at the University of Chicago for further evaluation. A neurologic examination and examination of the skin

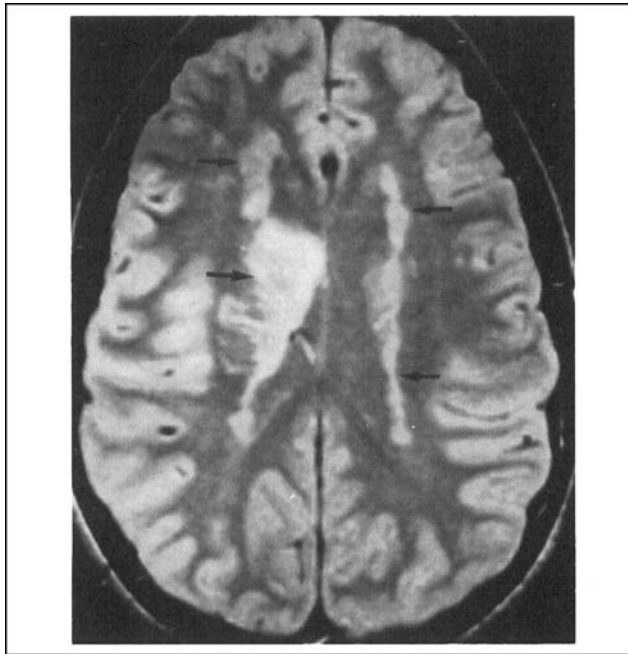


Figure 3. Brain MRI. Proton-density image, patient 5. Periventricular heterotopias are indicated by small arrows. There also is a large infarct involving the right frontoparietal cortex, internal capsule, and periventricular heterotopic tissue (large arrow).

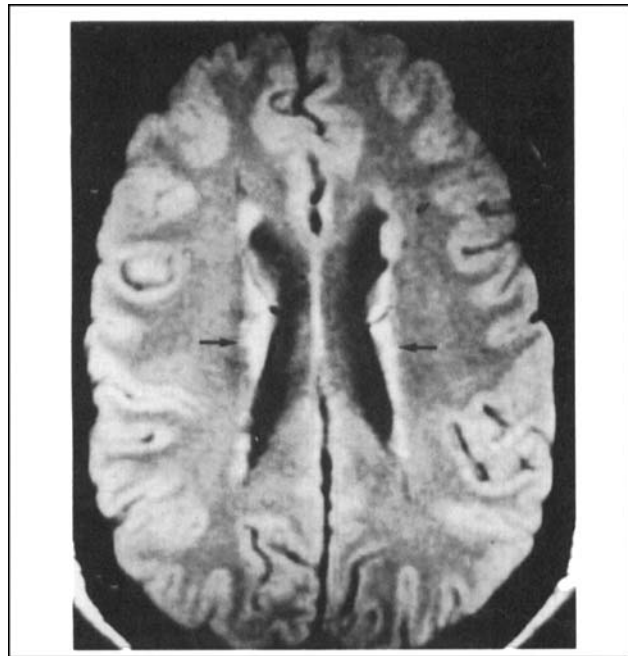


Figure 4. Brain MRI. T₁-weighted image showing periventricular heterotopias (arrows) in patient 7.

and eyes were normal. He had normal EEG, renal ultrasound, and echocardiogram. There was no family history of seizures or of the skin lesions of TSc. A cousin had Down's syndrome. Head CTs of both parents were normal.

Discussion. Nodular periventricular heterotopias and seizures are common findings in TSc. This diag-

Table. Reported cases of nodular periventricular heterotopia

Reference	N	Sex	Seizures	MR	Comments
Present cases, familial	6	6F	4	0	Stroke in 2 or 3; many miscarriages
Present case, sporadic	1	1M	1	0	
Zimmerman et al ⁶	2	2F	2	0	
Smith et al ⁷	6	Unknown	5	0	
Barkovich and Kjos ⁸	8	2M,6F	7	2 (mild)	Hypoplasia of corpus callosum in 1
Martin-Araguz et al ¹⁴	1	1F	1	0	
Total	24	3M,15F	20	2	

MR Mental retardation.

