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MR Imaging of Intracranial Tuberous Sclerosis

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The role of MR in evaluating tuberous sclerosis is reviewed in 15 patients. These studies were compared with CT scans, which were available in 14 patients. Four characteristic findings were noted on the MR images obtained. Subependymal nodules projecting into the lateral ventricles were seen in 12 of 15 patients on T1-weighted images. This was the most specific finding. Distortion of the normal cortical architecture was seen in 10 of 11 patients in whom T1-weighted images were obtained using a 256 × 256 matrix. These foci corresponded to multiple cortical areas of increased signal on T2-weighted images. Dilated ventricles were seen in five patients. In one patient, a known astrocytoma showed increased signal on the T2-weighted images, allowing differentiation from a benign subependymal nodule. MR depicted the cortical hamartomas more completely than did CT. The MR scans were abnormal in all cases, and a diagnosis could be confidently made in all 11 cases scanned using a 256 × 256 matrix. Our preliminary experience suggests that MR will at least equal and probably exceed CT, both for sensitivity and specificity, given the use of a 256 × 256 matrix.

Tuberous sclerosis (TS) was first described by von Recklinghausen in 1862 [1]. In 1880, Bourneville described the neurologic and gross pathologic findings, and coined the term "tuberous sclerosis of the cerebral convolutions" [1]. It wasn't until 1908, when Heinrich Vogt recognized the association of the facial adenoma sebaceum and the cerebral lesions described by Bourneville, that the diagnosis of TS was made during a patient's life (later confirmed by autopsy) [1].

For many years, the radiographic diagnosis of cerebral lesions in TS relied on plain-film radiography of the skull or pneumoencephalography. CT was a vast improvement, showing intracranial abnormalities in 87% of patients [2]. The clinical importance of diagnosis in these patients is threefold: first, it ends the need for further intensive work-up to diagnose the cause of a seizure disorder; second, it establishes the need to closely follow the patient, since characteristic subependymal lesions are known to undergo degeneration to malignant giant cell astrocytoma; and third, it suggests the desirability of genetic counseling, given the dominant inheritance factor of this disease.

MR has been shown to be more sensitive than CT in detecting many disease entities. In addition, it does not require intravenous contrast agents and is therefore less invasive than CT. To investigate the possibility that MR would be useful in evaluating patients with TS and to define the characteristic MR findings and role of MR in the evaluation and follow-up of patients with TS, we undertook a retrospective study of patients with TS imaged by MR.

Subjects and Methods

The MR scans of 15 patients (8 male and 7 female) with the clinical diagnosis of TS were reviewed. The youngest patient was 3 months old; the oldest was 17 years old. In 14 patients the MR images were acquired using a 0.35-T superconducting magnet. The images from one patient were obtained with a 0.5-T superconducting magnet. The images were acquired using

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a spin-echo (SE), multislice, multiecho technique [T1-weighted images: TR, 500–566 msec; echo time (TE), 28–40 msec; T2-weighted images: TR, 1500–2233 msec, TE 60–80 msec]. In 14 patients T1-weighted sequences were obtained. T2-weighted sequences were obtained in all 15 patients. The slice thickness was 10 mm. The MR images for the first four patients were obtained using a 256 × 128 matrix. A 256 × 256 matrix was used for the last 11 patients. CT scans were available for 14 of the 15 patients.

The studies were retrospectively reviewed with specific attention to presence and number of subependymal and cortical lesions; ability to detect calcification, or alteration of signal intensity indicating malignancy within the lesion; cortical architecture; and ventricular size. The signal intensity of both subependymal and parenchymal lesions was measured, as well as that of normal gray and white matter. In addition, a region of interest was drawn for both subependymal and parenchymal nodules as well as for that of the normal gray and white matter. T1 and T2 relaxation times were calculated when technically possible. This was done for nine patients. The calculation of T1 and T2 relaxation times using this imaging system has been described [3].

