MR Findings in Tuberous Sclerosis Complex and Correlation with Seizure Development and Mental Impairment

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PURPOSE: To correlate the findings on MR scans of the brain in patients with tuberous sclerosis complex with mental disability and the type and age at onset of the first seizure. **METHODS:** Patients with tuberous sclerosis complex who had MR brain scans were identified. The diagnosis was confirmed, and the clinical information on each patient was updated. The number, site, and area of abnormal signals were recorded on each scan. The presence of sulcal islands, gyral cores, and migration lines or wedges was recorded. **RESULTS:** Seventy-five patients were studied. Twenty-nine patients who had infantile spasms had more tubers than the 26 who presented with other types of generalized seizures. These patients had more tubers than the 15 patients with partial seizures. Significantly more tubers were found in patients with seizure onset before 1 year of age and mental disability. Gyral cores, sulcal islands, and radial migration lines or wedges were more common in patients with infantile spasms who had an early seizure onset and were mentally disabled. Patients who did not have seizures had no mental disability. **CONCLUSIONS:** A greater number of tubers occurred in patients who had infantile spasms, had their first seizure before 1 year of age, or had a mental disability. These features reflect the degree of cerebral dysfunction caused by the tubers. Gyral cores, sulcal islands, and migration lines or wedges also reflect cerebral dysfunction. MR scans correlate well with the clinical features and are valuable in assessing patients with tuberous sclerosis complex.

Index terms: Sclerosis, tuberous; Seizure disorders; Brain, magnetic resonance; Mental deficiency

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Tuberous sclerosis complex is a multisystem disorder that primarily affects the brain, retina, kidney, and skin. In the brain, tuberous sclerosis complex may be manifest by subependymal nodules in the walls of the lateral ventricles, cortical tubers in the cerebrum and cerebellum, and heterotopias (1) in the white matter. The subependymal nodules are well displayed by computed tomography (CT), and commonly patients are asymptomatic. In only 7% of patients with tuberous sclerosis complex does intracranial hypertension develop from subependymal nodules that continue to grow as a subependymal giant cell astrocytoma until one or both foramina of Monro are obstructed (2). The cortical tubers may be asymptomatic but are often associated with severe intractable seizures and mental disability. The capacity of magnetic resonance (MR) imaging to reveal change in tissue hydration of cerebral lesions, which makes them visible in normal tissue, gives this imaging method a definite advantage over CT scanning for displaying cortical tubers (3). For investigating patients with tuberous sclerosis complex, MR imaging and CT scanning of the head sometimes complement each other, because CT is more sensitive for displaying calcified lesions.

The number and anatomic location of cortical tubers may play an important role in the mental development and consequently the intelligence of individuals with tuberous sclerosis complex (4). Furthermore, the patient's age at seizure onset correlates with the degree of men-

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Fig 1. Multiple hyperintense tubers involving the base of the frontal and temporal lobes are much more obvious (*single arrow*) on T2-weighted images (*B*, 2200/80 [repetition time/echo time]) than on proton density–weighted images (*A*, 2200/30). Sulcal islands show hyperintense gyral white matter that is connected by adjacent subcortical white matter, whereas the intervening cerebral cortex appears spared (*arrowhead*).

tal disability (5); both symptoms reflect the cerebral dysfunction caused by the epileptogenic tubers.

To find support for the above statement, we studied the scans of patients with tuberous sclerosis complex seen at our institution since the introduction of high-resolution MR imaging and attempted to correlate structural changes with the patient's type of seizures, age at onset of seizures, and presence or absence of mental disability.

Methods

We identified all patients diagnosed with tuberous sclerosis complex who were seen at our institution and had a 1.5-T MR scan done before November 1, 1992. In each case, the scan was done with T1- and T2-weighted imaging sequences. We reviewed the clinical record of each patient to confirm that the diagnosis of tuberous sclerosis complex was made according to the published criteria (6), and we extracted data on seizures, if any, and mental status. Patients were considered to have *normal intelligence* if they did not require special education and were leading normal lives. All *mentally impaired* patients required special educational methods, or needed more than usual supervision, or completely depended on others to meet essential needs. No formal intelligence tests were done. However, all patients documented as having special needs were fully assessed by a multidisciplinary team. In patients with a history of seizures, we recorded the patient's age and type of seizure at onset and updated clinical information with a questionnaire by mail.

