AJNR

Radiologic screening in the neurocutaneous syndromes: strategies and controversies.

A D Elster

Commentary

Radiologic Screening in the Neurocutaneous Syndromes: Strategies and Controversies

Allen D. Elster[1]

The article by Egelhoff et al (1) in the current issue of this journal raises some important questions concerning what constitutes the proper radiologic screening and evaluation of patients with neurofibromatosis (NF). In this study, a surprisingly large number of occult spinal tumors were detected in patients with type 1 (NF-1) and type 2 (NF-2) neurofibromatosis. Does this mean that all patients with NF should undergo periodic magnetic resonance (MR) imaging of the entire brain and spine? Should their first-degree relatives also be scanned? How do the sophisticated new chromosomal marker tests for NF affect these imaging algorithms? Should we also rethink our approach to patients with other neurocutaneous syndromes, such as tuberous sclerosis and von Hippel-Lindau disease? To answer such questions, we must first review what is known about the natural history of these diseases, a limited and conflicting body of data that, for the present, must serve as our sole source of "truth."

Neurofibromatosis

In the hundred years since von Recklinghausen first described this entity, it has become clear that NF is actually a group of heterogeneous diseases (2–5). Chromosomal linkage studies have documented that NF-1 and NF-2 are genetically distinct, while clinical evidence supports the existence of as many as six additional subtypes of the disease. Any imaging algorithm or screening protocol that is eventually adopted, therefore, must take into account this great complexity and diversity in the genetic expression of NF.

Both NF-1 and NF-2 are transmitted as autosomal dominant traits with nearly complete penetrance (4). Approximately 90% of children who have inherited the NF-1 gene can be identified clinically after the age of 2 years when they develop café-au-lait spots, iris hamartomas (Lisch nodules), or cutaneous neurofibromas (6). However, children younger than 2 years with NF-1 and patients of all ages with NF-2 may manifest few external stigmata and be difficult to diagnose clinically. Fortunately, genetic tests for both NF-1 and NF-2 (costing approximately $1000 each) are now available by "mail order" from several centers. These tests require blood samples from both parents or two close relatives with NF, and hence cannot be used to detect the sporadic (noninherited) forms of the disease (that account for 40% to 50% of cases). Imaging evaluation, therefore, should be considered for two groups of patients: 1) those definitely diagnosed to have NF by clinical or laboratory methods, and 2) those in whom the diagnosis of NF remains in doubt even after such testing has been performed.

The optimal strategy for imaging such patients ideally should be based upon the natural history of the disease. Unfortunately, this natural history is imperfectly known, with the only certainty being that skin lesions and tumors at all sites in NF generally increase in size and number with advancing age (7). The course of NF in a given patient is thus largely unpredictable, and the presence or severity of any one feature of the disease only correlates poorly with the presence or severity of any other. Notwithstanding these uncertainties, a few general principles concerning the involvement of the central nervous system in NF are sufficiently well established to provide some rational basis for the timing of cranial imaging.

Optic gliomas are the most common intracranial tumor in NF-1, occurring in approximately 5% to 15% of patients (8). About 90% of these tumors are diagnosed between the ages of 1 and

7 years, making this period the critical time for initial cranial screening by MR (9). Visual fields testing, fundoscopy, and visually evoked responses are not sufficiently sensitive to make this diagnosis alone (3). **Therefore, we believe every patient with NF-1 needs a baseline cranial MR scan at some time during the first few years of life.** Since the optic gliomas of NF-1 are usually of benign histology and grow slowly, considerable latitude is permitted in the timing of MR imaging. In about 20% of cases, however, the optic glioma may behave aggressively, resulting in early patient demise (10). Such malignant behavior is usually apparent soon after discovery of the tumor, with the median time of death being 4 years after diagnosis. Thus, a single follow-up scan at about a year's interval will often provide considerable insight into the biologic behavior of an optic glioma.

