ORIGINAL ARTICLE

BRITTLE DIABETES CHARACTERISED BY RECURRENT HYPOGLYCAEMIA

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SUMMARY - There is little information on the clinical characteristics of “brittle” Type 1 (insulin-dependent) diabetic patients with predominantly hypoglycaemic instability. From a total cohort of 381 brittle diabetic patients from various parts of the United Kingdom, 64 (17 %) had life-disrupting instability due to recurrent hospital admissions with hypoglycaemia. Compared to brittle patients with recurrent ketoacidosis (DKA), who comprised 59 % of the total, those with recurrent hypoglycaemia were characterised by older mean age (34 ± 20 vs 22 ± 11 y, p < 0.001), and more equal sex distribution (53 % v 71 % female, p < 0.05). Patients with “mixed brittleness” (24 % of total) were intermediate between the other groups, in terms of both age and female predominance. Physicians in charge of patients with hypoglycaemic brittle diabetes considered psychosocial factors to be frequent underlying causes, though organic conditions such as lost hypoglycaemic warnings and alcohol abuse were also mentioned. Factitious insulin overdose was diagnosed in 3 patients. We conclude that hypoglycaemic brittle diabetes is a small but important sub-group of the overall brittle syndrome. It differs in age and sex distribution from the more common syndrome of recurrent DKA.

Key-words: type 1 diabetes, hypoglycaemia, brittle diabetes, ketoacidosis.

RÉSUMÉ - Diabète instable caractérisé par des hypoglycémies récidivantes.

Les caractéristiques cliniques du diabète de Type 1 (insulinodépendant) avec une instabilité due à des hypoglycémies sévères prédominantes sont mal connues. Dans une cohorte de 381 patients diabétiques instables recrutés dans différentes régions du Royaume-Uni, 64 (17 %) ont une instabilité majeure interférant avec la qualité de vie à la suite d’hypoglycémies graves récidivantes nécessitant des hospitalisations. Par comparaison avec les patients diabétiques instables en raison d’ épisodes répétés d’acidocétose (59 % des sujets de la cohorte), les patients avec hypoglycémies récidivantes sont caractérisés par un âge plus élevé (34 ± 20 vs 22 ± 11 années, p < 0.001) et par une distribution des sexes plus équilibrée (53 % vs 71 % de femmes, p < 0.05). Les patients avec une instabilité mixte (24 % du total) ont des caractéristiques intermédiaires entre celles des deux premiers groupes, à la fois en ce qui concerne l’âge et la prédominance féminine. Les médecins qui ont en charge des patients avec un diabète instable à prédominance d’hypoglycémies doivent tenir compte de facteurs psychosociaux comme causes fréquentes, mais ne doivent pas négliger des causes organiques comme la perte des symptômes d’appel de l’hypoglycémie et l’abus d’alcool. Des hypoglycémies factices liées à un surdosage volontaire en insuline ont été diagnostiquées chez 3 patients. En conclusion, l’instabilité liée à des hypoglycémies sévères récidivantes concerne un sous-groupe limité, mais néanmoins significatif, de sujets avec diabète instable. Ces patients diffèrent, du point de vue de l’âge et du sexe ratio, de ceux plus nombreux, où l’instabilité est liée à des épisodes répétés d’acidocétose.

Mots-clés : diabète de type 1, hypoglycémie, diabète instable, acidocétose.

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Received : November 5th 1998 ; revised : May 25th, 1999
The problem of hypoglycaemia in Type 1 (insulin-dependent) diabetes has in recent years received considerable attention. Diabetic patients on insulin treatment suffer disabling hypoglycaemia (needing external assistance for treatment) relatively frequently [1]. The controversy over human insulin and hypoglycaemia, though not proving a causal link, further drew attention to the neglected problem of insulin-induced hypoglycaemia [2], and in particular to the problem of hypoglycaemic unawareness which is now recognised as a major social and clinical problem [3]. Also the “dead in bed syndrome” has become recognised [4, 5] and though the cause of such unexplained nocturnal deaths in previously well subjects with Type 1 diabetes remains uncertain, hypoglycaemia (perhaps with associated cardiac arrhythmias) is thought to be the most likely aetiology [4]. Finally, the DCCT study has stimulated more intensive glycaemic control of Type 1 diabetic patients, although such intensified control was associated with an increased risk of severe hypoglycaemia [6].