A neuroradiologist reviewed the MR image of each patient and recorded from each scan the number, site, and estimate of volume of each abnormal cortical and subcortical signal on proton-density (Fig 1A) and T2-weighted (Fig 1B) sequences. These signals are known to represent cortical tubers (7). We estimated the volume of each tuber detected by MR by calculations using the area of measured signal change, the number of scans affected, and the section and skip thickness. For ease of handling, the tubers were grouped into those that were 1 cm or less, 1 to 2.5 cm, and 2.5 cm or more in size.

We also recorded the presence of sulcal islands (Fig 1), gyral cores (Fig 2), radial migration lines and wedges (Fig 3), and subependymal nodules (7). Gyral cores were more distinctive on T1 and proton-density than on T2 images. The center of the gyrus is hypointense to both white and gray matter on T1-weighted sequences but surrounded by isointense cortex. This gives the impression of an empty gyrus. On proton-density images, the tuber is hyperintense to white matter and sometimes slightly hyperintense to gray matter. On T2-weighted sequences, the gyral core and often the cortex are hyperintense to adjacent white and gray matter. Sulcal islands always involve two adjacent gyri and the intervening white matter. The white matter component of the lesion is hyperintense on T2-weighted sequences, whereas the cortex remains isointense to the adjacent cortex (8). The radial migration lines or wedges of signal hyperintensity span the white matter between the lateral ventricle and the cerebral cortex (9). We also reviewed the CT scan, when available, to determine the presence of subependymal nodules.

The results were analyzed by binary logistic regression.

Results

Seventy-five patients (38 male, 37 female) with tuberous sclerosis complex had an MR scan of the head in the course of their clinical evaluation. Seven patients were younger than 2 years of age, 22 were between 2 and 5 years of

