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Dupuytren's Disease

Abstract

Dupuytren's disease (DD) is a chronic condition in which fibrosis of tissue beneath the palm of the hand occurs. Causes and mechanisms of this disease's development are still not entirely understood. However, symptoms and the negative impact on individuals' quality of life are evident. While existing therapies for DD have been established to prevent and slow its progression, further research is needed to effectively address it on a wider scale.

Keywords

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Comments

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Part I: Scientific Research Review

Introduction

Dupuytren's disease (DD), also known as Dupuytren's contracture, is a chronic condition characterized by fibrosis of tissue beneath the palm of the hand. This tissue is known as the palmar fascia or palmar aponeurosis, and it is responsible for connecting the palmaris longus muscle of the forearm to ligaments in the palm (Mathew, 2016). Fibrosis causes cellular nodules to form that are replaced by acellular, tendinous cords as the disease progresses. These structures thicken and shorten the palmar fascia. When overlying skin binds to abnormal tissue, knots and cords form that pull fingers into a permanent contracted position (Bayat, 2016). Over time, this contracture becomes more severe and can progress to the point where individuals cannot fully extend their hand.

Resulting hand deformities complicate everyday activities, affecting everything from putting ones' hands in pockets to doing manual work. These challenges are exacerbated by instances in which both hands are affected, which account for approximately 45% of cases (Mathew, 2016; Loos, Puschkin, & Horch 2007). Despite DD's impact on patients' quality of life, it is non-lethal disease that primarily affects middle-aged men of Northern European descent and 4-6% of Caucasians globally (Mathew, 2016). An estimated ten million Americans and thirty million people worldwide are affected by it (Dupuytren's Foundation, 2017). Even though it is widespread, it is still not well understood and requires further research.

Etiology

The causes of DD are unclear and officially considered unknown. However, several non-modifiable and modifiable factors are suspected to be related to its onset. Genetics is one of the most widely recognized and believed to be most strongly related. Individuals with a known

family history are genetically predisposed with an 80% risk of heritability (Larsen et al., 2015). This estimate is based on comparisons of instances of DD between identical monozygotic and fraternal dizygotic twins. Identical twins had higher instances of DD among them, suggesting that genes do play a significant role since they share all of their DNA compared to their fraternal counterparts (Larsen et al., 2015).

People with a genetic predisposition for DD tend to not only require treatment but require treatment at an earlier age. For instance, in Becker et al.'s (2015) findings, these individuals required surgical intervention three times as much as patients without a family history of DD. They experienced symptomatic recurrence of the disease two times greater than their non-genetically predisposed counterparts. These results suggest genetics not only contribute to DD but contribute to a more aggressive form of it. These findings are further supported by observed upregulation in MafB gene in DD patients but is not yet fully understood (Matthew, 2016).

However, modifiable lifestyle factors may also contribute to the development of DD for those with and without genetic predisposition but are highly disputed. Factors such as smoking, alcohol consumption, hypertension, diabetes, and repetitive motions or vibrations are all considered possible causes. While some studies argue that hypertension and smoking have been implicated (Becker et al., 2015), others have found no statistical significance associated with any potential modifiable factors (Loos et al., 2007). Even though these factors are controversial, theories based on them have been created to attempt to explain DD's pathogenesis.

One plausible theory is individuals with genetic predisposition for DD affected by a secondary factor experience microvascular ischemia in the palmar fascia (Matthew, 2016). This serves as a catalyst for the conversion of xanthine dehydrogenase to xanthine oxidase, which oxidizes hypoxanthine to xanthine and uric acid. Oxidization also produces free radicals. They

stimulate an inflammatory immune response that causes an increase in the production of cytokines such as interleukin-1 (IL-1), transforming growth factor beta (TGFB), and platelet-derived growth factor. Together these substances prompt increased production of fibroblasts and differentiation into myofibroblasts. Stimulation and high density of fibroblasts promotes increased production of type III collagen, which is associated with DD (Matthew, 2016).

