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ORIGINAL ARTICLE - PERIPHERAL NERVES

Histopathologic changes inside the lateral femoral cutaneous nerve obtained from patients with persistent symptoms of meralgia paresthetica

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Abstract

Background In patients with persistent symptoms of meralgia paresthetica, a neurectomy of the lateral femoral cutaneous nerve (LFCN) can be performed to alleviate pain symptoms. The neurectomy procedure can be performed either as a primary procedure or after failure of a previously performed neurolysis or decompression of the LFNC (secondary neurectomy). The goal of the present study was to quantify the histopathologic changes inside the LFCN obtained from patients with persistent symptoms of meralgia paresthetica, and specifically to compare to what extend these changes are present after primary versus secondary neurectomy.

Methods A total of 39 consecutive cases were analyzed microscopically: in 29 cases, the neurectomy had been performed as primary procedure, in 10 cases, after failed neurolysis. Intraneural changes were quantified for the (1) thickening of perineurium, (2) deposition of mucoid, and (3) percentage of collagen. Analysis was performed at three levels: proximal to, at, and distal to the previous site of compression. In addition, correlations were investigated for the duration of symptoms and the body mass index (BMI) of the patient.

Results Intraneural changes were found consistently in all cases. There was no significant difference for the primary and secondary neurectomy groups. There was also no relation with the previous site of compression. There was a weak correlation between the occurrence of intraneural changes and the duration of symptoms, although this difference was not statistically significant.

Conclusions Histopathological changes in this study were found in all patients with persistent symptoms of meralgia paresthetica regardless of a previously performed neurolysis procedure. This finding suggests that the intraneural changes that occur in persistent meralgia paresthetica are largely irreversible and support the surgical strategy of neurectomy as an alternative to neurolysis, also for primary surgical treatment and not only after failure of neurolysis.

Keywords Pathology · Transection · Neurolysis · Decompression · Entrapment

Introduction

Decompression or neurolysis of the lateral femoral cutaneous nerve (LFCN) frequently is the surgical treatment of choice in patients with persistent symptoms of meralgia paresthetica despite conservative treatment [10]. If neurolysis fails to relieve pain symptoms, a neurectomy can be performed [5]. There still is discussion whether neurectomy can also be performed in the primary surgical treatment [4, 7].

At present, it is not clear why decompression sometimes fails to provide adequate pain relief. One explanation is that chronic compression has led to so many changes inside the nerve (as for example thickening of the perineurium and the deposition of mucoid and collagenous nodules that decompression alone does not provide sufficient pain relief) [2].

This study has been presented at the American Society for Peripheral Nerve (ASPN) this year in AZ.

This article is part of the Topical Collection on *Peripheral Nerves*

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The goal of the present study was to quantify the intraneural changes in the LFCN from patients with persistent symptoms of meralgia paresthetica. We thereby compared the results for patients that underwent the neurectomy as a primary procedure and patients that underwent the procedure, because of insufficient pain relief after a previous decompression or neurolysis. In addition, we investigated the relation between these changes and the previous site of compression, and we also looked at potential correlations with the patient's body mass index (BMI) and duration of symptoms. The latter was investigated because a longer duration of symptoms may have a negative impact on the patient outcome after neurolysis [3].

Methods

Patient inclusion

Between August 2012 and May 2017, a total of 45 patients consecutively underwent a neurectomy procedure in our hospital. All cases were performed by the first author (GdR). The first six cases were excluded, because for these cases, the microscope slides had been cut in a transverse direction. After analysis of the slides by the pathologist (SvD), it was decided to cut the segments longitudinally for further analysis (we found that, specifically, the measurement of perineurium thickness in these cases was less precise, because of potential tangential cut slides). Informed consent was obtained before the surgery. Therefore, a total of 39 consecutive cases were included. In 29 of these cases, the neurectomy had been performed as a primary procedure, either because the patient preferred this option (in 23 cases) or because the patients had been randomized to this group (in 6 cases) as part of the STOMP trial.[1] In 10 patients, the procedure was performed as a secondary procedure after a previous neurolysis procedure that had not resulted in sufficient pain relief at a mean interval of 6 months after the first surgery. Information on the duration of the clinical symptoms was obtained preoperatively in the outpatient clinic, as well as the length and weight of the patients to calculate the BMI.

