AJNR Am J Neuroradiol 19:541–546, March 1998

Usefulness of Contrast Material in MR of Patients with Neurofibromatosis Type 1

Cara Bonawitz, Mauricio Castillo, Cynthia T. Chin, Suresh K. Mukherji, and A. James Barkovich

PURPOSE: **Our objective was to determine the usefulness of routine administration of contrast material in brain MR imaging for the evaluation of areas of probable myelin vacuolization and neoplasms in patients with neurofibromatosis type 1 (NF-1).**

METHODS: **We retrospectively reviewed 112 consecutive contrast-enhanced brain MR studies obtained over a period of 7 years in 109 symptomatic and asymptomatic patients compiled from two institutional NF-1 data bases. MR studies were analyzed for areas of probable myelin vacuolization, with attention to degree of enhancement and its impact on lesion detection and characterization. Usefulness of contrast material was graded as 0 = not useful, 1+ = somewhat useful, and 2+ = useful.**

RESULTS: **Of 112 studies, 45% (n = 49) were normal. In the remaining 63 studies, 88 regions of probable myelin vacuolization and 52 tumors were identified. Enhancement was not observed in any regions of probable myelin vacuolization. Enhancement was present in 31% of tumors, and, of these, was found to be useful in 44%, somewhat useful in 12%, and not useful in 44%. For enhancing tumors, contrast agent was useful for lesion detection in 19% and for lesion characterization in 25%.**

CONCLUSION: **Contrast administration is useful in baseline MR studies to maximize tumor detection and characterization, to add confidence to the diagnosis of benign probable myelin vacuolization, and to document stability of neoplasms on follow-up examinations.**

Neurofibromatosis type 1 (NF-1) is an autosomal dominant disorder involving tissues of ectodermal origin and accounting for over 90% of neurofibromatosis cases. Diagnosis is primarily clinical (1). Involvement of the CNS is common, and some studies have advocated screening with magnetic resonance (MR) imaging of the brain for baseline evaluation and as an adjunct in the assessment of asymptomatic patients when clinical criteria are not met (2–5).

Commonly observed intracranial abnormalities in NF-1 patients include astrocytomas of the optic pathways and other locations in approximately 10% to 15% of cases. Areas of abnormal T2 signal intensity are observed with high frequency and once were thought to represent hamartomas or heterotopias (6–9). These T2 signal abnormalities are transient and may represent foci of abnormal myelination that are eventually replaced with more normal myelin during adolescence and adulthood (6, 8). DiPaolo et al (7) reported that spongiotic or vacuolar changes in the myelin are probably responsible for these transient signal abnormalities. Progression of these lesions into the second decade of life or the presence of enhancement dictates the need for close follow-up to exclude neoplasia (6).

Contrast administration is commonplace in brain MR imaging studies of adult patients (9–12). The safety of contrast material in adults has been well established, and preliminary data suggest that it is also safe for use in children. Current guidelines recommend contrast administration when precontrast studies show abnormalities, when improved lesion delineation is warranted, when tumor is suspected, and when postoperative evaluation is required to ascertain tumor recurrence (13–15). The usefulness of routine administration of contrast agent for MR imaging of patients with NF-1 has not been investigated. We reviewed a large number of MR imaging studies in patients with NF-1 to investigate the usefulness of routine administration of contrast agent in the evaluation of regions of probable myelin vacuolization and neoplasms.

Methods

We retrospectively reviewed 112 consecutive contrast-enhanced brain MR studies in 109 symptomatic and asymptom-

Received July 3, 1997; accepted after revision September 28.

From the Department of Radiology, University of North Carolina, Chapel Hill (C.B., M.C., S.K.M.) and the Department of Radiology, University of California, San Francisco (C.T.C., A.J.B.).

Address reprint requests to M. Castillo, MD, Department of Radiology CB 7510, University of North Carolina, Chapel Hill, NC 27599.

