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Pathogenesis of neuropathy in Dupuytren's contracture

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Objective To review pathomorphological characteristics of the nerves of the palmar aponeurosis in Dupuytren's contracture and develop a hypothesis of injury mechanisms. **Material and methods** The study included retrospective analysis of medical charts and surgical records of 123 patients with Dupuytren's disease grades 2-4 who underwent partial aponeurectomy, light microscopic micrography of histological preparations of nerve trunks of palmar aponeurosis stained with hematoxylin and eosin. **Results** Three major types of nerve injury to palm aponeurosis were identified in Dupuytren's disease including (1) active and residual perineuritis (41.6 %), (2) necrosis of endoneurial blood vessels and endoneurium (22%), and (3) fibromatosis of nerve sheath (37.4%). Higher rate of bilateral fascial fibromatosis and right-side involvement in unilateral fibromatosis ($p < 0.05$) was observed in Group 2 as compared to Group 3. The mean time interval of contracture formation was shorter in Group 3 by 21/2 years as compared to Groups 1 and 2 ($p < 0.05$). **Discussion** Perineurial lymphocyte and histiocyte infiltration was shown to be an additional criterion of fascial fibromatosis. Necrosis of endoneurial blood vessels was easily suspected in combination of bilateral fibromatosis (strong evidence for familial predisposition) and chronic hand injury of manual handling. Fibromatosis of nerve sheath indicated to aggressive course of the disease. **Conclusion** Pathomorphological characteristics of neuropathy in Dupuytren's disease allowed assessment of fibromatosis and prognosis of the course of the disease in an individual patient to administer postoperative immunocorrective and neurally mediated therapy for optimization of wound healing and recurrence prevention.

Keywords: Dupuytren's contracture, palmar aponeurosis, sensory neuropathy

INTRODUCTION

Dupuytren's contracture is the most common type of superficial fibromatosis [1] affecting palmar aponeurosis and fascias of the hand and fingers. Common characteristics of the disease include fibromatosis nodules and cord-like structures or bands causing flexion contractures of the metacarpophalangeal and proximal interphalangeal joints that usually occur in individuals with genetic susceptibility, unfavourable lifestyle choices and micro-trauma to the palmar tissue sustained manual labour. An electroneurographic study performed in patients with Dupuytren's disease showed decreased conduction velocity in the sensory fibres of the median and ulnar nerves in both digit-wrist and wrist-elbow segments [2]. A spiral cord can cause neuropathy of digital nerves [3, 4] or Dupuytren tissue can compress the palmar digital nerves against relatively inelastic deep transverse metacarpal ligament. Impaired tactile sensibility is reported in 65 out of 99 patients with total active extension deficits of 60 degrees or more from Dupuytren contracture [5], low or absent protective sensation observed in 6 cases; no improvement in sensitivity seen after elimination of contracture. Immunohistochemical evidence of pathological palmar aponeurosis revealed sprouting of nociceptive nerve fibres, mast cells and Langerhans cells [6], an abundance of cells in areas of nerve growth factor expression [7] and higher density of free nerve endings [8]. Nerve branches passing into or crossing the cords or nodules were seen in patients with painful fibromatosis nodules [9]. Nerve fibres normally pass through palmar aponeurosis into hypodermal tissue as a component of nerve trunks – palmar branches of the median and ulnar nerves and dermal branches of digital nerves [9], but no evidence of histological changes in nerves of patients with Dupuytren's disease could be found in the available literature.

Objective To review pathomorphological characteristics of the nerves of the palmar aponeurosis in Dupuytren's contracture and develop a hypothesis of injury mechanisms.

