DUPUYTREN'S DISEASE RISK FACTORS

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Dupuytren's is a common problem, but little is known about its aetiology. We have undertaken a large case-control study to assess and quantify the relative contributions of diabetes and epilepsy as risk factors for Dupuytren's in the community. Cases were patients with a diagnosis of Dupuytren's disease and, for each, two controls were individually matched by age, sex, and general practice. Our dataset included 821 cases and 1,642 controls. Five hundred and eighty-eight (72%) of the cases were men. The mean age at diagnosis was 62 (range 24–97) years. Diabetes was a significant risk factor for Dupuytren's disease (OR = 1.75) and there was an increased risk for medicinally treated diabetes (metformin – R = 3.56; sulphonylureas – OR = 1.75) and particularly insulin controlled (OR = 4.39) rather than diet-controlled diabetes. Epilepsy (OR = 1.12) and anti-epileptic medications were not associated with Dupuytren's disease. Ascertainment bias in previous studies may explain the reported association with epilepsy.

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INTRODUCTION

A number of putative risk factors for Dupuytren's disease have been proposed, but at present its aetiology remains unclear. Diabetes (Arkkila et al., 1996, 1997; Chammas et al., 1995; Caligero et al., 2002; Gamstedt et al., 1993; Noble et al., 1984; Renard et al., 1994; Ross, 1999; Yi et al., 1999) and epilepsy (Arafa et al., 1991; Critchley et al., 1976; Lund, 1941) might increase the prevalence of this condition, but the evidence is inconsistent (Gordon, 1954; Hueston, 1960; Laplane and Carydakis, 1985; Thurston, 2003). We have undertaken a case–control study using the West Midlands section of the UK General Practice Research Database (GPRD) to establish more clearly whether diabetes and epilepsy are associated with Dupuytren's disease in the community.

PATIENTS AND METHODS

The UK General Practice Research Database (GPRD) represents the largest source of continuous data on illness and prescribing habits in general practice in the United Kingdom (Walley and Mantgani, 1997). It contains prescribing and diagnostic information collected as part of routine patient care for over 3 million patients, approximately 5% of the UK population. For this study we have used the West Midland section of the GPRD, which represents approximately 10% of the total dataset, or approximately 383,000 patients.

Patients

We identified all patients with a recorded diagnosis of Dupuytren's disease within the West Midlands section of the GPRD who had greater than 12 months of follow-up data. We excluded cases diagnosed under the age of 20 years to prevent misdiagnosis due to the presence of camptodactyly. Our data was extracted using the Oxford Medical Information System (OXMIS) codes, which are derived from the International Classification of Diseases (version 8) and Read codes. These are hierarchic codes commonly used in GP practices. We identified all possible controls for each case on the basis of age, sex, general practice and duration of available data, and then used random sampling to select two matched controls per case. Each case was assigned a date of diagnosis, which was defined as the date of Dupuytren's disease first being recorded, and matching controls were assigned an identical "pseudo date of diagnosis". Each matched case and controls were assigned a common start date for data collection, defined as the date at which the practice started to contribute data to the GPRD or the date that the case or controls registered with the practice, whichever was later. In this study all patients had greater than 1 year of follow-up data. If the start dates for the case and matching controls differed the data were truncated to ensure that, within each case–control set, the duration of prescribing data was the same.

Demographic data on all patients in the study was extracted from the database. We calculated the body mass index (BMI) and coded this according to the World Health Organisation classification for obesity (World Health Organisation, 1997): under-weight, BMI

< 18.5; normal weight, BMI 18.5 to 25 (our reference range); mildly obese, BMI 25.1 to 30; moderately obese, BMI 30.1 to 40; and severely obese, BMI > 40.1. We extracted information for all diagnoses of diabetes, and prescriptions for insulin and oral hypoglycaemic medication (grouped as sulphonylureas and metformin), and all diagnoses of epilepsy and prescriptions for anti-epileptics (grouped as carbamazepine, phenytoin, sodium valproate and barbiturates).

Statistical analysis

The association between Dupuytren's disease and each exposure was analysed using conditional logistic regression, with the STATA (Version 7) computer program. We adjusted for mean annual consulting rates to assess the impact of ascertainment bias. We then repeated our analyses restricting our cases to those patients who also had codes indicating that their Dupuytren's disease had been operated on, to examine the impact of increasing the specificity of the diagnosis.

Ethical approval

Information within the GPRD is patient related, but is anomynised for the purpose of research studies. The protocol was reviewed and approved by the GPRD's own Ethical review committee, the Scientific Ethical Advisory Group.

