Acta Orthop. Belg., 2016, **82**, 643-648

ORIGINAL STUDY

Comorbidity in Dupuytren disease

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In this report, a possible association between Dupuytren's disease (DD) and other health problems was investigated. The health problems included in this study are : cardiac ischemia, hypertension, hyperlipidemia, diabetes mellitus, epilepsy, gout, rheumatoid arthritis, malignancy, asthma and COPD. The data of 725 patients with DD were collected from Intego, a database including all morbidity presented to the General Practitioners (GPs) in Flanders. The control group of 2900 age and sex matched non-DD patients was selected from the same database. A possible influence of severity of DD was evaluated by comparing the data of 333 patients operated for DD with the group of Integopatients with DD. This study showed a significant association of every single studied health condition with DD. Comparison of the operated group with the group from Intego with DD, demonstrated only some significant associations, a difference which may be explained by the difference in data collection.

Keywords : Dupuytren's disease ; comorbidity ; epidemiology.

INTRODUCTION

It is generally considered that Dupuytren's disease (DD) is more common in patients with certain conditions.

Knuckle pads, fibrous formation in the plantar fascia (Ledderhose disease) and fibrous changes in the penis (Peyronie's disease) are believed to be related conditions (*22*). Numerous reports indicate an increased prevalence of DD in patients with diabetes mellitus (*4,12*), epilepsy (*11-6*), hand trauma (*7,9*) and frozen shoulder (*18*).

Our aim was to look for the suggested associations and for new associations between DD and other health problems. We therefore studied comorbidity in a primary care population with and without DD, including the following possible comorbid conditions : ischaemic heart disease, hypertension, hyperlipidemia, diabetes mellitus, epilepsy, gout, rheumatoid arthritis, malignancy, asthma and

Conflict of interest : All authors certify that they have no financial interests and no benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article. There were no forms of financial support, commercial or financial involvements relating to the submission, including pharmaceutical company support. There are no agreements with any sponsor of the research reported in the Contribution that prevents the authors publishing both positive and negative results or forbids the authors from publishing this research without the prior approval of the sponsor.

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COPD. In the primary care DD population, the severity of the DD in the hands was unknown. The group was therefore compared to a group of patients treated surgically for DD.

METHODS

Study population

In a retrospective database study we investigated age and sex matched primary care patients with and without DD and patients operated for DD. Primary care patients were collected from Intego, a database including all morbidity presented to general practitioners (GPs) in Flanders. Intego was established at the Department of General Practice at Leuven University in 1994. Fifty-five GPs spread over Flanders continuously register all diagnoses in their electronic medical records, which are then collected in a central database. These data-collecting practitioners have been selected based on the superior quality of their registration. Diagnoses are classified according to a very detailed diagnostic thesaurus and converted into a comprehensive classification list (ICPC-2 codes), which is generally used by GPs all over the world. All patients included in the database between 1994 and 2011 were eligible for this study. 215,251 different patients are included in the database. Of all the patients included in this database 725 were diagnosed with DD. This gives a prevalence of 0.34%. For each of these 725, four patients were randomly collected with the same sex and birth year as a control group. These patients were only chosen on these matching criteria without knowledge of their clinical details. Only the conditions which were diagnosed before the diagnosis of DD were included in the analysis.

In this database group of patients with DD, no information on the severity of DD was available. To examine a possible influence of the severity of DD on the presence of diagnosed comorbidity, the primary care group of patients was compared to a group of patients operated for DD making the assumption that DD must be quite severe for the patient to want surgical correction. We investigated a total of 359 patients who had surgery for Dupuytren's disease between January 1992 and July 2006 at the orthopedic department of Leuven university hospitals. A hand surgeon diagnosed Dupuytren disease and the presence of comorbidity was based on self reported information from a mailed questionnaire in 2006, sent to all included patients. The questionnaire was based on the 19 conditions of the Charlson Index present before and after the diagnosis of DD. This index estimates the risk of death from comorbid disease (5). No adjustment was made for age and sex in this analysis.

Questionnaires (surgical patients) and information available from the database (Intego) were evaluated and compared. These provided information on ischaemic heart disease, hypertension, hyperlipidemia, gout, asthma and COPD. Special attention was paid to the presence of diabetes mellitus type 1 and 2, epilepsy, malignancy and rheumatoid arthritis because of the assumptions made in literature.

Statistical Analysis

We estimated the odds ratios with a 2 × 2 table and their 95% confidence interval (CI) for the presence of comorbidity as a function of Dupuytren's disease. Statistical significance of differences between groups were tested with a Mantel-Haenszel test.

