AJNR

MR evaluation of tuberous sclerosis: increased sensitivity with fluid-attenuated inversion recovery and relation to severity of seizures and mental retardation.

J Takanashi, K Sugita, K Fujii and H Niimi

This information is current as of August 18, 2025.

AJNR Am J Neuroradiol 1995, 16 (9) 1923-1928
http://www.ajnr.org/content/16/9/1923

MR Evaluation of Tuberous Sclerosis: Increased Sensitivity with Fluid-Attenuated Inversion Recovery and Relation to Severity of Seizures and Mental Retardation

Jun-ichi Takanashi, Katsuo Sugita, Katsunori Fujii, and Hiroo Niimi

PURPOSE: To evaluate the utility and possible increased sensitivity of fluid-attenuated inversion recovery (FLAIR) images for the detection of tubers in patients with tuberous sclerosis, compared with standard T2-weighted images, and to evaluate whether the tubers are correlated with neurologic symptoms. **METHOD:** We examined the number, size, and location of tubers in five tuberous sclerosis patients using T2-weighted and FLAIR images. Their intelligence quotients, ages at the onset of the first seizure, seizure types, and epileptic severity also were studied retrospectively. **RESULTS:** The number of tubers observed ranged from 4 to 17 on T2-weighted images, and from 10 to 33 on FLAIR images. All the tubers, other than the myelination line on T2-weighted images, were remarkably demonstrated as high-intensity lesions on FLAIR images. No correlation was found between the neurologic outcome and the number, size, or location of tubers on FLAIR images. **CONCLUSION:** FLAIR images were very sensitive for the detection of tubers, especially small subcortical ones, the number, size, and location of which are not related to the neurologic symptoms.

Index terms: Sclerosis, tuberous; Magnetic resonance, technique

AJNR Am J Neuroradiol 16:1923–1928, October 1995

Tuberous sclerosis is an autosomal dominant disease, clinically characterized by seizures, mental deficiency, and adenoma sebaceum (1, 2). The four major intracranial manifestations of tuberous sclerosis are cortical tubers, white matter abnormalities, subependymal nodules, and subependymal giant cell astrocytomas. Magnetic resonance (MR) imaging has improved the detection of these lesions, especially cortical tubers and white matter lesions, compared with computed tomography (3–6).

Recently, fluid-attenuated inversion recovery (FLAIR) images have been shown to be more sensitive for evaluation of a wide range of diseases, such as multiple sclerosis, infarction, herpes simplex encephalitis, sarcoidosis, and optic neuritis (7–11), when compared with conventional T1- and T2-weighted images.

The purpose of this study is to evaluate the utility of FLAIR images for the detection of cortical tubers and white matter abnormalities in tuberous sclerosis patients, compared with conventional T2-weighted images. We also examined whether the number, size, and location of lesions detected on FLAIR images are related to the epileptic severity and mental disability.

Patients and Method

There were five patients with a clinically established diagnosis of tuberous sclerosis who were under treatment for epilepsy and/or mental retardation at Chiba University Hospital in 1994. All five were female patients, 13 to 25 years of age. In addition, five patients with epilepsy or headache (10 to 15 years of age) but without intracranial lesions also were evaluated as controls using the same MR sequences.

MR was performed with a 1.5-T superconducting magnet. Axial T2- and proton density–weighted images (3000/

Received January 24, 1995; accepted after revision May 17.

From the Department of Pediatrics, Faculty of Medicine, University of Chiba, Chiba, Japan.

Address reprint requests to J. Takanashi, MD, Department of Pediatrics, Faculty of Medicine, University of Chiba, 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba 260, Japan.

