ELEPHANTIASIS NEUROMATOSA IN NEUROFIBROMATOSIS TYPE I

MRI findings with review of the literature

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SUMMARY

We report the case of a patient with NF-1 who presented with gross elephantiasis neuromatosa of her right leg. Prior to plastic surgery, Magnetic Resonance Imaging and Angiography (MRI and MRA) were performed to provide a detailed assessment of the extension as well as the vascular and muscular involvement of the neurofibroma.

Key words: neurofibromatosis, magnetic resonance (MR), elephantiasis neuromatosa.

RÉSUMÉ

Eléphantiasis neuromatosa et neurofibromatose de type I. Aspect en IRM et données de la littérature


Mots-clés : Neurofibromatose, IRM, éléphantiasis neuromatosa.

INTRODUCTION

Neurofibromatosis is a phakomatosis or neurocutaneous syndrome with autosomal dominant inheritance that affects the neuroectoderm as well as the mesoderm with a frequency of approximately 1 in 3,000 births [11]. Neurofibromatosis is classified into two distinct types that differ in clinical and genetic characteristics [10]: neurofibromatosis type 1 (NF-1), known previously as Von Recklinghausen disease, a peripheral neurofibromatosis and neurofibromatosis type 2 (NF-2), a central neurofibromatosis.

Cutaneous lesions, skeletal abnormalities and multiple nerve sheath tumors characterize NF-1. Three types of neurofibromas are found in patients with NF-1: the most common is the localized neurofibroma, the least common is the diffuse neurofibroma, and the most characteristic lesion of the disease is the plexiform neurofibroma. This lesion, in its most extreme form, may involve an entire extremity with gigantic hypertrophy of the skin, soft tissues and the underlying skeleton [7]; it has been described as a bag of worms and may become very large and deforming, therefore, named as “elephantiasis neuromatosa” by Virchow [11].

CASE REPORT

A 41 year-old woman with known neurofibromatosis type 1 presented to our hospital in December 2001 for excision of a recurrent large and disabling right leg plexiform neurofibroma which had recently undergone skin ulceration. The right leg plexiform neurofibroma, slowly increasing in size since childhood, necessitated debulking surgery in 1991. However, postoperatively, the lesion continued to grow and in December 2001, gross limb enlargement became so disfiguring that it resulted in the patient’s partial inability to walk. Additionally, the patient had also known optic chiasm glioma that was treated in 1994 with radiotherapy that left her with partial visual field cut (figures 1a and 1b).

Physical examination revealed multiple cutaneous neurofibromas with “café au lait” spots over her trunk. The right leg was markedly enlarged, predominantly involving the calf with several superficial varicosities and skin ulcerations posterior to the medial malleolus.

MRI study with MR angiographic sequences was performed prior to surgery to determine the relationship between the lesion and the adjacent neurovascular and muscular structures. The MRI study of both legs was performed with a body coil on a vision 1.5 T imaging system (Siemens Medical Systems, Erlangen, Germany). Pre and post-contrast fast spin-echo (FSE) T1 weighted imaging (T1WI) (TR=740, TE=12), FSE T2 weighted imaging (T2WI) (TR=2000, TE=50) and STIR sequences (TR=5,993, TE=29, TI=180) in the coronal and the axial planes were also performed. MR angiography was then performed from the level of the iliac arteries to the proximal ankle using a three-dimensional (3D) gradient-echo fast imaging sequence acquired in the coronal plane. Images were obtained before and immediately after intravenous injection.
of gadolinium-DOTA (0.2mmole/kg at 2ml/sec) using a power injector. Two consecutive MRA sequences were obtained in the arterial and venous phases. The total examination time was approximately 30 minutes. Vascular reformations were subsequently performed using maximum-intensity-projection (MIP) imaging processing.

All MRI sequences demonstrated extensive soft tissue abnormalities and hypertrophy of the right leg, extending from the knee to the ankle which measured approximately $35 \times 27$cm in transverse dimension at its maximum diameter, four times larger than the left side; the remainder of the right lower limb appeared normal. The mass infiltrated the subcutaneous fat and multiple muscular compartments limiting differentiation between individual muscles. The mass showed iso- to high signal intensity on non-enhanced T1WI when compared to muscle and relatively high signal intensity on T2WI (figure 2a). The dynamic contrast-enhanced MR angiographic sequences demonstrated hypertrophy of the right lower limb vessels; all main arteries were enlarged but patent (figures 3a and 3b). There were multiple tortuous collateral branches that infiltrated the soft tissues of the calf and showed early arterial enhancement. The post contrast images, in the venous phase, showed multiple small lakes of contrast accumulation within the soft tissue mass with several enlarged draining veins, suggesting progressive and extensive capillary pooling of contrast throughout the hypervascularised mass (figure 3c). Post-contrast T1WI with fat saturation (figures 2b, 2c and 2d) demonstrated enhancement of more than 90% of the mass. The right tibia and fibula showed hypertrophy of the marrow and irregular, thickened cortices. No bone destruction was seen. The surgeons were notified about the hypervascularity of the lesion, to avoid certain areas with abnormal vessels. The patient had partial tumor resection and 3.8kg of the lesion was removed. The histopathologic evaluation revealed neurofibromatous tissue with no evidence of malignancy. The patient is doing well 5 months after surgery.

