New Findings in Lipomatosis of Nerve: A Review of 52 Cases Evaluated at One Institution

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MAYO CLINIC

Background

Lipomatosis of nerve (LN) is part of a spectrum of adipose lesions of nerves[1], wherein the nerve is enlarged by fibrofatty proliferation within the epineurium[2, 3]. This has been variously called lipofibromatous hamartoma, fibrolipomatous hamartoma, intraneural fibrolipoma, fibrofatty tumor, among other names, and was recently redefined by the World Health Organization as lipomatosis of nerve[4].

LN is a histologically benign condition which may be variably associated with overgrowth phenomena within the nerve territory, such as macrodactyly[5]. The combination of massive enlargement of nerve, adipose tissue and skeletal overgrowth is routinely referred to as macrodystrophia lipomatosa (MDL) [6]. One of the unique features of this associated overgrowth is that it respects the territory of a major peripheral nerve[7], unlike other overgrowth syndromes like Proteus or congenital lipomatous overgrowth, vascular malformations, and epidermal nevi (CLOVE syndrome). LN is most commonly found in the median nerve as well as digital nerves of the hands or feet.

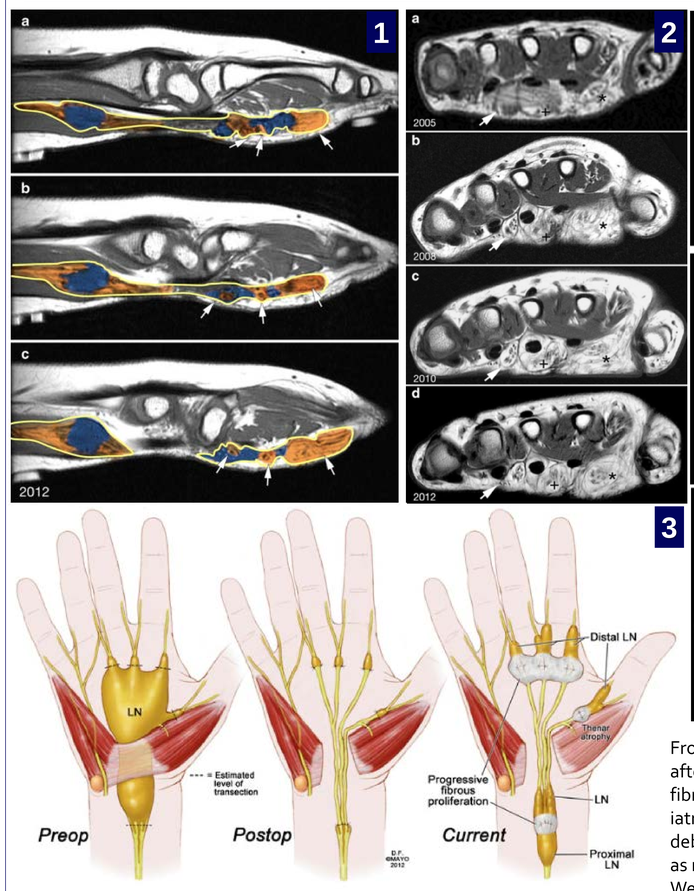
We sought to characterize the clinical manifestations of this disorder through review of cases at a single institution.

Methods

Electronic records from our institution's clinical patient database from 1992 to 2012 were searched for candidates for study inclusion. Patients were found by using the diagnosis keywords "lipofibromatous hamartoma", "fibrolipomatous hamartoma", "macrodactyly", "hyperostotic" and "Proteus-like", as many practitioners may misdiagnose LN as a different hypertrophy syndrome. All records containing some or all of these terms were reviewed to determine patients to be included in this study. Additionally, patients known or suspected to have LN from paper records or other materials predating 1992 were included for possible inclusion. Exclusion criteria included patients that were found to have dermatologic findings including café-au-lait spots, axillary freckling, cerebriform connective tissue nevi, vascular or lymphatic nevi; a history of arteriovenous fistulae or malformations or visceral involvement not limited to lipomas; or pathology, genetic mutation analysis or pedigree consistent with neurofibromatosis or other heritable disorder.

Medical records were reviewed and coded for nerve territory involvement; presence or absence of bone overgrowth, soft tissue overgrowth or other deformities; location of macrodactyly and, if macrodactyly present, which digital nerves were afflicted. Patient histories regarding date(s), indication(s), type(s) of surgery, outcome(s) and complication(s) and pathology report(s) were collected.

Fig 1: Fibroproliferative neuromas associated with LN



A patient referred to our institution had previously undergone resection and sural nerve grafting of the distal median nerve in an attempt to remove LN. We have followed his recovery with serial MR imaging over a five year period and documented the redevelopment of LN along the intact, native median nerve as well as the sural grafts. We also noted the progressive enlargement of fibrous neuromas at the proximal and distal graft coaptation sites[8].