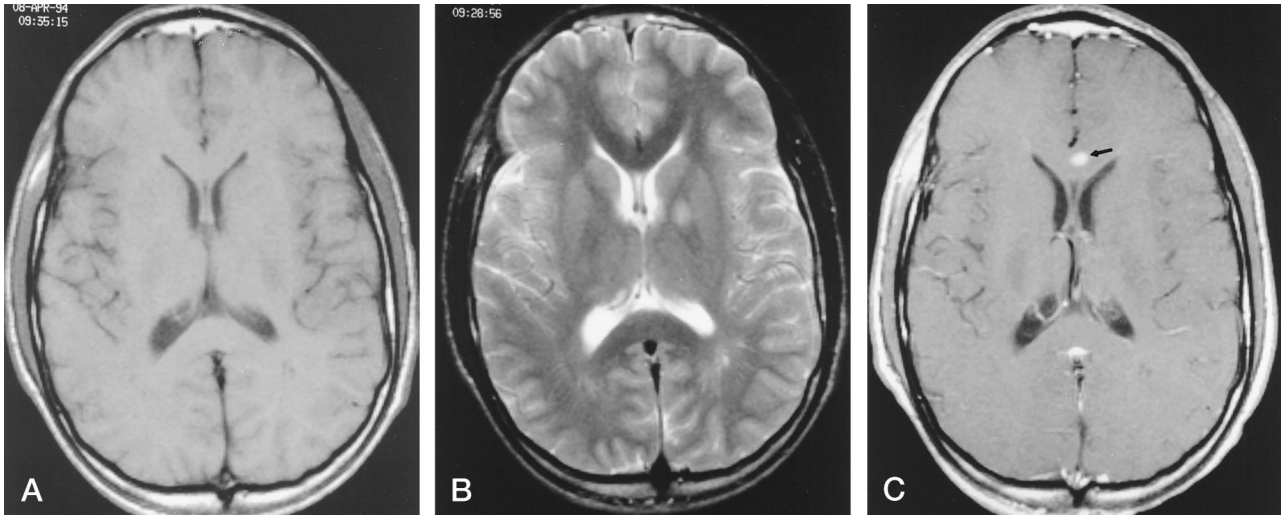

FIG 1. 15-year-old asymptomatic boy with presumed astrocytoma detected only on postcontrast MR images.

A, Axial T1-weighted image (600/15/1) shows no abnormality.

B, Corresponding T2-weighted image (3500/90/1) shows a presumed area of vacuolar myelin in the left globus pallidus. The genu of the corpus callosum appears normal.

C, Corresponding contrast-enhanced T1-weighted image shows a small focal enhancing lesion (*arrow*) in the genu of the corpus callosum, presumed to be an astrocytoma. Despite the recommendation for closer follow-up imaging, the patient did not return. The area of vacuolar myelin does not enhance.

atic patients from two institutional NF-1 data bases. The cohort consisted of 67 males and 42 females, ranging in age from 2 months to 42 years (mean, 10 years). MR studies were analyzed for areas of probable myelin vacuolization, defined as regions having a normal to slightly increased T1 signal intensity, high T2 signal intensity, and no mass effect; and for tumors, defined as lesions showing low T1 signal intensity, high T2 signal intensity, and mass effect. Contrast enhancement was considered to be diagnostic for tumor because areas of probable myelin vacuolization do not enhance. Special attention was given to presence/degree of enhancement and its impact on lesion detection and characterization. Because this was a bi-institutional study, the imaging protocols varied. In all patients, MR imaging consisted of a minimum of sagittal and axial precontrast T1-weighted sequences (500–600/15–20/1–2 [repetition time/echo time/excitations]), axial T2-weighted sequences (2500–4000/19–30 and 80–105/1), and axial and coronal postcontrast T1-weighted images. Contrast material was given intravenously at a standard dose of 0.1 mmol/kg.

Usefulness of contrast administration was subjectively graded as 0 = not useful, 1+ = somewhat useful, and 2+ = useful with respect to lesion detection, characterization (suggestive of tumor or not), and extent. The addition of contrast material was considered useful if the lesion was only seen after its administration or if the enhancement pattern changed the probable diagnosis. Contrast administration was considered somewhat useful if it helped to further define tumor boundaries but was not necessary for tumor visualization and did not change the diagnosis. Follow-up MR studies (1 to 5 years after the initial imaging examination) were reviewed in 79 patients, and if unchanged were not included in the analysis. In patients in whom initial MR studies were normal, follow-up studies were not included unless new abnormalities were identified. Studies showing only extracranial neurofibromas (ie, a normal-appearing brain) were not included. All studies were reviewed in concert by two neuroradiologists, one at each of the institutions involved.