AJNR 16:1923–1928, Oct 1995 0195-6108/95/1609–1923
© American Society of Neuroradiology

100,30/2 [repetition time/echo time/excitations]) and/or coronal T2-weighted images (4000/100/2), T1-weighted images (500/30/2), and FLAIR images (7000/160, 192/2; inversion time, 2000) were obtained in all ten cases. FLAIR was performed with the use of a rapid acquisition with relaxation enhancement readout, which acquired 16 or 20 echoes per excitation, as was previously reported (7, 12) (den Boer JA et al, "Multislice Turbo-FLAIR in Brain Studies of Multiple Sclerosis," presented at the annual meeting of the Society of Magnetic Resonance in Medicine, Berkeley, Calif, 1993) with slight modification of repetition times, inversion times, and echo times, which was found consistently to null cerebrospinal fluid (CSF) signal. The parameters were as follows: matrix size, 256 × 256 for T2-weighted images and 256 × 192 for FLAIR; field of view, 25 cm; section thickness, 8 mm; and section gap, 2 mm.

A pediatric neurologist reviewed the MR image of each patient, whose identity and disease severity were unknown, and recorded the number, size, and location of tubers. FLAIR images and T2-weighted images were read as separate groups. The tubers were classified, in configuration, into the migration line and wedge, gyral core, sulcal island, white matter lesions (heterotopic islets), and unclassified subcortical tubers. The migration line was taken as the thin line of hyperintensity on T2-weighted images spanning the white matter between the lateral ventricle and the cerebral cortex, and the migration wedge as similar in extent but triangular in configuration. A gyral core tuber usually appeared as a zone of low intensity on T1-weighted images and high intensity on T2-weighted images occupying the inner core of an expanded gyrus with a normal overlying cortex. Sulcal islands always involved two adjacent gyri, which showed high intensity on T2-weighted images in the central gyral white matter and connecting subcortical white matter, whereas the intervening two cortical layers remained isointense. Tubers were arbitrarily classified as to size: large, greater than 30 mm; intermediate, between 10 and 30 mm; and small, less than 10 mm. The lesions were divided into frontal, temporal, parietal, and occipital lobe by location.

All five patients underwent standardized psychometric examinations with the Wechsler scales (WPPSI and WISC-R). Mental development was estimated as the full scale IQ, and intellectual disability was classified as severe (IQ less than 50), moderate (IQ = 50 to 70), mild (IQ = 70 to 85), and normal (IQ greater than 85), as previously reported (13) with a slight modification.

The age at the onset of the first seizure, seizure type, and epileptic severity also were studied retrospectively. Epilepsy was defined as severe, intermediate, or mild when seizures had occurred daily, every week, or less frequently than every week during the previous 3 years with anticonvulsant treatment, respectively, and favorable when the patient had been seizure free for at least 2 years, with or without anticonvulsant treatment.

TABLE 1: Neurologic manifestations of tuberous sclerosis

Patient	Sex/ Age, y	Epilepsy Onset, mo	Epilepsy Type	Epileptic Severity	Mental Ability
1	F/25		None	· · ·	Normal
2	F/20	4	Infantile spasmus	Favorable	Moderately impaired
3	F/14	6	Partial seizures	Favorable	Moderately impaired
4	F/18	4	Infantile spasmus	Intermediate	Severely impaired
5	F/13	3	Partial seizures	Severe	Severely impaired

Results

The neurologic findings in our five cases are summarized in Table 1 and the MR findings in Table 2.

One of the five patients (patient 1) had normal intelligence, but two patients (2 and 3) had moderate and the others (4 and 5), severe intellectual impairment. Patient 1 had no epileptic seizures, but the others had epilepsy with onset before 6 months of age. Patients 2 and 4 had infantile spasms with onset at 4 months of age and the other two patients had partial seizures with onset at 3 and 6 months of age. The epileptic severity was favorable in two patients (2 and 3), intermediate in patient 4, and severe in patient 5.

The number of tubers observed ranged from 4 to 17 on T2-weighted images and from 10 to 33 on FLAIR images. Proton density–weighted images were less sensitive than T2-weighted images for the detection of tubers. All the tubers, other than the myelination line on T2-weighted images, were remarkably demonstrated as high-intensity lesions on FLAIR images (Fig 1). But some myelination lines on T2-weighted images appeared as low-intensity lesions on FLAIR images, which represented the partial volume effect of the CSF (Fig 2). Some small tubers on T2-weighted images were recognized as intermediate size on FLAIR images, and some white matter lesions on T2-weighted images were recognized as larger myelination wedges on FLAIR images in patients 1 and 4.

