

ORIGINAL ARTICLES

Cranial magnetic resonance imaging in patients with tuberous sclerosis and normal intellect

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Abstract

The pattern of cerebral hamartomas among a population of patients with tuberous sclerosis and normal intellect was determined. All patients with tuberous sclerosis over 5 years old with normal intellect who were resident in the Bath health district were offered cranial scanning by magnetic resonance imaging. Cerebral axial and coronal images were obtained in 10 mm contiguous sections with a Picker 0.5 tesla magnetic resonance imaging unit. The number, size, and distribution of lesions found was recorded. Eleven of 13 eligible patients underwent scanning. Two patients had normal scans. Seven patients had between one and five subependymal nodules. Nine patients had between two and nine cerebral tubers best seen on T2 weighted images. Our findings suggest that the wrong conclusions may be drawn if the number of lesions alone is used to predict neurological outcome in tuberous sclerosis.

Tuberous sclerosis is an important cause of epileptic seizures and mental handicap in young children, and has an incidence of 1/6000 births.¹ The proportion of cases in whom these serious neurological sequelae develop is now believed to be lower than previously estimated.² Mental handicap usually occurs in children who suffer seizures in the first year of life. Among children with a history of early seizures it is very difficult to predict neurological outcome. Most will develop mental handicap and many have resistant seizures but a few develop normally with or without a continuation of seizures. It has been suggested that the number of lesions identified on cranial magnetic resonance imaging (MRI) may predict mental development.^{3 4}

Cerebral involvement in tuberous sclerosis is characterised by subependymal glial nodules, cortical and subcortical tubers, and giant cell astrocytomas. The relationship between the number of cerebral hamartomas and the clinical course has been examined. One large study of cranial computed tomography in children with tuberous sclerosis found little relationship between mental development and the incidence of subependymal glial nodules or of cortical and white matter lesions.⁵ Magnetic resonance imaging appears to be more sensitive than computed tomography in detecting parenchymal tubers,⁶ which may be more prone to cause seizures. Lesions with high signal intensity on images with long repetition times are characteristic (T2 images). The size and configuration of the signal abnormalities on cranial MRI have

been found to correlate exactly with the pathological findings seen grossly and microscopically. The MRI findings appear to be less affected by age than are the corresponding low attenuation changes seen on computed tomography.⁷

There is very little information about the pattern of cerebral lesions in tuberous sclerosis patients with normal intellect, and the pattern in patients with no history of seizures has not been documented. We present the cranial MRI findings in a population of patients with tuberous sclerosis with normal intellect, some of whom were free of seizures.

Subjects and methods**POPULATION**

Twenty two individuals known to be affected by tuberous sclerosis and resident in the Bath health district were previously ascertained for a prevalence study.¹ After an interview by the authors and a review of their academic, social, and (for adults), work history, 13 of these patients were identified as over 5 years old and not mentally handicapped. They were able to read and write, to make normal progress at school, and the adults were capable of gainful employment.² Eleven consented to cranial MRI. One patient was an obligate gene carrier with no clinical evidence of the disease⁸ but all the other patients fulfilled diagnostic criteria outlined by Gomez.⁹ Eight patients had no history of seizures. Two girls aged 6 and 8 years had both recently developed partial seizures with secondary generalisation and were free of seizures on antiepileptic medication; both girls were doing well in normal schools. One woman aged 38 had occasional nocturnal seizures which began when she was 19 years old and for which she had refused treatment. She had a part time responsible job and could read and write. The two patients not consenting to MRI scan were a girl of 12 years with a hemiplegia and generalised seizures and a woman of 35 years also with a history of generalised seizures.

METHODS

Ethical approval was obtained from the local ethical committee and informed consent received before the study from the patients or their parents. Images were obtained on a Picker magnetic resonance imaging unit with a 0.5 tesla magnetic field. Multiecho sequences were taken in axial section with a repetition time of 1800 ms and an echo time of 30 and 100 ms; and inversion recovery sequences in coronal section with a repetition time of 1500 ms, an echo time

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of 26 ms, and an inversion time of 500 ms. Axial scans consisted of 16 contiguous 10 mm slices, and coronal scans of eight contiguous 10 mm slices. Although the minimum resolution of the imaging unit is 2 mm, it is difficult to interpret lesions less than 4 mm in size. Therefore to avoid misinterpretation and allow comparison in future studies, the number, size, and distribution of lesions measuring more than 4 mm in greatest diameter were recorded. Lesions present in the same area on two contiguous scans were counted as one.

Results

Two patients had normal scans. Seven patients had between one and five subependymal glial nodules. Nine patients had between two and nine cerebral tubers. Three patients had some ventriculomegaly.

