Long-Term Progression of Lipomatosis of Nerve

Mark A. Mahan[1], Blake D. Niederhauser[3], Kimberly K. Amrami[2,3], Robert J. Spinner[2,4]

Key words
- Fibrolipomatous hamartoma
- Lipofibromatous hamartoma
- Lipomatosis of nerve
- Macrodactyly
- Macrodystrophia lipomatosa
- Peripheral nerve
- Volumetric

Abbreviations and Acronyms
LN: Lipomatosis of nerve
MDL: Macrodystrophia lipomatosa
MRI: Magnetic resonance imaging

From the [1]Barrow Neurological Institute, Phoenix, Arizona; and Departments of [2]Neurologic Surgery, [3]Radiology, and [4]Orthopedics, Mayo Clinic, Rochester, Minnesota, USA

To whom correspondence should be addressed: Robert J. Spinner, M.D. [E-mail: spinner.robert@mayo.edu]

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OBJECTIVE: **Lipomatosis of nerve (LN) is a condition of massive peripheral nerve enlargement due to proliferation of fibrous and adipose tissue within the nerve, the natural history of which is currently unknown. We measured the pattern of growth in individuals with long-term radiologic follow-up.**

METHODS: **Review of the searchable records for LN at our institution found 52 patients, confirmed by pathology or pathognomic appearance on MRI. Ten patients had serial MRI of the same anatomic region for more than 2 years of clinical follow-up. Volumetric analysis was performed using regions of interest on serially imaged segments of affected nerves. Adjustment for skeletal growth was performed for pediatric patients.**

RESULTS: **LN enlarged in 7 of 10 individuals, often both longitudinally along the nerve and in cross-sectional volume. Regarding cross-sectional volume, 2 of the 10 patients demonstrated volume growth more than doubling and 5 additional patients had a >20% increase in nerve volume; the remaining 3 patients were quiescent, where change in the nerve volume was within the error range of volumetric analysis. All cases with growth remained >20% after adjustment for skeletal growth. Five of 10 individuals had longitudinal extension, even with correction for skeletal growth. More significant growth was noted in younger patients ($P = 0.02$). Growth rates more than 5% per year correlated with surgery, without statistical significance in this small population ($P = 0.14$).**

CONCLUSIONS: **Serial MRI reveals progressive enlargement of LN. The rate of growth was more profound in youth, but also occurred in early adulthood.**

INTRODUCTION

Lipomatosis of nerve (LN) is a rare fibroadipose lesion of peripheral nerves that involves massive hypertrophy of nerves. The term LN was coined by the World Health Organization in 1999 to include what had been historically and variably called lipofibrohamartoma, fibrolipoharmartoma, lipofibromatous hamartoma, fibrolipomatous hamartoma, fibrofatty tumor, lipofibroma, and fibrofatty proliferation of a nerve (6, 20, 22, 32, 37, 38). It most commonly occurs in the distal median nerve and its branches (3, 22, 35, 38), although involvement of the cervical and brachial plexus (36, 40, 41), ulnar (31, 35), radial (19, 34), sciatic (14, 30) including peroneal and tibial divisions (13), thoracic (28), and cranial nerves (7) have been infrequently reported. LN represents part of a spectrum of adipose disorders of nerves, ranging from nerve-associated lipomas to lipomatosis (39).

LN is frequently associated with nerve-territory-oriented skeletal abnormalities like macrodactyly and bone exostoses (2, 3, 38, 41), referred to as macrodystrophia lipomatosa (MDL). Although histologically benign, the overgrowth associated with LN may be progressive. Patients may require multiple orthopedic procedures to restrict the growth, and may ultimately require amputation, either from massive disfigurement or loss of function due to nerve resection. Recent studies have implicated somatic mosaic mutation of the PIK3CA growth signaling pathway. Other mutations of this pathway have been implicated in other disorders of overgrowth such as Proteus syndrome.

The natural history of LN is not known. Most studies report single cases or small series without long-term clinical or radiologic follow-up. To our knowledge, no study has ever looked at the serial magnetic resonance imaging (MRI) of LN or, importantly, the change of LN during long periods of time. We sought to evaluate whether LN grew over time. If it did, we wondered whether 1) growth occurred along nerves or in cross-sectional area, 2) LN grew disproportionately to overall growth during childhood, 3) LN grew in adult patients, and 4) if nerve volume growth had any relationship with surgery.

METHODS

The purpose of this study is to define the longer term pattern of growth of this adipose lesion on MRIs of patients with LN.

Clinical Review

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 key words "lipofibromatous

hamartoma," "fibrolipomatous hamartoma," "macrodactyly," "hyperostotic," and "Proteus-like" as some 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. In addition, patients known or suspected to have LN from paper records or other materials predating 1992 were identified 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, malformations, or visceral involvement not limited to lipomas, or pathology, genetic mutation analysis, or pedigree consistent with neurofibromatosis or another heritable disorder.

