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Mini Review

Dupuytren's Contracture: Updated Comorbidity, Renin-Angoitensin System and Perspective on Pathogenic Treatment

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Abstract

Dupuytren's Disease (DD) is a fibro proliferative disorder damaging the palmar fascia of the hand and integumentary tissues leading to debilitating condition-fixed flexion contracture of the digits. In the last decades epidemiology and pathogenesis of DD was extensively studied. Together with genetic predisposition, life style factors, aging and co morbidity integrative regulatory systems (radical oxygen specimen and tissue renin-angiotensin system) are involved in disease development, its tumour-like behavior and progression through vascular inflammation, leakage, vasoconstriction, exacerbation of hypoxic conditions and compensatory angiogenesis. Despite a lot of surgical and mini-invasive treatment options for Dupuytren's contracture correction, fascial fibromatosis is incurable because it possesses infiltrative growth and frequent recurrence. There are growing evidences that tissue renin-angiotensin system pharmacological modulation may be effective adjuvant treatment of various stages of DD. Well-known organ protective and immunomodulatory effects of such therapy would improve the active life longevity of patients.

Keywords: Dupuytren's contracture; Palmar fascia; Fascial fibromatosis; Myofibroblasts; Vasoconstriction; Tissue renin-angiotensin system

Introduction

Dupuytren's contracture is progressive flexion contracture of the hand. Fingers bending towards palm and their extension became limited or even impossible. Fixed hand deformation is the end stage of DD (palmar fascial fibromatosis)- incurable fibroproliferative disorder which leads to nodular formation, thickening, shortening and fibrosis of palmar and digital fascia and overlying skin, when normal bands of palmar fascia transform to fibrous cords.

The main clinical problems of DD-suboptimal functional results of various treatment methods, high recurrency rates, high age-dependent co morbidity.

The objective of this review is to consolidate the well-known and present day literature to better understand the current management, epidemiology, old and new insights in pathogenesis and the future perspective of treatment strategies of DD.

Discussion

Current treatment of Dupuytren's contracture

Criteria of the correct treatment of Dupuytren's contracture are proper timing and choice of the most optimal option that ensures the maximal function with minimal morbidity and minimal risk for the patient [1]. Analysis of 26 studies, evaluating the effect of pharmacological therapy (n = 11), physical therapy (n = 5) and radiotherapy (n = 10) on early DD shows that evidence of physical therapy efficacy is insufficient, intralesional steroid injection and radiotherapy appeared to lead to softening of nodules and to retard disease progression but lacked rigorous evaluation [2]. Injections of collagenase into Dupuytren's cords are mini-invasive method for treating contractures of Metacarpophalangeal (MCP) and Proximal Interphalangeal (PIP) joints. In prospective cohort study assessing 2-year treatment effect durability, improvement was maintained in 72% of the treated hands, complete contracture correction was seen in more than 80% of the MCP but in less than half of the PIP joints [3].

Analysis of 20 studies, involving 1584 patients, have shown no difference in clinical outcome between patients treated with Percutaneous Needle Aponeurotomy (PNA) and those treated with collagenase clostridium histolyticum, PNA tended to provide higher patient satisfaction with fewer adverse events, but had a higher rate of recurrence compared with limited fasciectomy, currently there remains limited evidence to guide the management of patients with Dupuytren's contracture [4].

The open surgical procedures for treatment of DD indicated in patients with positive table top test and include limited, segmental and radical fasciectomy and dermo fasciectomy [1]. External fixators were used in two-stage or single-stage approach for patients with severe PIP contractures [5-7]. Amputation, most commonly of the little finger, can be performed when other procedures are not expected to achieve a sufficient degree of correction; one of the possible complications is the formation of a painful neuroma [8]. Another variant - joint arthrodesis - results in shortening of the finger but exclude recurrence.

Treatment choice depends on the severity of Dupuytren's disease and patient/surgeon's preference. Limited fasciectomy is preferred method [9], due to the lesser risk for neurovascular complications (versus needle fasciotomy), though the recurrence rate 20% after limited fasciectomy is important disadvantage [8]. "Neither a cure nor an optimum form of treatment exists" for Dupuytren's contracture [4].

