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LETTER TO THE EDITOR (BY INVITATION) - PERIPHERAL NERVES

Response to the Letter to the Editor "Lipomatosis of nerve and overgrowth syndrome: an intriguing and still unclear correlation"

Tomas Marek[1] · Mark A. Mahan[2] · Kimberly K. Amrami[3] · Robert J. Spinner[1]

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To the editor,

We appreciate the letter to the editor by Vetrano et al. [11] regarding our recent paper on lipomatosis of nerve (LN) [5]. Our group has been interested in LN as well as other adipose lesions of nerves for many years [3, 4, 9].

First, we agree with the authors that there is a great inconsistency in the terminology in the world's literature of LN. Besides the term lipomatosis of nerve, which has been proposed by WHO in 2002 [2], many other terms are regularly used including fibrolipomatous hamartoma, lipofibromatous hamartoma, neural lipoma, and macrodystrophia lipomatosa, for a spectrum of pathologies. This terminology problem was one of the major reasons that we decided to compile the world's literature and perform the systematic review (which included the recent case by Vetrano et al. [10]). Our systematic review is now published in JNS [6]. This study strengthened the association of LN and nerve-territory overgrowth. We then utilized the raw data from this large database to conduct a follow-up study to analyze the presence (or absence) of nerve-territory overgrowth between two groups of cases (i.e., LN affecting so-called predominant sensory nerves and motor (mixed) nerves.) We believe that the findings reported in the paper (i.e., predominance of motor (mixed) nerve affected by LN and associated nerve territory overgrowth present) is interesting and worthy of future investigation.

Second, systematic reviews are always subject to limitations, as are all studies. Yet, reviews are able to achieve synthesis of often conflicting or confusing medical literature, which was our goal. We address the specific limitations of our systematic review, including the variable amount of information about individual cases reported in the articles (ranging from the available clinical information to the imaging (e.g., MRI and/or ultrasound), and the availability of operative photographs. As stated in the materials and methods section of our discussed paper, we performed Fisher's exact test [1] for the analysis, using JMP software (version 13, SAS Institute Inc., Cary, NC). Fisher's exact test is used for the analysis of dichotomous categorical variables. It is performed in situations when chi-square test would be less precise such as when one or more analyzed sample sizes are small (typically 5 or less) and/or when the samples are not normally distributed [8]. To address the authors' comment regarding the "imbalance between (affected) median nerve and all other nerves", we now performed a separate statistical analysis excluding the two major sites of LN in the median nerve (and branches) at the wrist/palm and the tibial nerve (and branches) at the ankle/foot, including only cases affecting nerves proximal to those sites. This analysis consisted of 17 cases in the predominant sensory group (15 superficial peroneal, 1 superficial branch of the radial, and 1 sural nerves; only 1 of these cases had overgrowth); and 50 cases in the mixed (motor) group (21 proximal median, 8 proximal ulnar, 7 brachial plexus, 6 sciatic, 3 tibial proximal to ankle, 2 proximal radial, 1 lumbosacral plexus, 1 obturator, and 1 femoral nerve: in this subgroup, 26 did not have overgrowth and 24 had overgrowth). Statistical analysis (Fisher's exact test performed in JMP software) also showed a statistical significant difference, favoring the mixed (motor) nerves and presence of the overgrowth ($p = 0.0015$), consistent with the 2 other statistical analyses reported in our paper [5].

Third, we strongly agree with their advocacy of advanced imaging techniques to promote diagnosing LN. In their recent case report [10], they described their experience with diffusion tensor imaging (DTI) to diagnose LN. This form of functional imaging,

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✉ Robert J. Spinner
spinner.robert@mayo.edu

[1] Department of Neurologic Surgery, Mayo Clinic, Gonda 8-214, Rochester, MN 55905, USA

[2] Department of Neurologic Surgery, University of Utah, Salt Lake City, UT 84132, USA

[3] Department of Radiology, Mayo Clinic, Rochester, MN 55905, USA

like elastography, may have a potential value in the future. Our group has been recommending anatomic imaging to assess the extent of the LN lesion and to better assess tissue composition of the lesion. The MR appearance of LN has long been considered pathognomonic [7]. We believe that improved MRI sequences and higher resolution (e.g., 7 T MRI) can provide additional information when researching LN and other adipose lesions affecting peripheral nerves. Spectroscopy might be another technique that may be of interest as it could potentially help to quantify the fat content of the LN lesion.

We hope that our responses clarify these key points regarding this fascinating pathology. There are "many unanswered questions", and hopefully, fewer unquestioned answers.

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