Neuroimaging Manifestations of NF1 — A Pictorial Review

William T. O'Brien, Sr., D.O.

Department of Radiology, David Grant USAF Medical Center, Travis AFB, CA
Department of Radiology, University of California, Davis School of Medicine, Sacramento, CA

Background

Neurocutaneous syndromes encompass a group of disorders that affect the embryonic ectodermal plate, which includes the central and peripheral nervous systems, as well as the overlying skin. Mesodermal and endodermal structures may be involved, depending on the type and severity of the specific neurocutaneous syndrome. Common developmental abnormalities include dysplasias and often an increased incidence of neoplasms.

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease, is the most common of the neurocutaneous syndromes with an incidence of approximately 1 in 2,600 to 1 in 3,500 live births.[1-3] Men and women are affected equally. NF1 is inherited in an autosomal dominant fashion with variable pathological and clinical expression. Approximately half of all cases result from spontaneous mutations of the NF1 gene.[4] The genetic defect affects chromosome 17q12 and results in decreased production of neurofibromin, which acts as a tumor suppressor. The disease affects the brain, skull, orbits, spine, musculoskeletal system, and skin/integumentary system, although there is significant variability in the type and severity of clinical manifestations.[3] Diagnostic criteria for NF1 include the presence of 2 or more of the following: first degree relative with NF1, 6 or more café-au-lait spots, 2 or more neurofibromas (NFs) or 1 plexiform neurofibroma (PNF), optic pathway glioma, bony dysplasia, axillary or inguinal freckling, and 2 or more Lisch nodules.[5,6] Central nervous system (CNS) abnormalities occur in approximately 15%-20% of NF1 patients.[7]

Intracranial Manifestations of NF1

Parenchymal Involvement and Neoplasias

Intracranial CNS manifestations include characteristic NF1 "spots" and low-grade neoplasms. The NF1 "spots" are regions of signal abnormality involving the basal ganglia, thalami, dentate nuclei, cerebellar peduncles, optic radiations, and brainstem in children and adolescents; they are thought to represent regions of myelin vacuolization **(Figure 1)**. They are hyperintense on T2 sequences and typically iso- to mildly hyperintense on T1 images. There should be no mass effect or enhancement, as enhancement or significant mass effect suggests development of a low-grade glioma. The lesions may wax and wane for the first decade of life or so and then regress.[8] They are uncommon after the second decade of life.

The most common CNS neoplasm associated with NF1 is a low-grade optic pathway glioma (OPG). The majority of children with OPGs have NF1,[9,10] while approximately 20% of patients with NF1 have OPGs.[11,12] The presence of bilateral optic nerve gliomas is considered pathognomonic for NF1. The tumors cause enlargement, elongation and "buckling" of the optic nerve, resulting in the "dotted i" appearance on axial images **(Figure 2)**. Enlargement and benign bony remodeling of the optic canal may also be seen. Although low-grade, the lesions may extend to the optic chiasm, and along the optic tracts and radiations **(Figure 3)**. Visual loss and interval change in size are the most important considerations in terms of managing OPGs. The tumors are hypointense on T1 and hyperintense on T2 sequences. Expansion of CSF within the optic nerve sheath complex may be seen, possibly due to CSF trapping. Enhancement characteristics are variable, especially in the