Results

Of 112 MR studies, 45% (n = 49) were normal. In the remaining 63 studies, 88 regions of probable myelin vacuolization and 52 tumors were identified. In the 52 patients with presumed tumors, seven were proved at biopsy (six were astrocytomas and one a dysembryoplastic neuroepithelial tumor), and the rest were followed clinically. Regions of probable myelin vacuolization were located in the posterior fossa (50%), basal ganglia (40%), and other sites (10%). Tumors were located in the optic apparatus (40%), brain stem (30%), hypothalamus (15%), cerebellum (4%), corpus callosum (4%), and cerebral hemispheres (6%).

Enhancement was not observed in any regions of probable myelin vacuolization. Enhancement was present in 31% of tumors (n = 16), and judged to be useful in 44% (n = 7), somewhat useful in 12% (n = 2), and not useful in 44% (n = 7). Enhancement was present in 33% of tumors in the optic apparatus (n = 7), 14% in the tectum (n = 1), 38% in the hypothalamus (n = 3), 50% in the posterior fossa (n = 1), 11% in the brain stem (n = 1), 100% in the cerebral hemispheres (n = 3), and 50% in the corpus callosum (n = 1).

In seven tumors, contrast administration was judged to be useful (2+). For enhancing tumors, contrast material was helpful for lesion detection in 19% (n = 3) and for lesion characterization in 25% (n = 4). In two cases, precontrast studies were interpreted as normal, and the tumors were only detected after contrast administration (Fig 1). One of these was located in the genu of the corpus callosum and the other in the left medial parietal cortex. In retrospect, only the latter lesion had minimal mass effect, but both were less than 5 mm in diameter and displayed no T1 prolongation. Despite our recommendation, both patients were lost to follow-up and imaging studies were not available for review. In another patient, a posterior fossa tumor showed only T1 pro-

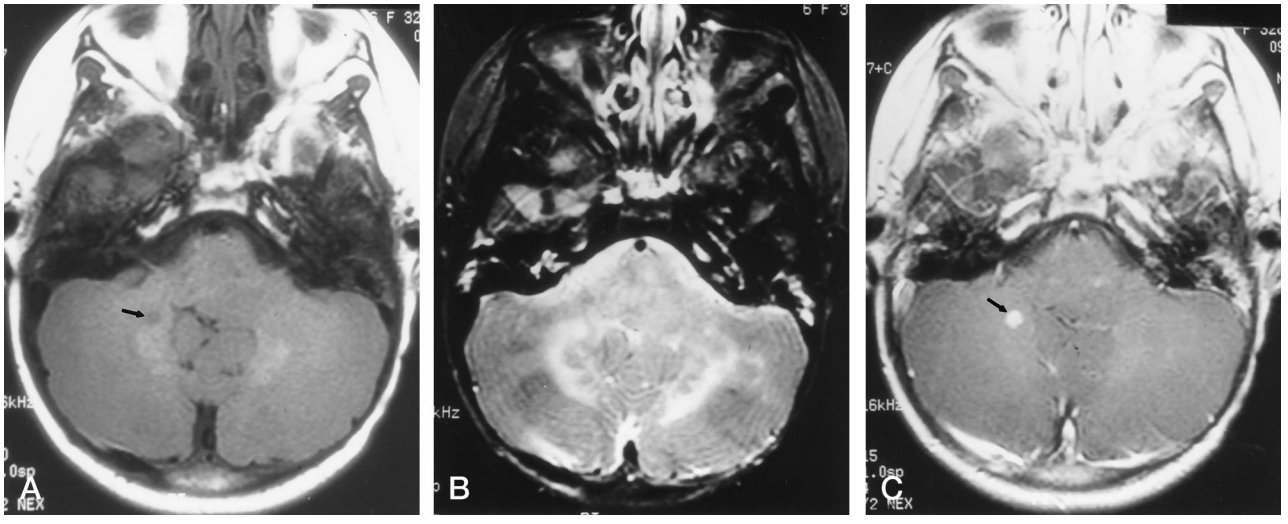

FIG 2. 6-year-old girl with ataxia and slurred speech, presumed to have an astrocytoma located amid areas of probable vacuolar myelin, seen only on postcontrast images.