The group with DD and without DD from the Intego database were compared with containing the matching in the analysis. As previously mentioned the operated group was un-matched. The level of significance was set on $p < 0,05$.

RESULTS

All 725 patients, born between 1900 and 1999 with DD, were gathered from the Intego database, 451 male (62%) and 274 female (38%), 77% born between 1930 and 1959. The control group contained 2900 patients without DD with the same age and sex distribution as the group with DD collected from the Intego Database.

For the operated population 723 patients operated for DD included in the registration of the hospital were contacted, 359 of them sent the questionnaire back and 13 patients died before returning the questionnaire (response rate 51%). Patients who didn't complete the questionnaire were excluded, leaving 333 patients available for this study. Of the 333 patients, 273 were male (82%) and 60 female (18%). The average age at time of questioning was 66 years (28-95), 79% was born between 1930 and 1959. (Table I).

We compared the cases with DD and the controls of the Intego database for the presence of comorbidity (OR and 95% CI). This resulted in : ischaemic heart disease OR = 1.31 (1.01, 1.71 ; p = 0.045),

Table I. — Study population

	Surgical	Intego +DD	Intego -DD
Total number	333	725	2900
Men	273 (82%)	451 (62%)	1804 (62%)
Women	60 (18%)	274 (38%)	1096 (38%)

hypertension OR = 1.67 (1.40, 1.99 ; $p < 0.001$), hyperlipidemia OR = 2.35 (1.95, 2.83 ; $p < 0.001$), diabetes mellitus (DM) type 1 or 2 OR = 1.91 (1.53, 2.41 ; $p < 0.001$), epilepsy OR = 1.23 (0.62 to 2.42 ; $p = 0.56$), gout OR = 1.96 (1.46, 2.62 ; $p < 0.001$), malignancy OR = 1.55 (1.16, 2.07 ; $p = 0.003$), rheumatoid arthritis (RA) OR = 1.39 (0.82, 2.36 ; $p = 0.22$), asthma OR = 1.89 (1.46, 2.44 ; $p < 0.001$), COPD OR = 1.73 (1.28, 2.34 ; $p < 0.001$).

The comparison between the operated group with DD and the group from the Intego database with DD (OR and 95% CI) resulted in : ischaemic heart disease OR = 1.25 (0.84, 1.84 ; $p = 0.27$), hypertension OR = 0.14 (0.09, 0.22 ; $p < 0.001$), hyperlipidemia OR = 0.86 (0.65, 1.15 ; $p = 0.31$), diabetes mellitus (DM) type 1 or 2 OR = 0.53 (0.27, 0.67 ; $p < 0.001$), epilepsy OR = 1.80 (0.74, 4.41 ; $p = 0.19$), gout OR = 0.95 (0.62, 1.48 ; $p = 0.83$), malignancy OR = 0.81 (0.50, 1.29 ; $p = 0.37$), asthma OR = 0.27 (0.15, 0.50 ; $p < 0.001$), COPD OR = 1.56 (0.06, 0.39 ; $p < 0.001$). There were no results available on rheumatoid arthritis in the operated group. An overview of the study results is displayed in Table II.

DISCUSSION

Comparison of the primary care group with DD to the control group without DD diagnosis, demonstrated that the prevalence of most comorbid condition in this study was significantly higher in the group with DD.

The major strengths of our study are the large size and the quality of the morbidity data registered by GPs, which make false associations very unlikely. Another strength is the diagnosis of DD in the operated group made by a hand surgeon which may imply a high sensitivity and specificity.

There are, however, some shortcomings. The control group was a group with no formal diagnosis of Dupuytren's disease but DD may be present in some of the patients anyhow because the group wasn't investigated in detail for a possible presence of DD. This was addressed by a high age and sex matched rate of 4 to 1 of the control group in comparison to the DD group. The accuracy of diagnosis of DD in the Intego database can be questioned. Each diagnosis was made on a clinical base such as for most conditions used in our study. It would not have been possible to construct such large routine data - based database if all diagnoses would have to be based on formal and predefined criteria. So mistakes could be made by interpretation of the conditions discussed in our study. Interpretation of the results of the operated patients requires some caution because comorbidity was reported by means of a questionnaire which may reduce the reliability of the associations and there was no adjustment for age and sex for this part of the analysis. It is possible that patients with severe comorbidities were not fit enough for surgery or for referal by the GP, so that worst cases aren't included in the operated group. Although the numbers are not expected to be high. We also directly asked about some conditions which could increase the prevalence in the operated group, whereas the conditions in the other groups are only noted if and when they are entered in the patient's file by the GP. Because the questionnaire didn't contain any details on the onset of the comorbidity, no assumptions could be made on the comorbidity or DD being a risk factor for each other. A possible identification of true risk factors is also obstructed by the fact that DD and most comorbidities are chronic which makes it hard to determine which condition first started.