Results

There were four characteristic findings seen in our patients with TS. The first and most specific finding, multiple subependymal nodules, was best appreciated on short TR images and was seen in 12 of the 15 patients (Figs. 1 and 2). The nodules were seen in all 11 patients in whom scans were acquired using a 256 × 256 matrix, but in only one of three patients in whom a 256 × 128 matrix was used. The subependymal nodules were difficult to detect on the long TR images (Fig. 1), where they were relatively isointense when compared with gray matter. The T1 relaxation time of these subependymal nodules tended to be between those of gray and white matter. In most cases there was slight prolongation of the T2 relaxation time in these nodules (up to 15%) compared with gray matter (Table 1). As one would expect, the presence of calcification in these nodules usually was not detected; however, this did not hamper the detection of the nodules with MR, when compared with CT (Table 2). In one patient, a large, very intense subependymal nodule was observed to be distinctly different from the other subependymal nodules (see Fig. 4). This high intensity was due to a markedly prolonged T2 (Table 1), and the lesion proved to be a gemistocytic astrocytoma at surgery.

The second characteristic finding in our patients was the presence of multiple cortical and subcortical foci of increased signal intensity seen on T2-weighted images. These cortical tubers represented the most sensitive finding, being seen in all 15 patients (Figs. 1–4). Some patients had only three or four such cortical foci; however, most had numerous (more than eight) ill-defined foci that were difficult to separate from one another and therefore could not be precisely quantitated. Many of these lesions, easily seen on T2-weighted MR images, could not be detected even retrospectively on the corresponding CT images. One such cortical focus in a 3-month-old male was biopsied. The lesion proved to be a hamartoma consistent with TS.

TABLE 1: **Relaxation Times**

Lesion	Number Studied	T1 (msec)	T2 (msec)
Subependymal nodule	7	537 ± 96	68 ± 9
Subependymal astrocytoma	2	1434 ± 33	121 ± 5
Cortical nodule	10	957 ± 110	70 ± 13
Normal cortical gray matter	9	848 ± 91	55 ± 13
Normal white matter	9	487 ± 26	66 ± 11

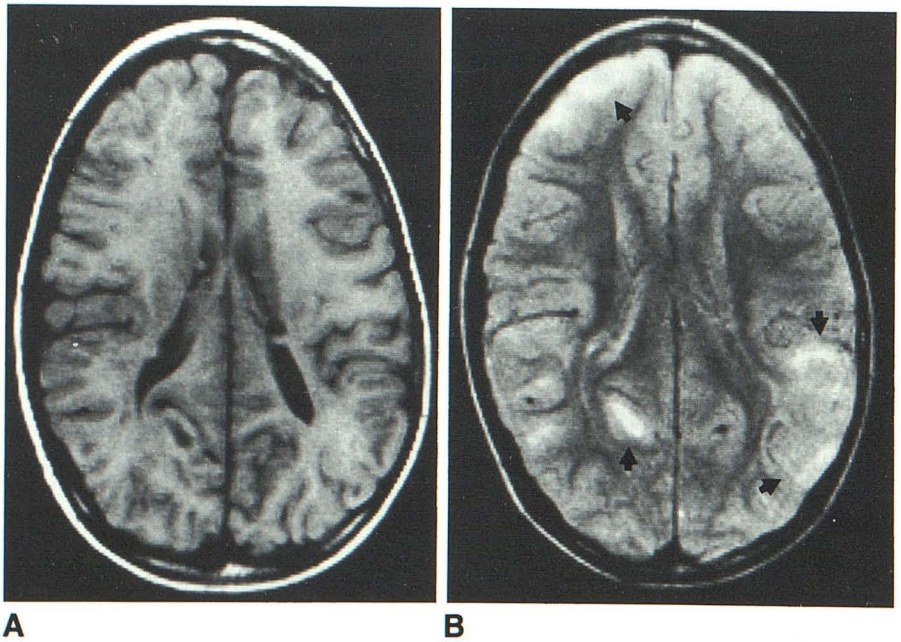

Fig. 1.—*A*, SE 500/30, 256 × 256 matrix. Transaxial image shows subependymal nodules projecting into lumen of lateral ventricles.

