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49.1 Introduction

Ledderhose Disease, also known as plantar fibromatosis or 'Dupuytren of the foot', consists of fibroma in the plantar fascia, usually, but not exclusively located on the medial part under the arch of the foot. The disease was named after the German physician Georg Ledderhose who described it in his publications in 1894 and 1897. In 1894 Ledderhose called it a fasciitis without linking to Dupuytren Disease in the hand, as none of his patient had hand symptoms (Ledderhose 1894). All 10 patients had developed pain and nodules in the plantar fascia after having an injury to the foot or having a plaster cast or splint applied to their lower leg. However, after examining some of the nodules histologically, he realized that the same cell types were found in the plantar as in the palmar fascia nodules. By 1897, he had seen 50 cases, some even with contracture of the fascia (Ledderhose 1897). Though spontaneous regression was observed, this did not happen often, and Ledderhose concluded the condition was the same as Dupuytren Disease. Guillaume Dupuytren himself had been aware of the foot-related disease and had promised to discuss it ('When opportunity presents, we shall speak of retraction of the toes, which is also caused by a crisping of the plantar aponeurosis' (Dupuytren 1832)) but died before he had the chance.

Research since then has been case studies mainly with low number of patients (Pickren et al. 1951).

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Not much research has been done into the immune histochemistry or cell structure of Ledderhose tissues (Allen et al. 1955), instead it is generally assumed to be the same as Dupuytren tissues. Very few clinical trials or studies into different treatments have been done so far, mostly investigating radiotherapy (Atassi et al. 2003; Heyd et al. 2010; Seegenschmiedt et al. 2012) or surgery (Wapner et al. 1995; Sammarco and Mangone 2000; Beckmann et al. 2004; Van der Veer et al. 2008) or the combination of both (de Bree et al. 2004).

Ledderhose Disease can be pain-free, but especially as the fibromas get larger, many patients experience a considerable amount of pain standing and walking on the affected foot. There is little information about prevalence available, but it is classed a rare disease by the Office of Rare Disease of the American National Institute of Health (ORD of the NIH), meaning it affects less than 200,000 people in the USA.

The aim of this survey was to assess the patients' experiences of the available treatment options and counselling, risk factors of Ledderhose Disease (LD), the relationship between LD and other conditions and needs of Ledderhose patients in general. This survey was part of an international survey that also addressed patients suffering from Dupuytren Disease described in part 1 of this book (Wach and Manley 2016).

49.2 Survey

49.2.1 Overview of the Survey

The international patient survey is described in part 1 of this book (Wach and Manley 2016). Patients with Ledderhose Disease (LD) and/or Dupuytren Disease (DD) were asked to fill out an online questionnaire. Patients were invited to participate via websites, forums and mailing lists by the supporting organizations (Wach and Manley 2016).

Overall the survey addressed for Ledderhose Disease:

- Quality of treatments
- Quality of counselling
- Family history
- Effect of lifestyle (smoking, drinking)
- Related diseases
- Needs of patients (open ended questions)

Patients were asked whether they are suffering from Ledderhose Disease, without requiring details about their diagnosis, although nodules in the foot can have a wide variety of causes (Macdonald et al. 2007). The survey did not specifically distinguish between nodules that have the same root cause as Dupuytren Disease and similar ones, maybe, for example, due to trauma (Gross 1957).

49.2.2 Surveyed Treatment Options

Treatments for plantar fibromatosis are in part different to those for Dupuytren Disease and have the aim of keeping the patient comfortable and mobile. In our LD survey, we inquire specifically:

