Increased Incidence of Carpal Tunnel Syndrome up to 10 Years Before Diagnosis of Diabetes

MARTIN C. GULLIFORD, FRCP[1]
RADOSLAV LATINOVIC, BSC[1]
JUDITH CHARLTON, MSC[1]
RICHARD A.C. HUGHES, FRCP[2]

The frequency of carpal tunnel syndrome (CTS) is increased in patients with peripheral neuropathy from a variety of causes (1). Abnormal glucose metabolism may be implicated in the etiology of "idiopathic" polyneuropathy in subjects who do not have diabetes (2). We investigated whether the incidence of CTS, Bell's palsy, and other peripheral nerve disorders is increased before the diagnosis of diabetes.

RESEARCH DESIGN AND METHODS

— A cohort study was implemented (3) using THIN, a database containing medical records from family practices in England and Wales (4). The study was approved by the South East Research Ethics Committee. Data were analyzed for 114 family practices with 644,495 registered patients aged ≤100 years. Diabetes cases were selected if their diagnosis date was between 1 November 2003 and 31 October 2004 and if they were aged between 30 and 89 years at diagnosis and had never been prescribed insulin or diagnosed with type 1 diabetes. These criteria produced 2,655 cases. Two control groups were randomly selected, matching for age, sex, and practice, from subjects who were never diagnosed with diabetes or prescribed oral hypoglycemic drugs or insulin. Eight cases, for whom two respective control subjects could not be identified, were omitted.

Each patient's medical record was searched for first occurrences of CTS, including carpal tunnel release and carpal tunnel injection (5). We also identified new occurrences of Bell's facial palsy. Other peripheral neuropathies were grouped, including mononeuritis of the upper limb excluding CTS, mononeuritis of the lower limb, mononeuritis multiplex, and peripheral neuropathy (including idiopathic progressive polyneuropathy, polyneuropathy, peripheral neuropathy, other idiopathic peripheral neuropathy, hereditary or idiopathic peripheral neuropathy not otherwise specific, and inflammatory and toxic neuropathies) (5).

The entry date to the study was the earlier of the start of the Windows-based medical record or the date of the first prescription following registration (up to a maximum of 10 years before the diabetes diagnosis date). There were 82 subjects who were diagnosed with CTS, 23 with Bell's palsy, and 28 with other peripheral nervous disorders before the entry date to the study, and these subjects were omitted. The interpretation did not differ if analyses were restricted to the Windows-based record only, but this resulted in exclusion of an additional 45 cases of CTS and 7 of Bell's palsy. Proportional hazards models were fitted to estimate the relative risk of each neuropathy in pre-diabetic subjects compared with control subjects. Analyses were adjusted for known risk factors for CTS (6), including BMI category (<25, 25.0–29.9, and ≥30 kg/m^2 and not known) and whether the subject ever had a diagnosis of thyroid disease, rheumatoid arthritis, osteoarthritis, or previous wrist fracture before the diagnosis of CTS. Robust SEs were estimated according to the identifier for each triplet, of one case and two control subjects, which was unique across all practices. There was no evidence from any analysis that the proportional hazards assumption was invalid.

RESULTS

— There were 2,647 subjects with pre-diabetes who were later diagnosed with diabetes in 2003–2004 and 5,294 control subjects matched for age, sex, and practice. The mean (±SD) age was 62.4 ± 13.1 years, and 49% were women. The mean duration of follow-up contributed by each subject was 8.9 ± 1.7 years for pre-diabetic cases and 8.8 ± 1.7 years for control subjects. The incidence of CTS was 425.1 per 100,000 person-years in pre-diabetic and 260.0 per 100,000 in control subjects (Table 1). The relative risk was 1.63 (95% CI 1.26–2.11, $P < 0.001$). After adjusting for known risk factors for CTS, the relative risk was 1.36 (1.02–1.81, $P = 0.039$). The incidence of Bell's palsy in pre-diabetic subjects was nearly twice that for control subjects. This increased risk of Bell's palsy in pre-diabetic subjects was not independent of elevated BMI, which is itself a cause of pre-diabetes (Table 1). There were 85 incident cases of other peripheral nerve disorders, including 29 in pre-diabetic and 56 in control subjects. The relative risk was 1.02 (0.65–1.58, $P = 0.939$). However, there were only 20 cases of "peripheral neuropathy" (7 in pre-diabetic and 13 in control subjects) and no recorded cases of "idiopathic progressive polyneuropathy."