A, Axial noncontrast T1-weighted image (500/20/1) shows small focal area (*arrow*) of relatively low signal intensity. The medial aspects of the cerebellar hemispheres show some increased signal intensity.

B, Corresponding T2-weighted image (3500/90/1) shows multiple areas of increased signal intensity in the medial cerebellar hemispheres, compatible with probable vacuolar myelin. The previously described focal abnormality is not seen.

C, Corresponding contrast-enhanced T1-weighted image (500/20/1) shows that the focal abnormality has enhanced (*arrow*), suggesting that it is a tumor. Patient was treated with radiation therapy.

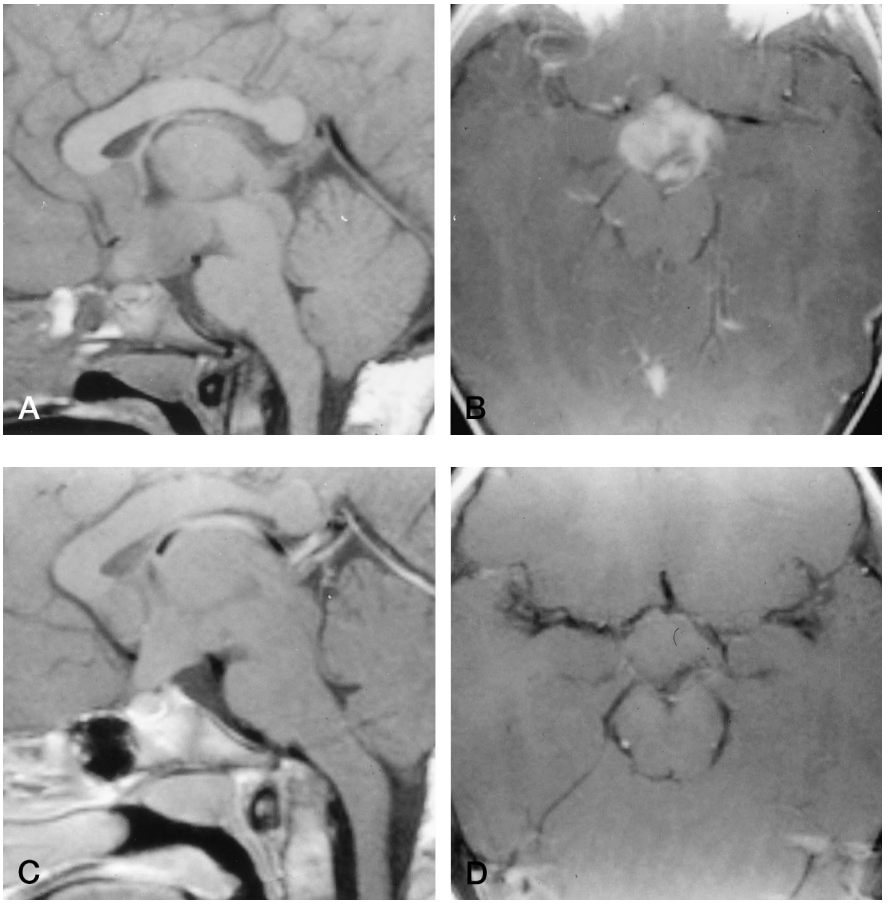

FIG 3. 8-year-old boy with amblyopia and reduced vision in the left eye with a pale disk fundoscopically. Involuting optic chiasm/hypothalamus astrocytoma was indicated by resolution of contrast enhancement.

A, Noncontrast midsagittal T1-weighted image (500/20/1) shows a mass in the region of the optic chiasm/hypothalamus. Incidentally, a Chiari type 1 malformation is present.

B, Axial contrast-enhanced T1-weighted image (500/20/1) shows enhancement of the tumor.

C, Midsagittal contrast-enhanced T1-weighted image (500/20/1) obtained 2 years after *A* and *B* shows diminishing size of the tumor and lack of enhancement.

D, Axial contrast-enhanced follow-up T1-weighted image (500/20/1) at similar level as *B* shows lack of tumor enhancement. There was progressive decrease in size and resolution of enhancement, suggesting a benign process, such as a hamartomatous malformation or astrocytoma.