Patients with NF-1 are also at considerable risk for developing gliomas elsewhere in the brain, about half of which become malignant. These gliomas occur over a much broader range of ages than optic gliomas, with about 75% of cases presenting before 40 years (11). Those which develop in the cerebellum are said to have a particularly poor prognosis (12). Because nonoptic gliomas occur over such a wide range of ages and have such variable clinical courses, no particularly cost-effective or efficient imaging strategy has yet been developed for their early detection. **We do not routinely scan asymptomatic adult patients with NF-1 in order to detect such occult gliomas. We do, however, maintain a very low threshold for imaging these patients when they present with headaches or subtle neurologic complaints.**

Another unresolved issue in the screening and follow-up of patients with NF-1 concerns how to deal with the incidental discovery on T2-weighted MR images of high-signal lesions in the basal ganglia and brain stem, which occur in as many as 60% of cases (2, 3, 13, 14). In the radiologic literature, these lesions have been speculatively identified as hamartomas, heterotopias, schwannosis, gliosis, glial nests, or glial nodes. When one *critically* analyzes the pathologic literature cited in support of these claims, however, it immediately becomes apparent that none of these named pathologic entities has ever been reported with frequencies approaching 60%, and most have never been described to occur in the basal ganglia (where the lesions seen on MR are most common). Furthermore, some of these disorders (such

as intramedullary and perivascular schwannosis) occur principally in NF-2, where high-signal lesions are seldom seen. Russell and Rubinstein have reported glial cell rests in the basal ganglia of patients with NF-2 and meningioangiomatosis, but state that glial ectopias in NF-1 are seen only "most exceptionally" (13).

Whatever their origin, it is generally believed that most of these lesions tend to regress with aging (14) and, thus, are only infrequently encountered in adults (2). It is entirely possible, therefore, that these lesions do not represent any fixed pathologic entity at all, but are merely transient areas of disordered glial proliferation or defective myelination that resolve with aging. Until the true nature of these lesions is established, perhaps we would be better off calling them by another name free of pathologic implications, such as UNOs ("unidentified neurofibromatosis objects").

How, then, can we reconcile these disputed pathologic findings or develop any intelligent strategy for following UNOs? When typical, benign-appearing UNOs (small, no mass effect, no contrast enhancement) are encountered on an initial MR scan as the sole abnormality, **one is probably safe in ignoring these lesions and obtaining a follow-up study only if clinically indicated.** (Being cautious, however, we continue to obtain a single follow-up scan at 1 year to confirm their stability). Occasionally, however, we encounter UNOs that, by virtue of their larger size, mass effect, or proximity to an optic pathway glioma, seem somewhat atypical. In these cases, we believe closer follow-up should be performed, since it is possible that some of these lesions may represent gliomas or focal extensions of an optic pathway tumor rather than benign UNOs.

Our strategy for cranial imaging in NF-2 differs from NF-1 since the types of tumors encountered and the natural history of the two diseases are distinct. In NF-2, the dominant intracranial tumor is the acoustic schwannoma, occurring in essentially 100% of patients (by definition). These tumors typically become symptomatic during or soon after puberty, and their rapid growth may be witnessed during pregnancy (15). In general, however, acoustic schwannomas grow slowly (16), and watchful waiting under yearly MR monitoring has been recommended for neurologically stable cases (15). A similar strategy may apply when intracranial meningiomas and schwannomas of other cranial nerves are encountered; this must be tempered, of course, based on the loca-

tions and initial sizes of the lesions. Ependymomas, the other common tumor in NF-2, will likely require a more aggressive therapeutic approach and imaging strategy.

Until the paper by Egelhoff et al (1), the world has remained generally blinded to the frequency of spinal tumors in either NF-1 or NF-2, except for one similar small series that reached the same conclusions (17). We now know that spinal neurofibromas, schwannomas, and meningiomas are much more common in both types of NF than anyone previously suspected. What is even more alarming is that occult spinal tumors are present in over half of asymptomatic patients. Should everyone with NF therefore undergo total spine MR imaging on a yearly basis regardless of symptoms?