Neurectomy procedure

Surgery in all cases was performed under general anesthesia with the patient in a supine position. A 5-cm incision was made, parallel situated, below the inguinal ligament. The LFCN was identified and followed back to where it passes through the inguinal ligament and where the nerve exits the pelvis. Anatomical variations in the course of LFCN were noted according to the classification by Asmzann et al. [1]. During revision surgery, the presence of a potential incomplete release was noted. In the primary cases, the inguinal ligament was incised over the nerve, similar to the procedure performed during neurolysis. The site where the nerve runs through the ligament was marked intra-operatively with a surgical marker, also in the revision cases (Fig. 1a). The nerve was transected several centimeters distal to the inguinal ligament. The proximal nerve end was slightly pulled out of the pelvis with a clamp (Fig. 1b) and transected as far proximally as possible, leaving a resected nerve end of about 3–5 cm with the previous site of compression marked in the middle of the segment. Three segments of a nerve of about 6–8 mm were cut from this resected piece of LFCN; one segment proximal to the previous site of compression, one segment at the previous site of compression, and one segment distal to the previous site of compression (Fig. 1c). All segments were separately labeled and sent for histopathologic analysis by the neuropathologist (SvD).

Fixation and slides

All segments were fixed in formalin and embedded in paraffin. Longitudinal sections of about 6 μm were cut, and slides were stained with hematoxylin&eosin (H&E). In addition, an alcian blue stain for mucoid depositions was performed on separate slides (that were available in 29 of the 39 cases).

Quantification

All 39 × 3 H&E-stained slides of the 39 patients were scanned with the IntelliSite Pathology Ultra Fast Scanner 1.6 RA and analyzed with Image Management System (Philips, The Netherlands). One nerve sample on each microscopic slide was carefully selected, avoiding tangentially cut areas and artifacts. First, the thickness of the perineurium on both side of the nerve segment was measured (Fig. 2a). The largest value was selected and used for further analysis. Second, the total area of the nerve segment and the areas containing collagenous nodules were measured to determine the percentage of collagenous nodules (Fig. 2b). Third, areas containing mucoid were measured using program ImageJ (Fig. 2c). With IMS-view, print screens of the nerve segments were taken with × 2 magnification. In ImageJ, the nerve segment was selected and analyzed using color deconvolution to segregate the alcian blue staining from the H&E staining. The threshold ranged from 200 to 215, depending on the intensity of the alcian blue staining.

Statistical methods

All data (age, body mass index (BMI), duration, percentage of collagen, and percentage of mucoid and thickness of perineurium) were reported as medians with range, except for gender, which was reported as frequencies. The intraneural changes were measured in primary, secondary, or STOMP procedure at

[1] We are currently investigating the effectiveness of the neurolysis and neurectomy procedures in a randomized controlled trial, named the STOMP trial (Surgical Treatment Options for Meralgia Paresthetica).