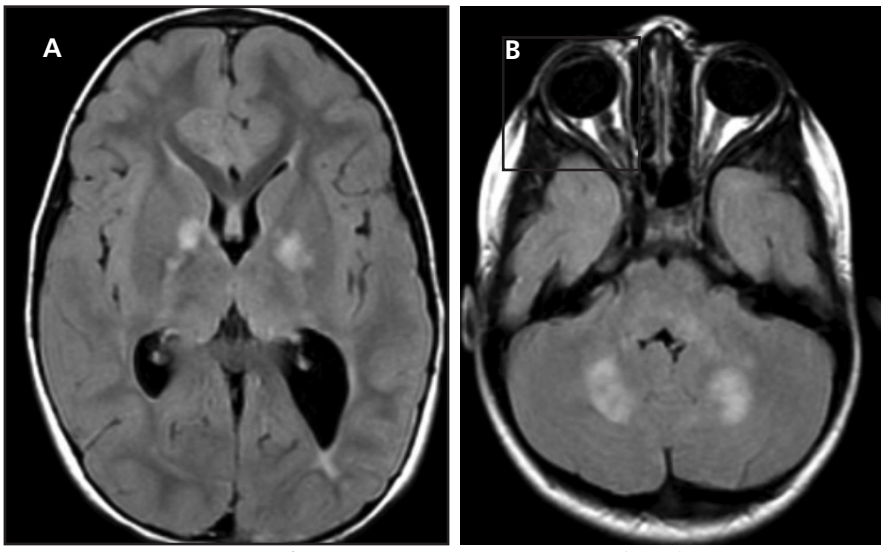

FIGURE 1. *NF1 "spots." Axial fluid-attenuated inversion recovery (FLAIR) images demonstrate multiple foci of increased signal intensity without mass effect involving the basal ganglia and deep white matter tracts (A), as well as the cerebellum (including dentate nuclei) and the brainstem (B).*

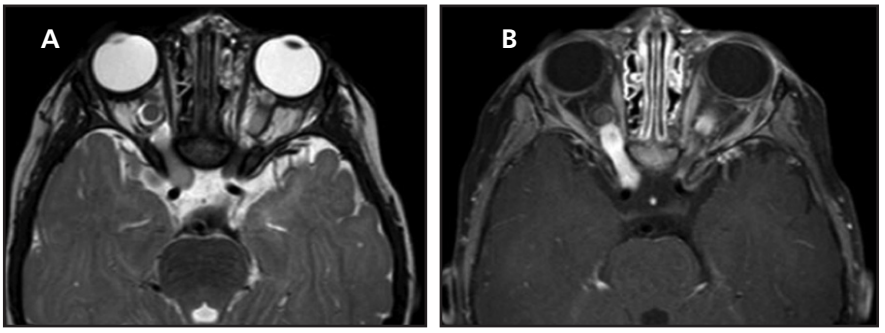

FIGURE 2. *Optic pathway glioma. Axial T2 image (A) demonstrates enlargement and buckling of the bilateral prechiasmatic and intraorbital segments of the optic nerves, resulting in the "dotted i" appearance. There is also increased CSF signal intensity within the right optic nerve-sheath complex. Axial T1 postcontrast image with fat suppression (B) reveals abnormal enhancement of the enlarged optic nerves. Reprinted with permissions: O'Brien WT.* Top 3 Differentials in Neuroradiology. *New York: Thieme, 2015.*

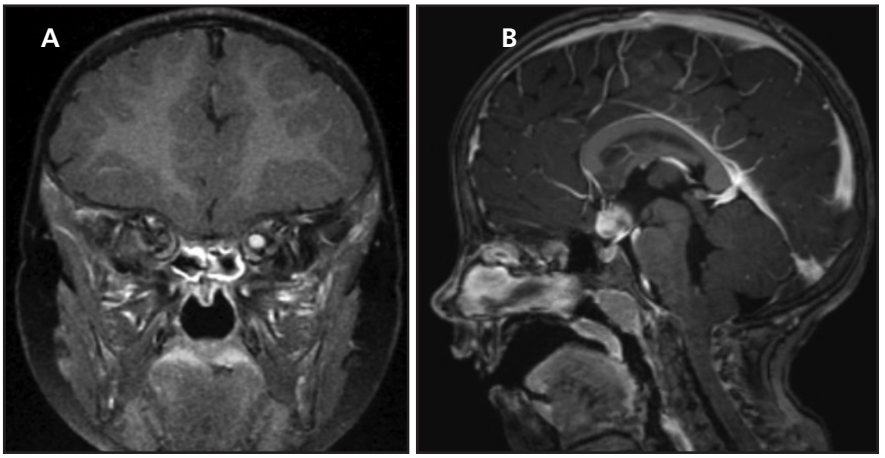

FIGURE 3. *Optic pathway glioma. Coronal T1 postcontrast image with fat suppression (A) shows abnormal enlargement and enhancement of the intraorbital left optic nerve. Sagittal T1 postcontrast image with fat suppression in a different patient (B) reveals an enhancing suprasellar mass centered within the optic chiasm.*

setting of ongoing treatment, and are less reliable in terms of directing treatment decisions compared to a change in tumor size or extent. Treatment options include chemotherapy, surgery, and radiation therapy, although radiation therapy is generally avoided in patients with NF1.[13]