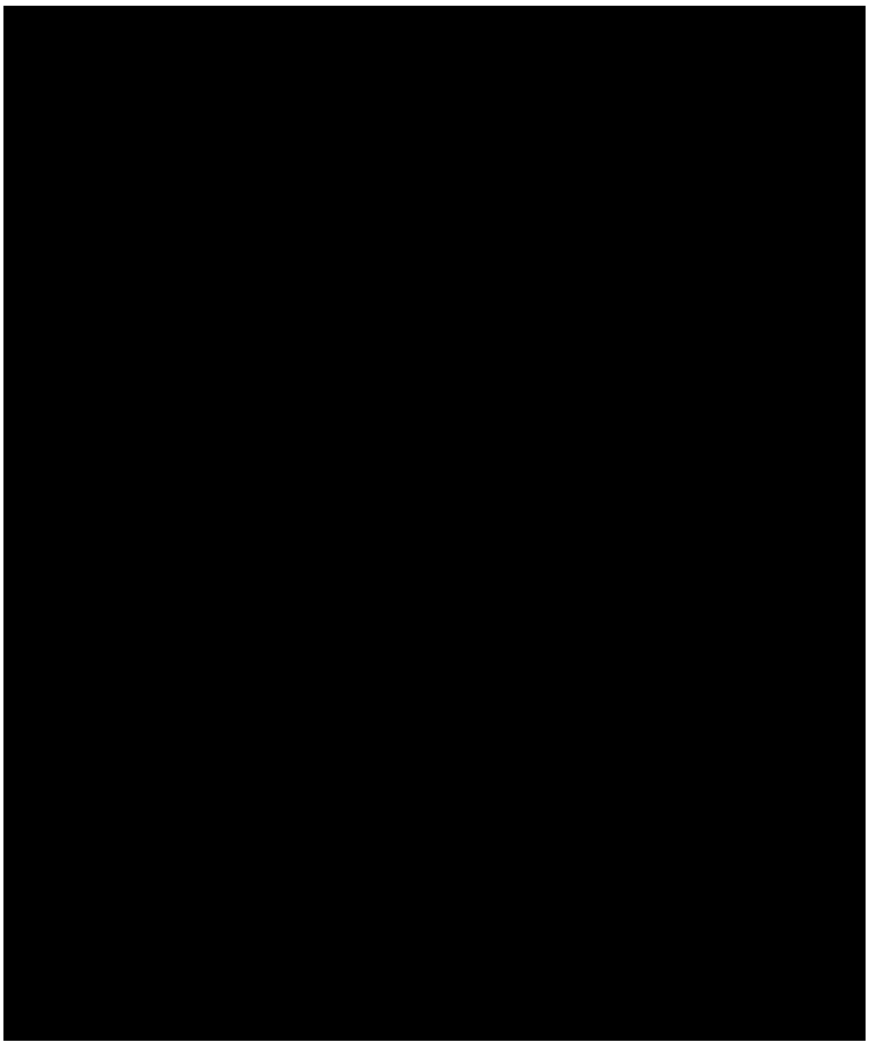

Fig 2. Multiple, at least three, evolving gyral core lesions (*C* and *D*, *arrows*) involving the right frontal, left frontal, and right paramedian parietal lobes were not obvious on either proton-density (*A*, 2000/30) or T2-weighted sequences (*B*, 2000/80) at age 3 months but are evident on these sequences (*C*, 2000/30; *D*, 2000/80) at age 26 months. Also note multiple subependymal nodules (*A*, *C*, and *D*) and large hypodense area in right frontoparietal region caused by progressive calcification within a tuber.

Fig 3. Multiple, faint radial migration lines on proton-density (*A*, 2200/30) and T2-weighted (*B*, 2200/80) sequences that extend through the centrum semiovale and appear to connect the ventricle with the gyral white matter.

Table 1: Relationship between seizure type at presentation and number of tubers seen in different brain areas

Type of Seizure at Presentation (Number of Patients)	Average Number of Tubers at Each Location (Numbers of Patients with Tubers at Each Site)					Median Number of Tubers	Number of Patients with Impairment
	F	AT	PT	P	O		
Infantile spasms (29)	5 (29)	2.8 (26)	3.7 (25)	5.6 (29)	0.5 (10)	4.4 (27)	25
Generalized seizures (26)	2.9 (19)	2 (13)	3 (12)	3.7 (20)	0.8 (10)	3.3 (12)	13
Partial seizures (15)	1.3 (9)	0.9 (7)	0.9 (6)	2.3 (13)	0.5 (4)	1.3 (8)	6
No seizures (5)	3.4 (4)	0.8 (1)	0.4 (2)	3 (1)	0.2 (1)	1.8 (4)	0

Note.—AT indicates anterior temporal lobe; F, frontal lobe; O, occipital lobe; P, parietal lobe; and PT, posterior temporal lobe.

age, and 46 were older than 5 years of age when the scan was done.

The number of tubers ranged from 1 to 46. On the external surface, the region most commonly affected, the parietal lobe, contained tubers in 65 patients (87%); 61 (81%) had frontal tubers, 51 (68%) had tubers in the medial or parasagittal area, 47 (63%) had tubers in the anterior or posterior temporal lobe, and only 20 (27%) had lesions detected in the occipital lobe.

The number of tubers was recorded for each patient, and from this an estimate was made of the volume of each tuber on the basis of the area of signal distortion. Analysis of the results showed that tuber volume did not give additional information for correlation of the MR appearances and clinical features.

Table 1 shows the relationship of the initial seizure type to the average number of tubers identified at each site. The seizure types were divided into five groups: (*a*) infantile spasms; (*b*) myoclonic seizures; (*c*) generalized seizures other than myoclonic or infantile spasms; (*d*) febrile seizures; and (*e*) partial seizures. For the purpose of statistical analysis, to determine the relationship of the site and the number of tubers detected on MR scan and the type of presenting seizure, groups 2, 3, and 4 were combined. This showed that the likelihood of the first seizure being an infantile spasm increased in parallel with the total number of tubers ($P < .001$). Partial seizures were associated with tubers in any one of the cerebral lobes except the frontal ($P < .01$) and generalized, myoclonic, or febrile seizures were associated with tubers in any lobe except the parietal ($P < .01$).

Table 2 indicates that a greater number of patients with infantile spasms as the presenting seizure type had sulcal islands, gyral cores, and migration lines or wedges.