- *Orthotics*: Insoles either just with padding under the foot or with a cut-out area to reduce the pressure on the fibroma when bearing weight.
- *Steroidic injection*: Intralesional injections with anti-inflammatory effect, aiming at reduction of nodule size and pain relief.
- *Verapamil gel*: Applied topically for 6–12 months to reduce nodule size.
- *Cryosurgery*: Freezing the lump under a nerve block (Spilken 2012).
- *Shockwaves*: High-energy focussed extracorporeal shockwaves intending to soften the nodules and reduce pain as tested in a small study (Knobloch and Vogt 2012).
- *Collagenase injection*: Occasionally CCH (collagenase *Clostridium histolyticum*) injections into LD nodules are used off-label to soften the nodule.
- *Surgery*: Traditionally the treatment offered to most patients where conservative treatment is ineffective. The types of surgery used are local

excision, partial fasciectomy or (sub)total fasciectomy for patients with recurrence or more than one fibroma in the same foot (Beckmann et al. 2004). Recurrence after surgery, defined as re-appearance of nodules in the operated area, is frequent (25–75%) and early, ‘all within 14 months of surgery’ (Aluisio et al. 1996).

- **Radiotherapy (RT):** Is still controversial in some countries, mainly because of the feared potential long-term risks and reluctance to treat a benign condition with RT. However, there is growing demand for it from patients as it has the ability to shrink the fibroma(s), reduce pain and allow return to normal life and even sport.

49.3 Results

49.3.1 Participating Patients

To achieve maximal participation, the responses for Ledderhose Disease were re-extracted in December 2015. Patient responses were mainly from Europe and the USA, with Canada and Australia contributing larger numbers of responses. Within Europe, the largest contributions were from the UK and Germany. After eliminating double entries, a total of 1000 Ledderhose patients responded (Table 49.1), 456 men with an average age of 53.8 and 544 women with an average age of 56.2.

Data correction was performed as described in part 1 (Wach and Manley 2016). Note that patients did not have to answer all questions; therefore, for any question the number of responses might be less than the total number of participants.

49.3.2 Age of Onset for Ledderhose Disease

The effect of gender, positive family history and having other (related) fibromatoses on the age of onset of Ledderhose Disease was evaluated. 888 patients specified their age of onset for LD, with an average age of onset of 44.6.

Table 49.1 Participants with Ledderhose Disease by country

Country	<i>N</i>	Country	<i>N</i>
USA	471	UK	163
Canada	46	Ireland	10
Australia	36	France	7
Germany	190	Other Europe	26
Holland	14	Africa	8
Austria	11	Rest of the world	18

49.3.2.1 Influence of Gender

Figure 49.1 shows that men develop Ledderhose Disease earlier than women. The average age of onset found for men is 41.4 (median = 43) and for women 47.5 (median = 50).

49.3.2.2 Family History and Concurrent Dupuytren Disease

Having a family history means that close relatives have or had Dupuytren and/or Ledderhose Disease. 528 patients reported having family history, 214 stated that they don’t know (‘unknown’) and 251 had no family history or were not aware of any relatives with DD or LD. Below we are counting ‘unknown’ and ‘no’ as having no (known) family history. Patients with family history have an average age of onset of 43.3 and without family history an average age of onset of 46. Note that these are not prevalence data, i.e. having a family history might well mean that the chances to develop LD (or DD) are much higher, but the average age of onset is only a few years earlier.

78.2% of the LD patients report suffering also from Dupuytren Disease. Overall, concurrent DD does not seem to have strong effect: the average age of onset for patients also suffering from DD is 45.4, even a little but not significantly later than the total average of 44.6. A strong difference appears when it is additionally taken into account which disease started first: patients with concurrent DD who had Ledderhose first report an onset of LD at 38, and if DD came first, the onset of LD was at 49.4. That difference is to some extent ‘natural’ because those with an early onset of Ledderhose Disease are all in the group