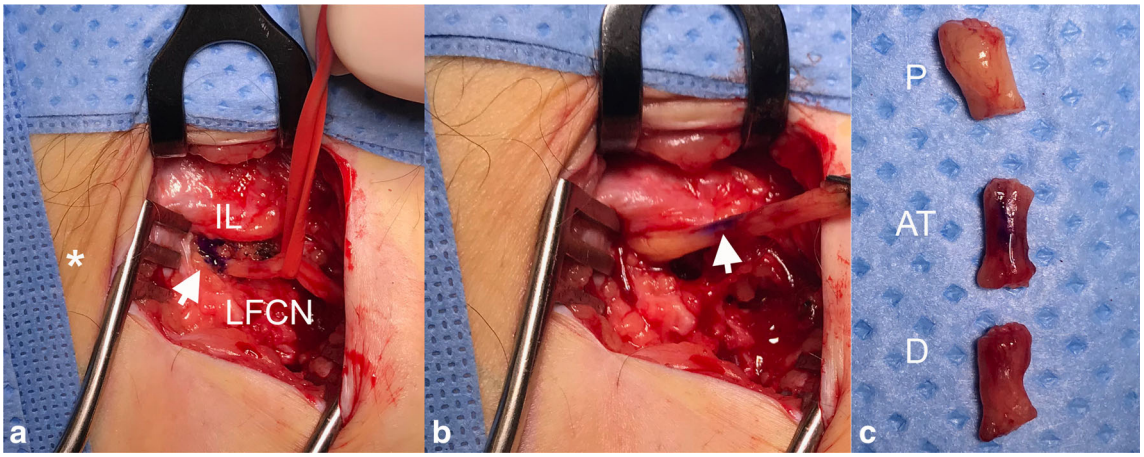

Fig. 1 Intraoperative photographs illustrating the different locations that were analyzed separately in this study. **a** Arrow points at the marked passage of the LFCN through the inguinal ligament; the inguinal ligament (IL) is retracted. The asterisk marks the position of the SIAS. **b** After distal transection, the LFCN is slightly pulled out of the pelvis (clearly visible in this case is the proximal thickening of the nerve). **c** The nerve segments that were separately sent for histopathologic analysis (P proximal to previous site of compression, AT at the previous site of compression, and D distal to previous site of compression)

three locations ("proximal," "at," or "distal" to the previous site of compression). The Kruskal-Wallis one-way analysis was used to investigate the intergroup differences of intraneural changes over the three locations and later used to evaluate the intergroup differences between treatment procedures at location "at the site of compression." Subsequently, for the analysis of duration of clinical symptoms, data were split for duration ≤ 1 year and duration > 1 year, and, for the analysis of the BMI, the data was split for BMI ≤ 30 and BMI > 30. These cut-offs had been determined before the start of the STOMP trial [3]. The Mann-Whitney test was performed to investigate the intergroup differences of the thickness perineurium, percentage collagen, and percentage mucoid. Spearman's correlation was used to investigate potential correlations, the occurrence of the different intraneural changes, and the duration of the clinical symptoms and the BMI.

Results

In the case of secondary neurectomy after failed neurolysis, no residual compression was noted during the surgery. There were no anatomical variations in the coronal plane other than types B, C, and D according to classification by Asmzann et al. [1]. The baseline characteristics for different groups of primary, secondary, and primary STOMP trial neurectomy were not significantly different (Table 1). Also, the results of the quantitative analysis were not significantly different, although the percentage of collagen was relatively low (0.55%) in the primary STOMP trial neurectomy group, compared to the primary (4.5%) and secondary (3.5%) neurectomy groups (Table 1).

Combined analysis of the groups for the site of compression showed no difference for the occurrence of intraneural changes proximal, at, and distal to the previous site of compression (Table 2). Further analysis on the duration of symptoms and BMI was therefore performed on the sections obtained "at" the site of compression.

As for the "duration of symptoms," no significant differences in thickness of perineurium, percentage of collagen, and percentage of mucoid were found for groups "duration of symptoms ≤ 1" and "> 1 year" (Table 3). There seemed to be a trend towards more intraneural changes for a longer duration of symptoms, but the Spearman correlations were not significant (Fig. 3).

As for the "BMI," there were no significant intergroup differences in thickness of perineurium, percentage of collagen, and

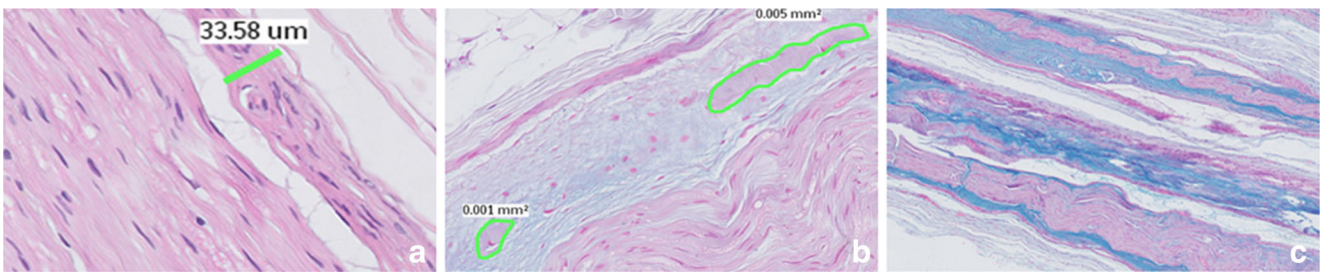

Fig. 2 Microscopic images (× 40, × 20, and × 10 magnifications, respectively) of H&E (**a** and **b**) and alcian blue (**c**) stains showing measurements for thickness of perineurium (a), presence of collagen nodules and deposition of mucoid (c)