Patients with comorbidities probably visit their GP more often than more healthy individuals. This could increase the diagnose of DD in the group with comorbidities. This is an indication bias that was noticed and should be taken into account when interpretating the results.

Another weakness is that there is no sufficient information available in Intego on lifestyle variables, so in this study no assumptions could be made on the influence of smoking and alcohol consumptions

Table II. — Prevalences of comorbid disorders and differences between surgical DD patients, Intego Registry patients with DD and Intego Registry patients without DD (odds ratios and their 95% confidence intervals -CI)

	SURGICAL	INTEGO	
COMORBIDITY	(%)	with DD (%)	without DD (%)
	OR (95% CI ; p-value)		OR (95% CI ; p-value)
CARDIAL ISCHEMIA	13.5	11.17	8.76
	1.25 (0.84-1.84 ; p = 0.27)		1.31 (1.01-1.71 ; p = 0.045)
HYPERTENSION	7.2	35.03	24.38
	0.14 (0.09- 0.22 ; p < 0.001)		1.67 (1.40-1.99 ; p < 0.001)
HYPERLIPIDEMIA	27.4	30.48	15.72
	0.86 (0.65-1.15 ; p = 0.31)		2.35 (1.95-2.83 ; p < 0.001)
DIABETES MELLITUS	8.13	17.24	9.79
	0.53 (0.27-0.67 ; p < 0.001)		1.91 (1.53-2.41 p < 0.001)
EPILEPSY	2.71	1.52	1.24
	1.80 (0.74-4.41 ; p = 0.19)		1.23 (0.62-2.42 ; p = 0.56)
GOUT	9.6	10.07	5.41
	0.95 (0.62-1.48 ; p = 0.83)		1.96 (1.46-2.62 ; p < 0.001)
MALIGNANCY	7.8	9.52	6.34
	0.81 (0.50-1.29 ; p = 0.37)		1.55 (1.16-2.07 ; p = 0.003)
REUMA	Not available	2.62	1.9
	Not available		1.39 (0.82-2.36 ; p = 0.22)
ASTHMA	3.9	12.97	7.31
	0.27 (0.15-0.50 ; p < 0.001)		1.89 (1.46-2.44 ; p < 0.001)
COPD	1.5	8.97	5.38
	0.16 (0.06-0.39 ; p < 0.001)		1.73 (1.28-2.34 ; p < 0.001)

of our patients on their conditions. Several studies linked alcohol consumption and smoking to DD and as previously indicated this also is a possible reason for the presence of many chronic conditions in DD. The response rate of 51% must also be considered as a weakness.

It should be mentioned that patients operated for DD have a lower prevalence for hypertension and asthma, so both would be a predictor for not having surgery.

The patients who had surgery were interpreted as a group with a more severe disease because the patients with a mild deformity are less eager to want surgery than patient who's disease is inhibiting daily activities.

For calculating the results an adjustment for multiple testing wasn't used because the goal was to generate a hypothesis and not to check an existing hypothesis. If p-values were adjusted for multiple testing by Bonferroni only the association with cardial ischemia in patients with DD would no longer be significant. Odds ratio were used because the study is analysed as a case-control study and using a relative risk is therefore not appropriate. The Intego groups were matched for sex and age. The controls were not matched for GP practice. The administrators of the Intego database started matching for GP practice after the start of this study. This would have helped to take into account the socio-economic status of our patients which may be associated with the prevalence of the comorbid disorders.

Patients with DD had significantly more cardiovascular problems diagnosed. A previous report on 85 patients with DD indicated significantly higher mean serum triglyceride and cholesterol levels,

without a clear relation between serum lipid levels and the severity of the contracture (*17*). Our study confirmed the previous association in a much larger population. Also, a significantly higher prevalence of hypertension in patients with DD was seen. Although hypertension is well known to be associated with smoking, there is also evidence of hypertension being an independent epidemiologic factor for DD, but further study is necessary before drawing conclusions from the association between hypertension and DD (*20*). Reports on a relation between DD and coronary disease are infrequent. An association of DD and alcohol consumption, smoking and diabetes mellitus has also been suggested (*4,12*). These are all risk factors for developing ischaemic heart disease, so it is not unexpected that our patients with DD have a higher prevalence of ischaemic heart disease compared to non-DD patients. Unfortunately there was no information available on these risk factors in the database to verify this possible explanation.