Low-grade cerebellar, brainstem, tectal plate, and basal ganglia gliomas are also common and have an increased incidence in the setting of NF1; the vast majority are pilocytic astrocytomas, although high-grade gliomas may occasionally be seen as well. Pilocytic variants involving the posterior fossa, brainstem, and optic pathways commonly present as cystic tumors with an enhancing mural nodule **(Figures 4 and 5)**. Enhancement may be seen along the cyst wall as well, which often indicates tumor cells lining the cystic component **(Figure 5)**.[14] On MRI, tectal plate gliomas are typically T2 hyperintense and iso- to hypointense on T1 with no or minimal enhancement **(Figure 6)**. More aggressive gliomas most often present in the pons and appear as ill-defined, infiltrative masses with variable enhancement patterns. Higher-grade components demonstrate central necrosis with increased peripheral enhancement and perfusion, as well as restricted diffusion.[14] Obstructive hydrocephalus may result from mass effect associated with tectal plate, cerebellar, or brainstem gliomas or as a result of aqueductal stenosis, which has an increased incidence in patients with NF1.

Orbital Involvement

In addition to OPGs (described above), orbital findings include sphenoid wing dysplasia with associated pulsatile exophthalmos, buphthalmos (globe enlargement), and intraorbital extension of a plexiform neurofibroma. Sphenoid wing dysplasia is a characteristic finding of NF1 but is relatively uncommon. The greater wing of the sphenoid is most often involved. Although the precise etiology of sphenoid wing dysplasia is not entirely understood, recent studies suggest that the

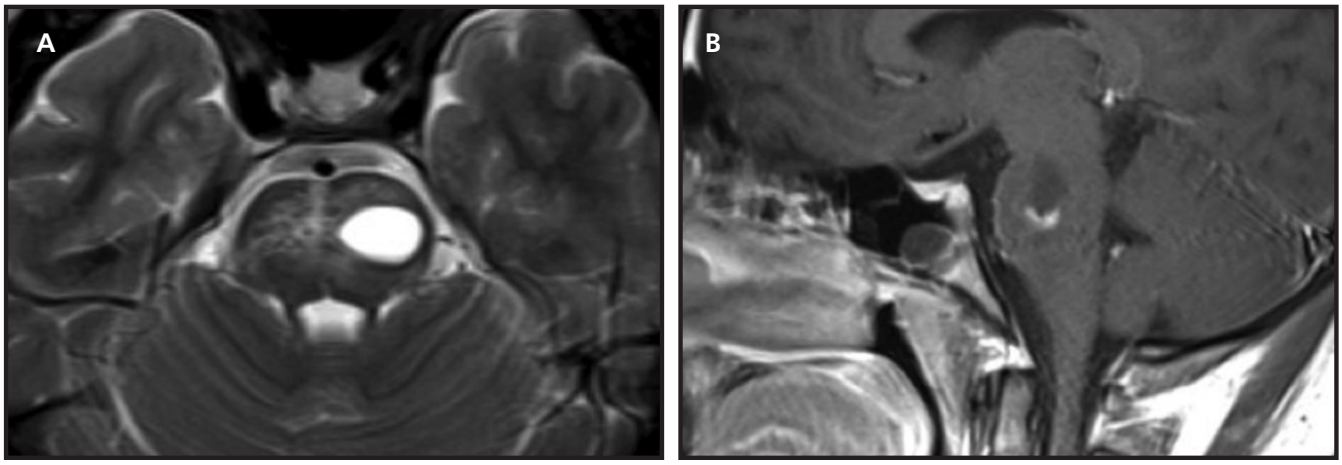

FIGURE 4. *Brainstem juvenile pilocystic astrocytoma. Axial T2 image through the pons (A) reveals a cystic lesion to the left of midline with mild mass effect and surrounding edema. Sagittal T1 postcontrast image (B) shows a nodular enhancing component along the inferior margin of the mass.*

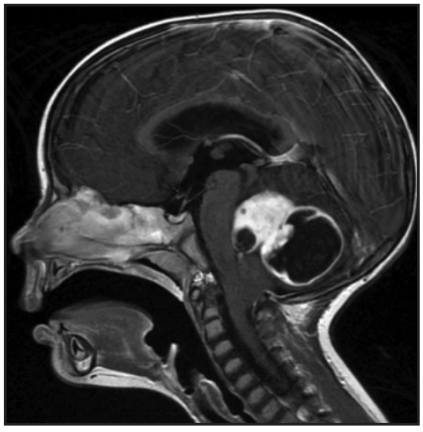

FIGURE 5. *Posterior fossa juvenile pilocytic astrocytoma. Sagittal T1 postcontrast image demonstrates a large cystic and solid posterior fossa mass with an enhancing nodular component along its anterosuperior margin, as well as enhancement along the wall of the cystic component. There is compression of the 4th ventricle and brainstem with obstructive hydrocephalus and inferior displacement of the cerebellar tonsils through the foramen magnum.*