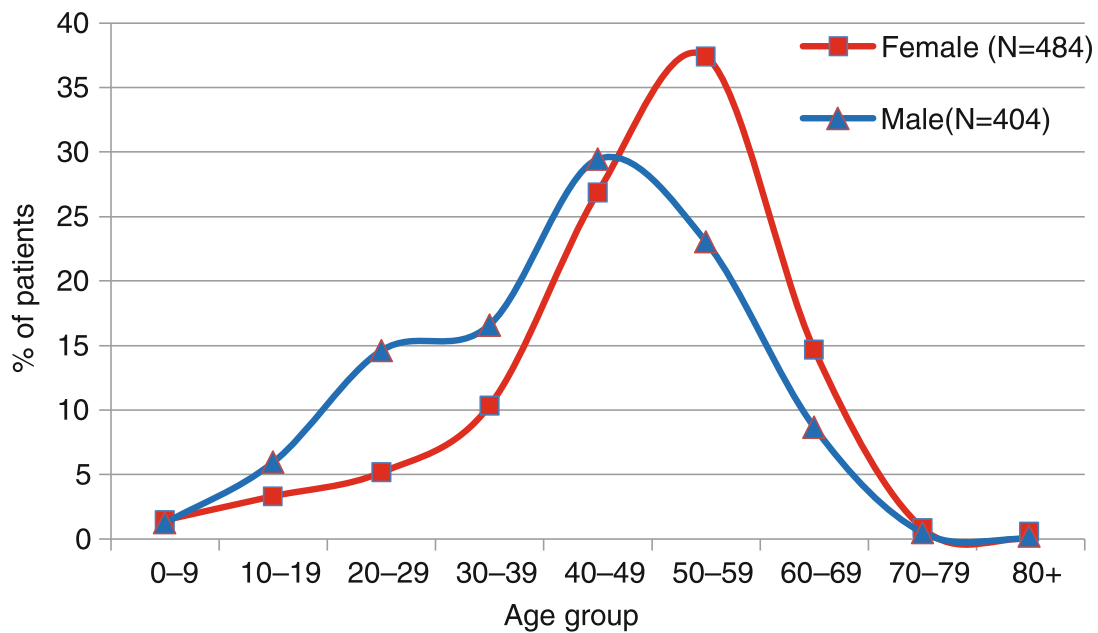


Fig. 49.1 Influence of gender on the age of onset of Ledderhose Disease

‘Ledderhose first’, thus lowering the average age of onset. If patients with an onset of LD <30 are excluded from the analysis, the average age of onset for the group with ‘Ledderhose first’ jumps to 46.8, while for ‘Dupuytren first’, the age of onset for LD increases only slightly to 51.

49.3.2.3 Lifestyle: Smoking and Drinking

Smoking is affecting the onset of Ledderhose Disease as shown in Fig. 49.2. For comparison also included in Fig. 49.2 are results for not smoking women without family history thus eliminating influences that might cause an earlier onset.

We found an average age of onset of Ledderhose Disease for smokers 40.2 (median=40), for nonsmokers 45.0 (median=48) and for nonsmoking women without family history 49.6 (median=52).

For alcohol consumption, we observed no significant effect on the age of onset of LD. The average was 44.7 if drinking more than 2 glasses of wine/pints of beer per day, 44.2 if drinking less than 2 glasses of wine/pints of beer per day and 45.2 if not drinking at all. Our survey did not inquire about specifically heavy alcohol consumption.

49.3.3 Related Diseases

Of the patients with Ledderhose Disease, 78% also have Dupuytren Disease, 22% have or had frozen shoulder (of the DD patients 18% have or had frozen shoulder), 26% had knuckle pads (DD patients: 15%), 16% had thyroid problems (DD patients: 12%), 5% had diabetes (same as for DD patients), 1.3% had epilepsy and 1.4% had liver problems. 7% of the male respondents have or had Peyronie disease (DD patients: 9.5%).

For diseases with more than 50 respondents affected, we tested whether this co-morbidity is affecting the age of onset of Ledderhose Disease (average age of onset for all patients=44.6, median=47). We did not find a significant effect, except maybe for knuckle pads (Table 49.2).