There is clearly no easy answer to this question until larger prospective studies are performed. For NF-1 at least, we take some consolation in the fact that surgery for spinal tumor is eventually required in only 2% to 6% of patients (3, 7, 11, 18). Furthermore, although malignant transformation of these tumors may occur, most cancer deaths in NF-1 are caused by malignant degeneration of peripheral soft-tissue neurofibromas, not spinal tumors. In fact, the most common spinal problem in NF-1 requiring surgery is scoliosis, not tumor (18). Therefore, it is arguable whether morbidity would be significantly reduced by the early diagnosis of these occult spinal tumors. A better case might be made for spinal screening in NF-2, where the natural history of spinal lesions has never been separately studied.

Tuberous Sclerosis

Tuberous sclerosis (TS) is an autosomal dominant disorder of variable expression and penetrance characterized by hamartomatous malformations of the skin, brain, heart, lung, and kidneys (4). Between 30% and 50% of cases appear to be inherited, while the remainder presumably result from spontaneous mutation of a locus on chromosome 11 (19, 20). The most serious consequences of TS are the neurologic ones: seizures, mental retardation, and brain tumors. Imaging studies play an important role in the diagnosis, management, and genetic counseling of families and patients with TS.

Unlike NF, where cutaneous manifestations are prominent and appear at an early age, the external stigmata of TS are more subtle and may not become manifest until late childhood (21). The most common skin lesion is the "ash leaf spot," a hypopigmented macule that may be found in 80% to 95% of patients when examined with a Wood's light. The best known skin lesion, the adenoma sebaceum (angiofibroma), occurs in no more than 80% of patients and is not usually seen before age 4. Periungual fibromas are nearly pathognomic of TS, but do not appear before puberty and then are seen in only 9% to 20% of patients. Seizures occur in 80% to 100% of patients, and, thus, are a common but nonspecific sign of the disease. While mental deficiency was previously thought to be an invariable feature of this syndrome, an increasing number of patients with TS are now being reported with normal or above normal intelligence (22). At present there are no commercial blood tests for TS similar to those available for NF.

Because the clinical signs and symptoms of TS can be subtle or nonspecific, imaging studies may be necessary to establish the diagnosis. Although computed tomography (CT) may detect subependymal calcifications to better advantage, MR imaging reveals parenchymal hamartomas and associated migrational anomalies so superiorly that it should be considered the imaging modality of choice for the initial diagnosis of this disorder (23, 24). MR imaging may also be of prognostic value at this early stage, since the number of cortical tubers detected by MR imaging in younger children appears to be predictive of the degree of eventual mental deficiency (25).

Imaging studies may also play an important role in the genetic counseling of parents whose child is afflicted by TS. Since fewer than half of cases of TS are inherited and no reliable genetic test for the disease yet exists, **it is important to examine parents carefully for subtle clinical signs when assessing their risk of giving birth to future offspring with TS.** A complete physical examination, preferably by experienced dermatologists and geneticists, remains the cornerstone for identifying parents who carry the TS gene. One group of investigators, however, reported finding occult cardiac rhabdomyomas by ultrasound in parents in three of seven families where sporadic occurrence of TS in a child was diagnosed by purely clinical criteria (20). In a prospective study performed at our institution, MR imaging allowed the diagnosis of occult TS in one parent who had no physical signs of the disease out of 30 families where at least one child was affected (26). On the basis of these data, **optimal genetic counseling would seem to require that**

ancillary cranial MR imaging and echocardiography be performed to detect parents who may silently carry the TS gene, although the anticipated yield of such procedures will be small.

After initial diagnosis is made, cranial imaging studies are required to diagnose a potentially lethal complication of TS, the development of a subependymal giant cell astrocytoma. These tumors occur in approximately 15% of patients with TS and are nearly always located near the foramen of Monro with a slight right-sided predominance (4, 23, 24, 27). The CT appearance of these lesions is 2- to 3-cm partially calcified mass with contrast enhancement. On MR, the signal characteristics of these tumors may be indistinguishable from other benign subependymal nodules, where contrast enhancement with gadolinium is also frequently identified. Because of the relatively high frequency and clinical significance of these tumors, **we recommend screening of patients with TS every 1–2 years with contrast-enhanced CT or MR,** or more frequently if clinical conditions warrant. This protocol should be followed at least **from ages 8 to 18,** which is the most likely time for giant cell tumors to develop.