The database revealed a higher prevalence of diabetes in patients with DD, a metabolic condition well known to be associated with DD (*4,12*). Published incidence rates of Dupuytren's disease in diabetic patients vary between 1.6% and 32% and 5% of Dupuytren's cases are diabetic (*16*). DD is often less severe in patients with diabetes mellitus, with less contractures and fewer patients requiring surgery. The reason of the association is thought to be attributable to the microangiopathy resulting in increased collagen production (*12*).

An association between epilepsy and DD was suggested by different authors (*6-11*) but the evidence is inconsistent (*8*). This was first reported by Lund (*11*). Later, DD prevalence rates ranging from 8 to 57% have been mentioned in patients with epilepsy, depending on the diagnostic criteria for DD (*2*). On the other hand, 3% of patients with DD also have epilepsy (*13*). In our study the prevalence of epilepsy is only 1.52% and showed no significant association with DD. There was no information available on the study population of the McFarlane and Ross study to explain this difference. The lower prevalence of epilepsy in our study may be explained by using other diagnostic criteria than the previous study.

There was also a significant association between gout and DD. No previous study reported a possible relation (*1*). Murrel introduced the hypothesis of a greater potential for hypoxanthine oxidase generated oxygen free radicals in Dupuytren's contracture (*14,15*). This hypothesis could not be confirmed in a clinical trial (*10*). The use of allopurinol inhibits the generation of free radicals which could cause a lower prevalence of DD in patient with gout (*15*). However, there was no significantly different use of allopurinol in our study groups to explain the association.

Previous studies showed an overall increased risk for all types of cancer of 23%. Our study showed an increase in prevalence of only 3% (9.5% against 6.3% in DD positive and DD negative patients) and because of the absence of information about the exact time of diagnosis of the malignancy we couldn't determine if DD is a risk factor for malignancy or the other way around. Several hypotheses for this increased malignancy rates can be made : lifestyle habits like smoking and alcohol and the association with DM. The hypothesis of free radicals as previously mentioned is another possible explanation of the increased prevalence of cancer in patients with DD because free radicals are a pathogenic factor in carcinogenesis of certain cancers (*21*).

Rheumatoid arthritis is the only condition so far with a lower reported DD prevalence. This has been attributed to the use of anti-inflammatory drugs, which inhibit the effect of free radicals on the prostaglandin cascade, a lower activity level and a possible genetic background (*3,19*). Our study based on a large GP-based morbidity database indicates higher prevalence rates, but not significant, for rheumatoid arthritis although this was somewhat unexpected based on earlier reports.

Respiratory problems like asthma and COPD are also significantly increased in patients with DD. There were no results found in literature but because of the association between smoking and COPD or asthma and smoking and DD it is no surprise to find this association. Further investigation will be necessary to look for a cause of this observed association, including the effect of smoking and other life style habits.

A higher prevalence of ischaemic heart disease was seen in the operated group but comparison of the operated group to the group of patients with DD in primary care showed no significant increase. The higher prevalence could probably be explained by a more developed DD and an older mean age in the operated group but no information was available on these data. Prevalences in the operated group must also be regarded with caution. Because of the difference in data collection, patients could have answered some questions false positive. Ischaemic heart disease could be a condition that isn't objectively identified but a condition that patients assume they have experienced. The results showed an increased prevalence of epilepsy however this association was not significant. Although these are the results of a questionnaire we can assume that epilepsy is a disease that isn't often wrongfully reported by patient interpretation. The patients with epilepsy are well aware of their condition and false positives are unexpected. All other conditions that were investigated showed a decrease in the operated group (with a possibly higher severity) and some conditions were even very rare in the operated group. Patients with diabetes have a lower need for surgery which is likely to explain the lower prevalence of diabetes in the operated group. Other lower prevalence rates in the operated group may be explained by the interpretation of the questions.

In conclusion, this study could be used as a pilot study for further associations with DD. Most comorbidities are linked to lifestyle variability, like smoking and alcohol, which are also linked to DD. It would be interesting to look for comorbidity in patients with and without these known risk factors separately. This study only looked for new associations without searching for a cause so next to lifestyle variability other explanations are a possible subject of research in the future.

Acknowledgments

We thank Steffen Fieuws for helpful comments and suggestions regarding our article and for his statistical advice.

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