Aspects of this theory are supported by current literature, which notes histological and blood chemistry changes consistent with inflammation. For instance, microvascular changes and the increased expression of mononuclear cells, such as T-cells and their receptors, have been observed in DD patients (Mayerl et al., 2016). This response is characteristic of immune response involving white blood cell infiltration and inflammatory factor expression in response to damage. While Bianchi et al. (2015) also noticed changes normally associated with inflammation, they differed slightly. For instance, increased expression of mononuclear cells and macrophages were not found. However, people with DD did have increased concentrations of circulating pro-inflammatory cytokines, such as IL-1, TGFB, and vascular endothelial growth factor. All of these secretions are needed for increase fibroblast and myofibroblasts proliferation associated with DD, which were also observed (Bianchi et al., 2015).

While theories, like the one previously discussed, are plausible, they are based on the pathophysiology of DD and what little is known. However, it fails to explain many details about DD. Lack of consensus among study findings is also unconvincing. Overall, more information on modifiable factors is needed for a better understanding of DD's causes.

Pathophysiology

The progression of DD consists of three stages in which fibroblasts are produced en masse due to an undetermined factor. During the proliferative phase, they differentiate into

myofibroblasts that form vascularized nodules on the fascia. Nodules are typically located under the skin near the metacarpophalangeal joint. It's followed by the involitional phase, in which nodules typically grow up toward the finger based on how tension is distributed within them. As they extend along the normal tendinous band of fascia, they form cords. In addition to being composed of myofibroblasts, cords are also made up of collagen secreted by excess undifferentiated fibroblasts. In the final residual phase, the cord continues to spread and begins to tighten due to collagen build up. An increase in nerve growth factor also causes a decrease in cyclic adenosine monophosphate concentrations and increases intracellular calcium levels, which lowers the threshold needed for myofibroblasts' contraction. Nodular tissue disappears, and the fibrous but acellular cord remains (Matthew, 2016; Bayat, 2016).

High concentrations of fibroblasts, myofibroblasts, and collagen are therefore present in the palmar fascia of individuals with DD (Bianchi, 2015; Alfonso-Rodríguez et al., 2014). DD patients also have higher concentrations of compounds associated with myofibroblasts, such as muscle actin and fibrillar components of the extracellular matrix (Alfonso-Rodríguez et al., 2014). The amount of each component varies depending on what stage the disease has reached, with more fibroblasts present initially and more myofibroblasts and collagen present in later stages. These characteristics are not unique to DD and are also seen in other conditions associated with fibrosis. However, the extent of their cell proliferation, differentiation, and build up remains less than that of DD patients' (Alfonso-Rodríguez et al., 2014).

Clinical Features & Diagnosis

As the palmar fascia thickens and shortens, nodule development is visible beneath the palm. They manifest as firm lumps of tissue that may be initially mistaken as calluses or arthritis (Matthew, 2016; WebMD, 2016). Any sensitivity or pain usually results from tissue buildup that

has formed around or displaced nerve fibers and/or tendons. As the disease progresses, these nodules form cords that extend from the palm onto the fingers, causing the hand to bend inward. Contraction is initially undetectable but can worsen and severely limit patients' range of motion. Normally, the ring and pinky fingers are solely affected, but the middle finger may also be if the condition is severe. The reason behind this phenomenon is not entirely understood.

DD can be diagnosed through a physical exam in which a physician can look and feel for skin puckering and knots (WebMD, 2016). A tabletop test may also be used in which patients are required to place their open hand on a flat surface (Mayo Clinic, 2016). If they cannot, this indicates that there is contracture. Other tests are not normally needed. Severity is divided among three grades. The first is characterized by the presence of nodules or cords, the second is when cords are present in the fingers and minimally impair finger movement, and the third is when an obvious contracture is present (Matthew, 2016).

Treatment

While there is no cure for DD, several treatment options are available for patients depending on their condition. The most common treatment is fasciectomy, which is a surgical intervention that consists of cutting excess tissue to relieve contraction and pressure (WebMD, 2016). Post-operative physical therapy is required to regain function and flexibility. This procedure is normally successful but depends on the severity of contracture. For instance, 96% of patients who have loss less than 30° of range of motion tend to have complete recoveries and are able to fully open their hand (Stepić, Končar, & Rajović, 2017). Patients with more severe contracture may not regain the same degree of range of motion.