RESULTS

Our dataset included 821 cases of Dupuytren's disease and 1,642 matched controls. 588 (72%) of the cases were men and 233 (28%) were women. The mean age at diagnosis was 62 (range 24–97) years (standard deviation = 12). The age-specific incidence of Dupuytren's disease peaked between 60–69 years. Seventy nine per cent of cases were aged between 50 and 79-years at diagnosis. The mean annual general consultation rates were a strong predictor for having a diagnosis of Dupuytren's disease (Table 1). The greater the number of consultations, the greater the risk of Dupuytren's disease being diagnosed. Diabetes was significantly associated with Dupuytren's disease (OR = 2.39; 95% CI, 1.66–3.44), and this effect remained after adjusting for consulting behaviour (OR = 1.75; 95% CI, 1.20–2.56). The impact of exposure to diabetic treatments was more marked than that for diagnosis. The use of insulin was strongly associated with Dupuytren's disease (OR = 6.00; 95% CI, 2.93–12.27), as was the use of oral hypoglycaemics grouped as metformin (OR = 4.22; 95% CI, 1.91–9.33) and sulphonylureas (OR = 2.30; 95% CI, 1.44–3.67). This association was reduced when adjusted for consultation rates, but the effect still remained (Table 1). Cases of Dupuytren's disease were more likely to have a diagnosis of epilepsy than controls, but this effect was removed after adjusting for consulting behaviour. None of the treatments for epilepsy was significantly associated with Dupuytren's disease (Table 1).

Table 1——Initial case-control analysis

Variable	*Case*	*Control*	*OR*	*95% CI*	*Adj OR*	*95% CI*
Total	821	1642				
Conrate 1	80	537	Ref			
Conrate 2	224	390	3.89	2.89–5.24		
Conrate 3	251	365	4.92	3.65–6.64		
Conrate 4	266	350	5.59	4.13–7.57		
BMI <18.5	7	10	0.88	0.32–2.46	0.87	0.29–2.60
BMI 18.5–25	210	275	Ref			
BMI 25.1–30	127	232	0.73	0.55–0.96	0.69	0.51–0.92
BMI >30.1	36	63	0.77	0.49–1.20	0.73	0.46–1.16
BMI no data	441	1062	0.51	0.41–0.64	0.73	0.57–0.92
Diagnosis of epilepsy	10	12	1.67	0.72–3.86	1.12	0.47–2.66
Carbamazepine	13	25	1.04	0.53–2.05	0.67	0.33–1.37
Phenytoin	10	8	2.5	0.99–6.33	1.45	0.56–3.77
Valproate	5	9	1.11	0.37–3.32	0.96	0.31–2.98
Barbiturates	8	6	2.67	0.93–7.69	1.82	0.61–5.37
Diagnosis of diabetes	64	54	2.39	1.66–3.44	1.75	1.20–2.56
Insulin	30	10	6	2.93–12.27	4.39	2.11–9.14
Sulphonylureas	38	33	2.30	1.44–3.67	1.75	1.08–2.81
Metformin	19	9	4.22	1.91–9.33	3.56	1.59–7.97

Adj OR = odds ratio adjusted for mean annual consulting rates; REF = reference group; Conrate = mean annual consultation rate; Conrate 1 = 0–1.7; Conrate 2 = 1.8–4.1; Conrate 3 = 4.2–7.9; Conrate 4 = 8.0–66.

The analysis was repeated limiting it to those patients with Dupuytren's diseases who had undergone surgical treatment for the condition, after adjusting for mean annual consulting rates (Table 2). There were 123 cases that had undergone surgical treatment, (15% of all Dupuytren's cases), of which 72% were men. The results in this group were very similar to those of the 821 cases of Dupuytren's for each of the risk factors analysed (Table 2). There was little change to the odds ratios for insulin and metformin use, after adjusting for consultation rates (Adj OR = 3.65 and 1.88, respectively).

DISCUSSION

Using The West Midlands Section of The UK General Practice Research Database, we have investigated a number of risk factors commonly believed to be important in the aetiology of Dupuytren's disease. Our study, which represents one of the largest case–control studies of Dupuytren's, found that diabetes mellitus and medicinally treated diabetes were a strong risk factor. Contrary to previous reports epilepsy, anti-epileptic medication and body mass index were not associated with Dupuytren's.

The data in our study is derived from the computerized general practice records used in routine clinical care. This has the advantage of reflecting real life experience rather than the research setting, and being a prospective continuous data collection, which avoids recall bias. One disadvantage however, is that the general practitioner may misdiagnose Dupuytren's disease though the condition is easily recognized. In addition bias may also have occurred if our cases included patients without Dupuytren's disease, but with other problems that are related to the various risk factors studied. General practitioners may have introduced bias if they were more likely to have diagnosed Dupuytren's because of prior knowledge of an earlier condition, but this would seem unlikely due to the poor understanding of its aetiology. Specific diagnostic criteria were not supplied for any of the illnesses reported by the participating doctors. However, data from practices is routinely validated by internal checks, and there are also specific audits of data supplied by individual practices. Only data meeting the minimum standards are added to the research database (Walley and Mantagani, 1997). It is likely that the diagnosis of Dupuytren's disease in this study has good specificity but low sensitivity, which is important for a case–control study. When we restricted our analysis to Dupuytren's cases that had undergone surgical treatment, in order to increase the specificity of the Dupuytren's diagnosis and check the validity of the diagnosis of Dupuytren's in the population studied, the results were very similar.