All the lesions detected solely on FLAIR images were small, and most were overlooked or misdiagnosed as the partial volume effect of the CSF on conventional T2-weighted images. But some of them could not be differentiated from normal gray matter retrospectively on T2-weighted images (Fig 3).

TABLE 2: MR findings in tuberous sclerosis patients

Patient	Number of Tubers			Size of Tubers			Location of Tubers		
		T2-weighted	FLAIR		T2-weighted	FLAIR		T2-weighted	FLAIR
1	MW,ML	0	1	L	0	0	F	2	5
	GC	1	1	I	1	2	T	1	2
	SI	0	1	S	3	10	P	0	3
	SC	1	8				O	1	2
	WM	2	1						
	Total	**4**	**12**						
2	MW,ML	2	2	L	3	3	F	3	8
	GC	3	4	I	3	5	T	2	3
	SI	2	2	S	3	10	P	3	5
	SC	2	10				O	1	2
	WM	0	0						
	Total	**9**	**18**						
3	MW,ML	1	2	L	2	2	F	6	12
	GC	7	11	I	4	8	T	2	5
	SI	1	1	S	11	23	P	4	8
	SC	7	18				O	5	8
	WM	1	1						
	Total	**17**	**33**						
4	MW,ML	2	3	L	1	1	F	5	10
	GC	2	4	I	2	5	T	1	2
	SI	0	0	S	5	9	P	2	3
	SC	3	8				O	0	0
	WM	1	0						
	Total	**8**	**15**						
5	MW,ML	0	0	L	0	0	F	4	6
	GC	1	1	I	0	1	T	0	0
	SI	0	0	S	6	9	P	1	2
	SC	5	9				O	1	2
	WM	0	0						
	Total	**6**	**10**						

Note.—MW indicates myelination wedge; ML, myelination line; GC, gyral core; SI, sulcal island; SC, unclassified subcortical tuber; WM, white matter lesion; L, large; I, intermediate; S, small; F, frontal lobe; T, temporal lobe; P, parietal lobe; and O, occipital lobe.

The region most commonly affected was the frontal lobe, with the parietal lobe being next. MR demonstrated no obvious abnormal parenchymal lesions in the five control patients on either T2-weighted images or FLAIR images.

MR in patient 1 with normal intelligence and no epilepsy demonstrated only 4 tubers, the least number of tubers on T2-weighted images, but there were 12 tubers on FLAIR images, this number being more than that in patient 5 with severe mental disability and epilepsy. There were no obvious correlations between the number, size, and location of tubers, and the mental and epileptic severity in FLAIR images.

Discussion

The T2-weighted version of FLAIR sequences nulls the signal from CSF and produces very heavy T2 weighting as a consequence of the very long echo time. FLAIR images have been recently reported to be more sensitive for the detection of abnormal lesions than conventional T1- and T2-weighted images in several neurologic diseases (7–11). Confidence that FLAIR findings reflected genuine lesions in the present study could be drawn from the fact that no lesion was observed in any controls, whereas every tuber without a myelination line detected on T2-weighted images was inevitably seen as a larger high-intensity lesion on FLAIR images. FLAIR images, however, demonstrated a CSF flow artifact attributable to the inflow of noninverted CSF, especially at the foramen of Monro; therefore, we did not evaluate the subependymal nodules in this study.

In our present series with tuberous sclerosis, FLAIR images demonstrated more numerous tubers, especially small subcortical and gyral core tubers, most of which were overlooked or misdiagnosed as the partial volume effect of the CSF on conventional T2-weighted images.