Von Hippel-Lindau Disease

Von Hippel-Lindau (VHL) disease is an autosomal dominant disorder with incomplete penetrance linked to a defect on chromosome 3 (28). Potentially lethal tumors may develop in multiple organ systems, including hemangioblastomas of the brain or spinal cord, renal cell carcinomas, and pheochromocytomas. There are generally no external manifestations of the disease, and no simple genetic tests are yet available. Imaging methods, therefore, are crucial both in the diagnosis of VHL and in the surveillance of patients at risk to develop it.

Jennings et al (29) have developed an elaborate protocol for the screening and follow-up of patients with VHL. In addition to regular clinical and ophthalmologic examinations, this protocol includes annual measurements of vanillylmandelic acid and catecholamines (to detect pheochromocytomas) and urinalysis (to detect hematuria from renal cell carcinoma). The initial diagnosis of VHL is significantly aided by a baseline abdominal CT scan (to look for characteristic cysts of the pancreas, liver, and kidneys, as well as to detect renal and adrenal tumors) and testicular ultrasound (to look for cysts and cystadenomas

of the epididymis). Since renal cell carcinomas develop in at least 30% of patients with VHL and are frequently bilateral or multiple, at least yearly screening by CT, MR, or ultrasound seems warranted throughout most of adulthood.

The imaging strategy to detect the central nervous system manifestations of VHL is somewhat different. Hemangioblastomas occur in about one-third of patients with VHL (29, 30), while about one-fourth of patients with hemangioblastomas prove to have VHL (31, 32). Since hemangioblastomas in VHL primarily involve the cerebellum (65%), brain stem (20%), and spinal cord (15%), MR imaging is clearly superior to CT for the evaluation of such lesions (32). Hemangioblastomas associated with VHL tend to present a decade or two earlier in life (mean age at presentation, 32 years) than those occurring in non-VHL patients. **Virtually all such tumors occur between the ages of 12 and 50 years,** and this should be the target time for imaging surveillance. Based on the relatively slow growth rate of these neoplasms, **we would recommend screening high-risk patients with contrast-enhanced MR no less frequently than every 2 years during this period.** The minimum MR examination **should include the cerebellum, brain stem, and upper cervical spine.** Prospective screening of the remainder of the spine could arguably be omitted since most VHL patients with spinal hemangioblastomas also have tumors in the posterior fossa.

Conclusions

In an ideal world with infinite resources, optimal medical care of patients with NF, TS, or VHL would include frequent examinations by clinical specialists as well as periodic comprehensive imaging studies of the brain, spine, and other organs at risk for neoplasia. In the real world, however, we are forced by economics to limit this screening and surveillance to a level where a high standard of care is maintained and costs are minimized. Because the natural histories of the phakomatoses are imperfectly known, and because their clinical courses are highly variable, no single imaging algorithm can be proved to be the "best." Our goal should be to develop "reasonable" imaging strategies that complement the level of clinical care at each institution—dynamic strategies that will be joyfully modified whenever new information becomes available.

References

1. Egelhoff JC, Bates DJ, Ross JS, Rothner AD, Cohen BH. Spinal MR findings in neurofibromatosis types 1 and 2. *AJNR* 1992;13: 1071–1077

2. Aoki S, Barkovich AJ, Nishimura K, et al. Neurofibromatosis types 1 and 2: cranial MR findings. *Radiology* 1989;172:527–534

3. Mulvihill JJ, moderator. Neurofibromatosis 1 (Recklinghausen disease) and neurofibromatosis 2 (bilateral acoustic neurofibromatosis): an update. *Ann Intern Med* 1990;113:39–52

4. Pont MS, Elster AD. Lesions of skin and brain: modern imaging of the neurocutaneous syndromes. *AJR* 1992;(in press)

5. Riccardi VM. Neurofibromatosis: clinical heterogeneity. *Curr Probl Cancer* 1982;7:1–34

6. Pulst S-M. Prenatal diagnosis of the neurofibromatoses. *Clin Perinatol* 1990;17:829–844

7. Riccardi VM. Von Recklinghausen neurofibromatosis. *N Engl J Med* 1981;305:1617–1627

8. Lewis RA, Gerson LP, Axelson KA, Riccardi VM, Whitford RP. Von Recklinghausen neurofibromatosis II: incidence of optic gliomata. *Ophthalmology* 1984;91:929–935

