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Dupuytren's Contracture And Prolonged Treatment With Phenobarbital

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Abstract:
Background*: Dupuytren's contracture is a progressive fibrotic condition affecting the palmar and digital fascia, leading to a progressive and irreversible flexion of the fingers. Antiepilepsy drug like Phenobarbital PB have been implicated in the development of Dupuytren's contracture.*
Clinical case report: *In our case report on two patients, we study the association between prolonged treatment with PB and Dupuytren's contracture.*
Conclusion: *Phenobarbital PB is implicated in palmar fibrosis. Development of Dupuytren's contractures may take longer after intiation of Phenobarbital.*
Key Words*: Dupuytren's disease, Phenobarbital, Aponeurectomy*

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I. Introduction

Dupuytren's disease is a pathology characterized by progressive fibrosis of the palmar fascia [1]. It is a slowly progressive benign fibroproliferative disease of the palmar fascia. The initial thickening of the fascia usually appears as a nodule in the palm, which can be painful or painless and often goes unnoticed. Joint stiffness and loss of complete extension develop insidiously over a variable period, usually several years.

As the process progresses, the nodules may progress, to form longitudinal bands called cords on the palmar fascia. The finger gradually loses its extension, with the appearance of contractures which cause one or more fingers to flex at the level of the metacarpophalangeal joint, the proximal interphalangeal joint, or both. The result is a deformation of the fingers in fixed flexion.

The cause of Dupuytren's disease is unknown; important factors include genetics, ethnicity, gender and age, and some environmental factors (Dolman et al, 2011) [2]. It most often affects subjects of Northern European ancestry, seems to have a pronounced genetic predisposition. In a study involving patients from the Netherlands, Germany and the United Kingdom, six of nine genetic loci associated with genetic susceptibility to Dupuytren's disease contained genes encoding proteins in the Wnt signaling pathway (Marike M van Beuge et al,2015) [3]. Overstimulation of this pathway, which can regulate cell proliferation, could potentially lead to fibroblast proliferation and nodule formation via effects on beta-catenin (vincenzo M Varallo et al, 2003) [4].

Pathologically, Dupuytren's disease is characterized by fibroblastic proliferation and disordered deposition of cartilage with fascial thickening. The formation of one or more nodules survives the early proliferative stage of the disease and constitutes the pathognomonic lesion of Dupuytren's disease. Nodules form due to the proliferation of fibroblasts in the superficial palmar fascia and are histologically composed of fibroblasts and type III collagen. Smooth muscle fibroblasts and myofibroblasts are present in the nodules; Accumulated concentrations of prostaglandins are also found in nodules and can influence myofibroblast contractility (Badalamente et al, 1988) [5]. The flexor tendons are not involved, but invasion of the dermis occurs and results in characteristic wrinkling and tethering of the skin.

The presence of CD3-positive lymphocytes and expression of major histocompatibility complex (MHC) class II proteins also reveal the possible role of a T-cell-mediated autoimmune response. (Baird KS et al, 1988) [6].

II. Clinical Case

Case 1:

A 45-year old male had a history of cryptogenic epilepsy with generalized seizure. Since the age of 20 years PB at 100 mg/day was used in monotherapy. No others significant risk factors for Dupuytren's contracture. The patient presented palmar fibromatosis of the right hand V and the left one (IV, V), severe extension deficit without pain. PB was substituted by Lamotrigine LTG 50 mg/day. Subsequently a partial aponeurectomy of the hand was performed.

Case 2:

A 29-year old male had a history of symptomatic epilepsy with focal seizures due to meningitis, was treated since the age of 5 years with PB monotherapy at 200 mg/day. No history of the risk factors for palmar fibromatosis. Flexion contracture without pain of the right little finger. PB was substituted by Levetiracetam LEV 1500 mg/day. Surgical treatment was performed by partial aponeurectomy

