Learning objectives

Illustrate and describe the characteristic lesions on MRI of neurofibromatosis type I, affecting both central and peripheral nervous system.

Propose a radiological follow-up management for children with NF-1.

Background

Neurofibromatosis type I is included in neurocutaneous syndromes or phacomatosis, of which it is the most frequent with an approximate incidence of 1/3000 live births\(^1\).

This disorder, also known as Von Recklinghausen’s disease, is caused by a mutation in the gene encoding the protein neurofibrin, located on chromosome 17. It has an autosomal dominant inheritance, although approximately 50% of cases are originated of new mutations\(^2\).

The clinical spectrum is highly variable, but its typical features are cafe-au-lait spots, axillary and inguinal freckles, Lisch nodules and neurofibromas.

Diagnosis is currently based on the clinical criteria agreed by the American NIH in 1988\(^3\). For the diagnosis of NF-1 there must exist at least two criteria (Fig. 1 on page 2). The definitive diagnosis is usually established by these criteria at around 4 years old, and by 11 years of age in 95% of cases\(^4\).

These criteria do not include imaging findings, although some authors\(^4\) believe some imaging criteria should be included, such as T2 sequence hyperintensities in MRI which correspond to areas of myelin vacuolation, due to its high frequency in these patients.

Images for this section:
### DIAGNOSTIC CRITERIA NF-1 (NIH)

<table>
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<th>Criteria</th>
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<tr>
<td>- Six or more café-au-lait macules</td>
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<td>- Freckling in the axillary or inguinal regions</td>
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<td>- Optic glioma</td>
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<td>- Two or more neurofibromas of any type or one plexiform neurofibroma</td>
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<td>- Two or more Lisch nodules</td>
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<td>- A distinctive osseous lesion such as sphenoid dysplasia or tibial pseudarthrosis</td>
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<td>- A first-degree relative with NF-1</td>
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**Fig. 1: DIAGNOSTIC CRITERIA FOR NF-1 (NIH)**
Imaging findings OR Procedure details

The affection of the CNS is a significant cause of morbidity in patients with NF-1. Imaging techniques, mainly MRI, are fundamental for management and monitoring of the disease. The most common findings are:

- **Areas of myelin vacuolization**

These lesions are observed as areas of hyperintense signal in T2 weighted MR images, and are present in 70% of patients with NF-1\(^5\). They are not usually observed in children under 2 years, and they increase in size and number until adolescence, when they frequently become smaller or even disappear. These lesions do not show mass effect or enhancement after the administration of gadolinium. They might be hyperintense in T1 weighted images, so it is advisable to obtain T1w sequences before contrast. The most common location is in the basal ganglia, particularly the globus pallidus, followed by the thalamus, brainstem, hippocampus and cerebellum (Fig. 2 on page 6).

- **Optic pathway gliomas**

Its incidence is estimated at 15%; only half of them are symptomatic\(^6\), usually in the first decade of life. Those that only affect optic nerves are usually asymptomatic, or cause loss of vision that normally does not progress. If there is chiasm and hypothalamus extension, precocious puberty can be associated. Optic pathway gliomas in NF-1 are low grade, but may progress to high grade malignancy. In MRI they present as thickening of the optic nerves, chiasm and/or optic tracts depending on the extent of the tumour. They are normally isointense to brain parenchyma on T1 and iso- or slightly hyperintense on T2. After the administration of intravenous gadolinium they rarely enhance, although there may be faint, diffuse or focal enhancement (Fig. 3 on page 7).

- **Other gliomas**

In patients with NF-1 there is increased incidence of astrocytomas compared to the general population, but with more indolent disease course and better prognosis. They are generally pilocytic astrocytomas or other low-grade gliomas. In addition to the optical path already commented, they may occur more frequently than in the general population in other locations (Fig. 4 on page 8).
They are usually hypointense in T1 weighted sequences and hyperintense on T2, with possible enhancement after the administration of contrast. If enhancement is present in a small lesion, we should suspect glioma instead of an area of myelin vacuolation typical of these patients. They often show little or absent perilesional oedema and mass effect.

- Vascular dysplasia

The most common cerebral vascular involvement in NF-1 is the result of proliferation of the intima with subsequent stenosis or occlusion of the internal carotid arteries and proximal portions of the middle and anterior cerebral arteries. Sometimes Moyamoya phenomenon may be observed with enlarged lenticulostriate arteries as collateral circulation (Fig. 5 on page 9). There may also be vascular involvement in other locations of the body, such as renal arteries. NF-1 is the second cause of renal artery stenosis after fibromuscular dysplasia in children\(^7\), so it is suggested to control hypertension in these patients.