CONCLUSIONS

— The present study had the strengths of a large sample size and a long duration of prospective data collection. Nevertheless, because of the relative rarity of these conditions, we have studied small numbers of cases and our estimates are imprecise. The main limitations are those of the clinical methods used for case definition and case ascertainment. We have used the term "pre-diabetes" to refer to the time before the diagnosis of diabetes. During this time, individual subjects may have normal glucose tolerance or varying degrees of hyperglycemia, including impaired fasting

From the [1]Division of Health and Social Care Research, King's College, London, U.K.; and the [2]Division of Clinical Neuroscience, King's College, London, U.K.

Address correspondence and reprint requests to Martin Gulliford, Public Health Sciences, Capital House, 42 Weston St., London SE1 3QD, U.K. E-mail: martin.gulliford@kcl.ac.uk.

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Abbreviations: CTS, carpal tunnel syndrome.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Incidence of CTS, Bell's facial palsy, and other peripheral nerve disorders during study period up to 10 years before diabetes diagnosis*

	n	Person-years	Events (no.)	Incidence rate (per 100,000 person-years)	Relative risk (95% CI)	*P* value	Adjusted relative risk (95% CI)	*P* value
CTS								
Pre-diabetic subjects	2,613	22,820	97	425.1	1.63 (1.26–2.11)	<0.001	1.36 (1.02–1.81)*	0.039
Control subjects	5,246	45,393	118	260.0				
Bell's facial palsy								
Pre-diabetic subjects	2,636	23,425	19	81.1	1.96 (1.04–3.70)	0.039	1.64 (0.87–3.11)†	0.128
Control subjects	5,282	46,163	19	41.2				
Other peripheral nerve disorders								
Pre-diabetic subjects	2,632	23,296	29	124.5	1.02 (0.65–1.58)	0.939	0.96 (0.60–1.52)†	0.857
Control subjects	5,281	46,038	56	121.6				

Results after omitting 82 prevalent cases of CTS, 23 prevalent cases of Bell's palsy, or 28 prevalent cases of "other peripheral nervous system disorders." *Adjusted for sex, age-group, BMI category, and whether subject had history of thyroid disorders, wrist fractures, rheumatoid arthritis, and osteoarthritis before CTS diagnosis. †Adjusted for sex, age-group, and BMI category only.

glucose, impaired glucose tolerance, or undiagnosed diabetes (7). The increased incidence of CTS in pre-diabetic subjects is comparable with the results of studies that have identified type 2 diabetes as a risk factor for CTS (6). However, previous studies generally included cases with diabetes of long duration. The present study makes the novel observation that the incidence of CTS is increased from before the time of clinical diagnosis of diabetes when exposure to hyperglycemia will generally have been less prolonged and less severe.

Additional analyses showed that corticosteroids were prescribed to a minority of patients following diagnosis of CTS or Bell's palsy with little difference in frequency between pre-diabetic cases and control subjects. The use of steroids for these indications is unlikely to have been of sufficient duration or dosage to cause diabetes. Adjustment for other risk factors for CTS, including obesity or history of arthritis, wrist fracture, and thyroid disease, partially accounted for the increased risk of CTS in pre-diabetic subjects. Missing and misclassified values were likely to lead to incomplete adjustment. However, while obesity is associated with increased risk of CTS (8,9), obesity is also a cause of hyperglycemia and is not a true confounder. Nondiabetic hyperglycemia may be associated with peripheral nerve dysfunction (2,10,11). The present results show an increase in two common peripheral nerve disorders, CTS and Bell's palsy, which are easily recognized in primary care. Hyperglycemia and associated metabolic abnormalities may contribute to causing these important focal peripheral nerve disorders before the diagnosis of diabetes.

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