“Brittle diabetes” is a term used to describe an uncommon sub-group of Type 1 diabetes, characterised by glycaemic instability of any type leading to life disruption [7], and recurrent and/or prolonged hospital admissions [8]. Such patients are enormously costly in terms of health care resources [9, 10], and most have recurrent attacks of diabetic ketoacidosis (DKA), and are usually young females [11, 12]. A smaller number, however, are known to suffer almost exclusively recurrent hypoglycaemic admissions to hospital [9, 13, 14]. No exclusive study of such patients has been carried out, though in wider reports of series of patients with brittle diabetes, Tattersall described 14 such patients [13], and 5 were reported by Gill [14].

In view of the interest and importance of hypoglycaemia in Type 1 diabetes and the lack of information on “hypoglycaemic brittle diabetes”, we report here the characteristics of a large group of patients with this apparent syndrome.

**PATIENTS AND METHODS**

We conducted a national postal questionnaire of United Kingdom (UK) diabetologists, to identify patients with “brittle diabetes”. This was defined as “severe glycaemic instability of any kind leading to life disruption and recurrent and/or prolonged hospitalisation”. The working definition was based on the widely accepted description by Tattersall in 1977 [7], concentrating on whether glycaemic instability (of any type) may lead to life disruption, normally by repeated hospital admissions interfering with work and leisure [8].

Questionnaires were sent to all consultant physicians and paediatricians running diabetic clinics in the UK, from lists at the British Diabetic Association. Responding consultants were asked to give details of any patients who fulfilled diagnostic criteria, together with age and sex. The predominant type of instability was also requested, defined as the major glycaemic reason for hospitalisations (“recurrent DKA”, “recurrent hypoglycaemia” or “mixed instability”). Finally, consultants were asked to speculate as far as possible on the patient’s reason for diabetic brittleness. The questionnaire is reproduced in the Appendix.

Permission was obtained from the local Ethical Committee. Statistical evaluation was carried out by students unpaired t test, and Chi squared tests with Yates’ correction.

**RESULTS**

**Frequency** — A 72 % questionnaire response was obtained (315 of 438 sent), and the 315 responding specialists provided details of 414 patients fulfilling brittle criteria (i.e. more than one “brittle” patient from some clinics). In 33 cases however there was no or insufficient detail as to the type of brittle behaviour. Of the remaining 381, 64 (17 %) were reported to have hypoglycaemic brittle diabetes. This compared with 225 (59 %) having recurrent DKA and 92 (24 %) mixed brittleness.

**Age and Sex** — Mean age of the hypoglycaemic brittle diabetes group was 34 ± 20 y (SD) with a range of 8–83 y. This was significantly higher than the recurrent DKA group, whose mean age was 22 ± 11 y (p < 0.001). There were 34 females (53 %) in the recurrent hypoglycaemic group, compared with 159 (71 %) with recurrent DKA patients - a significant female excess in the latter group (p < 0.05). The group with mixed brittleness were of intermediate age and female excess compared with the other two groups, but were not significantly different (Table I).

**Causes** — Possible causes of hypoglycaemic brittleness were given for only 38 patients (59 %). In 11 cases, organic problems were considered causative, and these comprised lost hypoglycaemia warnings [4], alcohol abuse [3], renal failure [1], gastroparesis [1], hypopituitarism [1], and senile dementia [1]. In 27 patients there were thought to be psychosocial aetiologies (2 causes were offered in 6 cases). The factors reported were: – poor compliance [11], family dysfunction [6], obsessional control [5], psychological problems [4], “life chaos” [3], factitious insulin overdose [3] and anorexia nervosa [1]. In one case of factitious overdose, the insulin was being given in excessive doses by a mother to her diabetic child (Munchausen’s Disease by Proxy).
DISCUSSION

The patients described here were reported from areas throughout Great Britain in response to a postal questionnaire. As such there are clearly problems of selection bias, and we can make no realistic attempts to assess the prevalence of hypoglycaemic brittle diabetes, nor to claim that our patients are entirely representative of the overall picture of severe hypoglycaemic instability in Type 1 diabetes. Nevertheless, our survey has gathered together a much larger group of Type 1 diabetic patients with disabling hypoglycaemic instability than has been previously reported.