Table 3 shows the relationship between the patient's age at seizure onset and the average number of cortical tubers determined by MR. Patients with seizure onset before 6 months of age had three times as many tubers as patients whose seizures began after 1 year of age. The likelihood of the first seizure occurring before 1 year of age increased relative to the total number of tubers ($P < .001$). If one patient (A) had one more tuber than another patient (B), then patient A was 1.3 times more likely to have a seizure before 1 year of age than B (95% confidence interval, 1.1 to 1.5).

Table 4 demonstrates the relationship between the patients' age at seizure onset and the presence of sulcal islands, gyral cores, and migration lines or wedges in their MR scans. All these findings were common in patients whose seizures started before 6 months of age and uncommon in patients whose seizures began after 1 year of age.

Forty-one patients were mentally disabled and had an average of 18.2 tubers each; 34

Table 2: Type of seizure at presentation and unique findings from MR imaging

Type of Seizure at Presentation (Number of Patients)	Number of Patients		
	Sulcal Islands	Gyral Cores	Migration Lines
Infantile spasms (29)	10	9	16
Myoclonic seizures (5)	0	0	1
Febrile convulsions (5)	0	1	0
Other generalized seizures (16)	2	3	3
Partial seizures (15)	3	0	1
No seizures (5)	1	0	1

Table 3: Age at onset of seizures and number of tubers

Age at Onset of Seizures, Mo	No. of Patients	Tubers
		Average No.
<3	14	19.2
3–6	21	19.8
6–12	11	15.7
12–60	16	6.9
>60	8	7.0

Table 4: Age at onset of seizures and findings from MR imaging

Age at Onset of Seizures, Mo	No. of Patients		
	Sulcal Islands	Gyral Cores	Migration Lines
<3	3	4	3
3–6	8	6	10
6–12	4	2	6
12–60	0	0	1
>60	0	1	1

patients had no disability and had 9.9 tubers each. The possibility of a patient being mentally disabled was directly related to the total number of tubers ($P < .01$). A patient (A) with one more tuber than another patient (B) was 1.1 times more likely to be mentally disabled (95% confidence interval, 1.0 to 1.1).

Table 5 portrays the number of mentally disabled patients who had sulcal islands, gyral cores, or migration lines or wedges on MR scans. All these features were more common in mentally disabled patients. Thirty-six patients had a CT scan as well: 22 patients showed subependymal nodules on both CT and MR; 11 patients, whose CT demonstrated subependymal nodules did not display them on MR; and in 3 patients no subependymal nodules were detected on either scan. All subependymal nodules detected on MR were also demonstrated by CT scan.

Discussion

There is definite evidence to show that the signal changes observed represent tubers. In a study by Nixon et al (7) in which postmortem MR scans were made with fixed brains of tuberous sclerosis complex patients, it was demonstrated that multiple focal areas of T2 signal correlated with cortical tubers. These were best seen on the white matter subjacent to the tuber. On some occasions increased signal was observed in the affected cortex. On T1 sequences, areas of signal disturbance occupied only the subcortical white matter. The study by Nixon et al (7) clearly showed that some tubers that do not involve the adjacent white matter are not detected on MR. Thus, our findings underestimated the number of cortical tubers.

Table 5: Relationship of mental impairment to findings from MR imaging

Mental Impairment?	No. of Patients	No. of Patients		
		Migration Lines	Sulcal Islands	Gyral Cores
Yes	41	13	10	15
No	34	3	3	5

In our seven patients younger than 2 years of age when the MR scan was done, the number of tubers detected likely was lower than the actual number. The evidence suggests that cortical tubers are present at birth, because they have been shown pathologically in the fetus (10). For detection of tubers on MR scan, the brain needs a greater myelination than what has occurred before 2 years of age. (Figure 2 shows the pattern of an evolving tuber.) However, because the scans of these seven patients did show several tubers, they were included in the study. The causal role of tubers in epilepsy has been demonstrated by finding clear topographic correlation between electroencephalographic spike foci and areas of abnormal MR signals (11).

There were large differences in the number of tubers found in patients with tuberous sclerosis complex. The frontal and parietal lobes were most commonly involved, as found in other studies (12). The occipital lobe, which is regarded as the least epileptogenic lobe, was less frequently involved.