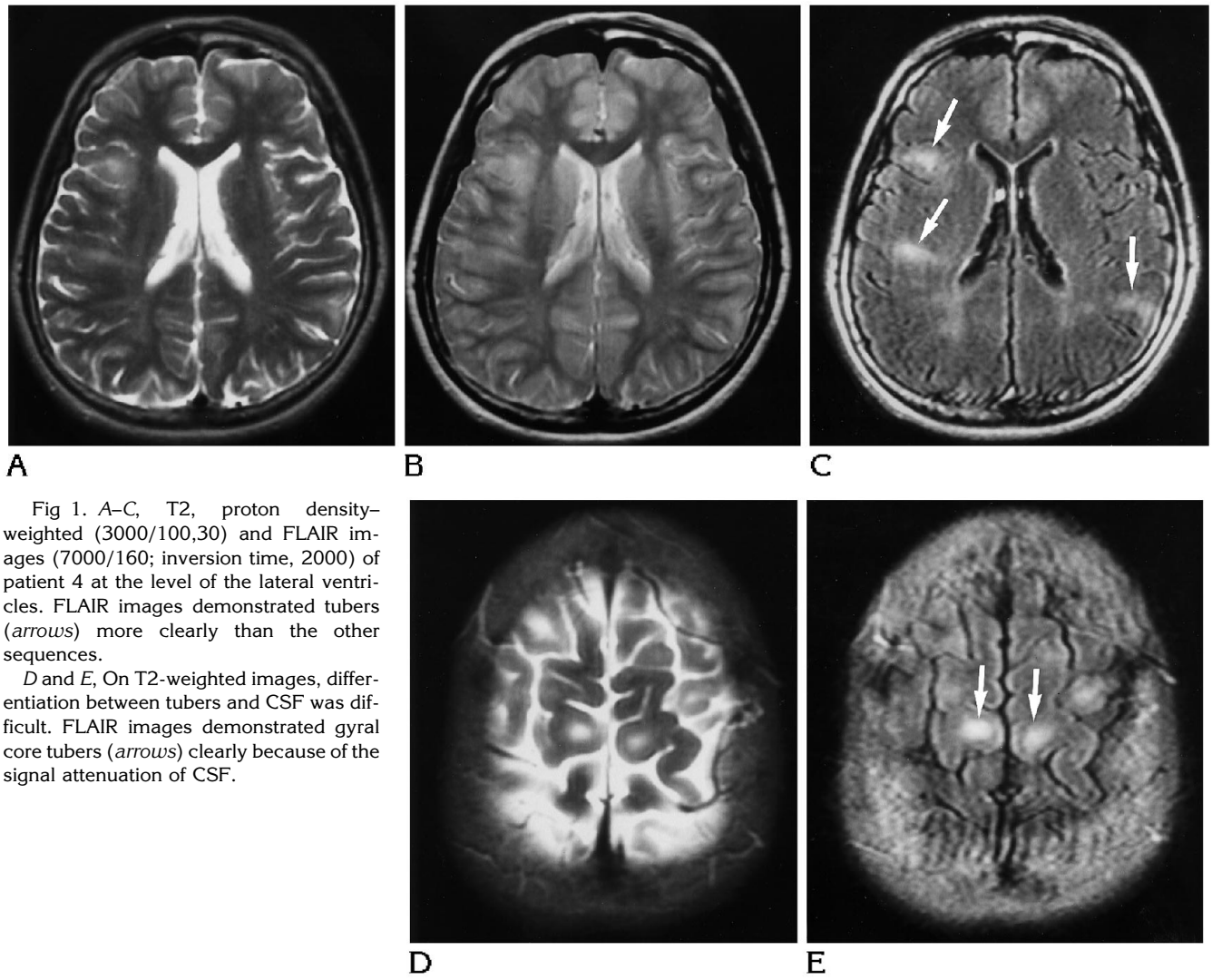

Fig 1. *A–C*, T2, proton density–weighted (3000/100,30) and FLAIR images (7000/160; inversion time, 2000) of patient 4 at the level of the lateral ventricles. FLAIR images demonstrated tubers (*arrows*) more clearly than the other sequences.

D and *E*, On T2-weighted images, differentiation between tubers and CSF was difficult. FLAIR images demonstrated gyral core tubers (*arrows*) clearly because of the signal attenuation of CSF.

Some of the lesions detectable only on FLAIR images, however, could not be seen even retrospectively on T2-weighted images (isointensity to the cortex). It is known that conventional MR may fail to visualize some pathologically demonstrated cortical tubers (14). The study by Nixon et al (15) clearly showed that some tubers that did not involve the adjacent white matter could not be detected on MR. Accordingly, some small tubers themselves might be recognized only on FLAIR images. In any case, FLAIR images are superior for the detection of small subcortical and gyral core tubers that might have been overlooked in previous studies involving conventional MR.