49.3.4 Patients’ Rating of Medical Counselling

Patients were asked ‘Given your experience to date, how would you rank the medical community’s knowledge and experience with Ledderhose

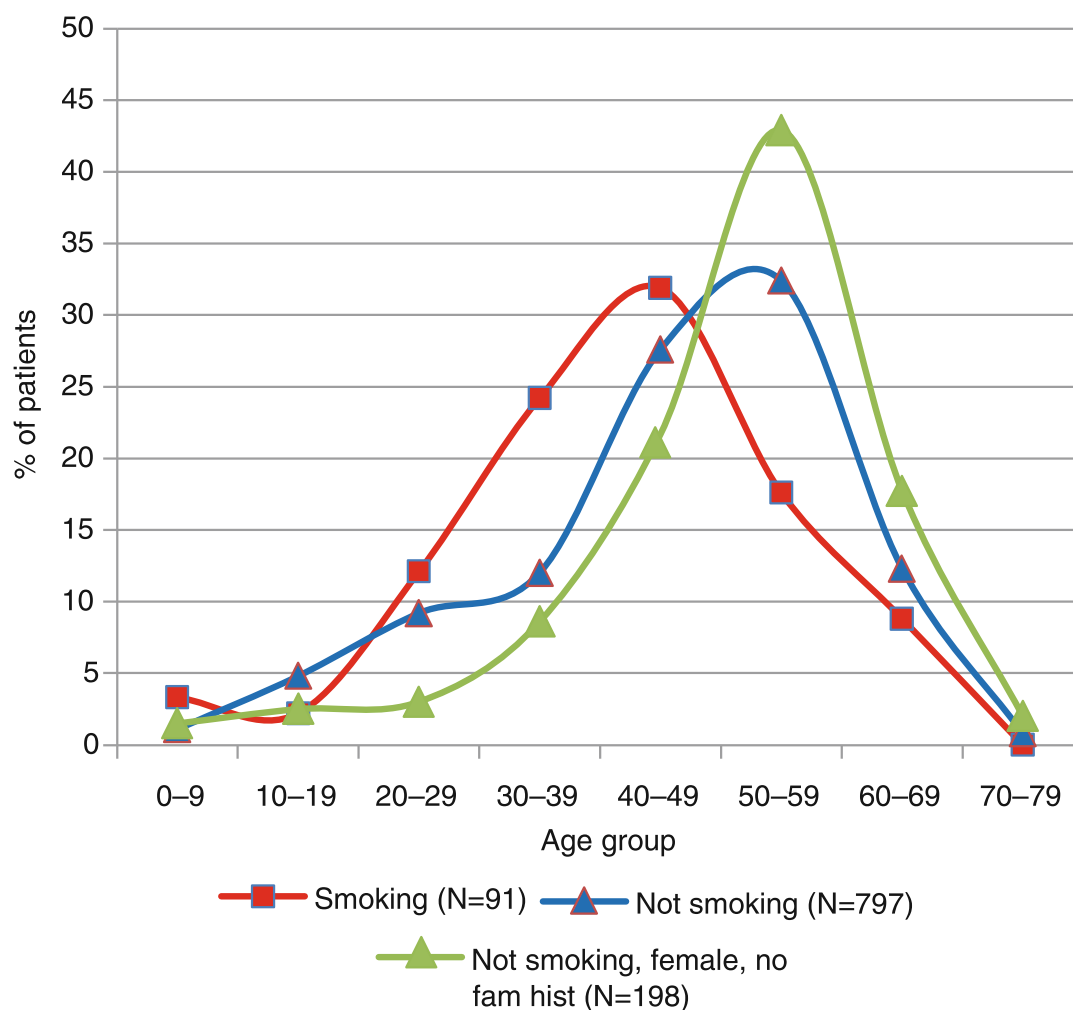


Fig. 49.2 Influence of smoking on the age of onset of Ledderhose Disease

Disease?’ on a range of 1–10 with 1=no knowledge and 10=knew everything. Figure 49.3 shows results by country, whereby countries with less than 100 respondents are omitted. For better overview, the ratings 1–3 (= bad; red), 4–7 (= medium; yellow) and 8–10 (= good; green) are combined.

The ratings in all three countries are very similar, with Germany scoring only slightly better. When asked more specifically about the doctor’s knowledge of the condition, various treatment options and associated conditions, the knowledge of the condition showed 16% good ratings, but information about various treatment options and associated conditions achieved only 5–7% good ratings (about the same for all 3 countries).