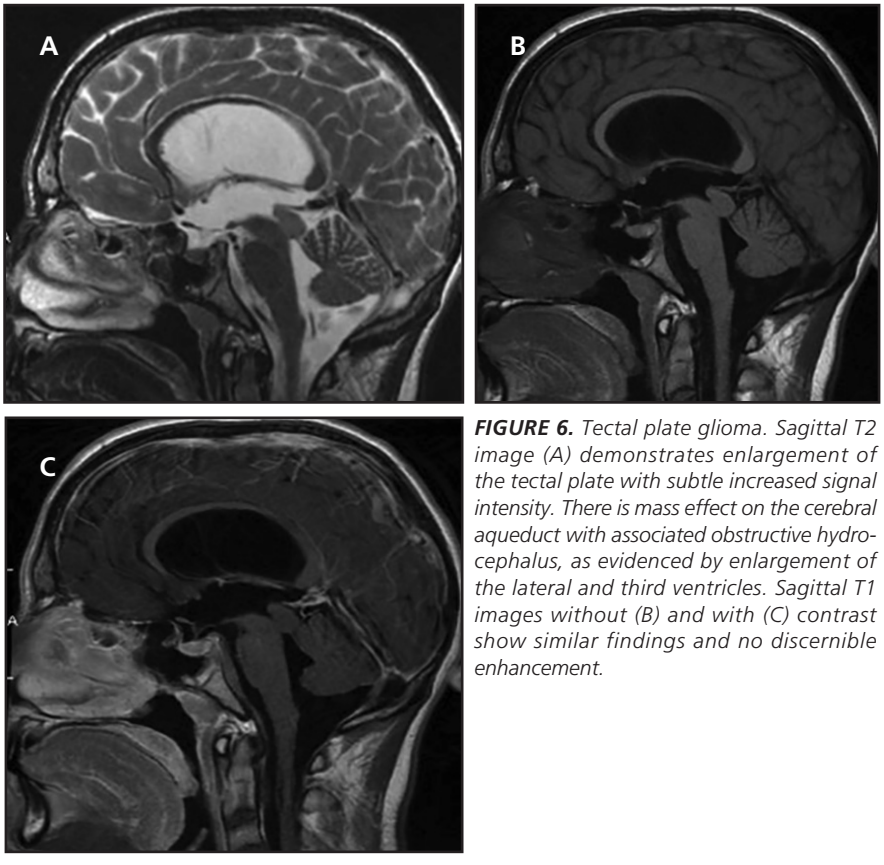

FIGURE 6. *Tectal plate glioma. Sagittal T2 image (A) demonstrates enlargement of the tectal plate with subtle increased signal intensity. There is mass effect on the cerebral aqueduct with associated obstructive hydrocephalus, as evidenced by enlargement of the lateral and third ventricles. Sagittal T1 images without (B) and with (C) contrast show similar findings and no discernible enhancement.*

process may be multifactorial with a combination of bony dysplasia, as well as an ipsilateral plexiform neurofibroma affecting growth and closure of skull base sutures.[15] Cross-sectional imaging demonstrates anterior displacement and thinning of the sphenoid bone with enlargement of the middle cranial fossa in the anteroposterior dimension **(Figure 7)**. Herniation of portions of the temporal lobe and overlying CSF into the posterior margin of the orbit results in pulsatile exophthalmos. Globe enlargement – buphthalmos – may also be seen in the setting of NF1 **(Figure 8)**.

As the name would imply, neurofibromas (NFs) are common in the setting of NF1. NFs are classified as benign peripheral nerve sheath tumors with subcategories, including localized, discrete superficial or deep NFs and diffuse plexiform neurofibromas (PNFs). NFs most often involve the orbits, head and neck, spine, and paraspinal soft tissues in patients with NF1. On MRI, they are hyperintense on T2 and hypointense on T1 sequences with heterogeneous enhancement. Compared to schwannomas, NFs are more likely to demonstrate the target appearance with central decreased and peripheral increased T2 signal intensity.[16]

PNFs refer to a network of nerve fascicles and thickened fibers that occur along the longitudinal axis of peripheral

