Familial bilateral periventricular nodular heterotopia mimics tuberous sclerosis

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Abstract

A mother and daughter with an initial diagnosis of tuberous sclerosis are described. The daughter presented with partial seizures at the age of 8 months. Computed tomography showed uncalcified periventricular nodules which on magnetic resonance imaging were ovoid, almost contiguous, of grey matter density, and did not enhance with gadolinium. Brain imaging of her asymptomatic mother was similar. Absence of severe mental retardation, extracranial hamartomas, and depigmented patches distinguishes familial bilateral periventricular nodular heterotopia (FNH) from tuberous sclerosis. FNH is probably inherited as an X linked dominant with lethality in males.

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The cerebral cortex develops from migration of primitive neuroblasts outwards from the germinal matrix starting from the eighth week of pregnancy. The wider availability of magnetic resonance imaging (MRI) has led to an increasing recognition of neuronal migration disorders during life. These disorders may be classified according to their appearance on neuroimaging and include lissencephaly, pachygyria, the bilateral perisylvian syndrome, the double cortex syndrome, and band and nodular heterotopias. Familial recurrence of each of these disorders has been reported suggesting an important genetic contribution to their aetiology.

Familial bilateral periventricular nodular heterotopia (FNH) is a recently described

condition and is characterised by irregular nodules in the periventricular white matter, mild mental retardation, and seizures (MIM 142510). Tuberous sclerosis is an autosomal dominant disorder in which there are hamartomas in multiple organs including brain, kidney, and heart. Periventricular nodules visible on computed tomography or MRI are common in both conditions.

We describe a mother and daughter whose abnormalities on neuroimaging were originally interpreted as evidence of tuberous sclerosis but who have a familial neuronal migration disorder distinguishable from tuberous sclerosis.

Case reports

CASE 1

A girl was born by caesarean section at 33 weeks' gestation because of intrauterine growth retardation. Birth weight was 1000 g and she was intubated and ventilated for 24 hours. At the age of 8 months she experienced two prolonged focal seizures each lasting around 90 minutes. Computed tomography (fig 1) showed an irregular outline to the lateral ventricles, although with no intracranial calcification, and the possibility of tuberous sclerosis was raised. Treatment was started with carbamazepine and she became free of fits for two years. At the age of 4 years she was re-evaluated because of frequent partial seizures. These began with abnormal movements of the left arm followed by her becoming quiet and distant. She would often say 'stop my arm moving it hurts'. There were other episodes where she would become quiet and unresponsive, fiddle with her hair or clothes, have repetitive chewing movements, and look frightened. No depigmented patches were visible under Wood's light and examination of the teeth, nails, and optic fundi were normal. An electroencephalogram was abnormal with sharp delta and spike transients in the left temporal region.

Echocardiography showed two bright echodense lesions in the right ventricle 'reminiscent of tuberous sclerosis'. Electrocardiography and renal ultrasound gave normal results. MRI (fig 2) showed multiple, irregular periventricular nodules that did not enhance with gadolinium. At the age of 5 years her intellect is normal and her seizures are partially controlled with carbamazepine and lamotrigine.

CASE 2

The mother of case 1 has never had a seizure. Her intellect is normal: she attended a

Figure 1 Computed tomogram of case 1 showing extensive uncalcified periventricular nodules.

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Table 1 Reported familial cases of bilateral periventricular nodular heterotopia

Author	Cases	Seizures	Intellect	Electroencephalography	Comments
DiMario <i>et al</i> ¹	Mother and daughter	Mother: complex partial seizures from age 21. Daughter: two febrile convulsions at age 3 and 5, complex partial seizures from age 10	Normal in 2/2	Daughter: bicentral paroxysmal activity with right sided predominance	Epilepsy in deceased maternal grandmother
Kamuro and Tenokuchi ²	Grandmother, mother, and daughter	Mother: febrile convulsion age 3, refractory complex partial and tonic clonic seizures from age 15. Grandmother and daughter (age 13) asymptomatic	Normal in 3/3	Mother: frequent right anterior temporal spikes	
Oda <i>et al</i> ³	Mother and two daughters	Mother: refractory complex partial seizures from age 13. Daughters: asymptomatic at ages 1 and 6 years	Normal in 3/3	Mother: multifocal spike and slow waves predominantly in left frontal and anterior temporal regions	Mega cisterna magna in 3/3
Huttenlocher <i>et al</i> ⁴	Six females in four generations	Four out of six with refractory tonic clonic seizures from ages 4, 5, 18, and 24; 1/6 asymptomatic (age 2); 3/6 stroke at age 19, 41, and 50	Normal in 6/6	Patient 3: epileptiform discharges arising from both temporal regions. Bitemporal and frontal background slowing	Eleven spontaneous abortions in five affected women; 3/6 stroke at ages 19, 41, and 50
This report	Mother and daughter	Daughter: simple partial, complex partial and minor motor status from 8 months. Mother: asymptomatic	Normal in 2/2	Daughter: sharp delta and spike transients in the left temporal region