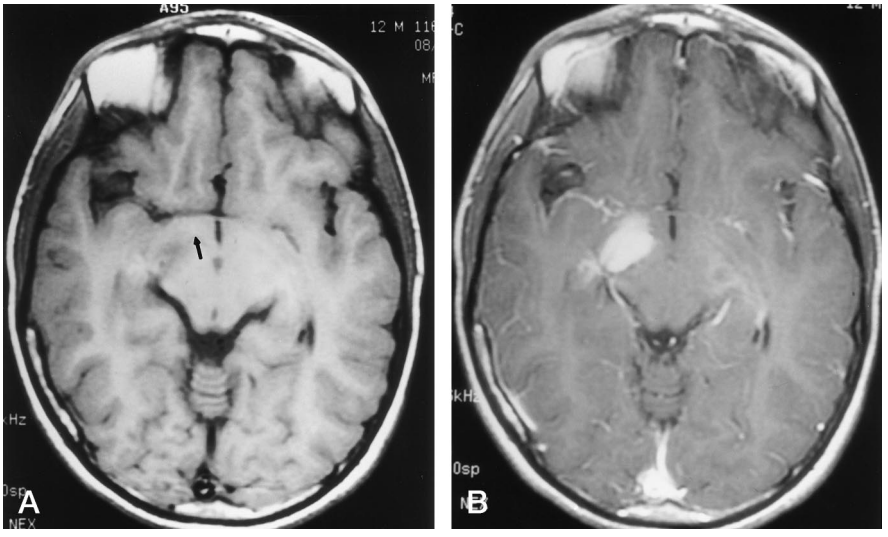

FIG 4. 7-year-old boy with right-sided ptosis, disconjugate gaze, and bilateral optic nerve atrophy.

A, Axial noncontrast T1-weighted image (500/20/1) shows thickening of the right optic radiation (*arrow*) and some inhomogeneous signal intensity to the right of the midbrain.

B, Corresponding contrast-enhanced T1-weighted image (500/20/2) shows enhancement of the right optic radiation, thus helping to define the borders of the tumor, which was proved to be a moderately anaplastic astrocytoma and was treated with chemotherapy.

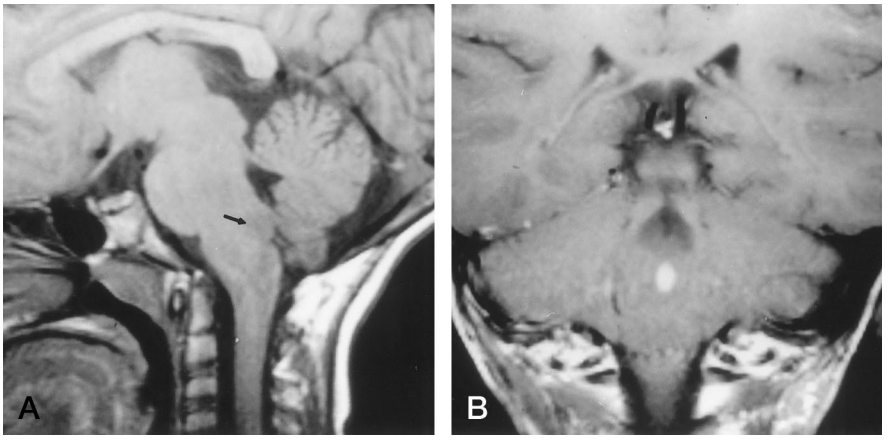

FIG 5. 7-year-old boy with signs and symptoms of increased intracranial pressure, slurred speech, and disequilibrium.

A, Midsagittal noncontrast T1-weighted image (510/15/2) shows a slightly hypointense lesion (*arrow*) in the brain stem with mass effect on the floor of the fourth ventricle.

B, Coronal contrast-enhanced T1-weighted image (510/20/2) shows the lesion has enhanced, with definition of its borders.

longation on noncontrast MR images and became more conspicuous after contrast administration (Fig 2). One lesion of the optic chiasm showed progressive resolution of enhancement and a decrease in size without treatment, suggesting an involuting astrocytoma (16) (Fig 3). In another optic tract tumor, contrast material aided in defining the boundaries (Fig 4). Enhancement was also judged useful in one hypothalamic tumor, in which the heterogeneous enhancement pattern suggested a higher-grade lesion, and in a brain stem lesion with mass effect, in which its borders were better defined after contrast administration (Fig 5).

