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ORIGINAL ARTICLE - PERIPHERAL NERVES

Lipomatosis of nerve and overgrowth: is there a preference for motor (mixed) vs. sensory nerve involvement?

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Abstract

Background Lipomatosis of nerve (LN) is a peripheral nerve disorder characterized by fibroadipose proliferation within the epineurium. It has been associated with nerve-territory overgrowth affecting soft tissue and/or bony structures. We sought to understand if there is an anatomical relationship associated with nerve-territory overgrowth.

Methods A review of the literature and our institutional LN cases was performed to determine the prevalence of nerve-territory overgrowth. Only cases with sufficient clinical and/or imaging data were selected. The cases were then subdivided into two groups and analyzed: (1) motor (mixed) nerve and (2) predominant sensory nerve, based on the anatomical location of the LN lesion. Subgroup analysis was performed on median nerves affected by LN, for a more homogenous population.

Results We identified 329 LN cases with sufficient information for analysis. Motor (mixed) nerve group (M) consisted of 287 cases (155 with overgrowth and 132 without overgrowth). Sensory nerve group (S) revealed group of 42 cases (4 cases with overgrowth and 38 without overgrowth). Statistical analysis comparing overgrowth status in the M and S nerve groups showed a statistically significant difference in overgrowth, favoring the M group for overgrowth ($p < 0.0001$). The analysis of median nerve group consisted of 225 cases in the M group (106 with overgrowth and 119 without overgrowth) and 20 cases in the S group (3 with overgrowth and 17 cases without overgrowth). A statistically significant difference in nerve-territory overgrowth status was present in the M vs. the S group, again favoring the M group for overgrowth. ($p = 0.0083$). Cases from our institution included 44 cases for this analysis. Forty-two cases in the M group (28 with overgrowth and 14 without overgrowth) and 2 cases in the S group (all 2 without overgrowth).

Conclusion We believe the association of LN and nerve-territory overgrowth might be explained by involvement of mixed motor nerves; however, the exact underlying mechanism is not known.

Keywords Lipomatosis of nerve · Peripheral nerve · Sensory nerve · Motor nerve · Overgrowth · Fibrolipomatous hamartoma

Introduction

Lipomatosis of nerve (LN) is a fascinating pathological entity that leads to massive enlargement of peripheral nerves and trophic effects of distal overgrowth. It is characterized by diffusely abundant fibroadipose tissue within the epineurium [45]. It is becoming increasingly recognized because of its pathognomonic appearance on MRI ("coaxial cabling" or "spaghetti-like" features on longitudinal plane) which eliminates the need for biopsy [30, 36]. The most commonly affected nerve is the median at the wrist and palm but many other nerves can be affected. Nerve-territory overgrowth is one of the hallmarks of this entity, and it has been recently reported to be present in 62% [35]. This leads to soft tissue and bony changes, such as subcutaneous lipomas, muscle

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lipomatosis, macrodactyly, exostoses, and osteochondromas. The overgrowth can be so severe that it results in movement restriction and multiple operations. Psychological problems can arise when massive overgrowth is present [29, 33, 34].

Treatment of this condition is symptomatic and typically includes nerve decompression when compressive neuropathy arises (carpal tunnel release is often performed for LN of the distal median nerve) [3]; soft tissue debulking; and/or bony procedures can address the nerve-territory overgrowth which may produce functional or cosmetic issues [3, 33, 34]; in some cases, amputation of appendicular structures (e.g., finger(s)) may be necessary [4].

Much of the pathogenesis of LN is unknown. We examined the specific type of nerve involvement (mixed motor or sensory) by LN in order to provide some insight into the overgrowth phenomenon.

Materials and methods

Inclusion criteria were LN affecting a specific nerve of any limb, known overgrowth status, and "adequate" clinical and/or radiological (MRI) data about individual cases. We subdivided cases based on affected nerves into two groups: (1) motor (mixed) nerve (M) and (2) predominant sensory nerve (S), and reviewed them for the presence of nerve-territory overgrowth.

A case was considered as part of the S group if the LN lesion was affecting a sensory nerve (e.g., palmar cutaneous branch) or the sensory continuation of a mixed nerve in a distal site where a motor contribution is no longer expected. Such examples are nerves located distally to these locations: median nerve (i.e., digital nerve) branches at the level of the mid-portion of the metacarpals or plantar nerve (i.e., digital nerve) branches at the level of the distal portion of the metatarsals; or the superficial radial or superficial peroneal nerve in the distal third of the forearm or leg, respectively. A case was also considered as part of the S group if an author(s) specifically claimed that only distal nerves (i.e., predominant sensory) were involved by LN (e.g., distal digital branches of median nerve or distal superficial peroneal nerve), even though no imaging data was provided. Cases with the LN involvement proximal to motor branches were included in the M group.