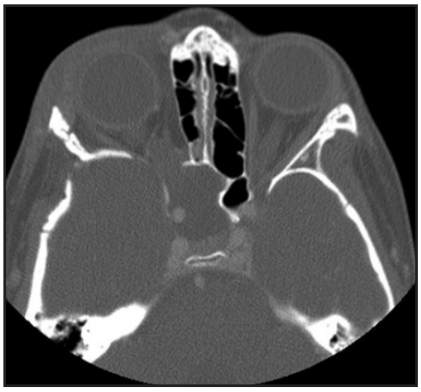

FIGURE 7. *Sphenoid wing dysplasia. Axial CT image in bone window reveals anterior displacement and thinning of the sphenoid bone on the right with enlargement of the middle cranial fossa in the anteroposterior dimension. A soft tissue mass extending through and expanding the right optic canal, consistent with an optic pathway glioma, is partially seen.*

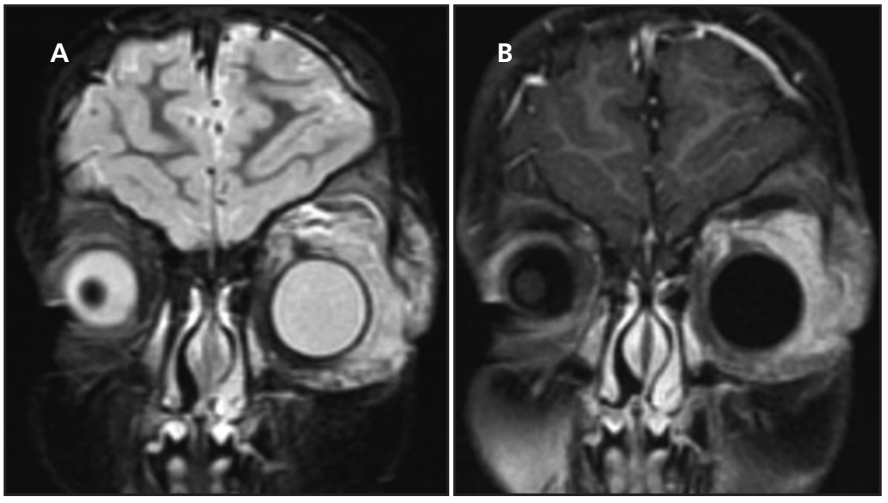

FIGURE 9. *Plexiform neurofibroma. Coronal fluid-sensitive T2 (A) and postcontrast T1 (B) images with fat suppression (A) demonstrate a large enhancing T2 hyperintense mass with intermediate to hypointense linear striations involving the pre- and postseptal compartments of the left orbit, as well as involvement of the suprazygomatic masticator space on the left. There is mass effect on the left with proptosis.*

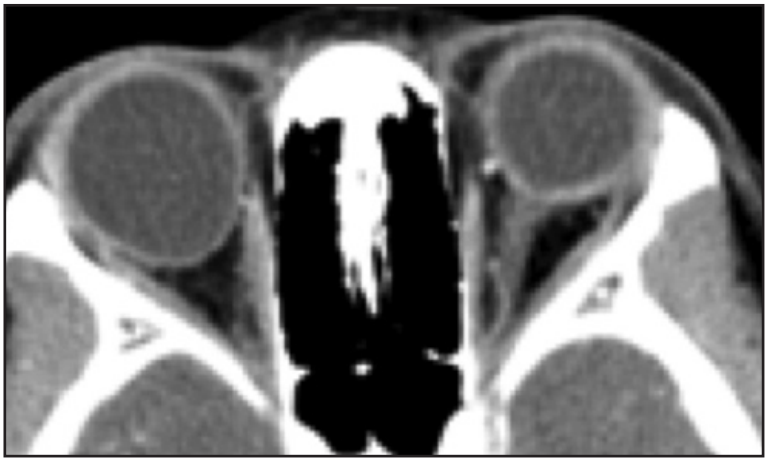

FIGURE 8. *Buphthalmos. Axial CT image reveals enlargement of the right globe in a young child with NF1, consistent with buphthalmos.*