Table 1 Baseline characteristics and results for different groups of patients

Median (range)	Primary neurectomy ($n = 23$)	Secondary neurectomy ($n = 10$)	STOMP trial neurectomy ($n = 6$)	P value
Age (years)	58 (23–83)	57 (29–76)	51 (25–62)	0.275
Male/female	10/13	3/7	2/4	0.736
BMI	28.0 (21–41)	30.5 (25–37)	27.5 (22–53)	0.458
Duration symptoms (years)	2 (0.25–20)	3.4 (0.21–7)	3 (0.52–13)	0.903
Thickness perineurium (μm)	21.5 (6.5–106.6)	19.8 (10.7–97.1)	18.4 (9.44–46.3)	0.685
Percentage collagen (%)	4.5 (0–11.7)	3.5 (0.01–10.76)	0.55 (0–4.5)	0.095
Percentage mucoid (%)	7.3 (1.1–30.7)	6.1 (2.1–17)	2.1 (0.01–28.4)	0.207

percentage of mucoid, although the median "percentage of collagen" was higher in patients with a BMI ≤ 30, whereas the median "percentage of mucoid" was higher in patients with a BMI > 30 (Table 4). Spearman correlation coefficients for thickness of perineurium, ratio of collagen, and percentage of mucoid were all positive for patients with a BMI ≤ 30, whereas these correlations were all negative for patients with a BMI > 30 (Fig. 4). These differences however were not statistically significant.

Discussion

In this study, histopathologic changes were found consistently inside the lateral femoral cutaneous nerve (LFCN) obtained from patients with persistent symptoms of meralgia paresthetica. There was no significant difference for patients that had previously undergone a neurolysis procedure and for patients that underwent neurectomy as a primary procedure. This finding suggests that these changes are largely irreversible. This could be an explanation why the neurolysis procedure frequently fails to alleviate the pain symptoms [9]. Possibly, the presence of these intraneural changes forms a pain generator that is not relieved by decompression of the nerve alone and requires the removal by a neurectomy procedure.

Before the start of this study, we expected that the intraneural changes would increase with duration of symptoms. Although results showed a trend towards more intraneural changes for a longer duration of symptoms, this correlation was not statistically significant. On the basis of the present study, we thus cannot say that patients with longer duration of symptoms (> 1 year) are better off with a primary neurectomy procedure. Hopefully, the STOMP trial that also includes a sub-analysis of patients with duration ≤ and > 1 year will provide more information on this [3]. Interestingly, the percentage of collagen in the STOMP trial group in this study was lower than for the group of patients that choose a primary neurectomy and group of patients that underwent the neurectomy after failed neurolysis.

Other interesting findings were that there was no relation for the occurrence of intraneural changes and the site of compression and the difference in occurrence between patients with a BMI of ≤ and > 30. These two findings will be separately discussed below. The discussion ends with the shortcomings of this study.

The site of compression

In this study, no significant differences were found inside the LFCN in relation to the previous site of compression. This is an interesting finding, because it suggests that compression in meralgia paresthetica is not merely a static phenomenon, but may be subjective to movement. Analogous to the ulnar nerve at the elbow in patients with cubital tunnel syndrome, the LFCN may glide through the tunnel, in this case the inguinal ligament, during movement, which might have an effect on different parts of the nerve. This explanation is supported by the variable occurrence of symptoms in patients: some patients report that symptoms mainly occur during walking, while others report symptoms occur mainly during sitting position with flexion of the hip (for example when driving a car) or with extension of the hip (for example when lying in bed). But also, by the different mechanisms of

Table 2 Results of the Kruskal-Wallis one-way analysis for thickness of perineurium, percentage of collagen, and percentage of mucoid for the different locations: "proximal," "at," and "distal to the site of compression"

Median (range)	Proximal	At	Distal	P value
Thickness perineurium (μm)	18,5 (2.9–117)	20.0 (6.5–107)	27.1 (8.83–83.5)	0.056
Percentage collagen (%)	2.78 (0.00–11.9)	3.70 (0.00–11.7)	2.21 (0.00–17.8)	0.489
Percentage mucoid (%)	4.38 (0.35–32.9)	4.98 (0.01–30.7)	4.49 (0.86–19.6)	0.603