Exclusion criteria included cases of appendicular LN unilaterally or bilaterally affecting one or multiple nerves with inadequate imaging and/or operative and/or clinical data to reliably localize the lesion (i.e., M or S group). The most common exclusions were cases in which the proximal extent of LN could not be determined—e.g., no imaging done; an amputation of a digit(s) was performed; and LN was identified in the section margin or no description where normal appearing nerve was located was provided. Cases of LN affecting axial neural structures, or intra- and extraneural lipomas were also excluded.

Overgrowth was determined by the presence of soft tissue and/or bony overgrowth [45]. Cases without soft tissue or bony overgrowth but with cutaneous lesions associated with LN [45] were labeled as "no overgrowth."

For statistical analysis, we performed Fischer's exact test using JMP (version 13, SAS Institute Inc., Cary, NC). A p value of less than 0.05 was considered significant.

Literature review

Cases in the literature were identified using raw data from a recent systematic review of LN [35]. The cases in this systematic review were divided into two major groups: (1) definite LN cases (i.e., cases with confirmed diagnosis of LN) and (2) probable LN cases (i.e., LN suspected but no definite proof provided). Each of those groups was further subdivided into a specific case (SP) group (papers with detailed information about individual cases) and into an aggregate case (AGG) group (papers with information about cases being pooled together). We chose to include and analyze only definite LN cases from the so-called SP LN cases group (Fig. 3 in Marek et al. [35]. These cases were further subdivided into two groups: (1) all cases of LN (upper and lower limbs) and (2) LN affecting the median nerve and its branches (without other nerves involved). The median nerve was selected for separate analysis because of the frequency of occurrence of LN in this distribution.

Institutional review

LN cases in our institution were identified using ACE (Advanced Cohort Explorer), a Mayo Clinic–developed software for patient database search. The following terms were used: fibrolipomatous hamartoma, lipofibromatous hamartoma, lipomatosis of nerve, hamartoma and nerve, and macrodactyly. Cases from our institution that were previously published were excluded for duplicity as they were included in the literature review part of this study.

Results

Literature review

We identified 483 published cases of definite LN in the SP group using our database from our recent systematic review on LN [35]. One hundred fifty-four cases were excluded for insufficient imaging and/or operative data to determine LN extent. Thus, we included 329 cases of LN for analysis of nerve anatomy and overgrowth.

All LN cases

When subdivision of cases was performed, there were 287 were in the M group and 42 in the S group. The M group comprised median ($n = 220$), ulnar ($n = 22$), plantar ($n = 16$), brachial plexus ($n = 7$), sciatic ($n = 6$), median bilaterally ($n = 5$), median and ulnar ($n = 3$), tibial ($n = 3$), radial ($n = 2$), lumbosacral plexus ($n = 1$), obturator (n = 1), and femoral ($n = 1$) nerves. The S group included the following nerves: digital branches of the median nerve ($n = 17$) [1, 3, 6, 9–11, 15, 16, 18, 22, 24, 25, 27, 39, 46, 47], superficial peroneal nerve ($n = 15$) [2, 4, 5, 7, 8, 12–14, 17, 23, 26, 38, 40, 41], digital branches of the plantar nerves ($n = 3$) [20, 31, 37], palmar cutaneous branch ($n = 2$) [3, 18], superficial branch of the radial nerve ($n = 2$) [19, 42], superficial branch of ulnar nerve ($n = 1$) [50], bilateral digital branches of the median nerve ($n = 1$) [21], and sural nerve ($n = 1$) [43]. In the M group, 155 cases had signs of overgrowth present and 132 did not; in the S group, there were 4 cases with overgrowth and 38 cases without signs of overgrowth (Table 1).

Statistical analysis comparing overgrowth status in the M and S nerve groups showed a statistically significant difference in overgrowth, favoring the M group for overgrowth ($p < 0.0001$).

LN affecting the median nerve and its branches

Subgroup analysis was performed on median nerve cases. There were 225 cases in the M group (106 with overgrowth and 119 without overgrowth). Two hundred and twenty cases were unilateral median involvement and 5 cases were bilateral median involvement. The S group consisted of 20 cases (3 with overgrowth and 17 cases without overgrowth) that had sufficient information for the anatomical evaluation (Table 1). Cases in the S group included median digital branches involvement ($n = 17$), the palmar cutaneous branch ($n = 2$), and bilateral digital branches of median nerve ($n = 1$). A statistically significant difference in nerve-territory overgrowth status was present in the M vs. the S group, again favoring the M group for overgrowth ($p = 0.0083$).