nosis was entertained initially in the present cases. However, the findings on imaging studies of the brain excluded TSc. The periventricular heterotopias in the present cases are more diffuse, imparting an irregular outline to the lateral walls of the body of the lateral ventricles. Calcifications have not occurred in these lesions, in contrast to the subependymal heterotopias of TSc, which are almost always calcified past infancy. Periventricular heterotopias of TSc have heterogeneous signal intensity on MRI,^{9,10} whereas the lesions in the present cases always had signal characteristics of cortical gray matter. None of the present cases showed tumors near the foramina of Monro or the cortical-subcortical tubers that are typical of TSc.² Mental retardation did not occur in the present cases; the major clinical resemblance to TSc is the occurrence of seizures. Although there is evidence of vertical transmission of the disorder in the large family reported here, the pattern of inheritance appears to be that of an X-linked dominant gene with lack of viability in affected males rather than autosomal dominant inheritance as occurs in TSc. However, autosomal dominant inheritance cannot be excluded on the basis of this single pedigree. We also studied an apparently sporadic male patient with similar nodular periventricular heterotopias (patient 7). Dominant or X-linked dominant inheritance in this patient are ruled out by normal imaging studies of the brain in the parents. Family studies in other cases are needed to confirm the inheritance patterns and to determine the proportion of cases with genetic transmission. No genetic information is provided for previously reported cases of periventricular heterotopias, but review of published reports indicates an excess of affected females (table). The largest series reported to date, by Barkovich and Kjos,⁸ contains six females and only two males (table).

Although there have been several pathologic reports of cases with nodular periventricular heterotopias, these had insufficient clinical data for delin-

ation of a clinical syndrome. Greenfield³ provided an illustration of a pathologic specimen with the typical nodular lesions but did not give a clinical history for the patient. There are reports of nodular periventricular heterotopias in association with other developmental defects of brain including hydrocephalus, agenesis of the corpus callosum, micropolygyria, and megalencephaly.⁴ Meschede^{11,12} and Virchow¹³ provided early descriptions of widespread subcortical heterotopias. Histologic examination demonstrated occurrence of neurons and glia in such malformations.¹²

Recent radiologic studies provide some clinical information in addition to the imaging findings. Zimmerman et al⁶ briefly reported two unrelated girls with nodular gray matter densities protruding into the lateral ventricles. Both had histories of seizures since childhood. Smith et al,⁷ in a survey that included six imaging centers, identified six cases with bilateral subependymal nodules, including one with autopsy confirmation of ectopic gray matter. Five of the six had a history of seizures; in one, the periventricular heterotopias were an incidental finding in a tumor patient studied for possible CNS metastases. This report does not provide further details, such as the sex of the patients or the family history. Martin-Araguz et al¹⁴ reported a single case with seizures as the only clinical manifestation. Barkovich and Kjos⁸ recently reported eight patients with subependymal gray matter heterotopias, most of whom had both complex partial and generalized tonic-clonic seizures. These cases, as well as the ones reported here, suggest a high association between periventricular nodular heterotopias and epilepsy (table). The seizures have been generalized tonic-clonic in most of the reports that specified seizure type.

Seizure disorder as the only clinical manifestation of a cerebral migratory defect is somewhat unexpected, since mental retardation is a major finding in most other migratory disorders, including lissencephaly, laminar heterotopias, and TSc. However, Meencke and Janz^{15,16} reported subtle migratory disorders or microdysgenesis in a large proportion of cases with primary generalized epilepsy, and suggested that these may be causally related to the seizure disorder. The migratory disorder in our cases appears to be much more extensive. Nevertheless, sufficient normal cortical architecture seems to be assembled for the development of normal cognitive functions. The ectopic cells left behind in the periventricular (germinal matrix) zone may be predominantly glia, as in the subependymal nodules of TSc.² Gressens et al¹⁷ recently reported that, in the mouse, a late group of cells forms in the germinal matrix near term, after the completion of neuronal birth and migration, and migrates to the upper (supragranular) layers of cerebral cortex, where these cells form cortical astrocytes. In the mouse, damage to this cell population appears to affect neuronal function and survival. A migration disorder that starts late in development, during the late second and third trimesters, could therefore lead to a pure population of arrested glia. The possibility that the heterotopias

in the present cases are glial in nature derives some support from the fact that there is no zone of white matter interposed between the nodular heterotopias and the ventricular lumen. Such a band of white matter tends to form in defects of neuronal migration, such as laminar (band) heterotopias.¹

The occurrence of strokes early in life in three affected family members studied by us raises the question of whether stroke is part of the syndrome of periventricular heterotopia. We did not find any reports of strokes in cases of periventricular heterotopias other than in the family we studied. Stroke in this family is probably related to a separate genetic defect.

The family reported here appears to provide the first proof of genetic transmission of periventricular heterotopias. This malformation now needs to be considered in families with epilepsy in multiple generations.

Addendum. A family in which a mother and daughter both had periventricular heterotopias and seizures has recently been reported.¹⁸

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