***B*, SE 2000/60, 256 × 256 matrix. Transaxial image using long TR at same level as in *A* fails to show subependymal nodules. Several cortical and subcortical foci of increased signal are seen (*arrows*).**

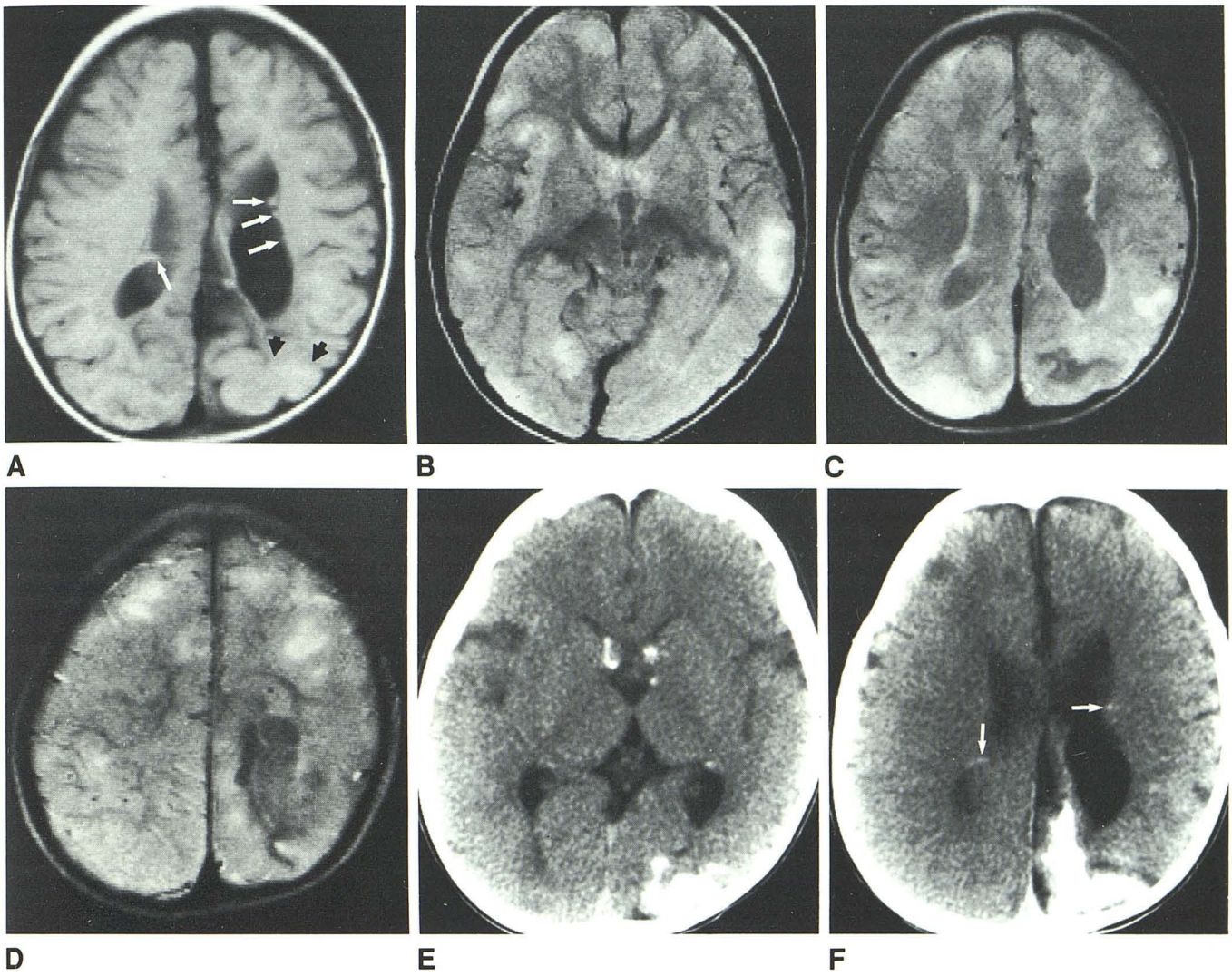

Fig. 2.—*A*, SE 500/30, 256 × 256 matrix. Transaxial image shows enlarged lateral ventricles with subependymal nodules (*white arrows*) and cortical architecture disruption (*black arrows*).