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MATERIAL AND METHODS

The study included retrospective analysis of medical charts and micropreparations obtained during pathomorphological diagnosis of operation material from 226 patients who underwent surgical procedure at the Russian Ilizarov Scientific Center for Restorative Traumatology and Orthopaedics between 2015 and 2017 and in the first half-year 2018. Patients provided voluntary informed consent for operative intervention that was documented in medical history. The patients aged from 27 to 84 years and the majority had grades II and III according to the classification of R. Tubiana [9], and four patients were diagnosed with grade IV contracture. Selective aponeurectomy was produced in most of the cases and one patient underwent total aponeurectomy. Inclusion criterion was histologically verified diagnosis of palmar fascial fibromatosis and presence of representative profiles of nerve trunks in slices of palmar aponeurosis (n = 123). Fragments of palmar aponeurosis excised during selective aponeurectomy were embedded in paraffin according to the standard practice. Sections of 5-7 μm were cut on a Reichert microtome (Austria) and stained with hematoxylin and eosin. Carl Zeiss Primo Star trinocular digital USB microscope, 3.1 Mpix UCMOS videocamera and MicroCapture Ver 6.6 software were used for light microscopy and for digitizing microscope slides.

RESULTS

Patients were subdivided into three groups depending on a pattern and extent of dominating histological changes in the nerves.

Group I (n = 51) included perineuritis with perineurium being infiltrated with macrophages and lymphocytes (Fig. 1, a–f) migrating from perivascular zone to the external perineurium layer (Fig. 1, a), to the regions between the layers (Fig. 1, d) and endoneurium onwards (Fig. 1, b). Images of macrophage opposition and perineurial cells (Fig. 1, b) indicated to necrosis of the latter. Destruction of both perineurial layers and collagenous layers in-between occurred in small fasciculi (Fig. 1, c). Multilayered perineurium appeared to be thick and stratified in nerve trunks with greater vascularity perforating perineurium (Fig. 1, d). Perineural fibrosis is one of outcomes of active perineuritis (Fig. 1, e, f) and it can be combined with obliteration of endoneurial vessels (Fig. 1, f). Perineuritis was accompanied either by axon and myelin degeneration (Fig. 1, a–d) or demyelination of nerve fibres (Fig. 1, e) with no evident increase in Schwann cells.

Group II (n = 27) included necrosis of endoneurial vessels and endoneurium. Fibrosis of perineurium was accompanied by both subperneurial and endoneurial edema and signs of necrotic death of endoneurial blood vessels (Fig. 2, a, b) in 27 patients followed by replacement of endoneurium with transparent basophilic finely granulated cavernous material (Fig. 2, c).

Group III included cases of nerve sheath fibromatosis (n = 45). The condition was likely to develop either after perineuritis (Fig. 3, a) or necrosis of endoneurium (Fig. 3, b). It was characterized by clusters of metabolically active and contractile fibroblasts in perineurial and endoneurial areas. Fasciculi appeared to be sclerotic in addition to excessive collagenous deposits with nerve sheath fibromatosis (Fig. 3, c).

The identified groups of patients were comparable by age at the onset of the disease, at the time of surgery and mean contracture grade (Table 1). The age of the disease was much less in patients of Group III as compared to that in Groups I and II, and frequency of bilateral involvement with palmar fascial fibromatosis and right-sided involvement in unilateral cases was significantly higher in Group II than in Groups I and III (Table 1).

There were no statistically significant differences in comorbidities between the groups and the comorbidities of the sample group are enlisted in Table 2. Arterial hypertension was most common for patients treated for Dupuytren contracture at the RISC “RTO”.