Table 2——Analysis of cases who had undergone surgery for Dupuytren's disease (Adjusted for mean annual consulting rates)

Variable	*Adj OR*	*95% CI*
BMI <18.5	4.27	0.28–65.03
BMI 18.5-25	Ref	
BMI 25.1-30	0.34	0.15–0.78
BMI >30	1.50	0.35–6.36
Diagnosis of epilepsy	2.61	0.41–16.59
Carbamazepine	0.84	0.16–4.87
Phenytoin	1.11	0.14–8.75
Valproate	5.46	0.55–54.6
Barbiturates	1.53	0.21–11.08
Diagnosis of diabetes	0.90	0.35–2.30
Insulin	3.65	0.66–20.27
Sulphonylureas	0.94	0130–2.99
Metformin	1.88	0.11–32.61

Adj OR = odds ratio adjusted for mean annual consulting rates.
Ref = reference group.

The mean age at diagnosis of Dupuytren's was 62 years, and the case sex mix was 3:1 male to female. It is generally accepted that Dupuytren's is more common in men than women (Lennox et al., 1993; Mackenney, 1983; Ross, 1999; Yost et al., 1955), with the incidence increasing with advancing age (Gudmundsson et al., 2000). Gudmundsson et al. (2000) found that men with a low body weight and body mass index were significantly correlated with the presence of Dupuytren's disease, but we found no significant association with BMI and Dupuytren's in our study (Table 1). The prevalence of soft tissue hand lesions, such as Dupuytren's disease, flexor tenosynovitis and carpal tunnel syndrome has been reported to be higher in diabetic populations than in control groups (Arkkila et al., 1996, 1997; Chammas et al., 1995; Caligero et al., 2002; Gamstedt et al., 1993; Noble et al., 1984; Renard et al., 1994; Ross, 1999; Yi et al., 1999). It has been reported that the incidence of Dupuytren's among diabetics varies between 1.6% and 32% (Yi et al., 1999) and that 5% of Dupuytren's cases are diabetic (type 1 and type 2) (Ross, 1999). Previous studies have reported that the prevalence of Dupuytren's was the same in insulin-dependant (type 1) and non insulin-dependant diabetes (type 2) (Arkkila et al., 1997; Caligero et al., 2002). Other studies have shown that Dupuytren's is more prevalent in insulin-dependent diabetics (Chammas et al., 1995; Renard et al., 1994). We have studied the use of anti-diabetic medication and insulin to assess the severity of diabetes mellitus and its association with Dupuytren's disease. Our study has shown that the impact of diabetes requiring antidiabetic medication or insulin was more marked than that the diagnosis alone, suggesting that medically treated diabetes carries a higher risk for Dupuytren's than diet-controlled diabetes. The use of insulin was strongly associated with Dupuytren's, as was the use of oral hypoglycaemics, suggesting that there is a stronger association with insulin-dependant diabetes (type 1), than non-insulin-dependant diabetes. This may reflect

the increased severity of insulin-dependant diabetes, and the fact that it occurs in a younger population than type 2 diabetes, and are therefore exposed to the disease and its processes for a longer period of time. Indeed type 1 and type 2 diabetes may have differing disease processes in Dupuytren's Disease.

A relationship between Dupuytren's disease and epilepsy was first described in epileptic inmates in 1941 (Lund, 1941). Since, evidence of such a relationship has been limited and inconsistent (Arafa et al., 1991; Crichley et al., 1976; Gordon, 1954; Hueston, 1960; Laplane and Carydakis, 1985; Lund, 1941; Thurston, 2003). Thurston's recent review of Dupuytren's found little conclusive evidence to link Dupuytren's disease with seizure disorders (Thurston, 2003). Previous studies have assessed chronic epileptics in residential centres (Arafa et al., 1991; Critchley et al., 1976; Lund, 1941), or in the outpatient setting (Laplane and Carydakis, 1985). We are unaware of any previous published case–control studies that have been performed assessing the epidemiological risk factors of Dupuytren's in the community. The incidence of Dupuytren's in epileptics has been reported as high as 56% (Critchley et al., 1976) and it has been suggested that it is directly related to the number of years that the seizure disorder has been present. The administration of anti-convulsants and in particular phenobarbitone has been implicated in the development of Dupuytren's in epileptics (Critchley et al., 1976; Lund, 1941), but this has never been adequately explained. Our study found that cases of Dupuytren's disease were more likely to have a diagnosis of epilepsy than controls, but this effect was removed after adjusting for consulting behaviour. None of the treatments for epilepsy were significantly associated with Dupuytren's disease (Table 1). We have shown that the mean annual consulting rates were a strong predictor for having a diagnosis of Dupuytren's disease, and it therefore seems likely that ascertainment bias explains the association found in our study and previous studies.

The aetiology and pathogenesis of Dupuytren's diseases remains poorly understood. Further studies are required to help answer questions about the cause and the potential prevention and treatment of Dupuytren's.

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