***B*, *C*, *D*, SE 200/60, 256 × 256 matrix. Transaxial images show multiple cortical foci of increased signal intensity.**

***E*, Unenhanced transaxial CT image shows multiple calcified subependymal nodules and large calcified cortical lesion.**

***F*, Unenhanced transaxial CT scan at same level as *A* shows calcified subependymal nodules (*arrows*) and large calcified cortical lesion that corresponds to area of cortical architecture disruption seen in *A*.**

Distortion of the normal cortical architecture was the third characteristic finding in our patients, and could be appreciated on T1-weighted images in 10 of the 11 patients scanned using a 256 × 256 matrix (Fig. 3). In none of the three patients scanned using a 256 × 128 matrix could this feature be seen. These areas of disrupted cortical architecture corresponded to foci of increased signal on T2-weighted images (Fig. 3).

The fourth characteristic finding, dilated ventricles, was seen in five patients. One had a gemistocytic astrocytoma at the foramen of Monro (Fig. 4). The other four were not associated with an obstructing lesion and were presumably secondary to dysplasia.

We compared high-resolution 256 × 256 matrix images obtained in 11 patients with low-resolution 256 × 128 matrix

TABLE 2: **Comparison of MR (256 × 256 Matrix) with CT in Eight Patients with Tuberous Sclerosis**

	Location of Pathology	
	Cortical/Subcortical	Subependymal
MR detected a greater number of lesions than CT	7 cases	3 cases
MR detected the same number of lesions as CT	1 case	2 cases
CT detected a greater number of lesions than MR	None	3 cases
Total	8 cases	8 cases

