IFSSH Scientific Committee on Dupuytren’s Disease

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Dupuytren resurrected

After many quiet years the whole subject of Dupuytren's Contracture has come to life with the publication and licensing of collagenase clostridium histolyticum (Xiaplex in USA, Xiapex in UK) as a minimally invasive treatment for this curious condition. This innovative approach has driven a reappraisal of what we know about Dupuytren's Disease and how we treat it. This has been evident by the publication of a number of new textbooks and sessions devoted to the topic at several National Society Meetings. A particular significance of this new treatment is the fact that after 20 years of thorough painstaking research, the team of surgeon Larry Hurst and scientist Marie Badalamente has achieved the holy grail of current grant funding strategies and made the transition from bench to bedside for collagenase.

We will return to this later but let us review what we know about the curious 'Maladie de Dupuytren' because it is one of the best examples of misquotation of scientific literature in medical practice. Ask any medical student for the cause of Dupuytren's Disease (DD) and the likely answer will be 'alcohol', which emphasises how medical texts oversimplify and pass down information without new research. The role of alcohol was brought to prominence by its finding in a relatively small cohort of patients with alcoholic liver cirrhosis. Some larger epidemiological studies, but not all, have found a statistical relationship with alcohol consumption but many patients are teetotal and can be offended by the suggestion. This is just one example of scholastic imprecision: many 'facts' being passed down from text to text. Almost every article on Dupuytren's quotes something of the history without bibliographic research and myths about Baron Dupuytren are perpetuated. The best historical review is contained within the literature by David Elliot who hunted down the original publications and enlisted language scholars to verify the accuracy of the translations. These articles (editors please note) are all that need to be cited in terms of history. Historically there have been many inaccuracies in the epidemiology such as 19th Century reports that it was not found in women, and 20th Century statements that it was not found in African or Asian ethnic groups, where it is much less common but not unknown. In reviewing the epidemiological evidence there are wildly different estimates of prevalence in different population groups and perhaps the most significant variable is not the disease incidence but the criteria for diagnosis. Whereas it is easy to diagnose a patient referred with nodules, cords and digital contractures, it is much harder on population studies to know whether to include patients with prominent fascial bands, skin pits, thick calloused skin, congenital and posttraumatic joint contractures. This was illustrated by Jonathan Noble, a hand surgeon who found that 42% of patients with signs of DD in a study group in which a rheumatologist had noted 18%.

There is no diagnostic test and the minor clinical signs are all debatable. And the apparent high incidence in Nordic countries may be due to the fact that these countries
have highly developed health care systems which undertake many epidemiological
studies of all types. In much of the world the incidence is unknown, other than by hand
surgeons’ impressions.

Tor Skoog in his extensive thesis of 1948 showed how the search for a simple cause and
effect relationship with some precipitating factor mapped out a history of fashionable
medical diagnoses in the 19th Century. Dupuytren himself suggested a link to chronic
trauma or injury and this was followed by syphilis, tuberculosis, chronic pulmonary
disease, sepsis in the palm and arteriosclerosis. These suggestions have been followed by
the 20th Century plagues of alcohol, smoking, connective tissue disease and HIV. What
seems clear is that there is no simple cause and effect relationship. John Hueston coined
the term ‘diathesis’ joining together family history, age and morphological features,
knuckle pads, Ledderhose’s disease, bilaterality, to indicate a more rapidly progressive
or extensive condition. The relevance of this to management is controversial, with some
authorities advocating a different choice of treatment option, but without outcome
measures to justify this.

Recently the apparent family and ethnic associations have been given factual support by
a New England Journal of Medicine paper identifying snips (SNP’s, single nucleotide
polymorphisms, effectively mutations) many of which are linked to WNT- genes, known
to be cellular signaling molecules involved in cell proliferation. Identification of the
cellular mechanisms may point the way to other treatment strategies for this and other
fibrotic diseases. After all, Dupuytren’s is just one of a whole constellation of diseases
affecting connective tissue structure, with quite individual clinical pictures and little if
any cross over; scleroderma, keloid, pulmonary fibrosis to name a few.

Surgical intervention

Up to the present time, the mainstay of treatment for Dupuytren’s Contracture has been
surgery, but every surgeon has a different approach to the optimum timing. Interestingly, a detailed study undertaken by Robert McFarlane reviewing the outcome
of 1000 operations by experienced surgeons showed that surgery on the little finger for a
contraction of <30 degrees was as likely to make the contracture worse than better.

All sorts of surgical interventions have been performed since Dupuytren’s original
simple fascial division, now termed ‘open fasciotomy’. Interestingly this was done with
the patient sitting in a chair, with the hand elevated, a position in which the arm can be
easily restrained from withdrawal (D’s operation preceded the development of anaesthesia). The huge variation in surgical approaches can be classified in three ways
as to procedures on the skin, fascia and PIP joint. Patterns of skin incisions are
numbered in hundreds with all varieties of serpiginous shapes. Perhaps the most popular are those of Bruner or a straight line incision with Z plasties.