We found a greater number of tubers in the frontal, medial, parietal, and temporal lobes of tuberous sclerosis complex patients presenting with infantile spasms than in tuberous sclerosis complex patients with any other type of generalized seizures or partial seizures. Statistically, the occurrence of infantile spasms rather than any other type of seizure was related to the total number of tubers and not to the number in any one area of the brain. This result was highly significant ($P < .001$). Twenty-five (86%) of the 29 patients with infantile spasms were disabled. Thus, it can be concluded that the greater number of cortical tubers in patients with infantile spasms causes more cerebral disruption and deficit.

Patients with other types of generalized seizures had fewer tubers than patients with infantile spasms and more than patients with partial seizures (Table 1). The patients with generalized seizures had significantly fewer tubers in their parietal lobes than did patients in the other two groups ($P < .01$).

Nine (60%) of the 15 patients with partial seizures were mentally disabled. Patients with

partial seizures had fewer tubers in the frontal lobe than did patients with infantile spasms, and fewer (37%) were mentally disabled ($P < .01$). This suggests that fewer tubers in the frontal lobes might be a favorable predictor for mental development, but it was not supported in direct analysis of the number of tubers versus disability. In a previous study in the west of Scotland (13), infantile spasms and generalized seizures as the first seizure type more often were associated with mental disability than were partial seizures. In our study, there was a definite inverse relationship between the patient's age at seizure onset and the total number of tubers (Table 3) ($P < .001$). Those who had seizures before 1 year of age had a significantly greater number of tubers than those whose seizures started later. There was a direct relationship between the number of tubers and the possibility of mental disability ($P < .01$). There was no significant localization to any particular region. No formal intelligence tests were possible to quantify mental disability. If a patient lived a normal life and attended a normal school, that was sufficient evidence of a normal intelligence. Any patient who attended or had attended a special school or who needed special educational help was considered mentally disabled. The assessment by the teachers and psychologists was rigorous and reliable. Mental disability in tuberous sclerosis complex, if present, often is severe and quite apparent (13).

Other observations from this study are that all tuberous sclerosis complex patients with mental disability had or have had some type of seizure, usually generalized and very often infantile spasms, and that none of the patients who never had seizures were mentally disabled. Although there were only five patients in the latter group, they had a median number of cortical tubers that was higher than for the patients with partial seizures. Further, the average number of frontal lobe tubers in this seizure-free group of patients was higher than for those with partial or generalized seizures, if the patients with infantile spasms are excluded. Thus, it appears that if patients with cerebral tuberous sclerosis complex have mental disability, there always is an association with seizures, suggesting that the seizures themselves play a role in the pathogenesis of the mental impairment.

Roach et al (14) were not able to link intelligence and the number of tubers directly. They reported considerable variation in the mental capacity of patients with 5 or fewer cortical lesions, but development was severely impaired in all patients with 10 or more cortical lesions. It is possible that in their study fewer lesions were detected because of less sensitive equipment.

In an MR study on persons with normal intellect (15), the frontal and parietal lobes were most frequently affected; the largest number of tubers detected was nine. In our study, the average number of tubers in patients with normal development was 9.9. Jambaqué et al (12), in a study of 23 cases, stated that the number of tubers detected was related to mental development, especially in cases of infantile spasms, as we found in our study. However, they did not state the total number of tubers found accurately, and there were three patients with an unfavorable outcome who had fewer than two tubers. They did not describe any patient who presented with generalized seizures other than infantile spasms; thus, the study did not give a complete picture.

We know of no radiologic-pathologic studies correlating sulcal islands, gyral cores, and migration lines or wedges with pathologic features. Sulcal islands and gyral cores are thought to represent tubers, and migration lines and wedges are thought to consist of neuronal heterotopia and dysmyelination or hypomyelination (9). The sulcal islands and gyral cores were not included in the total tuber count. Only the number of patients in whom these were seen is recorded, because these represent specific patterns in the subcortical white matter. Sulcal islands and gyral cores occurred more often in tuberous sclerosis complex patients with infantile spasms, those whose seizures began before 1 year of age and in those patients with mental disability (Table 2). Because these are believed to be tubers, this result supports the other findings of the study. Migration lines and wedges also occurred in patients with infantile spasms, mental disability, and seizures with onset before 1 year of age.

