Neurofibromatosis type 1 in childhood: diagnosis and complications

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Learning objectives

To describe and illustrate the imaging findings of neurofibromatosis type 1 (NF1) in childhood and some rare complications.

Background

NF1, firstly described by Von Recklinghausen, is a multisystemic and progressive disease and the most common of the phakomatoses, affecting 1 in 2500-3000 live births.

It is an autosomal dominant disorder, even though approximately half of cases are caused by spontaneous (de novo) mutations. NF1 is due to a mutation of the NF 1 gene on chromosome 17, which encodes a protein called neurofibromin, that appears to prevent cell overgrowth by turning another protein that stimulates cell proliferation.

NF 1 has a highly variable expression. Diagnosis is mainly clinical and is made according to the diagnostic criteria established by the National Institutes of Health Consensus Development Conference in 1987. Clinical diagnosis requires the presence of at least 2 of 7 criteria to confirm the presence of NF1. Table 1 on page 2

Images for this section:
### Table 1: Diagnostic criteria for NF 1.

<table>
<thead>
<tr>
<th>Criterion</th>
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<tbody>
<tr>
<td>Six or more café-au-lait macules (&gt; 0.5 cm in children individuals or &gt; 1.5 cm in adults)</td>
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<tr>
<td>Two or more neurofibromas of any type or one plexiform neurofibroma</td>
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<tr>
<td>Axillary freckling or inguinal regions</td>
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<tr>
<td>Two or more Lisch nodules</td>
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<tr>
<td>Optic pathway glioma</td>
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<tr>
<td>A distinctive osseous lesion: sphenoid dysplasia or long bone bowing with or without pseudoarthrosis</td>
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<tr>
<td>A first-degree relative with NF1 diagnosed by using the above criteria</td>
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</table>
Findings and procedure details

The clinical features that are considered diagnostic criteria are as follows:

CUTANEOUS MANIFESTATIONS:

- **Café-au-lait macules**: They are the first cutaneous sign. They may be present at birth or arise during the first months of life, increasing in number up to the 1-2 years of life. The presence of 6 cafe -au-lait macules > 0.5 cm in diameter fulfils one diagnostic criterion. Fig. 1 on page 6

- **Axillary or inguinal freckling**, arising between 3 and 5 years of age.

- **Cutaneous / subcutaneous neurofibromas**. Two or more cutaneous or subcutaneous neurofibromas or just one plexiform neurofibroma fulfils one diagnostic criterion.

Neurofibromas are benign nerve sheath tumors consisting mainly of Schwann cells. They can arise anywhere in the body and may show plexiform distribution.

When located along a spinal nerve root they manifest as intradural extramedullary lesions that may produce mass effect over the spinal cord, which can be displaced. They also can extend along the neural exit foramen producing foraminal widening and showing a typical "hourglass" shape Fig. 2 on page 7. They are well circumscribed lesions, often hyperintense on T2 weighted images and enhancing on postcontrast images.

Plexiform neurofibromas represent a tortuous expansion of a long nerve segment and its branches, with extension into the surrounding tissue. Typical sites of plexiform neurofibromas include the neck, pelvis, and limbs.

About 10 % of plexiform neurofibromas transform into malignant peripheral nerve sheath tumors. They are slightly hyperintense to muscle on T1-weighted images and heterogeneously hyperintense on T2-weighted images, occasionally showing a characteristic hyperintense rim and central area of low signal (target sign) on T2WI. Fig. 3 on page 8 They show an avid contrast uptake after its administration. Neurofibromas can be mistaken for venous malformations in diagnostic imaging. Fig. 4 on page 9

OPTIC MANIFESTATIONS:
- **Lisch nodules**: They are considered pathognomonic of NF1. These lesions are melanocytic iris hamartomas and detected by slit lamp examination. **Fig. 5 on page 10**

- **Optic pathway gliomas**: They are the most common intracranial tumors in NF1 patients, affecting about 15% of the children with NF1. They may be uni or bilateral and arise in any part of the optic pathway. On MRI they are seen as a fusiform thickening and elongation of the optic nerve. They are usually hypointense on T1-weighted images and iso or hyperintense on T2-weighted images. Enhancement is variable. Less than 50% of the patients develop visual symptoms. These tumors can regress spontaneously. **Fig. 6 on page 11**

**SKELETAL MANIFESTATIONS:**

Skeletal dysplasia **Fig. 7 on page 12**, bowing of the long bones and pseudoarthrosis are the features that are considered diagnostic criteria.

**FAMILY BACKGROUND:**

Since neurofibromatosis is an autosomal dominant disease, the presence of an affected parent, son or sibling is another diagnostic criterion.