Tubers occurred in all cerebral lobes, although most frequently in the frontal and parietal lobes (table). One patient had a cerebellar tuber. Most tubers (36/44) were less than 1.5 cm in greatest diameter and were frequently subcortical rather than cortical. Six lesions were in the deep white matter. Six of the patients each had between one and three other possible abnormal areas measuring less than 4 mm. These were all within the deep white matter and

were not included for analysis. Tubers were most easily seen on T2 weighted images where they appeared as areas of increased signal intensity (figure). Corresponding abnormalities on T1 weighted images usually appeared hypointense.

Tubers measuring 1.5 cm or greater were only seen in children. One girl aged 8 years had four tubers larger than 1.5 cm in size. This child is top of her class at school and has an Edinburgh reading age of 11 years. Another girl aged 13, with no history of seizures, was in the first 10 of her class for mathematics, English, and science and had three lesions 1.5 cm or larger.

Discussion

It is our experience that individuals who reach 5 years of age with normal development do not develop mental handicap from tuberous sclerosis and for this reason our patients are very unlikely to do so. The cranial MRI findings in patients with tuberous sclerosis with mental handicap and poorly controlled seizures is well documented.⁶ We have found similar lesions in a population of tuberous sclerosis patients with normal intellect, the majority of whom had no history of seizures.

We believe we have accurately identified hamartomas of at least 4 mm in size and that the number of cerebral lesions we found is sufficient to make cranial MRI unlikely to be a reliable predictor of clinical outcome. It is possible that the distribution and size of lesions may be of greater help. Both patients with temporal lobe lesions had seizures. We found very few occipital hamartomas and two of the four patients with occipital lesions had seizures. One study has suggested that abnormalities in this lobe correlate best with repeated interictal electroencephalogram abnormalities.¹⁰ We did not find that bilateral lobe involvement was associated with a poor prognosis. A small number of tubers in our study measured more than 1.5 cm and only three were greater than 2 cm. One previous report found many lesions more than 3 cm but size had not otherwise previously been mentioned.¹¹

We accept that none of our patients had more than 10 cortical lesions but it would seem unwise to extrapolate that this would never occur in affected individuals with normal intellect. One of our patients, who is a bright student, had nine cerebral tubers. Others have reported severely mentally handicapped patients with considerably fewer lesions.

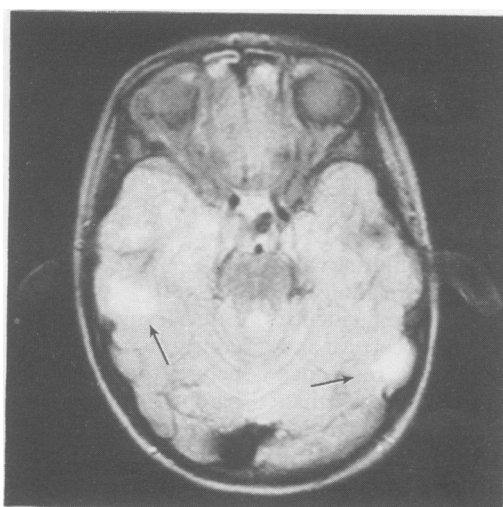
Some individuals may have an inherently higher seizure threshold which protects them from developing seizures at an early age despite multiple large or strategically located lesions. Neuronal heterotopias thought to represent neuronal arrest have been described in areas of the brain unaffected by cerebral tubers or subependymal glial nodules.⁹ These may be below the resolution of MRI imaging and their contribution to increased seizure potential or impaired cognitive function are unknown.

We have found that the cranial abnormalities in older patients were smaller, more frequently

Distribution of cerebral lesions on cranial MRI of patients with tuberous sclerosis and normal intellect

Age (years)	Frontal		Parietal		Occipital		Temporal		No of subependymal glial nodules
	Right	Left	Right	Left	Right	Left	Right	Left	
6*	2	1	2						5
8*	1	1	1	1	1	2	1	1	5
13	1		2	3		2			4
17		2	1	1					0
21									0
25	4								0
38	1		1	2					2
38*			2		1		1		4
45									0
51	1	1		1					1
78			1			1			2

*History of seizures.



T2 weighted axial cranial MRI scan showing two hyperintense cerebral tubers.

subcortical rather than cortical, and more difficult to identify. The cerebral lesions in tuberous sclerosis may become less obvious on MRI with advancing age as is the case for lesions seen on cranial computed tomography.⁷

Our findings suggest that the wrong conclusions may be drawn if the number of lesions alone on cranial MRI is used to predict neurological outcome in tuberous sclerosis. Our results provide a basis for comparison in future studies and we would recommend that both the number, size, and distribution of lesions should be recorded.

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