Figure 1: Contiguous sagittal imaging depicts regions of fibrous scar and lipomatosis of the median nerve, sural nerve grafts and digital nerves (yellow outline). The median nerve demonstrates lipomatosis of both the median nerve proximal, and the sural grafts distal, to the proximal coaptation, as well as lipomatosis of the digital nerves (orange overlay). Fibroproliferative response at the proximal and distal coaptation sites (blue overlay). Arrowheads (left to right) point to the radial digital nerve to the thumb, ulnar digital nerve to the thumb and the radial digital nerve to the index finger. **Figure 2:** Progressive lipomatosis of the digital nerves (radial digital nerve to index, asterisk; second common digital nerve, plus; third common digital nerve, arrowhead). Serial axial T1-weighted images at the metacarpal neck. There is progressive hypertrophy of the adipose elements within the proper digital nerves to the radial side of the index as well as the common digital nerves to the second and third webspaces. Panel A, 2004; panel B, 2008; panel C, 2010; panel D, 2012. **Figure 3:** Artistic representation of the patient's LN prior to surgery (based on 2005 MRI), presumed extent of resection (based on images from the published case report and operative report), and current architecture of the median nerve (based on 2012 MRI)

From this case, as well as historical reports of recurrence after nerve resection, we hypothesized that abnormal fibroproliferation may accompany surgery that involves iatrogenic injury to the nerve, e.g., nerve resection or nerve debulking, rather than surgery outside the epineurium, such as nerve decompression.
We found that mass-like neuromas were found on MR imaging, which correlated to the degree of iatrogenic injury to the nerve ($p<0.001$). Fascinatingly, these neuromas grew in volume over serial imaging. There was also a high incidence of hypertrophic scarring of the skin incision (21.3%) [9].

Figure 4: Panels A &B: Fibroproliferative neuroma (arrows) arising from the radial digital branch to the thumb following resection 27 years previously, axial (A) and sagittal (B) T1-weighted imaging Panels C & D: Fibroproliferative neuroma (arrows) in the course of the digital nerve branches to the index finger imaged 6 years after ray resection of the index, axial (C) and coronal (D), T1-weighted fast-spin echo. Note the classic appearance of lipomatosis of nerve depicted in median nerve (asterisk), partially obscured by plane of imaging, and in the superficial radial sensory branch (plus). Panels E & F: Fibroproliferative neuroma along the tibial nerve 3 months after decompression at the soleus sling for tibial neuropathy and fascicular biopsy. Focal fibroproliferation at the proximal end of the fascicular biopsy (D, T1-weighted fast spin echo) and focal contrast enhancement (E, spoiled gradient recall).

Results and conclusions

Review of medical records discovered 52 cases of LN, based on either pathologic review or pathognomonic appearance on MRI.

Detailed investigation into several clinical questions revealed the following conclusions:

- Surgical injury of LN appears to be strongly associated with the development of fibroproliferative neuromas. This was not seen in decompression surgeries for LN.
- Serial MR imaging reveals progressive enlargement of LN. The rate of growth was more profound in youth but also occurred in early adulthood.
- LN is not merely a finding in the distal extremities, but may be present in axial nerves, with resultant pleotropic effects
- LN may be associated with various forms of osseous overgrowth, ranging from joint related exostoses to osteochondromas of appendicular long bones.

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Fig 2: Growth of LN

The natural history of LN is not known. We sought to evaluate whether LN grew over time by volumetrically analyzing serial MRI.

With 10 patients who had serial MRIs (greater than 2 years apart) of the same anatomical region of LN, we found that LN grew in the majority of patients. The highest growth rates approached 10% per year; growth greater than 5% per year correlated with surgical intervention.

Growth was most impressive in younger patients, even after adjusting for skeletal growth. However, growth occurred even into the fourth decade of life; suggesting that LN may remain a dynamic disorder throughout life [10].

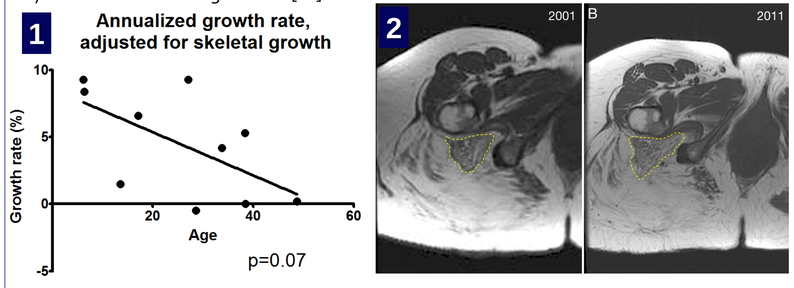

Figure 1: Graphic representation of annualized growth rate of LN (adjusted for skeletal growth) versus age at initial scan. **Figure 2:** Significant growth of LN : Axial T1 MR noncontrast imaging of the right proximal thigh , yellow outlines drawn around the epineurium of the sciatic nerve at the anatomical landmark of the ischial tuberosity (*). Imaging from 2001 shown in panel A; the cross-sectional area as outlined in yellow measures 1042 mm2. Imaging from 2011 shown in panel B; the cross-sectional area as outlined in yellow measures 1218 mm2.