- Neurofibromas

Neurofibromas are benign tumours that arise from the nerve sheath; they can have a paraspinal location, cutaneous and subcutaneous, visceral or along nerves. Cutaneous neurofibromas appear in up to 95% of adults with NF-1. Plexiform neurofibromas are typical of this disease, affecting approximately 30% of patients\(^8\). Up to 10% of plexiform neurofibromas have high risk of malignant transformation. Neurofibromas are shown in RM as circumscribed lesions iso- or discretely hyperintense to muscle on T1-weighted sequences, with "target" signal intensity on T2 (ring of hyperintensity and hypointense center due to central fibrocollagenous content) and heterogeneous enhancement (Fig. 6 on page 10, Fig. 7 on page 11, Fig. 8 on page 12, Fig. 9 on page 13).

- Other abnormalities in NF-1

There are other manifestations valuable in imaging like sphenoid bone dysplasia. This may cause herniation of the temporal lobes into the orbit, and is generally associated with orbital neurofibromas.

**MRI PROTOCOLS AND FOLLOW-UP IMAGING**

Brain MRI for evaluation of NF-1 should always include T2 FLAIR sequence and orbital study with a minimum thickness of 3 mm. In our centre, for patients with suspicion of NF-1 or follow up, we usually use the sequences described in the following table (Fig.
Whether there are brain focal lesions or optic pathway involvement, administration of intravenous gadolinium is recommended to assess enhancement of possible gliomas. If there is clinical or radiological suspicion of cerebral vascular involvement, study should be completed with arterial MRA of the circle of Willis using 3DTOF technique.

If growth is observed in plexiform neurofibromas, neurofibromas are painful or produce mass effect, MRI studies should include: T1 weighted and STIR sequences in planes depending on the location of the tumour and T1 fat-saturated imaging after administration of gadolinium.

NF-1 has a wide range of clinical behaviour and although there is no specific treatment, it is important to detect complications (Fig. 11 on page 15) at an early stage, so periodic reviews are recommended. We should consider that neurological and ophthalmologic examination in these patients can be significantly restricted by the condition of the patient (age, mental retardation, etc.), being the possible presence of optic pathway gliomas the (questionable) indication of control with brain MRI.

This indication of brain MRI is controversial; there are authors\(^9\) that consider there is no need for follow-up studies in asymptomatic patients with optic track glioma.

In our centre the indication of imaging depends on periodic clinical evaluation and the need or not for sedation to perform the MRI. As a general rule, an indication of neuroimaging is established every two years in the first 5-6 years of life if a complete eye examination cannot be performed. If the presence of optic pathway glioma is confirmed, control is performed every 6 months during 1 year, and one MRI per year until puberty. Afterwards, every two years. Visual evoked potentials do not replace MRI in the diagnosis and monitoring the evolution of optic pathway glioma.

MRI is not routinely indicated in other locations, except clinical findings suggestive of complications of the disease.