Skin may be replaced by grafting or occasional flaps and after operation can be closed or left open, credit for the latter being usually given to McCash, although Dupuytren did this first. The management of the fascial contracture depends on the surgeon’s philosophy as to whether the disease should be excised completely (the benefits of which are not supported by evidence) or whether the aim is to control the biology of the disease by release of contracture and of tissue tension, a practice for which there is at least in vitro experimental evidence.

A common practice has been to isolate the neurovascular bundles in the mid palm and excise all overlying diseased fascia while dissecting distally, described by Hueston as limited fasciectomy. This is only ‘limited’ in comparison with the radical resection performed at earlier times in the UK and currently still done by many surgeons in central Europe. Skoog encouraged the retention of the transverse fibres of the palmar aponeurosis (selective aponeurectomy) and many even more limited operations have now been described. There is a tendency now for therapy to veer in two directions, with a more minimal procedure for a contracture at the ‘easy’ end of the spectrum and a more radical dermofasciectomy at the ‘difficult’ end. This loose description of severity underlines the difficulty in classifying the features in the hand in a way which would inform clinical trials. Nodules and cords can be identified with some imprecision by external examination but hands are generally classified by the degree of preoperative joint contracture, which is largely dependent on the time at which the patient presents for treatment. There have been randomised studies comparing operations but not in multiple centres and we cannot be sure if the disease has the same characteristics in different regions, or given the lack of agreed diagnostic criteria referred to earlier, the case selections may be different in different centres, let alone facilities and practices for rehabilitation.

Although surgical intervention has been the mainstay of management, more recently needle fasciotomy has been introduced as a ‘minimally invasive’ alternative. This has been controversial as the concept of moving a sharp implement into the hand and moving it about seems intuitively dangerous to surgeons. Its strongest advocates report less damage than might be anticipated although a survey of hand surgeons in France has suggested that the incidence of nerve damage and tendon ruptures is higher than the series published by experts. The hand surgery community believes that this is not a procedure for general use, but it is appropriate for the patient to be assessed by a clinician who can offer the whole range of different treatments depending on the morphology of the contracture. The hand is anatomically a closely packed structure and the keynote studies by Robert McFarlane have demonstrated how contracting spiral
cords can displace neurovascular structures, particularly in the proximal segments of the digits, making them vulnerable to injury.

The possibility of a simpler treatment than fasciectomy however has been eagerly sought by patients, and by healthcare funders. Surgeons vary in their use of needle fasciotomy ranging from not at all, to selectively (prominent palmar bands) to more general application. It has been the use in the fingers which is most controversial because of the possibility of the nerve spiralling around a cord and therefore being vulnerable to injury. Performing the procedure with local anaesthesia of the skin alone, (or none at all) however gives remarkable protection to the nerve and nerve injury - if properly performed - is rare. The exact way in which the end of the needle is applied to the cord (stabbing or pendulum back and forth motion) will alter the ease of cord division, and possibly the likelihood of collateral damage but such variations depend on individual preference rather than scientific objectivity. There is also debate about steroid injection in addition to cord release.

**Alternative solutions**

And so to the new collagenase therapy. Had the world’s politicians and medical economists embraced the new treatment, and its cost, it would just have dropped neatly in to the hand surgeons’ armamentarium. But in these financially constrained times it is necessary to show a cost benefit analysis, the development of which has highlighted the lack of comparative evidence for all Dupuytren’s treatments in the areas of both cost and benefit. Hand surgeons have been happy to apply their own version of surgical treatment on the basis of a belief in the obvious short term outcomes. The lack of significant numbers of randomised trials has led to the UK National Health Service placing Dupuytren’s surgery on a list of procedures of ‘Limited Clinical Value’, interestingly alongside Inguinal Hernia repair, with instructions that funding should not be prioritised for treatments lacking an evidence basis established through trials. The challenge is to show benefit for treatment through randomised controlled trials and relative benefit for the various modalities. This challenge is made all the more difficult by a lack of agreement on measures of recurrence, there being different criteria in 49 different publications depending upon recurrence of cords or nodules, loss of extension range or a miscellaneous group of largely subjective or patient reported outcomes.

Many of the surgical debates may however be dwarfed by the introduction of collagenase which has a rather different methodology of action by producing a pharmacological break in contracted cords. The technique is that a needle is inserted into a cord as a means of injecting the active agent rather than depending on the needle’s use as a cutting tool. The exact injection protocol is tightly defined, and the commercial supplier has provided training in technique. The drug is injected directly into a palpable cord at
three sites, and presently only one linear or Y shaped cord is treated, although further trials may change this ruling. The injection is performed without anaesthesia to minimise the potential of injecting into a nerve, and it is important to avoid injection into a tendon or tendon sheath. The patient returns at 24-48 hours, local anaesthetic is administered and the treated digit is manipulated extending one joint at a time. There is a 11% incidence of skin ruptures or blood blisters but these heal rapidly with simple dressing. Good early results have been reported in clinical trials especially in the treatment of MCPJ contractures and long term benefits are awaited. Treatment is aimed at releasing cords and nodules are not treated.