Mental retardation occurs in about half of patients, being confined to those with epileptic seizures (13, 16, 17). The later mental function is known to be related to the early onset of epilepsy and the degree of its severity (17), although it is controversial whether there is a direct correlation between the level of mental ability and the number, size, or location of tubers. Roach et al reported considerable variations in the mentality of patients with fewer than 5 cortical lesions but that developmental functions were severely impaired in all patients with more than 10 cortical lesions (18). Jambaqué et al reported that 12 of 13 tuberous sclerosis patients with more than 4 tubers were mentally retarded but 6 of 9 with fewer than 2 tubers showed normal intelligence, consequently suggesting that mental retardation reflected the cerebral dysfunction caused by cortical tubers (16). Recently, Shepherd et al also reported that fewer tubers in the frontal lobes might be a favorable predictor for mental development in addition to a direct relationship between the

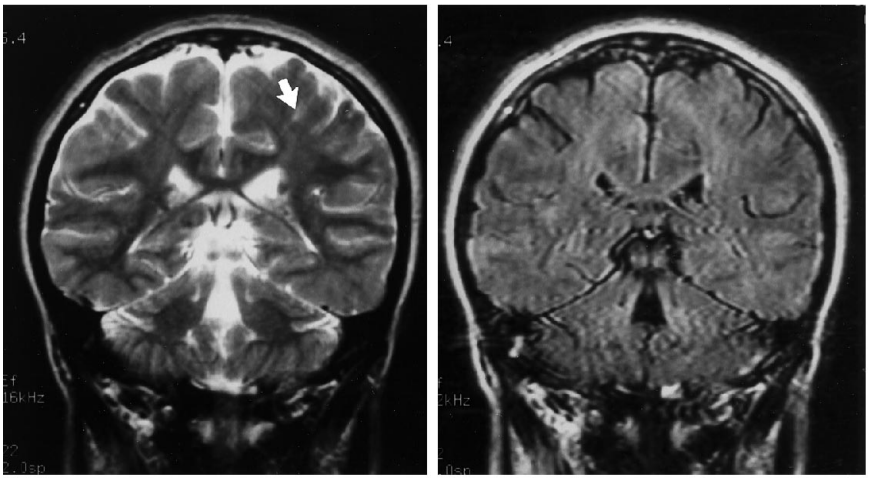

Fig 2. *A* and *B*, T2-weighted images (4000/100) of the brain of patient 2 showed a linear high-intensity lesion (*arrow*, *A*) in the left parietal region like a myelination line. But FLAIR images (7000/160; inversion time, 2000) demonstrated low intensity at the corresponding site, which represented the partial volume effect of CSF.

number of tubers and the possibility of mental disability (19). On the other hand, Martin et al (20) and Menor et al (21) demonstrated that there was no clear relationship between MR abnormalities and the neurologic evolution of tuberous sclerosis.

In our study, conventional T2-weighted images revealed four tubers in patient 1 with normal intelligence and more than 6 tubers in four patients with moderate or severe mental retardation, which suggested a positive correlation between the mental function and the number of tubers. FLAIR images, however, revealed more than 8 tubers in all five patients (12 tubers in patient 1). Therefore, no correlation could be found between the mental severity and the number, size, or location of tubers, including small subcortical tubers, detected only on FLAIR images. It is suggested that the mental disability in patients with tuberous sclerosis might be secondary to epilepsy or that small tubers do not cause brain dysfunction. In any case, further investigation is required, because our study was limited, involving only five patients.