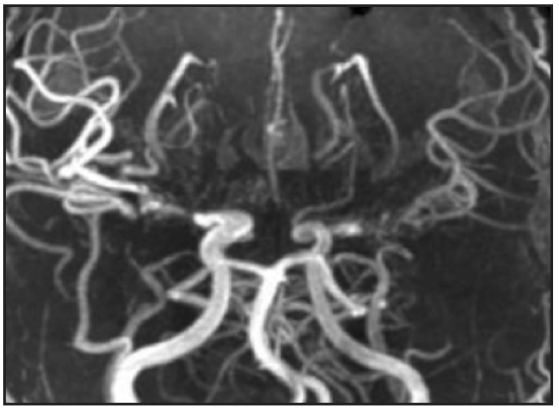

FIGURE 10. *Vasculopathy/moya moya. Reformatted image from an MR angiogram demonstrates occlusion of the terminal carotid and proximal cerebral arteries with multiple basilar and meningeal collateral vessels, consistent with moya moya.*

nerves. They appear more infiltrative on MRI with T2 hypointense septations and heterogeneous enhancement **(Figure 9)**. PNFs commonly involve the orbit, skull base, and spine. PNFs are clinically important, since approximately 10% will undergo malignant degeneration.[17]

Vascular Involvement

NF1 is known to affect the intracranial vasculature; however, the incidence of vascular abnormalities is relatively low. The most common vascular abnormalities include regions of stenosis or occlusion, often resulting in secondary moya moya disease. Additional vascular abnormalities include arteriovenous malformations and fistulae, dolichoectasia, as well as an increased incidence of aneurysms.[18]

Moya moya is characterized by progressive occlusion of the supraclinoid internal carotid artery and/or proximal cerebral arteries with development and enlargement of multiple basilar collateral vessels. The term "moya moya" means "puff of smoke" in Japanese and corresponds to the appearance of abnormal collateral vessels depicted on angiography when the entity was first described.[19] On MR angiography, there is loss of flow signal intensity at the carotid terminus and/or proximal cerebral arteries with multiple enlarged basilar collateral vessels, which have a smudgy appearance **(Figure 10)**. This results in the characteristic "puff of smoke" appearance. Patients are at risk of ischemia and subsequent infarcts, especially in a watershed distribution, as well as hemorrhage. Perfusion imaging can be used to monitor disease progression and determine whether or not there is an adequate vascular reserve.

Spinal Manifestations of NF1

Spinal manifestations of NF1 include multiple bilateral intraspinal and paraspinal neurofibromas. Spinal lesions may

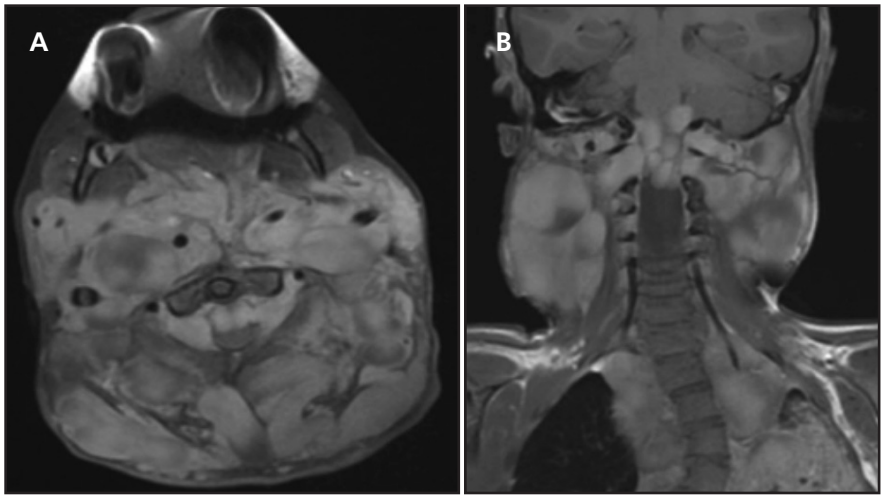

FIGURE 11. *Spinal (plexiform) neurofibromas. Axial (A) and coronal (B) T1 postcontrast images with fat suppression reveal multiple, large, lobulated, enhancing paraspinal, extradural, and intradural extramedullary masses. Cord compression is seen at the cervicomedullary junction. The coronal image (B) shows focal scoliosis within the upper thoracic spine associated with numerous paraspinal masses, as well as foraminal extension and expansion within the upper cervical spine. There is partial collapse of the left upper lobe.*