DISCUSSION

NF-1 is a hamartomatous disorder with the genetic defect localized to chromosome 17. The criteria for clinical diagnosis include the presence of a congenital or developmental neurofibroma (>2 simple or 1 plexiform type), “café-au-lait” spots (>6 in number, >5mm in diameter in a child or >15mm in an adult), axillary or inguinal freckles, pigmented hamartomas of the iris (Lish nodules), skeletal abnormalities (sphenoid dysplasia, cortical thinning), optic gliomas and an affected first-degree relative. The presence of two of the seven criteria establishes the diagnosis of NF-1 [11].

The discussion of multiple peripheral nerve tumors in neurofibromatosis is beyond the goal of this paper, but it would be useful to distinguish between neurofibroma and schwannoma that used to be the characteristic tumor of Neurofibromatosis type II.

In schwannomas, Schwann cells are the only proliferating cell type, mucopolysaccharide matrix is scanty or absent, and nerve fascicles are displaced rather than assimilated within the tumor. Multiple schwannomas are seen in approximately 5% of cases and are characteristic of Neurofibromatosis type 2 (NF2). They are round or lobulated, well delineated encapsulated and arise eccentrically from their parent nerve. They are considered resectable tumors,
where enucleation can be performed, and preserving the nerve continuity.

Neurofibromas are unencapsulated tumors, poorly circumscribed that diffusely infiltrate the nerve and the adjacent fat and muscle. As a result neurofibromas are usually unresectable tumors, where tumor resection is impossible without sacrificing the nerve tissue. Plexiform neurofibromas contain a mixture of Schwann cells, fibroblasts, reticulin and collagen fibers and a loose mucoid matrix interspersed between axons of the parent nerve. They typically affect a body region, usually a limb, but may also involve the trunk or bladder. Associated bone dysplasia is often encountered secondary to chronic hyperemia or as part of the mesodermal dysplasia [1]. Fusiform enlargement of multiple nerve fascicles and branches is characteristic. In contrast to schwannomas, neurofibromas rarely undergo fatty degeneration, cystic necrosis or hemorrhage. The MR appearance of a neurofibroma is variable. A solitary neurofibroma is a well-defined mass, isointense on T1WI, hyperintense on T2WI. Most of the deep-seated neurofibromas and only the benign neurofibromas show the characteristic target appearance, but some of the more peripheral neurofibromas, the large neurofibromas have a mixed signal intensity [10]. The target appearance represents geographic difference between the histologic zones of neurofibroma. The high signal intensity seen in the peripheral zone is likely related to the high water content of the myxomatous tissue [9], and the central low signal intensity is probably related to T2 shortening caused by the dense fibrocollageneous tissue. Plexiform neurofibromas characteristically show diffuse irregular infiltration into adjacent muscle and fat [4, 11]. This tumor has a locally aggressive behavior but the infiltrative pattern is not indicative of malignancy and has no histologic evidence of anaplastic or mitotic features [10]. It exhibits a heterogeneous hyperintense pattern on T2WI, reflecting the high water content of the myxoid matrix [12], and isointense signal to muscles on T1WI, although some neurofibromas may be hypo- or hyperintense to muscle on T1WI. On MRI schwannoma is sharply delineated, heterogeneous; two thirds of schwannomas are slightly hypointense to brain on T1WI, one third are isointense. Most schwannomas have increased signal intensity on T2WI and show intense enhancement following contrast administration [5].
The incidence of sarcomatous degeneration in neurofibromas has been estimated to range from 2 to 16%, whereas malignant transformation of schwannomas is extremely rare [6].

Plexiform neurofibromas are often hypervascular and can lead to massive spontaneous hemorrhage or severe bleeding during surgery. Studies have suggested that there are two varieties of plexiform neurofibroma: one variety with normal vasculature and the other demonstrating hypervascularity with abnormal blood vessels that are friable secondary to myxomatous degeneration. Those abnormal vessels are an integral part of the lesion along with the neural and fibrous elements constituting a hemangio-neurofibroma.