Table 3 Results of the Mann-Whitney analysis for thickness of perineurium, percentage of collagen, and percentage of mucoid for groups "duration of symptoms ≤ 1 year" and "duration of symptoms > 1 year"

Median (range)	Duration > 1 year ($n = 10$)	Duration > 1 year ($n = 29$)	P value
Thickness perineurium (μm)	20.1 (7.65–104)	19.4 (6.48–107)	0.475
Percentage collagen (%)	2.67 (0.00–11.0)	4.08 (0.00–11.7)	0.862
Percentage mucoid (%)	3.90 (0.01–19.2)	6.32 (1.10–30.7)	0.893

injury: in some cases intra-operatively, there is a clear compression of the nerve by the overlying inguinal ligament, but in other cases, the nerve may run over a hard rim of the underlying iliac fascia or the nerve may run through the inguinal ligament, which may cause compression during movement from the below. Intra-operatively, when performing a neurolysis procedure, all these potential compression sites must be inspected. In the case of an underlying rim of the iliac fascia, the fascia is incised to circumferentially decompress the nerve. This difference in compression depending on the position may thus explain that different parts of the LFCN may be compressed and not merely the site that was defined by the surgeon with the patient in a supine position. Further, potential clinical consequence of the finding that intraneural changes also occurred in the nerve segment taken proximal to the inguinal ligament is that it stresses the importance of very proximal transection of the nerve during the neurectomy procedure, by first opening the inguinal ligament over the nerve, and then, while slightly pulling the nerve out of the pelvis, to transect it as far proximally as possible (see Fig. 1). Another option would be to perform a neurexeresis instead of a neurectomy: a procedure that was performed in our hospital before the start of the neurectomy. The thought of pulling the nerve out of the pelvis was that the nerve breaks at different levels and that this prevents the formation of a neuroma [6], but another thought, as this study thus shows, is that it removes a longer nerve segment that may be affected by the intraneural changes than when the nerve is cut just proximal to the inguinal ligament. Possibly, the remainder of a distal nerve segment with intraneural changes may still provoke symptoms of meralgia paresthetica. More research is needed to further investigate this.

The potential influence of obesity

In this study, a significantly negative correlation for the thickness of perineurium was found for patients with a BMI > 30, whereas there was a weak positive correlation for patients with a BMI ≤ 30. This finding suggests a difference in pathogenesis