In two tumors, contrast was judged to be somewhat useful (1+). One tumor appeared entirely cystic on precontrast images but the enhancement pattern suggested a soft-tissue component as well (a surgically proved dysembryoplastic neuroepithelial tumor). In one tectal tumor, the postcontrast MR study helped to better define the borders. Thus, contrast enhancement was somewhat useful in further characterizing lesions in 12% (n = 2) of tumors. In the remaining five (44%) of 16 enhancing tumors, the presence or pattern of enhancement did not aid in lesion detection or characterization, change the diagnosis, or alter treatment.

Discussion

Signs and symptoms of brain involvement in patients with NF-1 typically include increased intracranial pressure, visual abnormalities, or seizures, thus prompting neuroimaging. Approximately 15% of all patients with NF-1 will have brain abnormalities on MR images (3). When lesions are present, they are often multiple (5, 17). Areas of probable myelin vacuolization, the most common brain abnormality, are present in 75% of these patients. Pathologically, these areas show spongiotic or vacuolar changes in the myelin (7). They occur in characteristic locations, such as the pons, midbrain, cerebellar white matter, internal capsule, and splenium of the corpus callosum. Positron emission tomography shows these areas to have normal metabolic rates and blood flow, suggesting that they are not related to edema or gray matter heterotopias (which have low and high metabolic rates, respectively) (18). While not usually present in infancy, these T2 hyperintensities increase in number until the second decade of life and then normalize. They are uncommonly, if ever, seen in adults with NF-1 (6–8, 19). The significance of areas of myelin vacuolization is not known. Some studies have shown a connection between the number and

size of T2 hyperintensities and impaired cognition and neuropsychological abnormalities (20, 21). Conversely, other studies have shown no relationship between the number and configuration of T2 hyperintensities and the patient's mental status (19, 22–24). The importance of imaging in these instances lies in recognizing that the T2 hyperintensities are not related to tumors, have a biologically benign behavior, and do not require therapy.

The second most common intracranial abnormality in NF-1 patients is astrocytoma. The primary criterion we use to differentiate these tumors from myelin vacuolization is mass effect. In patients with NF-1, astrocytomas most commonly occur in the optic chiasm/nerves but may be found anywhere in the brain. Of the NF-1 patients with brain abnormalities, lesions of the optic pathway are observed in approximately 20% to 35% (17, 25, 26). In addition, NF-1 patients with optic gliomas have more areas of probable myelin vacuolization than do those who have no brain tumors. Like the areas of probable myelin vacuolization, the optic pathway lesions may regress (16). Tectal tumors are slow-growing, but in our experience, they eventually compress the aqueduct and cause hydrocephalus, thus requiring close imaging follow-up. Cerebellar tumors may compress the brain stem and fourth ventricle (resulting in hydrocephalus) and may need to be treated surgically.

It may be difficult to distinguish between some presumed astrocytomas and areas of probable myelin vacuolization by MR imaging if the tumor is small and mass effect is difficult to appreciate. This is particularly true in locations such as the brain stem and cerebellar white matter, where areas of myelin vacuolization are common. Areas of probable myelin vacuolization show normal to slightly increased signal intensity on T1-weighted images, high T2 signal intensity, and lack of mass effect. Tumors, however, show low T1 signal intensity, high T2 signal intensity, and mass effect. Thus, the presence of high signal on T1-weighted images is another characteristic of probable myelin vacuolization. Some areas of myelin vacuolization are isointense with brain on T1-weighted images, presumably because of partial averaging of fluid-filled vacuoles and normal surrounding tissues (7). The reason for the T1 hyperintensity of some areas of myelin vacuolization is not clear. When they are seen in the region of the globus pallidus, it has been suggested that the T1 hyperintensity may be due to the presence of microcalcifications (7). The lack of enhancement after contrast administration gives added confidence to the diagnosis of probable myelin vacuolization. It might be argued that some tumors, particularly brain stem tumors, do not enhance after contrast administration (18, 27); however, brain stem tumors produce significant T1 prolongation and mass effect that is easily detected by MR, facilitating differentiation from probable myelin vacuolizations. Overall, therefore, it appears that contrast enhancement is the least important factor in helping to differentiate tumors from regions of probable myelin vacuolization, particularly in the posterior fossa. However, if a tumor is suspected, administration of contrast material may be helpful to delineate its full extent and to aid in its characterization. Therefore, we sought to determine whether the use of contrast material is helpful in evaluating probable myelin vacuolization and tumors and whether its routine administration in patients with NF-1 is warranted.