9. Hoyt WF, Baghdassarian SA. Optic glioma of childhood: natural history and rationale for conservative management. *Br J Ophthalmol* 1969;53:793–798

10. Imes RK, Hoyt WF. Childhood chiasmal gliomas: update on the fate of patients in the 1969 San Francisco Study. *Br J Ophthalmol* 1986; 70:179–182

11. Sørensen SA, Mulvihill JJ, Nielsen A. On the natural history of von Recklinghausen neurofibromatosis. *Ann NY Acad Sci* 1986;486: 30–37

12. Ilgren EB, Kinnier-Wilson LM, Stiller CA. Gliomas in neurofibromatosis: a series of 89 cases with evidence of enhanced malignancy in associated cerebellar astrocytomas. *Pathol Annu* 1985;20:331–358

13. Russell DS, Rubinstein LJ. *Pathology of tumors of the nervous system*. 5th ed. Baltimore: Williams & Wilkins, 1989:776–782

14. Sevick RJ, Barkovich AJ, Edwards MS, et al. Neurofibromatosis type I: temporal evolution of white matter lesions. *Radiology* 1991; 181(P):193

15. Martuza RL, Eldridge R. Neurofibromatosis 2 (bilateral acoustic neurofibromatosis). *N Engl J Med* 1988;318:684–688

16. Valvassori GE, Guzman M. Growth rate of acoustic neuromas. *J Otol* 1989;10:174–176

17. Li MH, Holt AS. MR imaging of spinal neurofibromatosis. *Acta Radiol* 1991;32:279–285

18. Huson SM, Compston DAS, Harper PS. A genetic study of von Recklinghausen neurofibromatosis in south east Wales. II. Guidelines for genetic counselling. *J Med Genet* 1989;26:712–721

19. Smith MS, Smalley S, Cantor R, et al. Mapping of a gene determining tuberous sclerosis to human chromosome 11g14-11g23. *Genomics* 1990;6:105–114

20. Al-Gazali LI, Arthur RJ, Lamb JT, et al. Diagnostic and counselling difficulties using a fully comprehensive screening protocol for families at risk for tuberous sclerosis. *J Med Genet* 1989;26:694–703

21. Lucky AW. Pigmentary abnormalities in genetic disorders. *Dermatol Clin* 1988;6:193–203

22. Roach ES. Usefulness of magnetic resonance imaging in tuberous sclerosis. *Arch Neurol* 1988;45:830–831

23. 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

24. Nixon JR, Houser OW, Gomez MR, Okazaki H. Cerebral tuberous sclerosis: MR imaging. *Radiology* 1989;170:869–873

25. Roach ES, Williams DP, Laster DW. Magnetic resonance imaging in tuberous sclerosis. *Arch Neurol* 1987;44:301–303

26. 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

27. McMurdo SK, Moore SG, Brant-Zawadski M, et al. MR imaging of intracranial tuberous sclerosis. *AJR* 1987;48:791-796

28. Hosoe S, Brauch H, Latif F, et al. Localization of the von Hippel-Lindau disease to a small region of chromosome 3. *Genomics* 1990; 6:634–640

29. Jennings AM, Smith C, Cole DR, et al. Von Hippel-Lindau disease in a large British family: clinicopathological features and recommendations for screening and follow-up. *Q J Med* 1988;251:233–249

30. Horton WA, Wong V, Eldridge R. Von Hippel-Lindau disease: clinical and pathological manifestations in nine families with 50 affected members. *Arch Intern Med* 1976;136:769–777

31. Neumann HPH, Eggert HR, Weigel K, et al. Hemangioblastomas of the central nervous system: a 10-year study with special reference to von Hippel-Lindau syndrome. *J Neurosurg* 189;70:24–30

32. Elster AD, Arthur DW. Intracranial hemangioblastomas: CT and MR findings. *J Comput Assist Tomogr* 1988;12:736–739