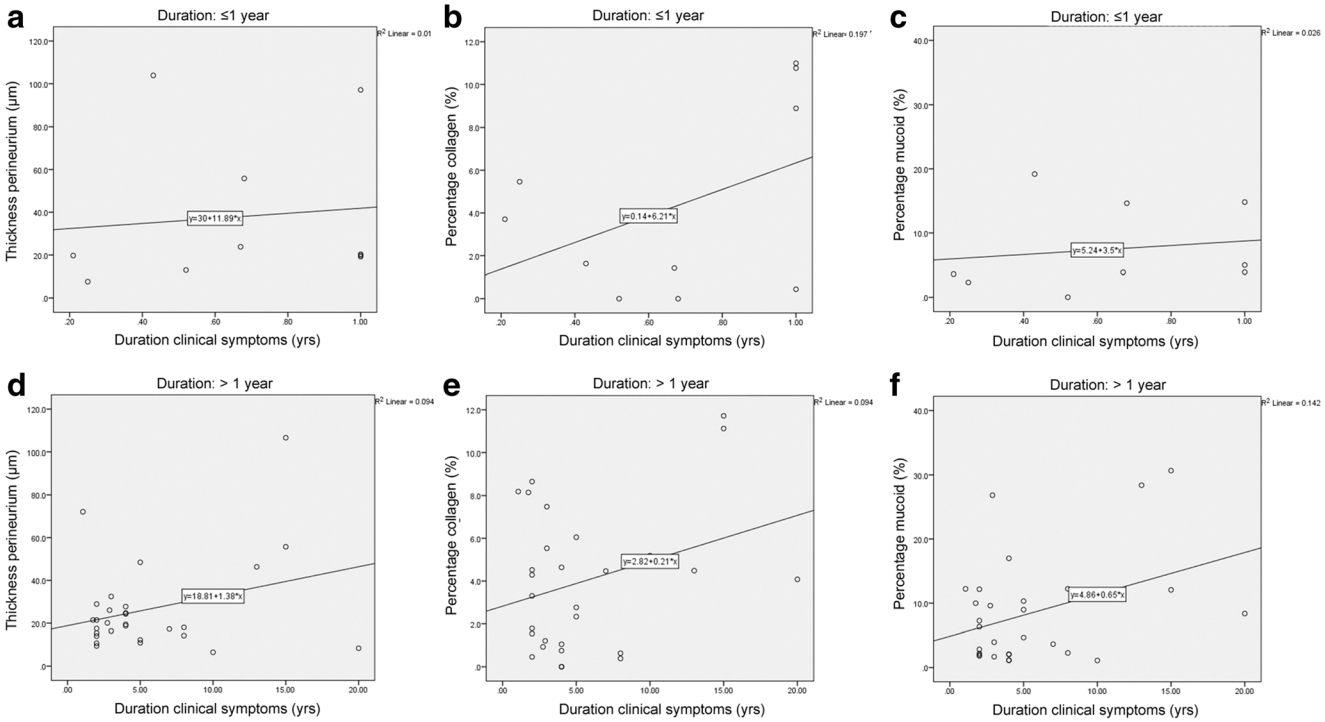

Fig. 3 **a**–**f** Scatter plots showing the occurrence of different intraneural changes for the duration of symptoms for patient with symptoms of 1 year or less and patients with symptoms for more than 1 year

Table 4 Results of the Mann-Whitney analysis for thickness of perineurium, percentage of collagen, and percentage of mucoid for groups "BMI ≤ 30" and "BMI > 30"

Median (range)	BMI ≤ 30 ($n = 26$)	BMI > 30 ($n = 13$)	P value
Thickness perineurium (μm)	19.5 (7.65–107)	20.1 (6.48–55.8)	0.965
Percentage collagen (%)	4.18 (0.00–11.7)	1.42 (0.00–8.90)	0.255
Percentage mucoid (%)	3.90 (0.01–30.7)	9.60 (1.10–26.8)	0.314

between these two patient groups. As already noted by Keegan [8] in obese patients, the cause for meralgia may be different, because it is not so much caused by direct compression at the inguinal ligament, but rather, by traction onto the ligament. This traction is caused by the weight of the abdominal fat, which is surrounded by the deepest layer of the superficial fascia, called the fascia of Scarpa (Fig. 5b). This fascia attaches 1–2 cm below the inguinal ligament to the fascia lata. In a standing position, the abdominal fat may thus cause a downward pull of the inguinal ligament and thereby indirectly compress the nerve. Probably this intermittent traction leads to different intraneural changes (mucoid deposition rather than the formation of collagen nodules). The clinical consequence of this finding could be that meralgia is more likely to resolve in patients with obesity than in patients without, but of course again, more research is needed to investigate this hypothesis. Nevertheless, it stresses the importance of weight reduction in obese patients with meralgia paresthetica as a first conservative treatment measure.

Shortcomings study

Obviously, our study has several shortcomings that could not be resolved, because it concerns a clinical study and not an experimental study on nerve compression. First of all, before the start, we expected to find a more significant influence of the duration of symptoms on the occurrence of intraneural changes. Difficulty, however, in determining the effect of duration is that this is determined by the recollection of patients at intake. Further, some patients experience severe symptoms for a relatively short period of time, while others report exacerbation of symptoms after years of relatively mild symptoms. Then, there is "the chicken-and-egg causality dilemma": do the intraneural changes develop due to compression while the patients have symptoms or are the intraneural changes the cause for the occurrence of pain symptoms? This issue could not be solved by this study. The latter explanation seems less likely, because neurolysis still provides pain relief in about 60% of the cases. Hopefully, subgroup analysis for patients