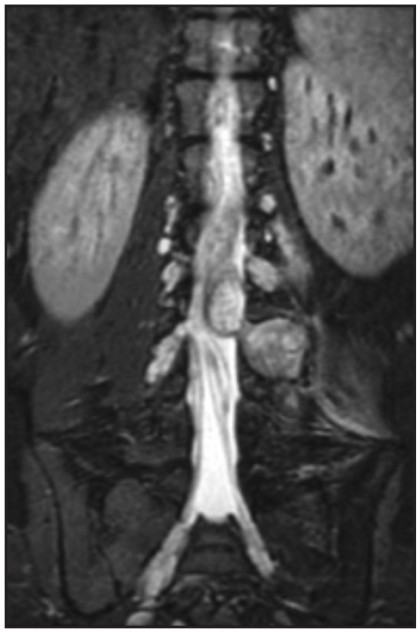

FIGURE 12. *Malignant peripheral nerve sheath tumor. Coronal T2 image demonstrates a large dumbbell-shaped mass extending through and expanding a neural foramen within the lumbar spine on the left. The superior portion of the intraspinal component is ill-defined and increased in size from comparison examination. Multiple NFs are seen at adjacent levels.*

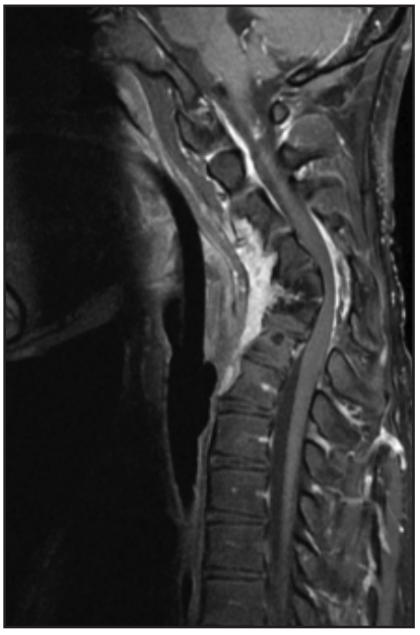

FIGURE 13*. Kyphoscoliosis. Sagittal T1 image with fat suppression reveals bony dysplasia of the mid-lower cervical spine with a focal kyphotic gibbus deformity. There is underlying cord compression at the apex of the bony deformity, as well as abnormal enhancement within the epidural and paraspinal soft tissues, consistent with NFs.*

be intradural, intradural and extradural, or purely extradural. On imaging, smaller lesions are often T2 hyperintense with prominent enhancement, similar to schwannomas. Larger lesions are more heterogeneous in signal intensity and enhancement patterns. As with NFs elsewhere and as discussed above, neurofibromas are more likely than schwannomas to demonstrate the "target sign," which refers to peripheral increased and central decreased T2 signal intensity. Intra- and extradural lesions extend through and expand the bony neural foramina with benign bony remodeling **(Figure 11)**.

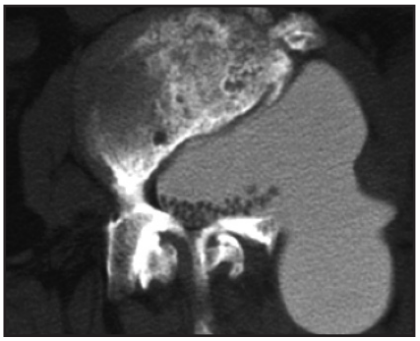

FIGURE 14. *Lateral thoracic meningocele. Axial image from a CT myelogram demonstrates a large meningocele extending through and expanding the left neural foramen and into the adjacent paraspinal soft tissues. Image courtesy of Paul M. Sherman, M.D.*

Although the majority of cases of malignant peripheral nerve sheath tumors occur in the setting of neurofibromatosis, the estimated incidence of malignant peripheral nerve sheath tumors in NF1 patients is approximately 5%.[20] Malignant lesions tend to be larger, more ill-defined and heterogeneous, and grow fairly rapidly with regions of central necrosis **(Figure 12)**. Large retroperitoneal PNFs may be present and are prone to malignant degeneration, which is best characterized by interval growth on subsequent imaging.

Additional spinal manifestations include kyphoscoliosis **(Figure 13)**, dural ectasia with posterior vertebral body scalloping, and lateral thoracic meningoceles. The bony manifestations of NF1 may be due to a primary bony dysplasia and/or bony changes associated with adjacent neurofibromas.[21] Lateral thoracic meningoceles are thought to result from dural ectasia/meningeal dysplasia **(Figure 14)**.

Extra-CNS Manifestations of NF1

Extra CNS and spinal manifestation are beyond the scope of this review, but include cutaneous abnormalities, such as cutaneous neurofibromas and café-au-lait spots; pseudoarthroses and bowing deformities affecting the long bones of the extremities; "ribbon" ribs;

and overgrowth or hypertrophy of all or a portion of a limb. NF1 is associated with an increased incidence of neoplasia, to include pheochromocytoma, gastrointestinal stromal tumors, leukemia, and lymphoma.