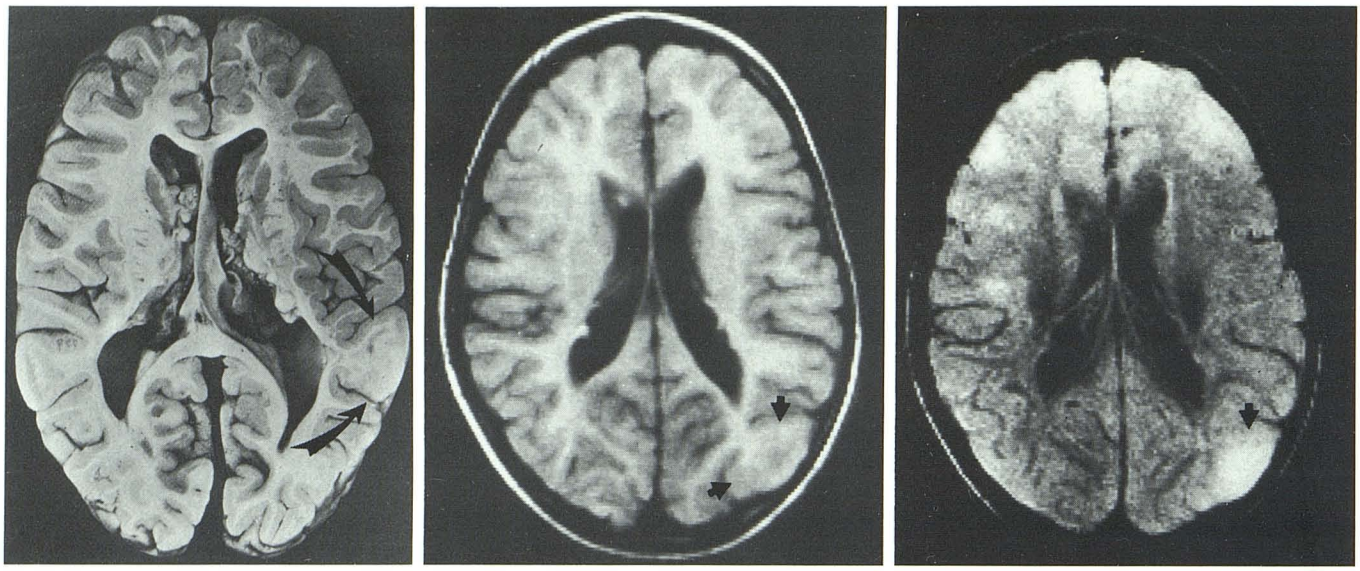

Fig. 3.—*A*, Gross anatomic specimen from a patient with tuberous sclerosis shows multiple subependymal nodules. There is a large cortical tuber posteriorly on left (*arrows*) that disrupts normal cortical architecture. This contrasts with normal cortical architecture in left frontal lobe with normal gray-white differentiation. (Reproduced with permission. From Reagan TJ, Neuropathology. In: Gomez MR, ed. *Tuberous sclerosis.* New York: Raven Press, 1979: p. 73.)

B, SE 500/30, 256 × 256 matrix. Transaxial image from a different patient than in *A* looks quite similar. There is disruption of normal cortical architecture posteriorly on left (*arrows*). Also shown are subependymal nodules.

C, SE 1500/60, long TR image at same level as *B*. Large focus of increased signal (*arrow*) corresponds to region of disrupted cortical architecture in *B*.

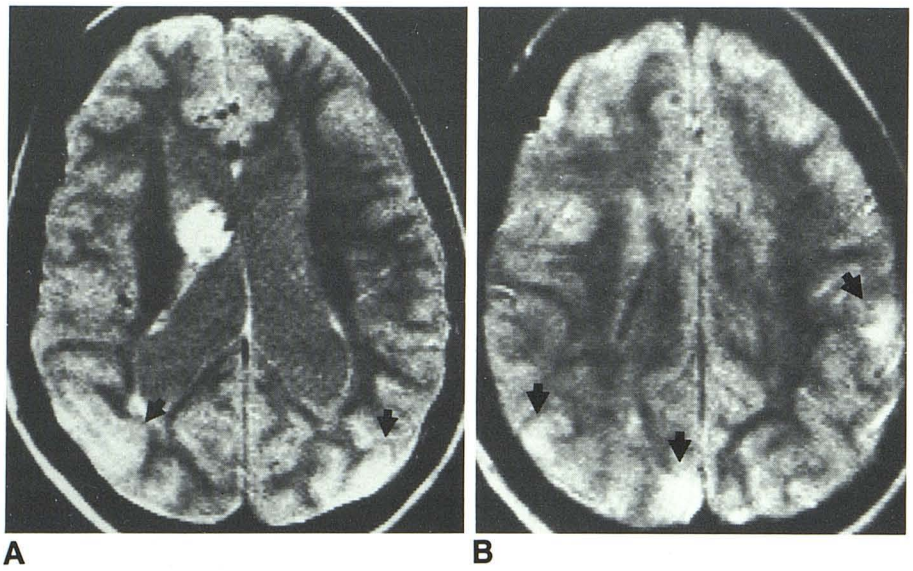

Fig. 4.—*A* and *B*, SE 2000/60. Transaxial images in this patient with tuberous sclerosis and a gemistocytic astrocytoma show tumor to be extremely intense. Multiple cortical foci of increased signal are seen (*arrows*).

images obtained in four patients. It was possible to make a specific diagnosis of TS in only two of the four patients scanned using a 256 × 128 matrix; however, on the basis of the constellation of features described above, a specific diagnosis was possible in all 11 patients scanned using a 256 × 256 matrix.

There were eight patients in our series in whom both a high-resolution (256 × 256) matrix MR scan and a CT scan were obtained within 5 months of each other. These were compared and the results are summarized (Table 2). MR demonstrated a greater number of cortical and subcortical lesions in seven of the eight cases. There were no patients in whom CT demonstrated more cortical or subcortical lesions than MR. MR was found to be equal to CT in the detection of subependymal nodules.