**There are other typical manifestations that are not considered as diagnostic criteria but are very often seen in these patients:**

**CENTRAL NERVOUS SYSTEM MANIFESTATIONS:**

- **White matter signal alterations** they are the most common neurorradiologic finding in NF1 (43-93% of the patients). They are areas with increased T2 signal and they are usually localised in cerebellum, brain stem, basal ganglia (more likely in globus pallidus), splenium of corpus callosum and periventricular white matter. They typically show no mass effect or enhancement after contrast administration **Fig. 8 on page 13**. Their etiology remains uncertain.

They typically appear from 2 years of age, show a rapid increase in number and size during the 10-12 years of life, and they show regression and eventually disappear during adulthood.
Occasionally they can show mass effect and cause obstructive hydrocephalus secondary to compression of the Sylvian aqueduct Fig. 9 on page 14. Development of malignancy is a rare complication. Radiological follow-up is recommended.

- **Other intracranial gliomas:** They usually are low-grade gliomas and frequently have a more indolent course in NF1 than in general population.

They can arise at any location within the central nervous system, with a predilection for the brainstem and the cerebellum. They are hyperintense on T2 weighted images and show variable enhancement. Fig. 10 on page 15, Fig. 11 on page 16.

**MUSCULOSKELETAL MANIFESTATIONS:**

- **Scoliosis.** Though it is not a diagnostic criterion, it is the most frequent orthopaedic disorder in NF1 patients. It can be secondary to dysplasia in the vertebral bodies or to the presence of intra or paraspinal neurofibromas. Fig. 12 on page 17

**Images for this section:**
Fig. 1: Cutaneous manifestations in NF1: café-au-lait macules (black arrow) and cutaneous neurofibromas (blue arrow).
**Fig. 2:** Paraspinal neurofibroma in a 7-year-old child with NF1. (a) Axial and (b) coronal T2-weighted MR images demonstrate an extramedullary lesion of right C4 nerve root, which is markedly hyperintense and shows the typical "hourglass" (arrow).
Fig. 3: Thoracic plexiform neurofibromas in a 14-year-old patient. Axial T2 weighted MR images show several bilateral and multilevel hyperintense lesions arising from intercostal nerves.
Fig. 4: Pretibial plexiform neurofibroma in a 7-year-old girl. (a) Coronal T1 and (b) axial T2 fat-suppressed MR images demonstrate a lesion in the anterior subcutaneous fat of the left leg, which is hypointense on T1WI and hyperintense on T2 with a low-signal-intensity central target sign.
Fig. 5: Lisch nodules in patient with NF1.
Fig. 6: Optic glioma pathway. (a, b) 5-year-old child with NF1. (a) Axial proton density and (b) coronal T1 weighted-images show a marked thickening and elongation of the orbital portion of the right optic nerve, causing proptosing. (c, d) MRI of a 3-old-year boy. (c) Axial T2 weighted image demonstrates thickening of the left optic nerve. Furthermore, there is a plexiform neurofibroma on the ipsilateal eyelid (arrow head). (d) Contrast-enhanced T1 weighted image: left intracranial optic nerve glioma demonstrating avid enhancement.
Fig. 7: Sphenoid wing dysplasia in 3 year-old-patient. Axial T2WI shows signal intensity changes on the left greater wing of sphenoid compatible with osseous dysplasia. In addition, it shows a plexiform neurofibroma on the left eyelid (arrowhead). Eyeball is increased in size in relation to congenital glaucoma.
Fig. 8: Supra and infratentorial hyperintensities (a,b) Axial FLAIR MR images: (a) high signal intensities in both globus pallidus and hippocampus, (b) left frontal periventricular white matter, both globus pallidus and thalamus. (c,d) Coronal T2 FLAIR: high signal intensity areas in both globus pallidus (c) in pons, left middle cerebellar peduncle and medulla.
**Fig. 9:** Hydrocephalus in an 8-year-old patient with NF1. T2 FLAIR MR images: (a,b,) high signal hyperintensities in midbrain that exert mass effect over Sylvian aqueduct, causing hydrocephalus of recent diagnosis onset, visible on (c). (d) Brain MRI three years before showing a normal ventricular size.
Fig. 10: Hypothalamic glioma in a 3-year-old patient. (a) Sagital T1, (b) axial T2 axial, (c) coronal FLAIR(d) and coronal contrast-enhanced T1 images. There is an enlargement of the hypothalamic region, showing high signal intensity on T2WI and enhancing on post-contrast T1 image.
Fig. 11: Hypothalamic glioma in a 5-year-old patient with NF1. (a) Sagital and (b) axial T1WI show enlargement of the hypothalamic region with no enhancement after contrast administration, compatible with low-grade glioma.
Fig. 12: Teleradiography of the spine of a 14-year-old girl with NF 1, showing a several right convex thoracic scoliosis.
Conclusion

Although there are more clinical than radiologic diagnostic criteria, radiologists should know them and be aware of the possible complications of NF 1 for an accurate diagnosis and a right follow up strategy.

Personal information

References