Conclusion

Neurofibromatosis type 1 is the most common of the neurocutaneous syndromes, affecting multiple sites and organ systems. CNS manifestations occur in roughly 10%-20% of patients and include regions of myelin vacuolization (NF1 "spots"); multiple tumors, to include gliomas (optic pathway and spinal are the most common) and variants of neurofibromas; bony dysplasia; vascular abnormalities; and dural ectasia. Understanding the characteristic imaging findings, as well as their clinical significance and expected evolution, is critical in correctly interpreting neuroimaging studies in this patient population, and appropriately guiding management decisions.

References

1. Lammert M, Friedman JM, Kluwe L, et al. Prevalence of neurofibromatosis 1 in German children at elementary school enrollment. Arch Dermatol 2005; 141(1): 71-74.
2. Evans DG, Howard E, Giblin C, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Genet A 2010; 152A(2):327-332.
3. Jett K, Friedman JM. Clinical and genetic aspects of neurofibromatosis 1. Genet Med 2010 12(1):1-11.
4. Tonsgard JH. Clinical manifestations and management of neurofibromatosis type 1. Semin Pedatr Neurol 2006; 13:2-7.
5. Williams VC, Lucas J, Babcock MA, et al. Neurofibromatosis type 1 revisited. Pediatrics 2009; 123: 124 -133.
6. Ferner RE, Huson SM, Thomas N, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1 (NF1). J Med Genet 2007; 44: 81-88.
7. Braffman B, Naidich TP. The phakomatoses, part 1: neurofibromatosis and tuberous sclerosis. Neuroimaging Clin North Am 1994; 4:299-324.
8. Sevick R, Barkovich A, Edwards M, et al. Evolution of white matter lesions in neurofibromatosis type 1: MR findings. Am J Roentgenol 1992; 159:171-175.
9. Kornreich L, Blaser S, Schwarz M, et al. Optic pathway glioma: correlation of imaging findings with the presence of neurofibromatosis. Am J Neuroradiol 2001; 22:1963-1969.
10. Nicolin G, Parkin P, Mabbott D, et al. Natural history and outcome of optic pathway gliomas in children. Pediatr Blood Cancer 2009; 53:1231-1237.
11. Listernick R, Charrow J, Greenwald M, et al. Natural history of optic pathway tumors in children with neurofibromatosis type 1: a longitudinal study. J Pediatr 1994 ;125:63-66.
12. Blazo MA, Lewis RA, Chintagumpala MM, et al. Outcomes of systematic screening for optic pathway tumors in children with neurofibromatosis type 1. Am J Med Genet 2004; 127:224-229.
13. Avery RA, Fisher MJ, Liu GT. Optic pathway gliomas. J Neuro-Ophthalmol 2011; 31:269-278.
14. O'Brien WT. Imaging of primary posterior fossa brain tumors in children. J Am Osteopath Coll Radiol 2013; 2(3):2-12.
15. Jacquemin C, Bosley TM, Liu D, et al. Reassessment of sphenoid dysplasia associated with neurofibromatosis type 1. Am J Neuroradiol 2002; 23:644-648.
16. Carra BJ, Sherman PM. Intradural spinal neoplasms: a case based review. J Am Osteopath Coll Radiol 2013 2(3):13-21.
17. Evans DG, Baser ME, McGaughran J, et al. Malignant peripheral nerve sheath tumours in neurofibromatosis 1. J Med Genet 2002; 39(5): 311-314.
18. Rodriguez D, Poussaint TY. Neuroimaging findings in neurofibromatosis type 1 and 2. Neuroimag Clin N Am 2004; 14:149-170.
19. Burke GM, Burke AM, Sherma AK, et al. Moyamoya disease: a summar. Neurosurg Focus 2009; 26(4): 1-10.
20. Lin J, Martel W. Cross-sectional imaging of peripheral nerve sheath tumors: characteristic signs on CT, MR imaging, and sonography. Am J Roentgenol 2001; 176:75-82.
21. Sher BJ, Duncan IC. Neurofibromatosis type 1 – some cranial and spinal manifestations. SA J Radiol 2004; 8(3):32-35.

The views expressed in this material are those of the author, and do not reflect the official policy or position of the U.S. Government, the Department of Defense, or the Department of the Air Force.