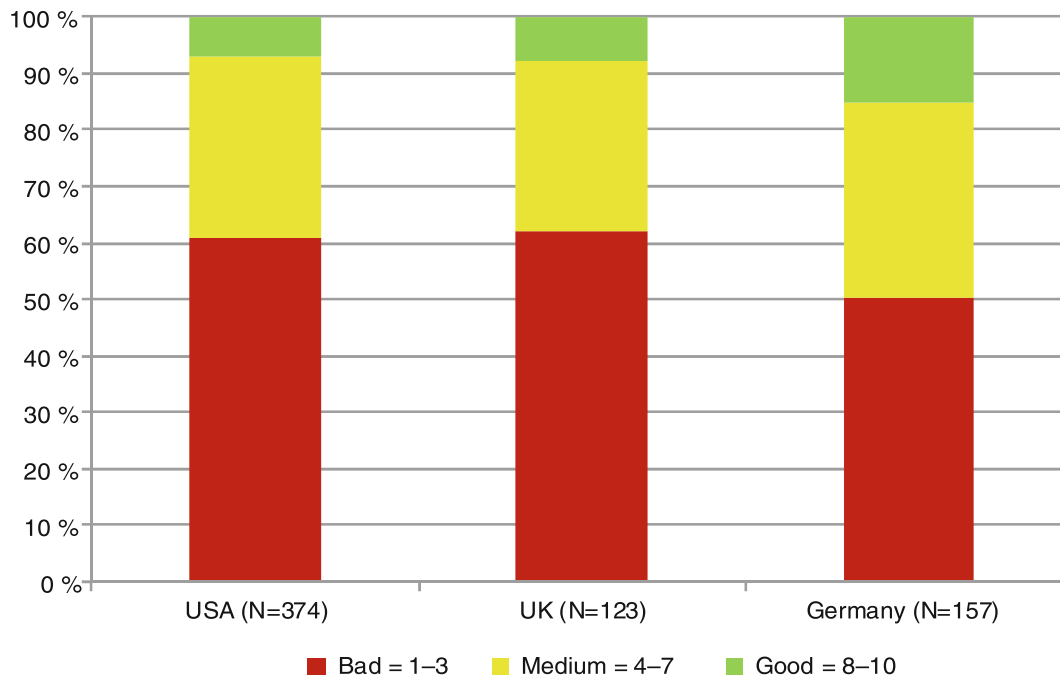
49.3.5 Patients’ Rating of Treatments for Ledderhose Disease

Patients were asked to rate the effect of the treatments they had, using a score from 1 and 10, with 1 being the worst possible outcome and 10 being the best possible. For analysis, the 1–3 ratings, 4–7 and 8–10 have been combined (Fig. 49.4).

Patients who responded to the survey were most impressed with the result of radiotherapy. Cryotherapy comes out as second favourite, but the total number patients is small ($N=15$). The ‘classical’ treatments surgery, orthotics and steroid injections all seem to be less effective than patients would like. Not included in Fig. 49.4 are 4 LD patients who reported injection of collagenase as

Table 49.2 Age of onset of LD for various co-morbidities

Co-morbidity	Frozen shoulder	Knuckle pads	Thyroid	Diabetes	DD=yes	DD=No	Peyronie
Ave. onset	45.7	39.4	48.4	44.3	45.4	41.7	44.8
Median	49	41.5	50	45	48	44	47
N	220	256	158	53	782	218	71

**Fig. 49.3** Patients' rating of the medical counselling for Ledderhose Disease

an off-label use but were not impressed by the outcome (75% bad, 25% medium ratings). The ratings from patients who decided to have no treatment at all are included for comparison.

Patients could also indicate that they had 'other treatments' and many commented on those. This evidence is only anecdotal; no treatment was frequently mentioned in this category. Positively rated therapies were massaging (twice), tissue plasminogen activator (twice), Nexavar, proteolytic enzyme therapy, laser + verapamil, serrapeptase and topical iodine (each once).