Discussion

Prior to the development of CT, patients with TS were evaluated radiographically by plain skull radiography and

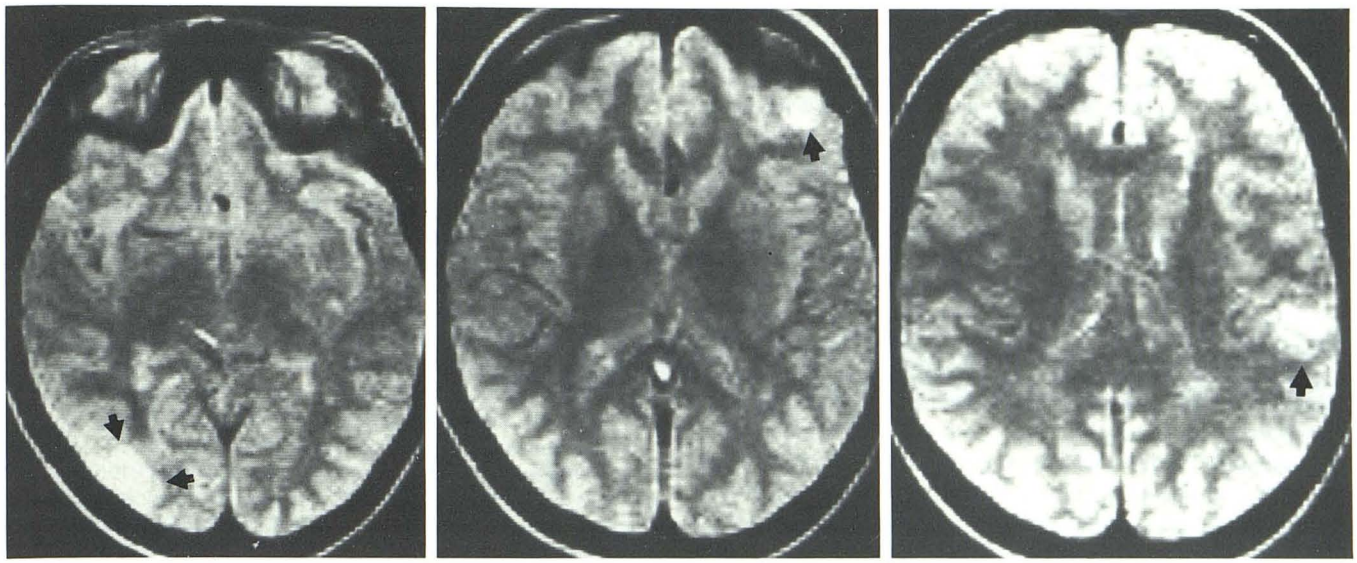

Fig. 5.—32-year-old clinically normal woman, with normal CT scan, and her daughter, who has tuberous sclerosis.
***A–C*, SE 2000/56, 256 × 128 matrix. Transaxial images at three levels show three areas of increased signal in cortex (*arrows*).**

pneumoencephalography. CT offered a highly sensitive, noninvasive technique with which to screen these patients, and it has become the "gold standard" [4–8]. CT demonstrates calcified subependymal nodules well, and allows one to easily make the correct diagnosis; but in many patients, it fails to demonstrate hemispheric lesions in spite of the presumed presence of such lesions in most of these patients. As shown in Table 2, MR is more sensitive than CT in demonstrating hemispheric lesions. Exactly what these cortical and subcortical areas of increased signal seen on MR correspond to pathologically is not yet entirely clear, although there is pathologic correlation in one 3-month-old male in whom a cortical lesion was biopsied. This proved to be a cortical hamartoma consistent with TS. Figure 3 shows the striking similarity between the MR examination of one of our patients and the gross anatomic specimen of another patient with TS and a large cortical tuber. This correlation suggests that at least some, if not all, of the cortical and subcortical abnormalities detected by MR do in fact represent tubers.