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Epidemiology and co morbidity of Dupuytren's disease

Roughly prevalence of DD is 3% to 6% of white population; the disease is rare in nonwhite people [10]. Large study of twin pairs has shown that genetic factors play a major role in the development of DD [11] but multiple cases without a family history also exist. Many other factors (advanced age, male sex, occupation, life style, comorbidities) have been discussed as contributing to ethio-pathogenesis of DD for many years in Western countries [12-17].

In Taiwan (Ethnic Chinese) the most common comorbidities in DD were hypertension (29.6%), diabetes mellitus (21.9%), hyperlipidemia (14.8%), ischemic heart disease (10.5%), and chronic obstructive pulmonary disease (8.0%) [18].

In Brasilian patients with DD coexisting diseases were: diabetes mellitus (49%), especially the insulin-dependent (62%), hypertension (55.2%), and dyslipidemia (19%). With regard to lifestyle, 22% were smokers and 9% were alcohol consumers [19].

Among 123 patients with Dupuytren's contracture operated in Russian Ilizarov's centre 40.3% were suffered from arterial hypertension, 11.3% from ischemic heart disease, 8.1% from insulin resistance and diabetes type 2, 6.5% - from chronic obstructive pulmonary disease, and 5.6% - from liver diseases [20].

Analysis of 33 publications has demonstrated associations between DD and diabetes mellitus, liver disease, and epilepsy [21]. Dupuytren's contracture was presented in almost equal percentage in patients with alcoholic and non-alcoholic biopsy-proven liver disease (25% vs 28%) [22].

The percentage of patients with Dupuytren's contracture was higher in the psoriasis population than in the non-psoriasis population (19.6% vs 3.6% respectively) [23].

Old and new insights in pathogenesis of Dupuytren's disease

From clinical point of view palmar fibromatosis are to be found in an intermediate position between benign fibrous tumors and fibro-sarcomas because it possesses infiltrative growth and frequent recurrence but never metastasize [24]. On molecular and cellular levels, Dupuytren's disease matches distorted wound-healing response rather than neoplastic process [25]. Regulatory growth factors strictly control hemostasis, cells proliferation and collagen deposition in normal wound scarring repair. Besides growth factors free radicals, metalloproteinases, sex hormones, mechanical stimulation, and gene modified expression considered to be responsible of an exaggerated cell activation, increased collagen synthesis and deposition in DD [26].

G. Gabbiani [27] was the first who discovered myofibroblasts in palmar fibromatosis and suggested that these cells are responsible for contraction of cords and excessive matrix deposition [28]. The marker of myofibroblasts is α–smooth muscle actin (α-SMA), similar to actin isoform of vascular smooth muscle cells [29]. In recent clinic-pathological study of 25 Dupuytren's contracture cases ki-67 proliferation index was 1-2% in 24 patients without recurrence and >5% in one patient with recurrence which also presented strong positive staining for α-SMA [30].

Many authors agreed that Dupuytren's disease is myofibroblastic disorder. In ultra structural study of 43 cases the majority of cells in the proliferative and the involutional nodules were myofibroblasts, in the involutional nodules they contained microfilament aggregates-probable result of actin filaments contraction; perivascular hemorrhages and hemosiderin together with macrophages lymphocytes accumulations were found in the proliferative nodules [31].

Detailed characterization of the inflammatory cells, pro-inflammatory and pro-fibrotic cytokines near markedly narrowed vessels in DD was obtained recently [32].

Progressive fibro-proliferative process causes strangulation of microcirculatory bed and larger vessels. The comparative study of hand hemodynamics in 15 healthy volunteers and 10 patients with Dupuytren's contracture by Pulsed Ultrasound Doppler Velocimetry (PUDVM) have shown signs of vasoconstriction at the level of superficial palmar arc in patients. This finding was in accordance with histological signs of the perforating palmar fascia arteries constrictive remodeling [33].

Constrictive remodeling of palmar fascia perforating arteries supplying the hypodermis was more severe in patients younger than 55 years old than in senior group, but compensatory changes of hypodermis capillarization were also more expressed [34]. The method of laser flowmetry revealed that the base capillary flow of the palmar skin in that group was increased compared to healthy control subjects and older group.

J.T. Hueston considered the skin in DD as "mediating neurovascular organ, and is not simply involved secondarily" [35]. Under transmission electron microscope observation myofibroblasts were found in the skin and subcutaneous tissues from Dupuytren's contracture patients who accepted dermofasciectomy [36].