The radiological modalities most often used in analyzing neurofibroma include computed tomography (CT) and MRI. Although CT is rarely helpful in making a specific diagnosis, it can provide a precise evaluation of the bone lesion, the extent of the soft tissue lesion; however, it is by far inferior to MRI in soft tissue contrast resolution and the visualization of tissue planes. Color Doppler ultrasound is very limited in the evaluation of a large mass, extending outside the range of the probe. Angiography is used mainly to assess the vascular supply of the tumor, the abnormal tumor vessels and to locate vessels suitable for preoperative intra-arterial embolization. However, preoperative intra-arterial embolization of plexiform neurofibroma is poorly discussed in the literature with no definite indication; consequently no attempt for embolization was undertaken for our case. The surgery team decided to perform a surgical resection because of the serious functional and cosmetic problem caused by the bulky mass and a preoperative MRA was used instead of conventional angiography to demonstrate the regional vascular anatomy and thus permit a plan to be drawn up for the resection procedure.

Dynamic contrast-enhanced 3D MRA represents a recent advance in imaging with rapid acquisition of high-quality angiographic images that permit a free choice of imaging planes and phases delineating the arterial and venous supplies, visualization of the abnormal changes of the vasculature in the affected limb, important landmarks in surgical planning. Post-contrast images show the extensive capillary pooling of contrast throughout the soft tissue mass corresponding to the plethora of abnormal vessels in “the haemangio-neurofibroma” and the large ectatic veins [12], which is a pathognomonic finding of a hypervascularised plexiform neurofibroma [7]. It should be emphasized that MRI and MRA may assist not only in the correct diagnosis of neurofibroma but also in imaging the vasculature of a plexiform neurofibroma which is essential in distinguishing between the two types, for proper surgical planning. Indeed, the surgical resection of this neurofibroma was performed under the placement of a tourniquet above the knee to garrote the calf vessels and thus decrease hemorrhage during the resection.

The common differential diagnoses in this case are other soft tissue tumors causing elephantiasis such as filariasis, macrodystrophia lipomatosa, lymphangiomatosis, vascular malformation such as hemangioma and massive subperiosteal hematoma described in a case report by Steenbrugge et al. [8].

Other dysplasia syndromes with hamartomatous disorders like Proteus syndrome and Klippel-Trenaunay-Weber syndrome should also be considered. The Proteus syndrome is a rare complex hamartomatous condition with postnatal overgrowth of many tissues.

**Fig. 3.** Dynamic contrast-enhanced MR angiographic images acquired in the coronal plane at the level of the right calf with vascular reconstruction using MIP. The arterial phase demonstrates enlargement of all main arteries of the right lower limb (a) and multiples tortuous collateral branches (b). c) Delayed post-contrast image shows multiples small lakes of contrast accumulation (capillary pooling within the soft tissue) with multiple enlarged draining veins.

**FIG. 3.** ARM dynamique injecté. Image acquise dans le plan coronal au niveau du mollet droit. Reconstruction MIP. Dilatation des artères principales du membre inférieur droit (a) et branches collatérales tortueuses (b). Images retardées (c) : multiples lacs de produit de contraste avec élargissement des veines de drainage.
It is characterized by partial gigantism of the hands, feet, or both; plantar hyperplasia; hemangiomas of the spleen, lipomas, lymphangiomas, varicosities, verrucous epidermal nevi, macrocephaly, cranial exostosis, asymmetry of the limbs because of long bone overgrowth and aggressive lipomatoses in different locations. Essentially, any tissue or organ can manifest overgrowth including the spleen, kidneys, thymus, gut and the brain as hemimegaly. The syndrome was given the name Proteus, which refers to the mythical Greek sea god who was capable of changing his bodily shape to avoid capture [3]. Proteus syndrome can be ruled out in this patient on the basis of the absence of exostoses, epidermal connective tissue nevi and the presence of three diagnostic criteria for NF I.

A triad of symptoms characterizes klippel-Trenaunay-Weber syndrome, also known as nevus vasculosus hypertrophicus: venous varicosities, extensive nevus flammeus or cutaneous hemangiomas, and hypertrophy of soft tissue and bones. Patients usually present during infancy with cutaneous hemangiomas; over time, chronic venous insufficiency develops, leading to various skin manifestations. Bone and soft-tissue hypertrophy develop later in life. The lower limb is the site of malformation in approximately 95% of patients. The hypertrophy involves the length as well as the circumference of the involved extremity and is caused by local hyperemia and venous stasis secondary to the vascular anomaly [2]. In this case, Klippel-Trenaunay-Weber syndrome can be ruled out given the absence of cutaneous hemangioma, absence of bone and muscle hypertrophy and the presence of diagnosis criteria for NF I.

RÉFÉRENCES