Epileptic seizures are the most common neurologic symptom of tuberous sclerosis, with an occurrence rate of 92% (17). The causal role of tubers in epilepsy has been demonstrated by the finding of a clear topographic correlation between electoencephalographic spike foci and areas of abnormal MR lesions (22), and an association was reported between the number of tubers and epileptic severity (16). Tuberous sclerosis patients with infantile spasms had more tubers than those with other type of seizures, who had more tubers than those without seizures (19). And patients with partial seizures

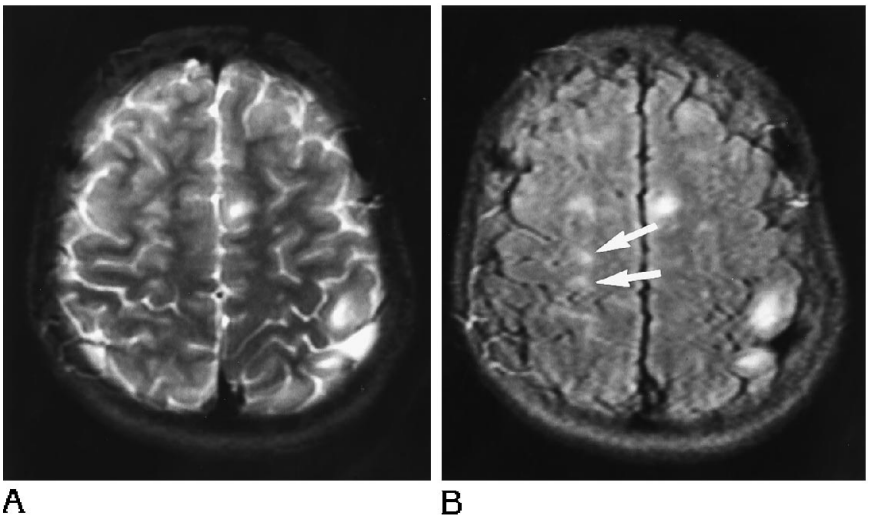

Fig 3. *A* and *B*, Small tubers detectable on FLAIR images (7000/160; inversion time, 2000) of patient 3 (*arrows*) could not be differentiated from normal gray matter on T2-weighted images (3000/100).

had fewer tubers in the frontal lobe than those with infantile spasms (19). Our present series, however, showed no clear relationship between the number, size or location of tubers and the type and severity of epilepsy, especially on FLAIR images. There was a definite inverse relationship between the patient's age at seizure onset and the total number of tubers (19). It is considered that in this study all four patients with epilepsy had an early onset of seizures (ie, younger than 6 months of age); therefore, they might have had more numerous tubers than patients with tuberous sclerosis in general.

Tuberous sclerosis is an autosomal dominantly inherited disease, although its clinical expression is highly variable. Estimates of the number of familial cases range from 14% to 44%, depending in part on the completeness of the evaluation of the probands' families (23, 24). MR was recommended previously to improve genetic counseling (25). Roach et al, however, reported only one parent among 60 couples (120 parents) whose diagnosis of tuberous sclerosis rested primarily on conventional MR findings (23). FLAIR sequences are strongly recommended to improve the rate of detection of small tubers in parents with "mild" tuberous sclerosis (forme fruste) who risk having other affected children.

In conclusion, FLAIR sequences are very sensitive for the detection of tubers in tuberous sclerosis patients, which are not related with their mental or epileptic severity. Further evaluation with FLAIR sequences is needed with larger numbers of patients, to improve genetic counseling for clinically silent parents.

Acknowledgments

We thank Huminori Morita, Yoshitada Nakano, and Teruyuki Ishii for their excellent technical support.