Fig 3: Axial, not appendicular, LN

Essentially the entire literature on this disorder has been based on cases of LN affecting nerves of the extremities. However, the axial body is similarly innervated and, therefore, nerves of the axial body would seem to be able to be affected by LN. This would include the proximal branches of the nerves of the extremities, which innervate axial structures. We therefore looked for axial involvement in two ways: pure axial nerve involvement and axial involvement due to proximal branches of LN-affected extremity nerves.

By investigating for cases of hypertrophy without regard to macrodactyly, we discovered a patient with thoracic nerve involvement. In looking for cases where the proximal sciatic nerve was affected by LN, we discovered the hallmarks of LN in the axial structures. These hallmarks, or sequelae, of LN are four-fold: 1) lipomatosis of nerve; 2) asymmetric and disproportionately abundant proliferation in visceral or subcutaneous fat, including lipoma formation; 3) fatty infiltration of muscle or muscle atrophy; and 4) osseous hypertrophy, particularly with predilection for joint exostoses and osteochondromas[11].

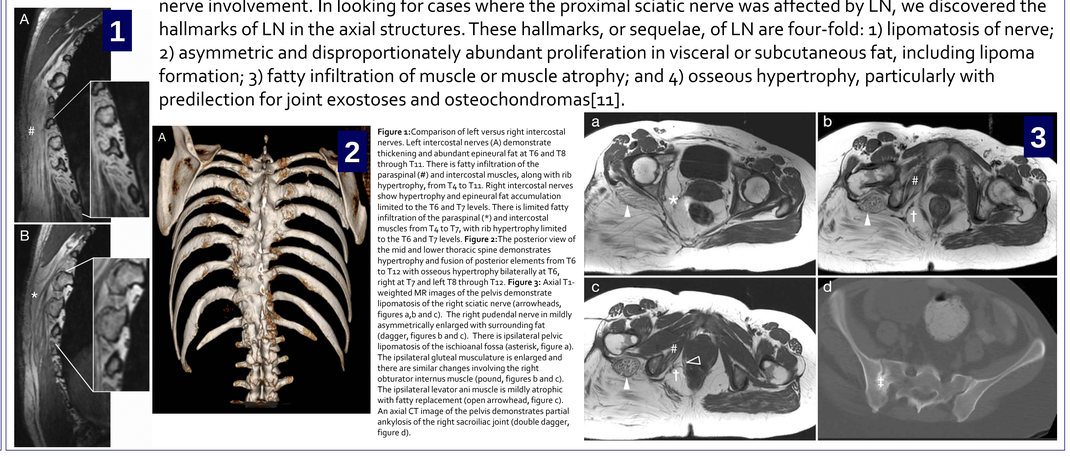

Figure 1: Comparison of left versus right intercostal nerves. Left intercostal nerves (A) demonstrate thickening and abundant epineural fat at T6 and T8 through T11. There is fatty infiltration of the paraspinal (#) and intercostal muscles, along with rib hypertrophy, from T_4 to T_{11}. Right intercostal nerves show hypertrophy and epineural fat accumulation limited to the T6 and T_7 levels. There is limited fatty infiltration of the paraspinal (*) and intercostal muscles from T_4 to T_7, with rib hypertrophy limited to the T6 and T_7 levels. **Figure 2:**The posterior view of the mid and lower thoracic spine demonstrates hypertrophy and fusion of posterior elements from T6 to T_{12} with osseous hypertrophy bilaterally at T6, right at T_7 and left T8 through T_{12}. **Figure 3:** Axial T1-weighted MR images of the pelvis demonstrate lipomatosis of the right sciatic nerve (arrowheads, figures a,b and c). The right pudendal nerve in mildly asymmetrically enlarged with surrounding fat (dagger, figures b and c). There is ipsilateral pelvic lipomatosis of the ischioanal fossa (asterisk, figure a). The ipsilateral gluteal musculature is enlarged and there are similar changes involving the right obturator internus muscle (pound, figures b and c). The ipsilateral levator ani muscle is mildly atrophic with fatty replacement (open arrowhead, figure c). An axial CT image of the pelvis demonstrates partial ankylosis of the right sacroiliac joint (double dagger, figure d).

Fig 4: Osteochondromas associated with LN

Disfiguring bony hypertrophy, particularly of the digits, is a well published consequence of LN. Interestingly, no previous research had investigated the occurrence of proximal osseous hypertrophy.

We found multiple cases where proximal ends of long bones had developed osteochondromas in the territory of a nerve affected by LN [12].

Figure 1: Patient with LN involving the brachial plexus (A) and multiple osteochondromas, including the choracoid process (B) and the proximal ulna (C and D) and distal radius, ulna, carpi and third metacarpal (E and F). **Figure 2:** Patient with LN of the sciatic and common peroneal nerve (B and C) along with a osteochondroma of the fibular head (A and D).