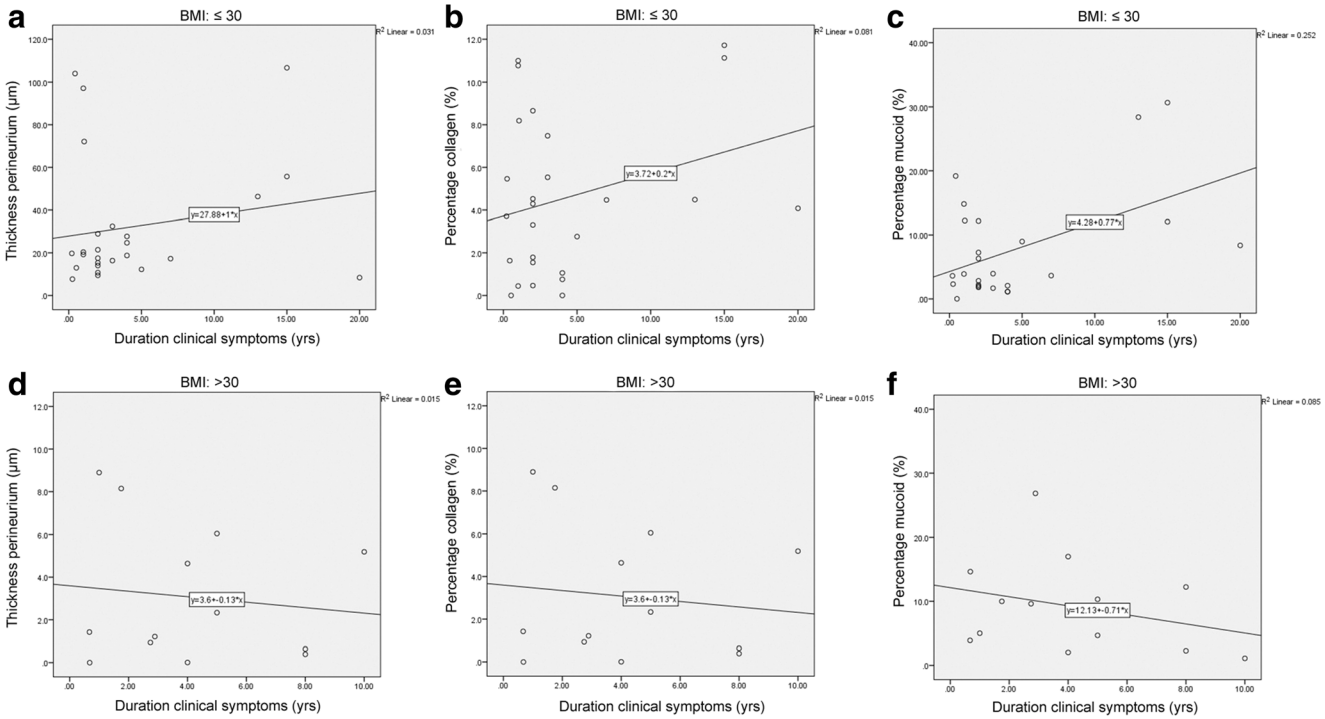

Fig. 4 **a**–**f** Scatter plots showing the occurrence of different intraneural changes for the duration of symptoms for patients with a BMI of 30 or less and patients with a BMI of more than 30

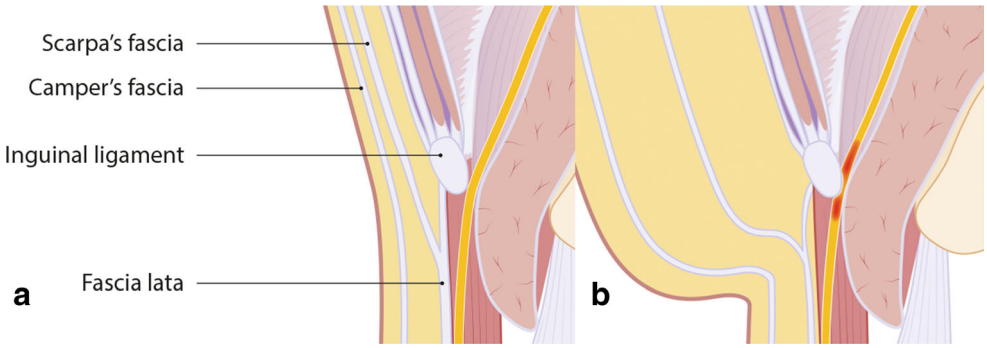

Fig. 5 Medical illustration showing the sagittal course of the LFCN in a normal situation (**a**) and in an obese patient (**b**). In (b), the abdominal fat, which is surrounded by Scarpa's fascia, causes traction onto the inguinal ligament through the attachment onto the fascia lata, which subsequently causes compression of the underlying LFCN

with ≤ and > 1 year of symptoms in the STOMP trial, that is still on-going, will provide more information into this.