The MR scans were not done at the same time as seizure onset, and thus we cannot assess how MR could be used to predict future disability. In patients who present with infantile spasms in the first year of life, not all tubers may be detected. This study equated the number of tubers and other MR features with seizures and mental disability in a large number of patients

and provided a basis for future studies to determine the mechanism of mental disability.

This study also confirmed the superiority of the CT scan over the MR scan in detecting subependymal nodules. In 11 of the 33 persons who had subependymal nodules detected on CT scan, these nodules were not detected on MR image, as reported previously (16).

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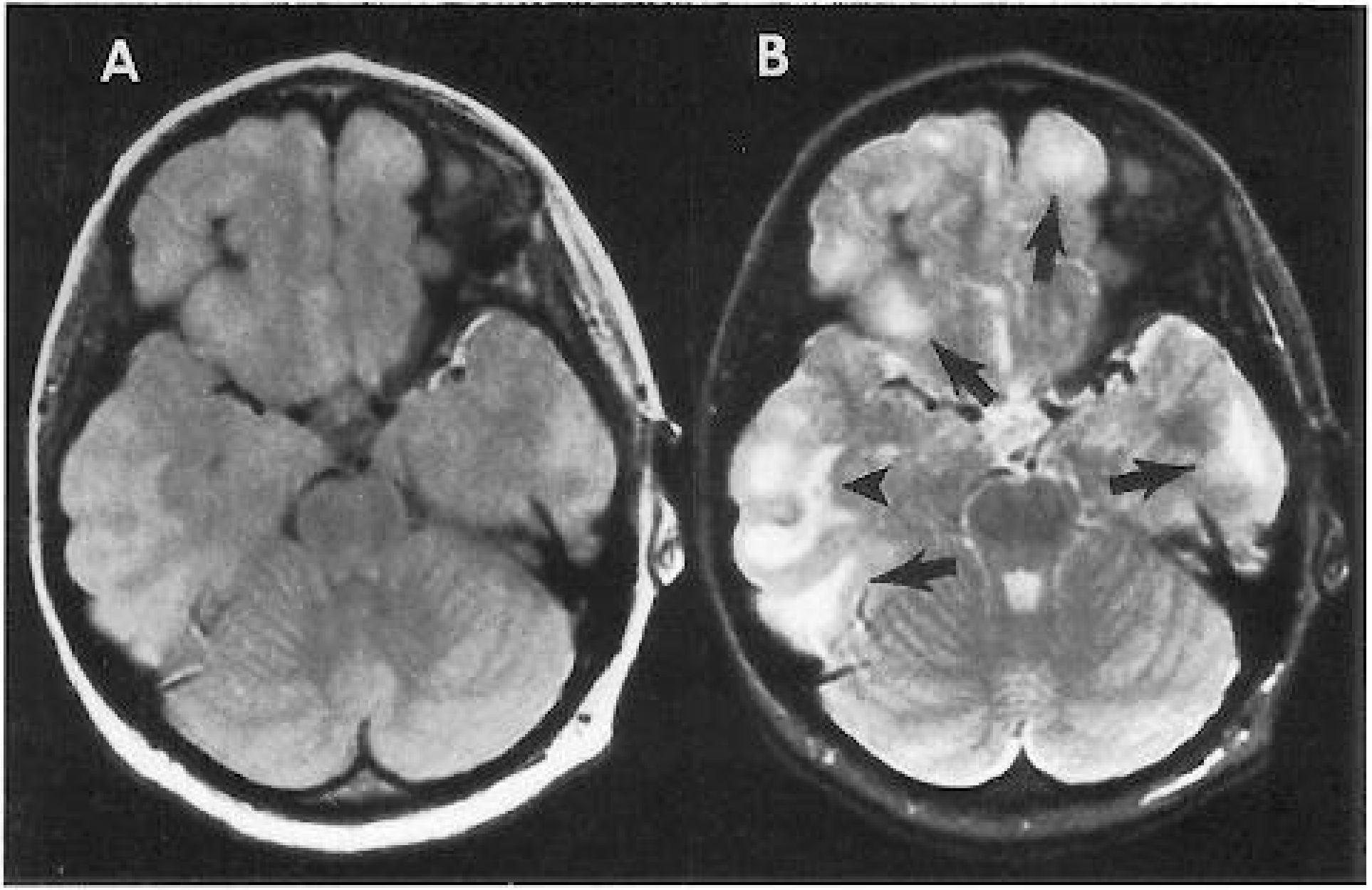
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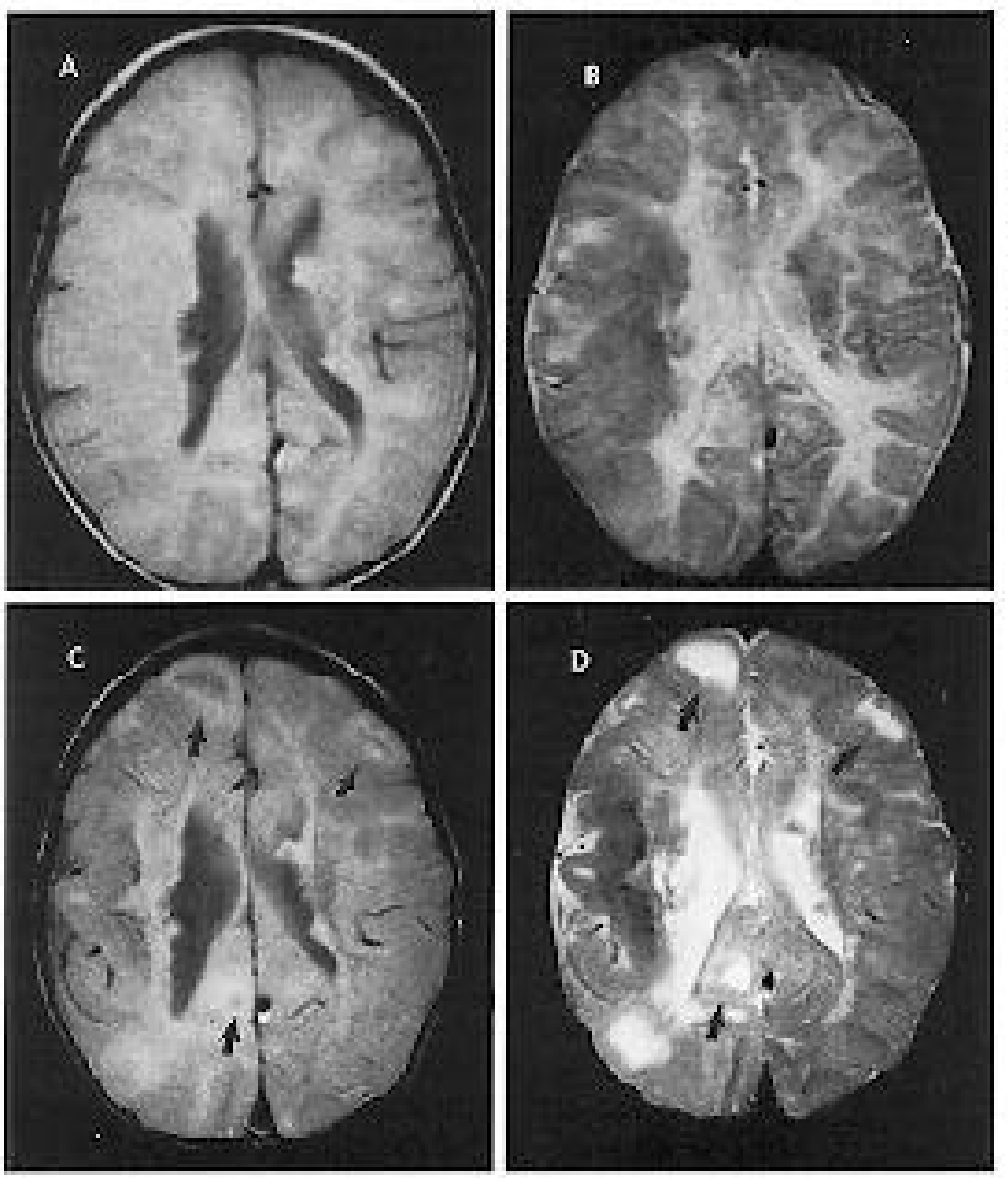
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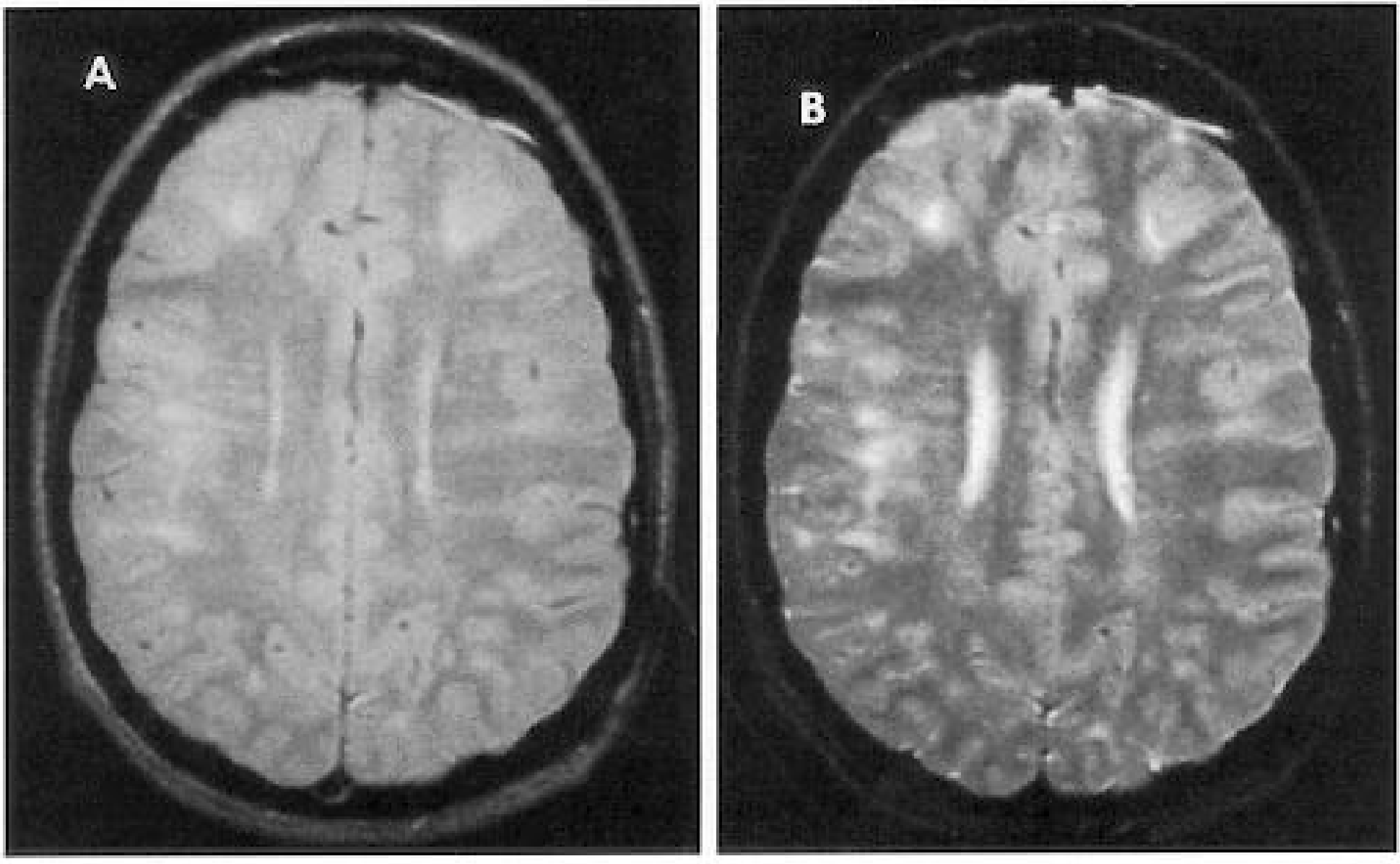
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