49.3.6 Comments and Suggestions by Patients

At the end of the survey, patients were asked what they would wish from scientists and doctors

and if they had any other remarks. Unsurprisingly many patients would like a cure, or failing that a lasting treatment that leaves them without pain. Better knowledge of disease and treatment options was requested by many patients, especially for general practitioners. Also suggested was earlier referral or treatment, not waiting until the condition causes real problems. Doctors should take family history into account, as patients with a strong family history have seen the devastating effects that Ledderhose and Dupuytren Disease can have.

More research was requested many times; patients appear unaware of what research is being done. Patients are also interested in alternative treatments, diet changes and possible anti-inflammatory or immune regulatory options to treat the condition. Many patients would like to see one doctor for all fibromatoses and regular

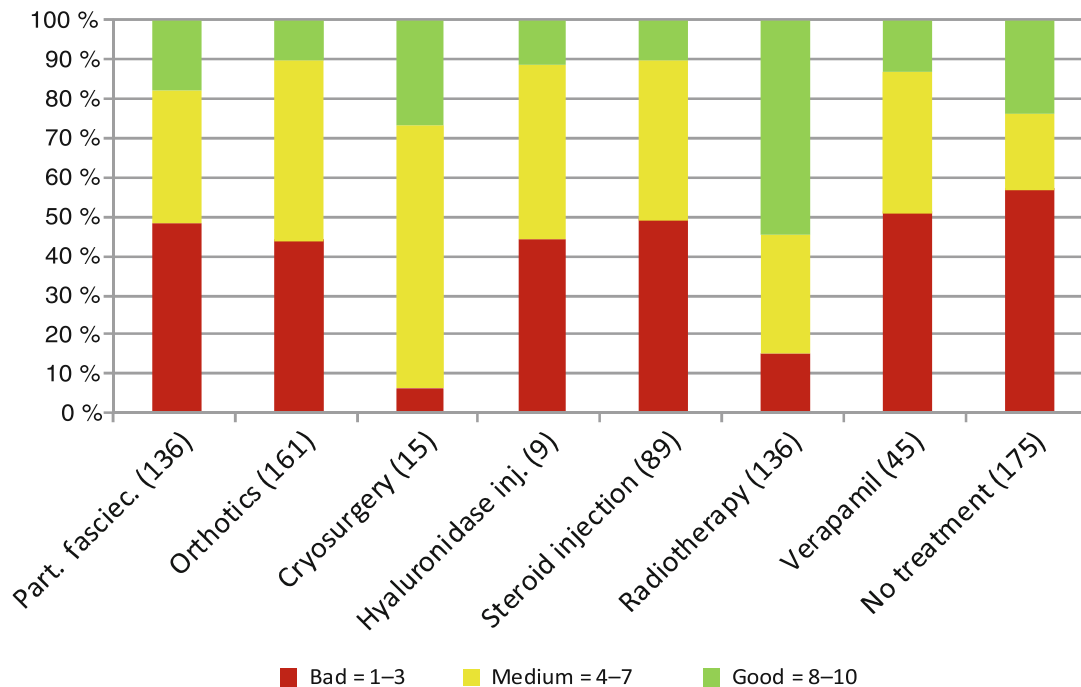


Fig. 49.4 Patients' rating of treatments for Ledderhose Disease

checks for patients once they have been diagnosed with one of the conditions. Last but not the least, stop thinking of Ledderhose (or Dupuytren) as a pain-free disease of alcoholics; neither statement is true.

49.4 Discussion

The goal of this survey was to assess the quality of counselling and treatments as perceived by patients. Additionally, the influence of potential risk factors should be explored. This was achieved by interviewing patients via an anonymous online survey. 1000 patients with Ledderhose Disease responded making this survey the biggest survey of LD patients so far.

49.4.1 Risk Factors

As patients were not selected for the survey on a statistical basis but were invited via mailing lists and websites, our survey is not suitable for providing reliable epidemiologic data. The World Health Organization states 'although plantar

lesions arise more commonly in men, the gender difference is not as great as that found in palmar lesions' (Goldblum and Fletcher 2002). This might explain why we had more men than women in the Dupuytren group (ratio 1.4) (Wach and Manley 2016) but less in the Ledderhose group (ratio 0.84).