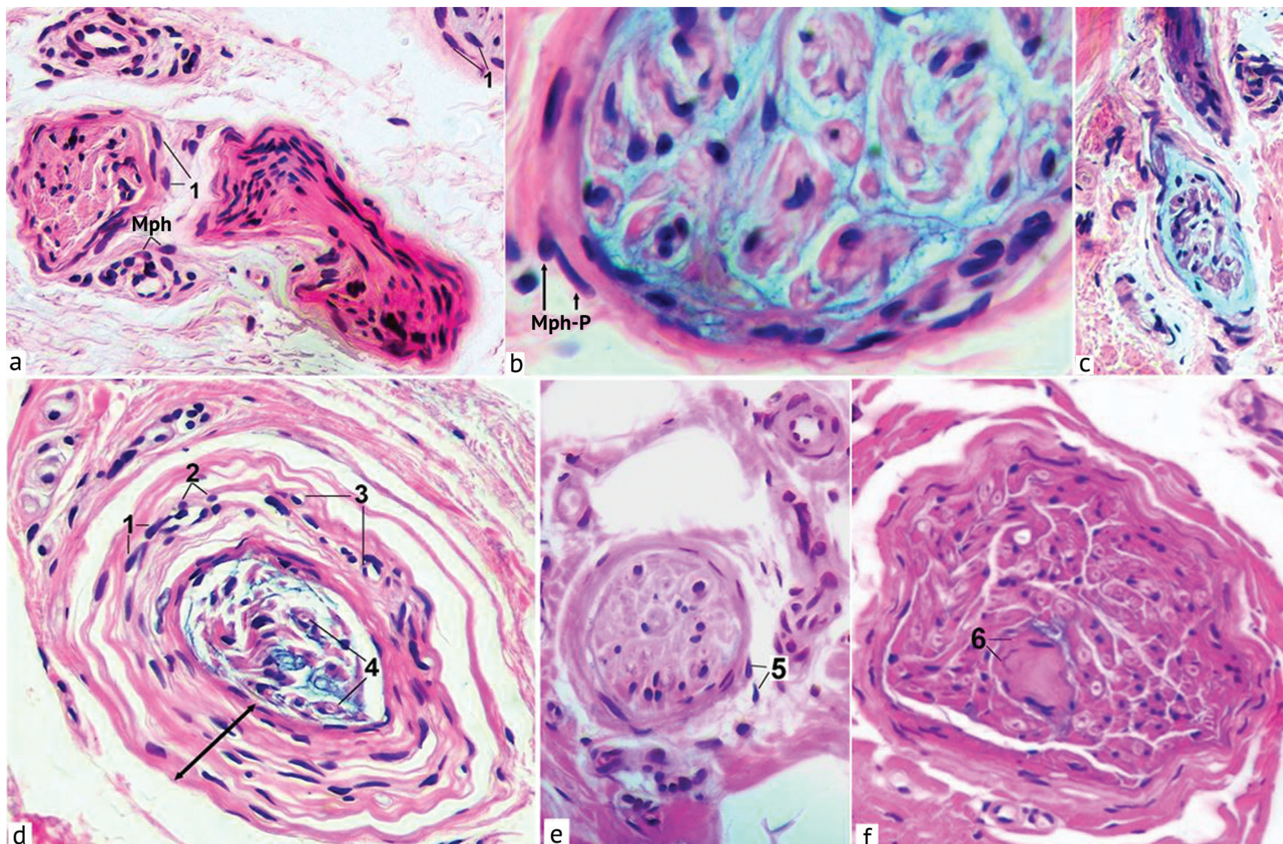

Fig. 1 Active and residual perineuritis: a-d – perineurium infiltrated with inflammatory cells, e, f – impaired lamellar structure and fibrosis of perineurium. Mph – macrophages in perivascular areas, 1 – macrophages in perineurium; Mph-P – apposition of macrophages and perineurial cells, 2 – lymphocytes in perineurium; 3 – blood vessels perforating perineurium; 4 – singular myelinated fibers preserved in endoneurium, double-edged arrow – thickened and stratified perineurium; 5 – migrating macrophages escaping from perineurium; 6 – obliterating endoneurial vessel. Stained with hematoxylin and eosin. Magnification 500× (a, c, d, e, f) and 1250× (b)