Conclusions

This study shows that specific intraneural changes occur in patients with persistent symptoms of meralgia paresthetica. Interestingly, no significant differences were found for patients that underwent neurectomy as primary procedure and patients, in whom previously a neurolysis procedure had been performed, which supports the surgical strategy of neurectomy, also as a primary procedure. Currently, there is no evidence on which procedure (neurolysis or neurectomy) can best be performed in patients with persistent symptoms of meralgia paresthetica [9]. Hopefully, the STOMP trial will provide more information on this.

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Compliance with ethical standards

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

Ethical approval All procedures performed in study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No ethical approval was required for the retrospective part of the study. For the STOMP trial, ethical approval was obtained before start of the study (Dutch trial registry: NTR4530).

References

1. Aszmann OC, Dellon ES, Dellon AL (1997) Anatomical course of the lateral femoral cutaneous nerve and its susceptibility to compression and injury. Plast Reconstr Surg 100:600–604
2. Berini SE, Spinner RJ, Jentoft ME, Engelstad JK, Staff NP, Suanprasert N, Dyck PJ, Klein CJ (2014) Chronic meralgia paresthetica and neurectomy: a clinical pathologic study. Neurology 82:1551–1555. https://doi.org/10.1212/WNL.0000000000000367
3. de Ruiter GC, Kloet A (2015) Comparison of effectiveness of different surgical treatments for meralgia paresthetica: results of a prospective observational study and protocol for a randomized controlled trial. Clin Neurol Neurosurg 134:7–11. https://doi.org/10.1016/j.clineuro.2015.04.007
4. de Ruiter GCW, Kloet F (2018) Anatomical considerations on transposition of the lateral femoral cutaneous nerve. Clin Anat. https://doi.org/10.1002/ca.23057
5. de Ruiter GC, Wurzer JA, Kloet A (2012) Decision making in the surgical treatment of meralgia paresthetica: neurolysis versus neurectomy. Acta Neurochir 154:1765–1772. https://doi.org/10.1007/s00701-012-1431-0
6. de Ruiter GC, Wurzer JA, Kloet A (2015) Recurrence of meralgia paresthetica years after a neurexeresis procedure: a case report. Br J Neurosurg 29:885–887. https://doi.org/10.3109/02688697.2015.1054358
7. Hanna AS (2017) Lateral femoral cutaneous nerve transposition: renaissance of an old concept in the light of new anatomy. Clin Anat 30:409–412. https://doi.org/10.1002/ca.22849
8. Keegan JJ, Holyoke EA (1962) Meralgia paresthetica. An anatomical and surgical study. J Neurosurg 19:341–345. https://doi.org/10.3171/jns.1962.19.4.0341
9. Payne R, Seaman S, Sieg E, Langan S, Harbaugh K, Rizk E (2017) Evaluating the evidence: is neurolysis or neurectomy a better treatment for meralgia paresthetica? Acta Neurochir 159:931–936. https://doi.org/10.1007/s00701-017-3136-x
10. Schwaiger K, Panzenbeck P, Purschke M, Russe E, Kaplan R, Heinrich K, Mandal P, Wechselberger G (2018) Surgical decompression of the lateral femoral cutaneous nerve (LFCN) for meralgia paresthetica treatment: experimental or state of the art? A single-center outcome analysis. Medicine (Baltimore) 97:e11914. https://doi.org/10.1097/MD.0000000000011914

Comments

This study correlates histopathological changes in the lateral femoral cutaneous nerves of patients who underwent either a primary neurolysis followed by a neurectomy due to persistence of symptoms and those who underwent a primary neurectomy. Most of the pathological changes seen in the nerves were similar in the two groups and also did not correlate with either duration of symptoms (although this can be somewhat difficult to assess as the authors point out) or BMI of the patient. These findings are important to report because they are not what one would necessarily expect or predict a priori and have important implications about treatment and further studies that need to be done.

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