To facilitate a high return rate, we deliberately kept our questionnaire simple, and did not seek information such as complications, treatment, glycaemic control etc. In fact, glycated haemoglobin levels would have been very difficult to interpret because of variations in assays and reference ranges. We also used the simple but well-accepted definition of “brittleness” suggested by Tattersall [7], using life disruption as the major criteria rather than factors such as admission rates.

The “polarisation” of brittle diabetic instability into hyperglycaemic (recurrent DKA) or hypoglycaemic behaviour is well described, with relatively few displaying characteristics of “mixed brittleness” [13, 14]. Previous studies have shown that over 90 % of hospital admissions in patients with recurrent DKA or recurrent hypoglycaemia are due to that particular type of glycaemic instability [14]. Our results show that hypoglycaemic brittle diabetes makes up 17 % of the total brittle spectrum. This compares with 12/22 (55 %) [13] and 5/42 (12 %) [14], from two previous smaller surveys. Compared with patients with recurrent DKA, hypoglycaemic brittle patients are significantly older; and were of approximately equal male:female ratio, compared with a female excess in recurrent DKA (see Table). Also of interest is that patients with mixed brittleness were intermediate in both age and sex-ratio, between the groups with recurrent DKA and recurrent hypoglycaemia.

The information on possible causation of hypoglycaemia in this study is of course very subjective. In some patients, direct and deliberate induction of hypoglycaemia was known or at least suspected (including one case in a child of Munchausen’s Disease by Proxy). Many of these patients may have what has been described elsewhere as “factitious hypoglycaemia” [16]. The problem of obsessional self-control was reported in 5 of our patients, and has previously been described [17]. With current attempts to optimise glycaemic control to reduce complication risks [6], this may become an increasing problem. Organic causes included alcohol abuse, renal failure, malabsorption and gastroparesis. As risk factors for hypoglycaemia, these have been previously drawn attention to [10]; as has glucocorticoid deficiency either due to hypothalamic or hypothalamic [18].

Though hypoglycaemic brittle diabetes is less common than other forms of brittle behaviour, it is clearly important. Such patients deserve a vigorous search for an organic underlying aetiology, though as with other types of brittle diabetes psychosocial problems appear to be common underlying factors. Patients with recurrent DKA have a tendency to spontaneous resolution, but nevertheless run a long-term risk of increased early death and diabetes-related morbidity [8]. Tattersall and colleagues reported 2 deaths in 12 years of follow-up in their 12 patients with recurrent hypoglycaemia (both deaths were hypoglycaemic in nature). Larger and more detailed outcome studies of these difficult patients would clearly be of great value.

| Table I. Comparison by age and sex of patients with recurrent ketoacidosis, mixed brittleness and recurrent hypoglycaemia (complete data on 381 patients) |
| Number | Age* | Female |
| Recurrent Ketoacidosis | 225 (59 %) | 22 ± 11 y** | 159 (71 %)*** |
| Mixed Brittleness | 92 (24 %) | 28 ± 18 y | 59 (64 %) |
| Recurrent Hypoglycaemia | 64 (17 %) | 34 ± 20 y | 34 (53 %)** |

* means ± SD
** the age difference between the recurrent ketoacidosis and recurrent hypoglycaemia groups was significant (p < 0.001)
*** the proportion female between these two groups was also significant (p < 0.05)
REFERENCES


APPENDIX

BRITTLE DIABETES QUESTIONNAIRE

Name of Diabetes Specialist
Name of Hospital

For this study we are defining brittle diabetes as follows

“TYPE 1 DIABETIC PATIENTS WITH GLYCAEMIC INSTABILITY OF ANY KIND LEADING TO LIFE DISRUPTION AND RECURRENT AND/OR PROLONGED HOSPITALISATION”

Do you have any patients in your clinic who are “brittle” according to this definition?

YES ———
NO ———

If so, how many such patients? ———

Please give age and sex ——— ———

Are control problems (please tick)
— Recurrent ketoacidosis?
— Recurrent hypoglycaemia?
— “Mixed” brittleness?

Please also state any known or possible causes: —————————————————————————