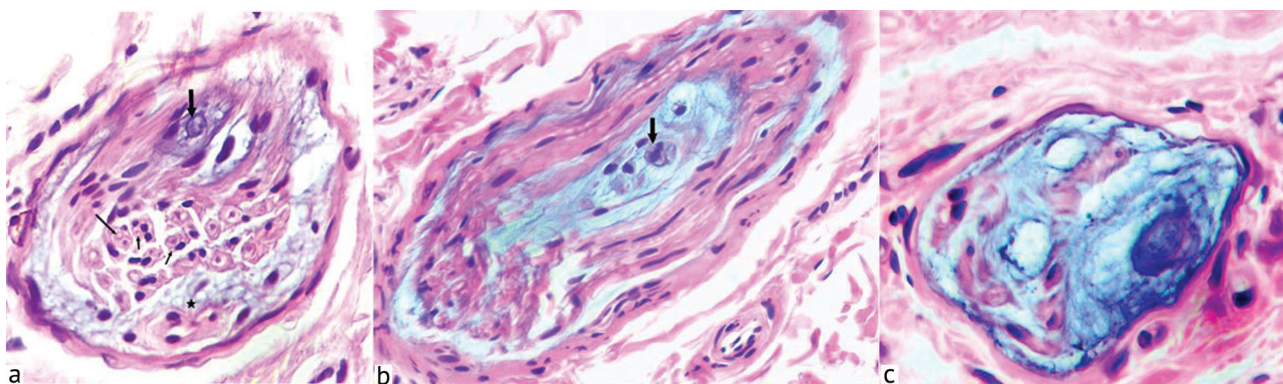

Fig. 2 Injuries to endoneurial vessels and necrosis of endoneurium: a – necrosis of endoneurial vessel (thick arrow) and fibrosis of endoneurium in the upper semicircle of the fasciculus section, preserved myelinated and regenerating hypomyelinated (thin arrows) nerve fibers and intact endoneurial vessel (starlet) in the lower semicircle; b – necrosis of endoneurial vessel and edema of endoneurium in the centre of fasciculus, Wallerian degeneration of nerve fibers, c – subtotal necrosis of endoneurium. Stained with hematoxylin and eosin. Magnification 500× (a, b) and 1250× (c)

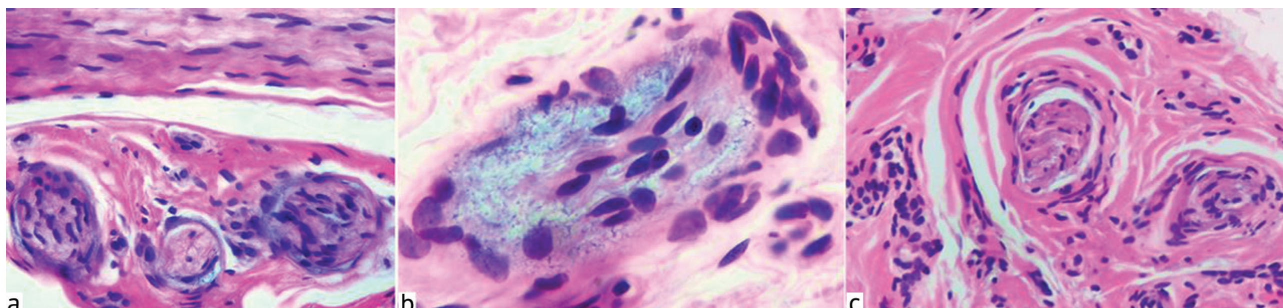

Fig. 3 Fibromatosis of nerve sheaths: a – outcome of perineuritis; b – outcome of endoneurium necrosis; c – collagenous deposits and sclerotic fasciculi. Stained with hematoxylin and eosin. Magnification 500× (a, c) and 1250× (b)

Table 1

Major clinical characteristics of patients in identified groups

Group/parameter	1. Active and residual perineuritis (n = 51)	2. Necrosis of endoneurial vessels and endoneurium (n = 27)	3. Fibromatosis of nerve sheaths (n = 45)
Age at onset of the disease (M ± σ)	53.92 ± 12.49	51.28 ± 10.50	51.52 ± 10,78
Age at the time of surgery (M ± σ)	59.87 ± 9.11	59.96 ± 10.65	57.78 ± 9.67
Age of the disease (M ± σ)	8.55 ± 0.933	8.67 ± 5.283	6.22 ± 5.04
Grade of contracture (M ± σ)	2.58 ± 0.08	2.74 ± 0.53	2.66 ± 0.56
Frequency of bilateral fibromatosis (%)	42.30	62.96[1,3]	35.55
Frequency of the involved right side in unilateral fibromatosis (%)	55.17	0.81[1,3]	48.28

Superscripts: 1 – difference between Group II and Group I at a tendency level ($p < 0.1$); 3 – statistically significant difference between Group II and Group III ($p < 0.05$).