However, demyelination has been described in patients with TS [9] and may account for some of the foci of high signal seen on the long TR sequences. Further proof will be difficult to obtain until the brain of a patient with TS who has had a premortem MR scan becomes available for pathologic examination and correlation.

Pathologically, the hemispheric lesions are similar to the subependymal nodules, although some controversy exists in the pathology literature [10, 11]. If the lesions are in fact identical (and noncalcified), one would expect the MR signal characteristics to be the same. That is not the case. The cortical and subcortical lesions tend to be considerably more intense on the long TR images than the subependymal nodules (presumably due to increased water content in the hemispheric lesions), lending support to the view that the lesions are not identical in composition. Alternatively, a partial volume effect from the adjacent CSF that surrounds these small nodules as they project into the lumen of the lateral ventricles could explain the lower signal intensity seen in the subependymal nodules (CSF returns signal equal to or less than that from gray matter when patients are imaged on our magnet with a TR of 2.0 sec or less).

Patients with TS have a propensity to develop tumors, most commonly giant cell astrocytomas at the foramen of Monro [8, 12, 13]. Some advocate routine CT scans every 2–3 years to detect the development of these tumors (and resultant hydrocephalus) as early as possible [8]. Contrast enhancement of a lesion on CT is the primary criterion used to distinguish a tumor from a benign subependymal nodule. We imaged one patient with a tumor at the foramen of Monro that was very intense on long TR images (Fig. 4). A possible explanation involves the breakdown of the blood-brain barrier. This allows contrast enhancement on CT, and should therefore allow the accumulation of water in the lesion. The increased water content of the lesion would result in an intense signal of the long TR images, distinctly different from the relatively isointense benign subependymal nodule. A larger series of TS patients with tumors, particularly giant cell astrocytomas, will need to be imaged using MR to investigate the potential for MR in the differentiation of tumor from benign nodules. The common complication of these tumors, hydrocephalus due to obstruction of the foramina of Monro, should be easily differentiated from dysplastic dilated ventricles by the presence of periventricular intense signal due to the transependymal flow of CSF in the former.

There were numerous calcified lesions, both cortical and subependymal, as verified by CT in our patients. These calcifications must be present in order to diagnose TS by CT. Fortunately, CT is extremely sensitive to small calcifications and it is not difficult to demonstrate these lesions. MR, on the other hand, has been shown to be extremely poor for the demonstration of calcifications [14]. However, the inability to detect these calcifications by MR in no way hampered our ability to make the correct diagnosis of TS. The greater number of lesions detected in most patients with the characteristic pattern allowed us to make the correct diagnosis with confidence.

Because of the superior sensitivity and lack of ionizing radiation, MR should be valuable for screening normal family members of patients with TS to detect the presence of the unexpressed TS gene for proper genetic counseling. In addition to the 15 patients in our series, we reviewed the MR and CT scans of a 34-year-old clinically normal mother of a child with TS. The CT scan showed no evidence of TS, but the MR scan showed three distinct areas of increased signal in the cortex (Fig. 5). Presumably this represents a "forme fruste" case of TS. The inability to detect such subclinical cases prior to the development of MR may partly account for the 50–80% incidence of sporadic cases of TS reported in the literature [6, 11]. The true incidence of sporadic cases may be much lower. It has been advocated that family members of patients with TS be imaged by CT for genetic counseling purposes [15, 16]. In view of the demonstrated superior sensitivity, MR should become the screening imaging technique of choice for genetic counseling.

In summary, we feel that presence of the four characteristic MR findings—(1) multiple subependymal nodules; (2) multiple cortical and subcortical areas of high signal intensity on long TR sequences; (3) disruption of the cortical architecture; and (4) dilated ventricles—is virtually pathognomonic for the MR diagnosis of TS. Our preliminary experience suggests that MR will at least equal and probably exceed CT, both for sensitivity and specificity, given use of a 256 × 256 matrix. In view of the lack of ionizing radiation, MR may be the preferred method for following these patients and for evaluating family members for genetic counseling.

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