Patients with MRI of LN were included for review. Patients with serial MRI studies of the same segment of nerve separated by at least 2 years were included for volumetric analysis. Patients with poor imaging quality, undecipherable anatomy, or inconsistent imaging of the same segment of the affected nerve were excluded from review.

Radiologic Review

All available MRIs in each case was reviewed by a fellowship-trained musculoskeletal radiologist and a neurosurgeon with expertise in peripheral nerve imaging. The MRI examinations were performed at our institution and referral centers during more than 20 years with the expected differences in technical parameters and resolution. All examinations included at least transaxial T_1- and T_2-weighted images.

Given the variability of imaging studies, different segments of the nerve involved by LN were imaged at different points of time. Therefore, all MRI examinations of the affected nerve were reviewed for suitability. The two MRI studies that contained both the longest consistent segment of the affected nerve and were separated by the most interval of time were selected for volumetric analysis. Usually, each examination started or stopped at different anatomic locations. Therefore, volumetric analysis was performed on segments identified by skeletal landmarks. The anatomic landmarks depicting the first and last axial slices of the volumetric analysis are described as the "Segment of nerve with serial imaging" in Table 1. If a patient underwent resection of a portion of the nerve during the radiologic follow-up, that segment of nerve was excluded from analysis. If a patient had affected nerve branches, only the principal nerve was analyzed to reduce in-plane volume averaging artifact.

Volume estimates were obtained by performing cross-sectional contour tracings (region of interest) on an Advantage Windows workstation (General Electric, Waukesha, Wisconsin, USA) or on a proprietary image display system (QREADS, Mayo Clinic, Rochester, Minnesota, USA) using T_1-weighted axial images. The boundary of the nerve was the identified epineurium, which is slightly hypertrophic in LN. Intraneural lipomas were excluded from the calculation. The volume of each nerve was calculated independently by a radiologist and neurosurgeon and averaged over iterations. Evaluation of the volumes was overseen by the senior radiologist.

Due to limitations of the end point of scans, the full distal extension was not included in the volumetric calculation. This was most commonly due to the position of the limb within the scanner. Anatomic landmarks served as consistent end points for cross-sectional volume calculation, not the longitudinal extent of LN. Longitudinal growth was not calculated, partially due to the skeletal growth in many of these patients and the absence of anatomically complete imaging in another set of patients. Longitudinal extension was noted in relationship to anatomic landmarks, not calculated distances.

For skeletally immature patients, volumetric analysis was performed of the fifth metacarpal, which was uniformly imaged in all skeletally immature patients, to serve as a control for skeletal growth. The volume of the nerve was divided by the volume of the fifth metacarpal to create an index for comparison between scans. The term skeletally adjusted in the present article refers to comparison of this quotient.

Statistical Analysis

For the purpose of statistical analysis, patients were categorized into one of three groups. Those patients whose nerve had undergone a factorial increase (i.e., an increase more than doubling in volume) were labeled as the factorial growth group. Patients whose nerve had undergone a statistically significant increase in volume were labeled as the significant growth group. When no certain change in volume was observed, the patient was placed in the quiescent group. The data were reviewed to determine whether the rate of LN growth correlated with surgical intervention. Skeletally adjusted annualized LN volume growth was used to stratify two groups for comparison.

Comparisons among groups were evaluated using Fisher's exact tests and were further summarized using odds ratios and 95% confidence intervals obtained from exact logistic regression. Statistical analyses were performed using the SAS software package (SAS Institute, Cary, North Carolina, USA). Analysis of variance (ANOVA) calculations were performed to assess whether the subgroups were distinct in clinical behavior.

Ethical Concerns

Institutional Review Board approval was obtained for this study, and it complies with all of this institution's policies governing research of human subjects (no. 12-005479).

RESULTS

Clinical Results

Fifty-two patients with a diagnosis of LN or MDL confirmed by pathology or pathognomic MRI were reviewed for availability of MRIs. Patient records spanned 1956 to 2012 and from the collected clinical records of 17 individual surgeons. Twenty-six patients (50%) had MRIs of the involved anatomic region (Figure 1). Fifteen of these patients had serial MRIs, of which 12 had serial MRIs for more than 2 years of follow-up. Two patients with long-term MRI surveillance were excluded due to indecipherable anatomy (1 patient) resultant from plexal location and extensive fatty infiltration of adjacent muscles, and serial imaging of different segments of the involved nerve (1 patient) that did not allow comparison over time. A total of 10 patients were included for volumetric review.

The anatomic locations of the affected nerves were median nerve in four patients,