We identified 88 areas compatible with probable myelin vacuolization on noncontrast MR images. As expected, the most common location for these abnormalities was the posterior fossa. None of the abnormalities thought to be areas of probable myelin vacuolization on precontrast studies enhanced after contrast administration, and the absence of enhancement supported/confirmed their benign nature. We believe that the lack of enhancement in a lesion with no mass effect and nearly normal signal intensity on T1-weighted images is a useful observation that supports the nonneoplastic nature of such a lesion. As recommended by Elster et al (3), in the presence of only probable myelin vacuolizations, routine follow-up imaging may not be necessary unless new symptoms develop.

We identified 50 lesions thought to be tumors on the basis of precontrast studies and 52 thought to be tumors after contrast administration. In two cases, these lesions were small and were not seen on any MR sequence before contrast administration (Fig 1). The findings of enhancement led to the recommendation of more frequent imaging follow-up by the radiologist interpreting the studies. In another patient, a lesion noted on precontrast images was made more conspicuous after contrast administration (Fig 2), and in two other tumors, the borders were seen more clearly on the postcontrast MR study (Figs 4 and 5). In two tumors, the pattern of enhancement suggested higher-grade lesions, leading to closer follow-up in one patient and to surgery in the other. The one tumor appeared entirely cystic on precontrast images but the enhancement pattern suggested a more extensive solid component (a surgically proved dysembryoplastic neuroepithelial tumor). In one hypothalamic tumor, the presence of irregular contrast enhancement and poorly defined lesion borders suggested a more aggressive lesion and dictated closer follow-up. This lesion has grown slowly but progressively on subsequent studies. However, the opposite finding (ie, decreasing contrast enhancement) is also useful. In one of our patients, a tumor in the optic chiasm showed decreasing size and resolution of enhancement (Fig 3), a finding that may support the notion that some of the tumors in this location may be more akin to a hamartoma than to a true neoplasm and that treatment is not always warranted (16). Therefore, contrast administration was judged to be useful and somewhat useful in nine (17%) of 52 tumors, but did not alter the diagnosis in 43 (83%) of them.

Conclusion

Nearly all tumors and all regions of probable myelin vacuolization were confidently identified on MR

imaging studies prior to contrast administration. The presence or absence of contrast enhancement helped us to characterize the tumors, define boundaries, and increase our confidence in the diagnosis of myelin vacuolization. Contrast administration is useful in baseline MR studies to maximize tumor detection and to document stability of neoplasms on follow-up examinations; however, contrast may not be necessary in patients with only myelin vacuolization unless new symptoms arise. In addition, the decision to administer contrast material in patients with NF-1 ultimately depends on the experience of the person interpreting the images. In a small number of patients, the enhancement patterns of a lesion may lead to changes in management.