While we cannot judge whether a specific influence like smoking or family history makes it more likely to develop Ledderhose Disease, we can evaluate the age of onset of LD. We find an average age of onset of 41.4 (men) and 47.5 (women), respectively, similar to DD where the averages are 46 (men) and 50.1 (women) (Wach and Manley 2016). Male patients develop Ledderhose Disease earlier, and also smoking and family history result in an earlier onset, while we found no effect of moderate drinking.

We did not observe a strong influence of comorbidities, maybe with the exception of knuckle pads. The connection with Dupuytren Disease is strong: 78% of the LD patients also suffered from DD. But suffering from DD did not strongly affect the age of onset (Table 49.2). There is a possibility that we are surveying two types of Ledderhose Disease: the one type could be the

aggressive form that makes Ledderhose Disease start early, e.g. onset in Fig. 49.2 at the age at 35 or earlier. The other group could be patients developing Dupuytren Disease first. Those will likely become sensitized by DD and observe their feet more thoroughly. They might find nodules that they would have never noticed without having DD. We suspect that this group might have a larger contribution of light LD with later onset. This is supported when looking at the severity of Ledderhose Disease (scale 1–10 with 1=least severe). The average severity of Ledderhose Disease if LD developed first was 4.9, while for those who developed DD first, the average severity was 3.7.

Based on this observation, we recalculated the age of onset for those who developed Ledderhose Disease *first*. If those patients did not develop DD, the age of onset of LD was 39.3. If they did develop DD, the age of onset of LD was slightly earlier, at 38. We conclude that developing both diseases is possibly an indication for a more aggressive disease, but the effect on the age of onset of LD seems small.

49.4.2 Quality of Counselling and Therapies

One of the most striking results of this survey is the perceived low quality of medical counselling. Patients are obviously very dissatisfied with the advice they received. In the medical community, a broader awareness of all therapeutical options and of related diseases would be very helpful for improving consultations.

Most of the surveyed treatments received bad rating in the 45–50% range and just 10–20% good ratings. Only radiotherapy with 54% good ratings and cryosurgery with 18% (and only 7% bad ratings) seem to offer better chances for success in treating Ledderhose Disease. Unfortunately for patients, these two treatments are lacking availability: radiotherapy is available in Germany, to some extent in the USA and very limited in the UK and a few other countries. Cryosurgery for LD seems to be available only in the USA, at least according to our survey. The treatment situation

of LD could thus be much improved by better availability of these two treatments and possibly by new effective treatments.

49.4.3 Potential Biases and Errors

For our survey, there is a variety of potential biases and errors. This includes that inviting patients via forums and mailing lists might create a bias towards dissatisfied patients because those might be the ones more likely checking the Internet for information. Further, in an Internet survey, typically the elder patients are underrepresented. As indicated in the discussion of the Dupuytren part of this survey (Wach and Manley 2016) an online, not assisted self-reporting (instead of medical records) may be subject to misunderstandings, entry errors and recall errors. Nevertheless, we believe that the ratings of medical counselling and treatments are based on a sufficiently high number of answers and are clear enough to indicate actual facts.

Conclusions

This survey should be seen as a guide towards patients' backgrounds, ideas and treatment preferences and can be helpful to doctors to better understand the relationship between Ledderhose and other conditions and what patients want from a doctor. The survey exhibited:

- The quality of medical counselling for Ledderhose Disease can be improved considerably.
- The typical LD treatments, orthotics, steroid injection and surgery seem to have only limited benefit and bad results in about 50% of cases.
- Radiotherapy and cryosurgery are perceived by patients as the relatively best treatments but have limited availability in most countries.
- Male gender, family history and smoking seem to cause an earlier onset of Ledderhose Disease. We did not find an effect of moderate alcohol consumption on the age of onset.

Acknowledgments and Conflict of Interest

Declaration The authors wish to thank all patients who took the time to fill in the survey and all organizations supporting this survey. The authors have no conflict of interest to declare.

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