Table 2

Frequency of comorbidity (%) in study patients (n = 123)

Condition	%
Arterial hypertension	40.3
Ischemic heart disease	11.3
Insulin resistance and type 2 diabetes	8.1
Chronic obstructive pulmonary disease	6.5
Liver and gall bladder diseases	5.6
Sensorineural hearing loss	4.0
Lower limb varicose vein disease	4.0
Extreme smoking	3.2
Urinary stone disease	2.4
Adiposis	2.4
Spondylopathies	1.6
Ectopic foci of fibromatosis (Ledderhose disease)	0.8

DISCUSSION

Constriction of microvessels and autoimmune dysfunction of vascular endothelium are considered initial factors involved in the pathogenesis of Dupuytren contracture that provoke proliferation of perivascular fibroblasts, pericytes and myofibroblasts under tissue hypoxia [12]. Examination of operation material from 123 patients with Dupuytren contracture indicated to perineurial cells as another target initiating autoimmune dysfunction in addition to microvessel endothelial cells.

Although peripheral nerve structure has been studied for the last two centuries the question of histogenetic nature of perineurial cells remains subject of discussion [13]. Comprehensive research on ontogenesis, behavior in tissue culture, reparative regeneration, reactive properties and ultrastructure of tissue components of peripheral nerve sheath allow for the cellular perineurium lining to be referred to borderline epithelium; epithelium determines specific features of peripheral hemato-neural barrier and provides homeostasis of endoneurium [14–17]. The findings were further supported by results of immunohistochemical studies: perineurial cells express epithelial membrane antigen [18], Glut-1 [19], a marker of solid compounds being characteristic of intercellular epithelial contacts and endothelial cadherin that regulates permeability of endothelial and perineurial cells and provides hemato-neural barrier functioning [20].

Perineurium contributes to the destruction of major hemato-neural barrier structures – lamellas of perineurial cells and endothelium of endoneurial blood vessels. Neuropathies with perineuritis are described in singular observations being associated with diabetes mellitus, nutritional abnormalities, rheumatological illnesses and malignancy [21]. In our study, nerve impairment was not associated with co-morbidities in patients with Dupuytren contracture. Perineuritis was likely to represent an initial stage of nerve impairment predestinating irreversible changes in the nerve conduction. Signs of remyelination and regenerative clusters of myelinated nerve fibers were

revealed in several observations and they were not accompanied by evident increase in Schwann cells, and spontaneous neuroregeneration in patients with Dupuytren contracture is equivocal. Perineurial fibrosis as an outcome of perineuritis results in disturbed circulation of endoneurial fluid, endoneurial edema, intrafascial pressure increase, rapidly progressing occlusion or necrosis of endoneurial vessels. This leads to death of nerve fibers and glial cells with endoneurial matrix being replaced with transparent basophilic finely granulated cavernous material [22, 23] that cannot serve as a substrate for nerve regeneration. The study showed that the likelihood of the changes was higher in combination of bilateral fibromatosis (including evident genetic susceptibility) and chronic hand traumatization.

Replacement of perineurium and endoneurium with clusters of metabolically active and contractile fibroblasts followed by collagenous deposits and sclerotic fasciculi (fibromatosis, and not fibrosis of nerve sheaths) occurred in cases of aggressive course of the disease. It is supported by the fact that the mean time of contracture formation was 2.5 years less in the group with fibromatosis of nerve sheaths as compared to patients of other groups.

Compression is seen as a major mechanism of nerve impairment in patients with Dupuytren contracture [3, 4, 9]. Histological manifestations of human chronic compression neuropathy include epineurial and perineurial fibrosis, thinning of myelin sheaths of myelinated fibers and appearance of small regenerating unmyelinated fibers [24]. Abnormal immune response and reparative process typical for Dupuytren disease [25] act as additional chains of pathogenesis of neuropathy and determine specific variants of nerve impairment being different from compression neuropathy and identified in our study (Fig. 4).