With the understanding that there are definable genetic mutations in this ‘Maladie’, it is apparent that the surgeon can treat Dupuytren’s Contracture but not Dupuytren’s Disease. It should therefore not be a surprise that the ‘Disease’ will recur. This is a traditional but false concept which has conditioned surgical thinking and led to vague definitions of recurrence as contracture or ‘disease’ in the operated area, versus extension as disease out with the operated area. It is no surprise that published recurrence rates vary from 0 to 100%. Such recurrence concepts are mentally rooted in cancer biology and are not appropriate for Dupuytren’s, as the entire palmar fascial continuum has the potential when appropriately triggered to become diseased and there is a lack of evidence for the benefit of radical excision of diseased tissue. This brings us to the operation of dermofasciectomy which is generally described as a radical operation. It is certainly radical in the treated area removing skin, fascia and fat; it should probably be termed dermolipofasciectomy when properly performed, but it is not radical in the sense of resection of all Dupuytren’s tissue, often leaving behind disease proximal and distal to the treated area. What this operation, as currently performed, seeks to do is to remove the tissue planes and palmar fascial ligamentous components in which contracture tissue propagates.

The action may be by prevention of the tension lines which develop in the genesis of joint contracture. Done in this way it has in some but not all studies the lowest return of joint contracture of all current operations. By contrast the insertion of a ‘firebreak’ skin graft without radical resection of the underlying fascial structures will not prevent the propagation of ‘fire’. Although dermo(lipo)fasciectomy is branded as a radical operation, it holds little terror for the surgeon routinely performing skin grafts and if done as a primary procedure, the areolar tissue around nerves and vessels is preserved making resection much simpler than in the case of the heavily scarred recurrence.

**Long term strategies**

What seems to be needed in treating Dupuytren’s is a different mindset. Our understanding of the pathology of the disease is a mixture of surgical intuition and a few laboratory observations. Luck’s description of nodules and cords has generally been
understood to suggest that the nodule is the active region of the disease applying traction on normal palmar fascial ligaments which become contracted cords. The essential cell, the myofibroblast, beautifully described by Gabbiani, seems to be responsible for the contraction process. We now understand that not only can fibroblasts be transformed to myofibroblasts but the process is reversible and tension seems to be required for the maintenance of the myofibroblast morphology. And not only tension, but a particular level of tension as Messina has shown that Dupuytren’s tissue can be elongated by an external traction system. It seems that contracture can be relieved by relief of tissue tension either through the traditional excision methods, by minimally invasive procedures, or alternatively by strong traction. Immediate recurrence can be prevented by preventing the linear continuity of the Dupuytren’s tissue. Longer term recurrence can be prevented by preventing the reestablishment of tension in the palmar fascial structures.

It is clear from the internet that the patient wants a simpler treatment with less ‘down time’, and if this can be delivered by minimally invasive treatments without complications, with an acceptable contracture-free-interval, and with no detriment to later surgery should this be necessary, then this is the way to go. Much more data is needed to define the principles of minimally invasive approaches, and to collect this data we need to establish better and standardised outcome measures. The starting point for this is to agree diagnostic and descriptive criteria.

Although seemingly straightforward, the diagnosis of Dupuytren’s can be debatable as there are no tests or uncontroversial clinical signs. The nodule was described by McFarlane as the pathognomonic diagnostic feature, but there are several types of nodules and their absence does not preclude the diagnosis. In patients presenting for treatment it seems important to map out the three components which will be the focus of treatment: nodules, cords and in particular individual joint angles of contracture. As these are the three components which will be treated, the immediate result can be judged by the presence or absence of cords or nodules and the release of however many angles of joint contracture. The longer term result should be measured by disease-free interval – either quantifying how much joint contracture exists at a fixed point in time, or alternatively measuring how long it takes for the contracture to reach the preoperative state.

What we now need are clinical trials of different treatments. But before these can have credibility, there is a need to obtain general agreement on diagnostic criteria and classification of disease. Tubiana has produced the most generally applicable classification, but it may be better to focus on the exact lesions to be treated rather than to consider the hand overall. In addition the concept of ‘recurrence’ needs to be shifted towards disease-free interval with the adoption of criteria allowing comparison of length of benefit of different treatments for relief of joint contracture. Trials then need to take
in to account different disease severity, which may be different in different geographic regions. Procedures of both intervention and of rehabilitation need to be standardised. It is possible that currently the variations in contracture morphology, skin incision, fascial dissection, PIP joint management and rehabilitation may mean that no two patients have ever had exactly the same treatment!

Meanwhile the choice of treatment is based on individual experience and it seems appropriate that the patient should benefit from consideration of all the options available, with selection dependent upon the variables of the hand, the contracture and the patient.

Suggestions for further reading