References

1. NIH Consensus Development. **Neurofibromatosis.** *Arch Neurol* 1988;45:575–578
2. Lund Am, Skovby F. **Optic gliomas in children with neurofibromatosis type 1.** *Eur J Pediatr* 1990;150:835–838
3. Elster AD. **Radiologic screening in neurocutaneous syndromes: strategies and controversies.** *AJNR Am J Neuroradiol* 1992;13:1078–1082
4. Truhan AP, Filipek PA. **Magnetic resonance imaging: its role in the neuroradiologic evaluation of neurofibromatosis, tuberous sclerosis and Sturge-Weber syndrome.** *Arch Dermatol* 1993;129: 219–226
5. Bognanno JR, Edwards MK, Lee TA, et al. **Cranial MR imaging in neurofibromatosis.** *AJR Am J Roentgenol* 1988;151:381–388
6. Sevick RJ, Barkovich AJ, Edwards MS, et al. **Evolution white matter lesions in neurofibromatosis type 1: MR findings.** *AJR Am J Roentgenol* 1992;159:171–175
7. DiPaolo, DP, Zimmerman RA, Rorke LB, et al. **Neurofibromatosis type 1: pathologic substrate of high-signal-intensity foci in the brain.** *Radiology* 1995;195:721–724
8. Itoh,T, Magnaldi S, White RM, et al. **Neurofibromatosis type 1: evolution of deep gray and white matter MR abnormalities.** *AJNR Am J Neuroradiol* 1994;15:1513–1519
9. Ferner RE, Chaudhuri R, Bingham J. **MRI in neurofibromatosis 1: the nature and evolution of increased intensity T2-weighted lesions and their relationship to intellectual impairment.** *J Neurol Neurosurg Psychiatry* 1993:56:492–495
10. Denckla MB, Hofman K, Mazzocco, et al. **Relationship between T2-weighted hyperintensities (unidentified bright objects) and lower IQs in children with neurofibromatosis-1.** *Am J Med Genet* 1996;67:98–102
11. Yasujima H, Komatsu M, Sakurai T, et al. **Relationship between child epilepsy and MRI findings in von Recklinghausen neurofibromatosis (NF1).** *Brain Dev* 1994;26:32–37
12. Moore BD, Slopis JM, Schomer, et al. **Neuropsychological significance of areas of high signal intensity on brain MRIs of children with neurofibromatosis.** *Neurology* 1996;46:1660–1668
13. Joy P, Roberts C, North K, de Silva M. **Neuropsychological function and MRI abnormalities in neurofibromatosis type 1.** *Dev Med Child Neurol* 1995;37:906–914
14. North K, Joy P, Yuikke D, et al. **Specific learning disability in children with neurofibromatosis type 1: significance of MRI abnormalities.** *Neurology* 1995;45:1029–1030
15. Elster AD, Moody DM, Ball MR, et al. **Is Gd-DTPA required for routine cranial MR imaging?** *Radiology* 1989;173:231–238
16. Felix R, Schorner W, Laniado M, et al. **Brain tumors: MR imaging with gadolinium-DTPA.** *Radiology* 1985;156:681–688
17. Graife M, Bydder GM, Steiner RE, et al. **Contrast enhanced MR imaging of malignant brain tumors.** *AJNR Am J Neuroradiol* 1985; 6:855–862
18. Brant-Zawadski M, Berry I, Osaki L, et al. **Gd-DTPA in clinical MR of the brain.** *AJNR Am J Neuroradiol* 1986;7:781–793
19. Powers TA, Partain CL, Kessler RM, et al. **Central nervous system lesions in pediatric patients: Gd-DTPA-enhanced MR imaging.** *Radiology* 1988;169:723–726
20. Bird CR, Drayer BP, Medina M, et al. **Gd-DTPA-enhanced MR imaging in pediatric patients after brain tumor resection.** *Radiology* 1988;169:123–126
21. Elster AD, Rieser GD. **GD-DTPA-enhanced cranial MR imaging in children: initial clinical experience and recommendations for its use.** *AJNR Am J Neuroradiol* 1989;10:1027–1030
22. Prazzini C, Triulzi F, Bianchini E, et al. **Spontaneous involution of optic pathway lesions in neurofibromatosis type 1: serial contrast MR evaluation.** *AJNR Am J Neuroradiol* 1995;16:1711–1718
23. Es SV, North KN, McHugh K, et al. **MRI findings in children with neurofibromatosis type 1: a prospective study.** *Pediatr Radiol* 1996; 26:478–487
24. Balestri P, Lucignani G, Fois A, et al. **Cerebral glucose metabolism in neurofibromatosis type 1 with [18F]-2-fluoro-2-deoxy-D-glucose and PET.** *J Neurol Neurosurg Psychiatry* 1994;57:1479–1483
25. Di Mario FJ, Ramsby G, Greenstein R, et al. **Neurofibromatosis type 1: MR imaging findings.** *J Child Neurol* 1993;8:32–33
26. Pollack IF, Shultz B, Mulvihill JJ. **The management of brainstem gliomas in patients with neurofibromatosis 1.** *Neurology* 1996;46: 1652–1660
27. Molloy PT, Bilaniuk LT, Vaughan SN, Needle MN, Liu GT, Zackai EH. **Brainstem tumors in patients with neurofibromatosis type 1: a distinct clinical entity.** *Neurology* 1995;45:1897–1902