Mesenchymal stem cells as potential source of myofibroblasts were also identificated in perinodular fat and skin [37]. These cells have the ability to differentiate into three mesenchymal lineages (osteogenic, chondrogenic and adipogenic). Metaplastic formation of cartilage and bone [38,39] and areas of lipomatosis in dense fibrous tissue of Dupuytren's cords [39] were described in surgical material.

Lessons from pathogenesis and co-morbidity

The strong participation of vessels narrowing, tissue ischemia and reactive oxygen species in the pathogenesis of DD was known for many years. This suggests that vasodilators, oxygen therapy and antioxidants could be effective in the treatment of this pathology. First of all it was noted that antioxidant allopurinol given for other reasons improved hand function in some Dupuytren's contracture patients [40]. Translation of allopurinol therapy of DD to clinical practice did not reach the expected success [41]. Total relief of symptoms of early DD was obtained with HBO treatment in one clinical case [42]. Possible prevention of tissue ischemia was achieved in two cases in which topical nitro-glycerine was used postoperatively [43]. Relief of Dupuytren's contractures of both hands over a 3-year period while taking antioxidant (coenzyme Q10) for other condition was described recently [44].

Successes achieved only in separate cases could be due to complexity of the condition. Besides hypoxia compensatory

angiogenesis plays also important role in both basic processes and in DD also [45]. In some patients pathologic variants of microcirculatory hemodynamic and injuries of micro vessels became irreversible [46] and vasogenic pharmacotherapy is problematic.

The findings that DD is associated with epilepsy, diabetes, cardiovascular diseases, Chronic Obstructive Pulmonary Disease (COPD), liver diseases and psoriasis mean that all mentioned diseases may have common factors that impact to their pathogenesis. Renin-Angiotensin System (RAS) is one of the probable such candidates, uniting all these diseases.

For many years RAS was defined as endocrine system involved in regulation of blood pressure and water/electolyte balance. Circulating RAS components (pressors renin and angiotensin) were known in past centuries, but in the last twenty years the local or tissue RAS and its new roles in inflammation, immunology and aging were discovered [47]. The tissue RAS has two codependent arms which signal through type 1 and type 2 receptors-one being pro-inflammatory and pro-fibrotic and one being anti-inflammatory and anti-fibrotic [48]. New roles of RAS in clinical pathology and effects of its inhibition in therapy of the diseases are being studied intensively in patients with cardiovascular diseases [49], epilepsy [50], diabetes and hypertension [51], COPD [52], liver diseases [53], and psoriasis [54].

There are several reports on the RAS receptors and effectors in Dupuytren's tissues. ATIIR1 (angiotensin II receptors type 1) have been demonstrated on the myofibroblasts [55]. Another research has shown that ATIIR1 was mildly positive only in one patient from 11 but all specimens were stained extensively for ATIIR2 [56]. Angiotensin II was among effective pharmacological promoters of contraction in cultured Dupuytren's disease myofibroblasts [57]. Expression of PRR (pro-renin receptor), ATIIR1, ATIIR2, and ACE (angiotensin-converting enzyme) was demonstrated on the embryonic stem cell–like cell population on the micro-vessels surrounding Dupuytren's disease nodules and cords by immune-histochemical staining [58].

ATIIR1 signaling stimulates vasoconstriction and VEGF-mediated angiogenesis in solid tumors, VEGF (vascular endothelial growth factor) increases vascular permeability and leakiness, these conditions exacerbate hypoxia and contribute to the spread of the tumor, but tagerting the RAS may improve cancer treatment [59]. Vascular inflammation and leakiness, constrictive arterial remodeling and hyper-vascularity of fat tissue are typical changes in palmar fibromatosis tissues [34].

The first selective nonpeptide AT2 receptor agonist-compound 21-was reported in 2004 [60]. Its anti-inflammatory and antifibrotic effects were investigated [61] and now this drug is in clinical trials [62]. Recently this substance was explored on the model of Dupuytren's disease using a xenograft and it was established that compound 21 significantly decreases expression of pro-fibrotic genes and myofibroblast proliferation [63].

Conclusion

In summary, the open surgery remains the treatment of choice of Dupuytren's contracture. Besides limited fasciectomy, adjuvant surgery (dermo fasciectomy and external fixations for deformity correction) should improve the long-term results. The recent advances in our understanding of disease pathogenesis have led to novel adjuvant therapy based on RAS modulation. We believe that well-known organ protective and immunomodulatory effects of such therapy would improve the active life longevity.

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