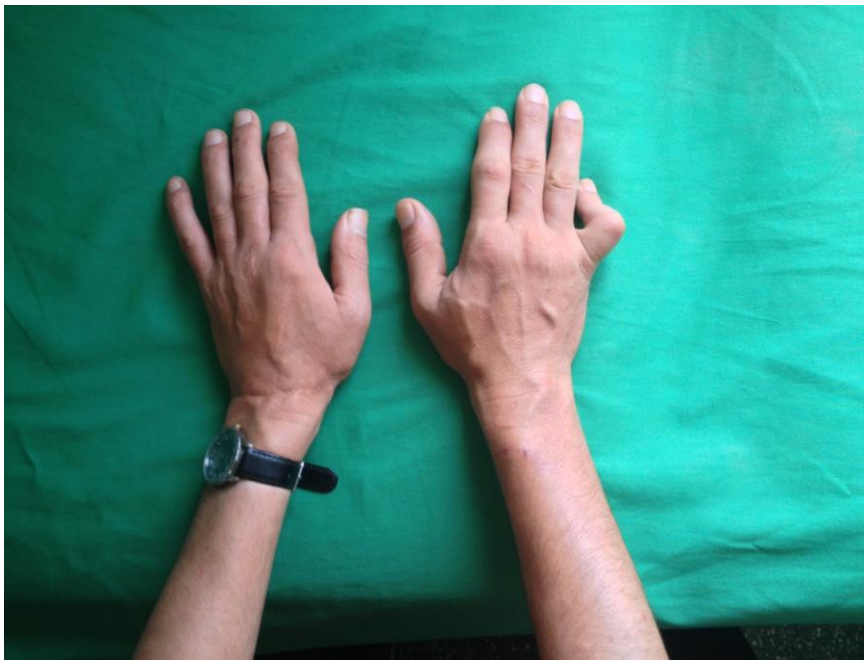

Figure 1. Palmar fibromatosis of the right hand V

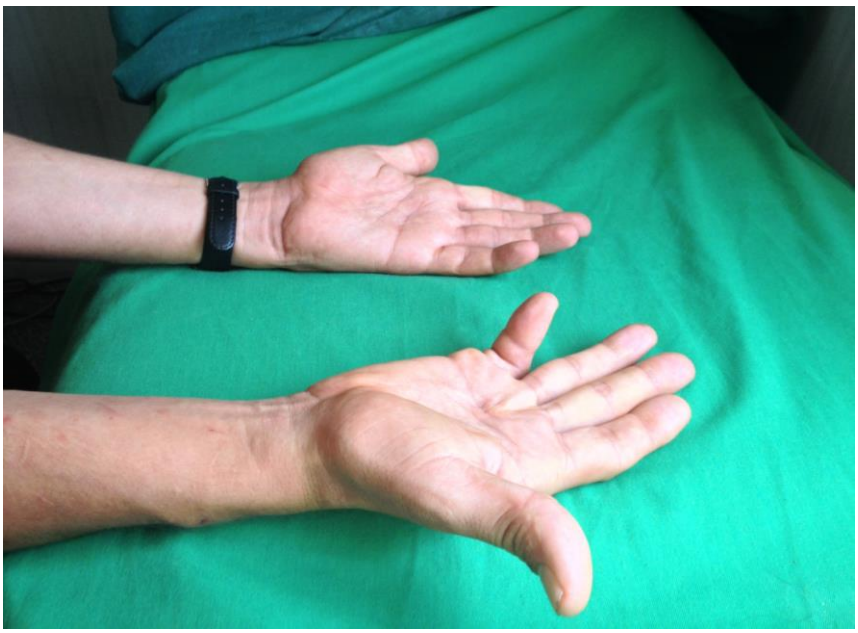

Figure 2. Palmar fibromatosis of the right hand V and the left one (IV, V)

III. Discussion

The first patient presented with palmar fibromatosis (Dupuytren's disease) of the right hand V and the left one (IV, V). He had been treated with phenobarbital monotherapy for 25 years.The palmar fibromatosis occurred after 24 years of drug therapy at dosage 100 mg/day.

The second patient presented with palmar fibromatosis(Dupuytren's disease) Flexion contracture without pain of the right little finger V . He had been treated with phenobarbital monotherapy for 25 years. The palmar fibromatosis occurred after 25 years of drug therapy at dosage 200 mg/day.

The association between the use of barbiturates and the development of joint stiffness was identified (Maillard et al, 1925) [7]. and later named (Gardenal rheumatism) (Beriel et al, 1934) [8].A clinical association between Dupuytren's disease and BP was initially postulated by Lund who examined a large Danish cohort (Lund, 1941) [9]. A comprehensive summary was given by Schmidt (Schmidt , 1983) [10], who attributed Dupuytren's disease, Ledderhose syndrome, and (frozen shoulder) to chronic BP use. He emphasized that the development of Dupuytren's disease can occur from 3 months to 20 years after the introduction of BP treatment, that it is dose-dependent.

Dupuytren's disease mainly affects men of northern European origin with a male-to-female ratio of 6 to 1 and a delay in onset of the disease in women of 10 years. In subjects of Asian, Arab and African origin, Dupuytren's disease remains rare (Brenner et al, 2001) [11].In Europe, the prevalence decreases from northern countries with around 2% in Germany (Brenner et al, 2001) [11] to becomes rare in Mediterranean region (Shaw et al, 2007) [12].

IV. Conclusion

Phenobarbital PB is implicated in palmar fibrosis. Development of Dupuytren's contractures may take longer after intiation of Phenobarbital. Therapeutic management consists of surgical excision (aponeurectomy) and substitution of another antiepileptic treatment for phenobarbital PB.