Institutional review Search of LN cases in our institution yielded 55 cases. After a detailed review, 11 cases were excluded for the following reasons: insufficient information to be sorted into the M or S group ($n = 6$), cases included in the "Literature review" section of this paper ($n = 3$) [28, 33, 34], and LN affecting axial structures ($n = 2$). Thus, there were 44 additional cases for this analysis. The M group consisted of 42 cases and included the following nerves: median ($n = 22$);

Table 1 Summary of LN cases in the literature and cases from our institution with subdivision to and motor (mixed) and predominant sensory nerve subgroups

M group	No.	S group	No.
Literature cases			
Median	220	Median (digital branches)	17
Ulnar	22	Superficial peroneal	15
Plantar foot	16	Plantar foot	3
Brachial plexus	7	Superficial branch of the radial	2
Sciatic	6	Palmar cutaneous branch	2
Bilateral median	5	Bilateral digital branches of the median	1
Median and ulnar	3	Superficial branch of ulnar	1
Tibial	3	Sural	1
Radial	2		
Lumbosacral plexus	1		
Obturator	1		
Femoral	1		
Mayo Clinic cases			
Median	22	Superficial peroneal	1
Sciatic	8	Ulnar digital of the ring finger	1
Median and ulnar	4		
Tibial	2		
Plantar	2		
Ulnar	1		
Superficial ulnar	1		
Brachial plexus and median	1		
Tibial, plantar and superficial, and deep peroneal	1		

sciatic ($n = 8$); median and ulnar ($n = 4$); tibial ($n = 2$); plantar nerves ($n = 2$); brachial plexus and median nerve ($n = 1$), ulnar ($n = 1$); superficial branch of ulnar nerve ($n = 1$); distal tibial, superficial peroneal (LN identified up to fibular neck), deep peroneal; and medial plantar ($n = 1$) (28 with overgrowth and 14 without overgrowth). The S group contained two cases and included superficial peroneal nerve ($n = 1$) (Fig. 1) and ulnar digital nerve of the ring finger ($n = 1$), (all 2 without overgrowth) (Table 1).

Fig. 2 This figure was reproduced from Ardakani et al. [5]. Overgrowth of the foot including toes can be appreciated. Based on these findings we strongly suspect more proximal or widespread nerve involvement by LN

Discussion

Lipomatosis of nerve, along with intra- and extraneural lipomas, comprise the spectrum of adipose lesions affecting peripheral nerves [45]. While LN is well-known for its association with nerve-territory overgrowth, recent papers from our group have shown that intraneural and extraneural lipomas are not associated with nerve-territory overgrowth [32, 45].

In our review of the literature and our institution's cases, we found a difference between the overgrowth status of LN cases associating M nerves and overgrowth and S nerves and no overgrowth. We believe (but cannot prove) that the 4 cases in the S group in the literature with overgrowth (one involving the superficial peroneal nerve in the distal leg [5] and 3 cases with "isolated involvement of the digital nerves" of the median nerve (case nos. 4, 7, and 10) [3]) can be explained on an anatomical basis. In these cases, clinical and MRIs were not performed of proximal nerves, which we know can be involved in LN [48]. In the superficial peroneal case, the overgrowth affected all toes and the foot (Fig. 2), suggesting to us more proximal and/or more widespread involvement. These 4 outlier cases identified in our literature review would not have met the criteria we used for own institutional series. Cases from within our institution demonstrated no signs of nerve-territory-oriented overgrowth in the S group, which we attribute to having adequate imaging of the proximal nerve to completely image the LN lesion.

There are some potential speculative mechanisms for the different predisposition of mixed motor-sensory nerves vs. sensory nerves in this disorder. Considerations include neurophysiological differences between motor and sensory innervation; volume of tissue affected by LN/innervated by the affected nerve; and all manners of hypotheses regarding limb development in a potentially somatic mosaic mutation disorder. For example, somatic activating mutations in PIK3CA, encoding the catalytic subunit of phosphatidylinositol 3-kinase (PI3K), have been reported in patients with LN-associated macrodactyly [44, 49]. These studies suggest that aberrant PI3K signaling may be implicated in LN