Figure 2 T1 weighted MRI scan of case 1 showing periventricular nodules of grey matter density (arrowed) that do not enhance with gadolinium.

mainstream school and was in full time paid employment. Examination under Wood’s light was unremarkable and there were no stigmata of tuberous sclerosis in her nails, teeth, or optic fundi. Renal ultrasound gave normal results; computed tomography showed an identical appearance to her daughter. Computed tomography of the father of case 1 was normal.

Discussion

Sixteen females with FNH from five families have now been reported (table 1).^{1–4} Partial and secondarily generalised seizures are most common, although some affected adults may

be seizure free. Seizures starting in infancy have not previously been reported. The variable expression of seizures in affected females may be related to differences in X inactivation. Febrile convulsions have occurred in 2/5 families.^{1,2} The cause of the seizures in FNH is unknown but the occurrence of 3 Hz spike and wave activity in some sporadic cases of nodular heterotopia⁵ suggests the possibility of a widespread disorder of brain function. Intelligence is not markedly reduced.

The absence of affected males combined with frequent spontaneous abortions in one family⁴ are compatible with X linked dominant inheritance with lethality in males. Sporadic nodular heterotopia has also been described.⁵ This may be distinguished from the X linked form by occurrence in males, later seizure onset, and fewer nodules.

In 3/5 reported families a previous diagnosis of tuberous sclerosis had been made.^{1,4} Diagnostic criteria for tuberous sclerosis have been established.⁶ Familial nodular heterotopia is distinguishable from tuberous sclerosis on clinical, radiological, and genetic criteria (table 2). Infantile spasms accounted for 60% of seizures in the first year of life in children with tuberous sclerosis in one series,⁷ but these have not been described in FNH. Early onset of seizures in tuberous sclerosis is commonly associated with severe mental retardation. Subependymal nodules are a primary feature of tuberous sclerosis and are usually calcified before the age of 2 years.⁸ The nodules are composed of glial cells in tuberous sclerosis and heterotopic neurones in nodular heterotopia. The different densities of these two tissues may not be detected on computed tomography but will be easily apparent on MRI. It is rare to see more than 10 periventricular nodules in tuberous sclerosis.⁸ Computed tomography is frequently abnormal in tuberous sclerosis but may be normal in nodular heterotopia. Tuberous sclerosis has an equal sex incidence.

Echocardiography has previously been shown to have a high false positive rate in the detection of cardiac rhabdomyomas in adults.⁹ In the daughter we have described the echodensities on cardiac ultrasound led to erroneous support for the diagnosis of tuberous sclerosis. Abnormal findings on echocardiography should be interpreted with care if the diagnosis of tuberous sclerosis is in doubt.

Table 2 Clinical features of FNH and tuberous sclerosis

	FNH	Tuberous sclerosis
Commonest seizure type	Partial seizures	Infantile spasms +/- partial seizures
Mental retardation	Mild if present	Severe if seizure onset <1 year of age
Skin lesions	Not reported	Common
Periventricular nodules	Best seen on MRI	Best seen on computed tomography
	Grey matter density on MRI, do not enhance	White matter density on MRI, enhance
	Uncalcified, may be contiguous	Usually calcified and discrete
Cortical lesions	Not reported	Common
Extra central nervous system hamartomata	Not reported	Common
Genetics	Males not affected (? lethal), X linked dominant	Equal sex incidence, autosomal dominant

The identification of familial neuronal migration disorders is important not only for accurate genetic counselling but also for the insight these disorders may give into the mechanisms of normal neuronal migration and the causes of epilepsy. Familial nodular heterotopia has been mapped to Xq28 by linkage analysis in one family.¹⁰ The identification of further families may permit positional cloning of the gene. A gene encoding a neural cell adhesion molecule (L1CAM) has previously been mapped to Xq28. Mutations in this gene give rise to three different neuronal migration disorders: X linked hydrocephalus, the MASA syndrome (mental retardation, aphasia, shuffling gait, and adducted thumbs), and one type of X linked spastic paraparesis.¹¹ L1CAM is therefore a candidate gene for FNH.

In the past it has been thought that genetic factors are more important in the primary generalised than the partial epilepsies. The frequent occurrence of partial seizures in FNH, and the recent description of a number of genetically determined partial seizure disorders,^{12 13} suggests that this may not be the case. Genetic counselling of families with partial seizure disorders may require MRI of first degree relatives.

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