Limitations of our study include absence of findings of transmission electron microscopy or immunohistochemistry supporting sprouting of unmyelinated fibers, however, increase in nociceptive fibers in patients with Dupuytren contracture was reported by some authors [6]. This phenomenon can be viewed as a temporary event because destruction of perineurium, partial or complete replacement of endoneurium with cell-free material or sclerosis of fasciculi lead to gradual collapse of nerve trunks in palmar aponeurosis. A. Florescu [2] reported impaired conduction in the nerves of the forearm in patients with Dupuytren contracture reflecting retrograde neurodegenerative changes. Objective clinical assessment of the magnitude is difficult enough, and transformation of cell bodies of primary afferent neurons being similar to delayed posttraumatic changes in experimental animals cannot be disregarded [26].

Cutaneous nerves control blood vessel remodeling [27] and wound healing [28] in addition to sensory innervation. Delayed wound healing is a most common postoperative complication of fasciotomy observed in 22.9 % of the cases reported in meta-analysis of 143 publications and is likely to be caused by denervation changes [29].

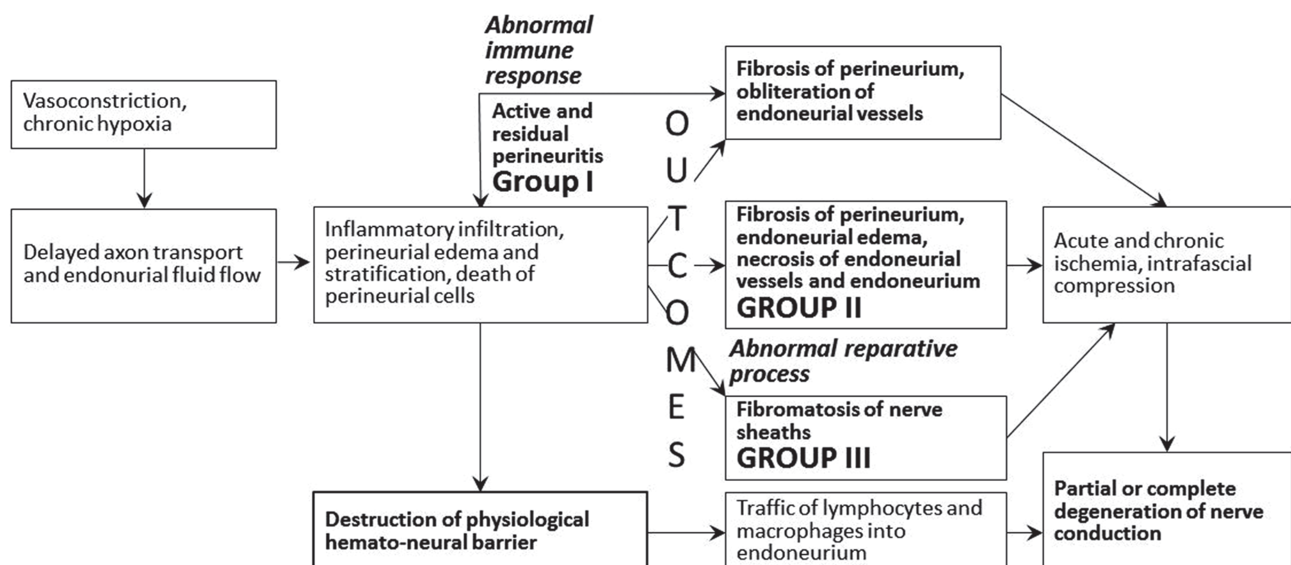

Fig. 4 Diagram of pathogenesis of neuropathy in Dupuytren contracture

CONCLUSION

Three major types of nerve impairment in palmar aponeurosis were first identified in patients with grades 2–4 Dupuytren contracture including active and residual perineuritis, necrosis of endoneural vessels and endoneurium, fibromatosis of nerve sheaths based on pathomorphological findings of operation material. Pathomorphological characteristics of neuropathy in Dupuytren's disease allowed assessment of fibromatosis and prognosis of the course of the disease in an individual patient to administer postoperative immunocorrective and neurally mediated therapy for optimization of wound healing and recurrence prevention.

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