References

1. Gomez MR. Criteria for diagnosis. In: Gomez MR, ed. *Tuberous Sclerosis*. New York, NY: Raven Press; 1988:9–19
2. Takanashi J, Katsuo S, Horiguchi H, Iai M, Niimi H. Neonatal tuberous sclerosis: report of a case studied by cranial MRI. *No To Hattatsu* 1992;24:571–574
3. Braffman BH, Bilaniuk LT, Naidich TP, et al. MR imaging of tuberous sclerosis: pathogenesis of this phakomatosis, use of gadopentetate dimeglumine, and literature review. *Radiology* 1992; 183:227–238
4. Nixon JR, Houser OW, Gomez MR, Okazaki H. Cerebral tuberous sclerosis: MR imaging. *Radiology* 1989;170:869–873
5. Inoue Y, Nakajima S, Fukuda T, et al. Magnetic resonance images of tuberous sclerosis, further observations and clinical correlations. *Neuroradiology* 1988;30:379–384
6. Houser OW, Shepherd CW, Gomez MR. Imaging of intracranial tuberous sclerosis. *Ann NY Acad Sci* 1991;615:81–93
7. Takanashi J, Sugita K, Fujii K, Takatsuna Y, Niimi H. Optic neuritis with silent cerebral lesions; availability of FLAIR sequences. *Pediatr Neurol* 1995;12:152–154
8. De Coene B, Hajnal JV, Pennock JM, Bydder GM. MRI of the brain stem using fluid attenuated inversion recovery pulse sequences. *Neuroradiology* 1993;35:327–331
9. Thomas DJ, Pennock JM, Hajnal JV, Young IR, Bydder GM, Steiner RE. Magnetic resonance imaging of spinal cord in multiple sclerosis by FLAIR. *Lancet* 1993;341:593–594
10. Hajnal JV, Bryant DJ, Kasuboski L, et al. Use of fluid attenuated inversion recovery (FLAIR) pulse sequences in MRI of the brain. *J Comput Assist Tomogr* 1992;16:841–844
11. De Coene B, Hajnal JV, Gatehouse P, et al. MR of the brain using FLAIR (FLAIR) pulse sequences. *AJNR Am J Neuroradiol* 1992; 13:1555–1564
12. Rydberg JN, Hammond CA, Grimm RC, et al. Initial clinical experience in MR imaging of the brain with a fast fluid-attenuated inversion-recovery pulse sequence. *Radiology* 1994;193: 173–180
13. Shepherd CW, Stephenson JBP. Seizures and intellectual disability associated with tuberous sclerosis complex in the west of Scotland. *Dev Med Child Neurol* 1992;34:766–774
14. Curatolo P, Cusmai R, Cortesi F, Chiron C, Jambaque I, Dulac O. Neuropsychiatric aspects of tuberous sclerosis. *Ann NY Acad Sci* 1991;615:8–16
15. Nixon JR, Miller GM, Okazaki H, Gomez MR. Cerebral tuberous sclerosis: postmortem magnetic resonance imaging and pathologic anatomy. *Mayo Clin Proc* 1989;64:305–311
16. Jambaqué I, Cusmai R, Curatolo P, Cortesi F, Perrot C, Durac O. Neuropsychological aspects of tuberous sclerosis in relation to epilepsy and MRI findings. *Dev Med Child Neurol* 1991;33:698–705
17. Gomez MR. Neurologic and psychiatric features. In: Gomez MR, ed. *Tuberous Sclerosis*. New York, NY: Raven Press; 1988:21–36
18. Roach ES, Williams DP, Laster DW. Magnetic resonance imaging in tuberous sclerosis. *Arch Neurol* 1987;44:301–303
19. Shepherd CW, Houser OW, Gomez MR. MR findings in tuberous sclerosis complex and correlation with seizure development and mental impairment. *AJNR Am J Neuroradiol* 1995;16:149–155
20. Martin N, Debussche C, De Broucker T, Mompoint D, Marsault C, Nahum H. Gadolinium-DTPA enhanced MR imaging in tuberous sclerosis. *Neuroradiology* 1990;31:492–497
21. Menor F, Martí-Bonmatí L, Mulas F, Poyatos C, Cortina H. Neuroimaging in tuberous sclerosis: a clinicoradiological evaluation in pediatric patients. *Pediatr Radiol* 1992;22:485–489
22. Seri S, Cerquiglini A, Cusmai R, Curatolo P. Tuberous sclerosis: relationships between topographic mapping of EEG, VEPs, and MRI findings. *Neurophysiol Clin* 1991;21:161–172
23. Roach ES, Kerr J, Mendelsohn D, Laster DW, Raeside C. Detection of tuberous sclerosis in parents by magnetic resonance imaging. *Neurology* 1991;41:262–265
24. Fleury P, deGroot WP, Delleman JW, et al. Tuberous sclerosis: the incidence of sporadic cases versus familial cases. *Brain Dev* 1980;2:107–117
25. Terwey B, Doose H. Tuberous sclerosis: magnetic imaging of the brain. *Neuropediatrics* 1987;18:67–69