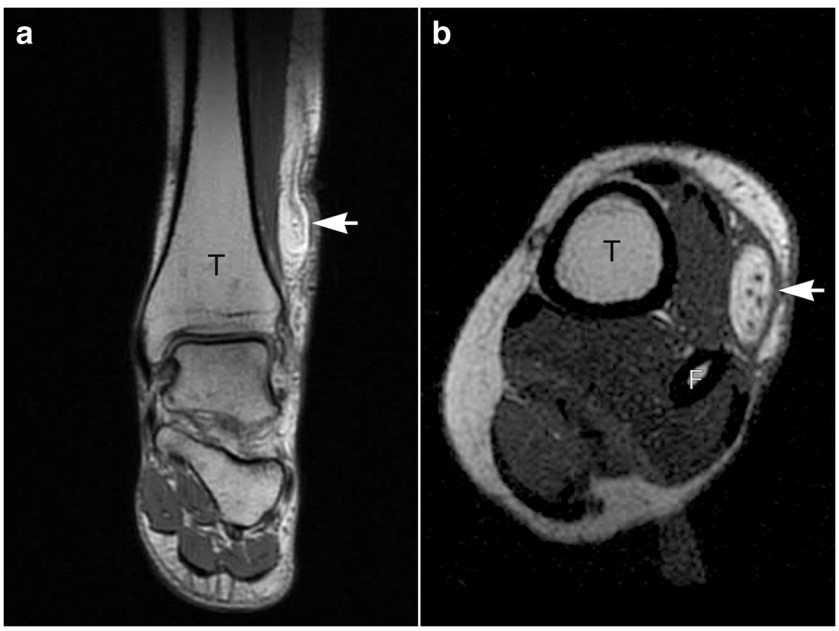

Fig. 1 T1-weighted MRI images showing LN of the superficial peroneal nerve (arrows) in coronal (**a**) and axial (**b**) planes. Image **b** demonstrates the co-axial cable-like appearance, a pathognomonic feature for LN. No associated nerve-territory overgrowth is present. T tibia, F fibula

pathogenesis. However, the overwhelming number of cases of LN involves single nerve [35] and there is convincing evidence that this syndrome is progressive, rather than strictly congenital [28, 30]. Thus, the anatomical distribution suggests that distal overgrowth is unique to the type of axons carried by the nerve. It is possible to consider that the type of innervation may have profound consequences to the distal tissues. Other possibilities for this phenomenon might include differential responsiveness to trophic signals from stem cells present in adult adipose tissue; differential effects of repulsive signs such as semaphorin 3 secreted from osteoblasts which may limit overgrowth of sensory and sympathetic axons; and differential molecular apparatus supporting cytoskeletal plasticity and membrane trafficking in motor and sensory axons (Fig. 3). It is important to say however that all of these are only hypotheses and that further research is needed to become to understand this process more.

Limitations

Although we attempted to be as specific as possible in our methods, we acknowledge that determining the "true" longitudinal extent of the LN lesion (and thus whether a case belongs to the M or S group) is difficult based on retrospective review; typically, the imaging is incomplete or of low resolution, and the interpretations of the imaging or operative findings are imperfect. Ideally, to best determine the true longitudinal extent of LN, we recommend obtaining MRI that evaluate for LN from spinal nerve origin to the most distal location of the affected nerve. For this study, while we tried to be inclusive utilizing the available data points, still, we excluded cases that were felt to have limited operative descriptions, inadequate MR images, or ambiguous levels of anatomic division. We also recognize the subdivision of groups (motor vs. sensory) is not a pure one. The motor group is mixed. The sensory group, while a predominant sensory, could well have some component of motor fibers due to anatomical variations.

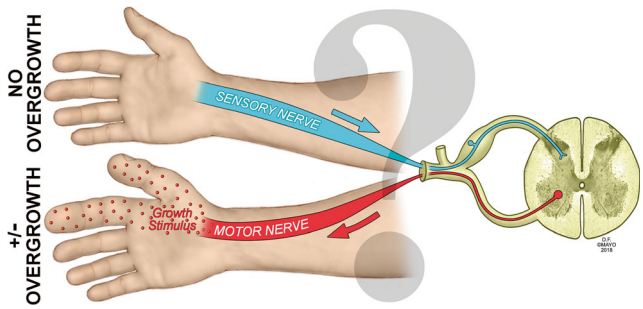

Fig. 3 An illustration showing the concept of nerve involvement (sensory vs. motor) and overgrowth. The exact mechanism is unknown; however, mixed (motor) nerves might play an important role in pathogenesis of overgrowth associated with LN (with permission, Mayo Foundation, 2018)

The number of cases in the sensory group is small as seen in our institutional cases.

Conclusion

We believe that involvement of mixed motor nerves affected by LN plays an important role in the pathogenesis of LN-associated nerve-territory overgrowth. The exact mechanism is unknown. Anatomical evidence suggests that it relates to the combination of presence of PIK3CA mutation in the overgrown tissue and LN of mixed motor nerves. Further research is needed to better understand the mechanism behind overgrowth associated with LN.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was retrospective. However, informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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