Other non-invasive therapies include collagenase *Clostridium histolyticum* (CCH) injections that are directly administered to affected areas (Bainbridge et al., 2012). The

collagenase breaks down collagen deposition and has yielded positive results both on its own and in conjunction to fasciectomy (Tay, Tien, & Lim, 2015; Watt, Curtin, & Hentz, 2010). Immune-targeting therapies are promising, especially in light of DD's association with inflammation. For instance, treatments targeting cytokines, tissue proliferation, and T-cell activity could be beneficial as suggested by Alfonso-Rodríguez et al. (2014) and Mayerl et al. (2016) respectively. Intralesional steroid injections, consisting of corticosteroids, have already been shown to soften nodules (Bale et al., 2010). Radiotherapy appears to have the same effect (Bale et al., 2010). It also appears to be effective in preventing the progression of the disease, but to be of no effect for more advanced cases (Betz et al., 2010). While these methods have been effective, more research is required to understand their long term effects.

Prevention

DD does not have any established prevention methods. While collagenase injections and radiotherapy may be used proactively in the future, monitoring and early intervention are the current consensus.

Part II: Living with Dupuytren's Disease

Amidst all of the Thanksgiving festivities this past November, my uncle came to our house to celebrate with his right hand bandaged in white gauze. My aunt and cousin, concerned about how it was healing, urged him to show his sister/my mother, who works as a nurse and is familiar with wound healing. Seeing the thick dark stitches that criss-crossed his palm and laced up his two lateral fingers was the first time I learned of his diagnosis as well as my family's familiarity with Dupuytren's Disease (DD). Over the past week I had the opportunity to gain insight into his experience with DD and, by extension, the reality of many others affected by DD.

My Uncle Dave is a 53-year old Caucasian male of Northern European descent. He currently resides in Western Connecticut with his wife and daughter, working as an electrical technician a few towns over. His work is physically demanding and requires careful coordination to ensure that it is done correctly. His father was French-Canadian and had lived with DD during his lifetime, which most likely predisposed my uncle to the condition. While a case could be made regarding DD and his occupation, current literature doesn't provide a sufficient basis for that claim. Even though he was aware of this family history, he had never really paid it much mind.

It wasn't until four or five years ago that he began to notice minute changes on the palm of his right hand. At the time, he didn't realize that they were initial signs of DD and continued to go about things unconcerned. They were not painful and hardly detectable. What eventually felt like a soft lump beneath his palm grew into a more solid lump over a year, and that solid lump into a solid cord over the course of several years. These very gradual changes never seemed to be an issue. He learned how to adapt to them at work and in daily life. Even as his Dupuytren's progressed and extended to his ring and pinky finger, he found ways to work around

them and their slow but steady contraction. DD had become a part of life that he eventually acknowledged but remained unconcerned about. He saw no reason to take time off work when it didn't really bother him and he was preparing to pay for his daughter's college tuition.

At some point, however, he was no longer able to compensate for the severe contracture that compromised not only his pinky and ring finger but also middle finger. He was unable to open his hand, which impaired his ability to not only work but also perform daily activities. Simple movements like shaving, driving, and opening doors became challenging. He decided to seek out treatment and, due to the severity of the contraction, underwent a fasciectomy. While the surgery went well, he did come away with nerve damage in his fingers because the cords had progressed so severely. For the first few months afterward, he regularly attended physical therapy two times a week. He currently continues to do physical therapy on his own and check in with his physician twice a month as his insurance will no longer cover physical therapy.

Since his surgery, he has been able to fully extend his right hand with minimal discomfort. His only complaint is that his little finger doesn't bend as well as it used to because of the nerve damage. Overall, though, he has had a successful recovery and has returned to work. Whether he experiences a recurrence in his right hand has yet to be seen. He plans to be more proactive in seeking out treatment after this experience, paying special attention to the palm of his left hand where a small knot has begun to grow. Its callus-like appearance seems benign, but he's all too familiar with the consequences of letting things get out of hand.

My uncle's story is a window into what life with DD is like. Although his case was very severe, it serves as an example of how its slow progression masks its severity. Despite the fact that DD doesn't cause pain and isn't something people seek a physician for, as they would with a cold or infection, it needs to be taken seriously. In its own way, it is a very debilitating chronic

disease that affects everything patients do with their hands. Its complications are an additional burden for middle-aged and older people who may already be facing other chronic health problems.

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