Images for this section:
Fig. 2: AREAS OF MYELIN VACUOLATION. a) and b) Axial T2 FLAIR sequence. Hyperintensities in both hippocampi, pallidum nuclei and thalami. In a) thickening of the chiasm and left optic tract (arrow) is shown. c) Coronal T2 weighted image. Hyperintensity in both cerebellar dentate nuclei. d) T1w MTC axial image in the same localization than 1b. The areas of myelin vacuolation in palidum nuclei and thalami show significant T1 hyperintensity.
Fig. 3: OPTIC PATHWAY GLIOMA. a) Coronal T1 weighted sequence. Asymmetry in the caliber of optic nerves due to thickening of the left nerve caused by glioma (arrows). b) Coronal T1w image. Glioma affecting the left hemichiasm (arrow). c) Axial STIR. Thickening of the cisternal portion of the right optic nerve (arrow). d) Axial fat-saturated T1w after intravenous gadolinium administration. Glioma of the left hemichiasm and optic tract, without significant enhancement.
Fig. 4: Right frontal GLIOMA in patient with NF-1. a) Axial T2 FLAIR image. Hyperintense defined focal tumor of 2 cm diameter with minimal mass effect and without perilesional edema. b) Axial T1 MTC after administration of gadolinium. The lesion shows enhancement, suggestive of glioma.
Fig. 5: CEREBRAL VASCULAR DYSPLASIA. a) Severe stenosis of the left middle cerebral artery (arrow). b) 3D T1 sequence after administration of gadolinium shows prominent vessels (arrowheads) at location lenticulostriate arteries (Moyamoya phenomenon). c) and d) Signs of chronic hypoperfusion. In c) hyperintense signal is observed in cortical sulci in T2 FLAIR with enhancement after administration of gadolinium (d).
Fig. 6: Multiple NEUROFIBROMAS. Coronal T2 images in (a) and STIR (b) of the chest and upper abdomen. Many paravertebral, intercostal, and a bilateral subcutaneous tumors and left hemithorax mass are observed; they are lobulated and with "target" appearance: hyperintense with central hypointensity, typical of neurofibromas.
**Fig. 7:** NEUROFIBROMA in the right arm. a) Sagittal T1 weighted image. A subcutaneous soft tissue tumor in axillary region and internal part of the arm is noted. It is lobulated and isointense to muscle. b) Sagittal STIR. The lesion shows marked hypersignal intensity. c) Sagittal T1 with fat suppression after administration of intravenous gadolinium. The neurofibroma shows diffuse and irregular enhancement.
**Fig. 8:** Left facial NEUROFIBROMA. Hyperintense soft tissue mass in STIR sequence (a and c) with intermediate signal on T1 (b and d). It affects the subcutaneous tissue and parotid, sublingual and masticator space of the left side.
**Fig. 9:** Sciatic NEUROFIBROMA. T1w axial image (a) and fat-suppressed T1 after administration of gadolinium (b) at the middle third of the right thigh in a patient with NF-1. An enlarged sciatic nerve (arrows) is observed with intense contrast enhancement, consistent with neurofibroma.
## HNJS Protocol for Brain MRI in NF-1

| Routine Brain Protocol including | Sagittal T1 FLAIR  
|                                | Axial T2 FLAIR  
|                                | Coronal T2  
|                                | Axial T1 MTC  
|                                | Diffusion B1 and B1000 |
| Orbital MRI study (3mm thickness) | Axial or coronal T1  
|                                | Coronal or axial STIR |
| If focal lesions or optic pathway affected: administration of i.v gadolinium | 3D T1 post-contrast  
|                                | Axial T1 MTC post-contrast  
|                                | Axial or coronal fat-suppressed T1 of the orbit |

**Fig. 10:** Hospital Infantil Universitario Niño Jesús Protocol for Brain MRI in NF-1
### Complications in NF-1

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<th>SYSTEM</th>
<th>COMPLICATIONS (% Frequency)</th>
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<tr>
<td><strong>CENTRAL NERVOUS S.</strong></td>
<td>Learning difficulties (30-60%), IC &lt;70 (4-8%), epilepsy (6-7%), aqueductal stenosis (1.5%), others: deficit secondary to tumors, medullary compression</td>
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<tr>
<td><strong>PERIPHERAL NERVOUS S.</strong></td>
<td>Malignant tumors of peripheral nerves (2-5%)</td>
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<tr>
<td><strong>OUTANEOUS</strong></td>
<td>Cosmetic concern, prunus</td>
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<tr>
<td><strong>CARDIOVASCULAR</strong></td>
<td>Hypertension (renal artery stenosis 2%)</td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td>Bleeding or obstruction due to neurofibromas, constipation</td>
</tr>
<tr>
<td><strong>ENDOCRINE</strong></td>
<td>Short stature, neuroendocrine disorders due to hypothalamic tumors, abnormal puberty, pheochromocytoma (2%)</td>
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<tr>
<td><strong>ORTHOPEDIC</strong></td>
<td>Scoliosis (10%), bowing of long bones and/or pseudoarthrosis (2%), bone cysts, fibroids, bone overgrowth, osteoporosis</td>
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<tr>
<td><strong>VISUAL</strong></td>
<td>Optic malformations, optic glioma (15%)</td>
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**Fig. 11:** Complications in NF-1
Conclusion

MRI is the fundamental imaging technique in detection and follow-up of lesions in patients with NF-1.

References


9.- Blanchard G et al. La realisation systématique de l’imagerie par resonance magnétique cérébrale a a-t-elle un intérêt chez l’enfant attaint de neurofibromatose de type 1? - Usefulness of systematic brain magnetic resonance imaging in children with neurofibromatosis type 1?. Arc Ped.2009;2359:1-6.

Personal Information