

PAPERS

Neurological aspects of insulinomas

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Summary

Neurological involvement occurred in every one of a series of 30 patients with an insulinoma. The episodic nature of the hypoglycaemia caused symptoms and signs to fluctuate and often led to delay in diagnosis (mean length of history was 3 years). The commonest feature at first presentation was confusion (20 instances), but as the illness evolved, coma (16 instances) and convulsions (8 instances) became more frequent. Objective weakness was found in 7 patients, with 3 examples of hemiparesis and 2 each of paraparesis and monoparesis; in all, the weakness resolved over a period of 1 hr to 3 days when normoglycaemia was maintained. Other neurological features included subjective visual disturbances, headache, dysarthria and ataxia.

220 patients with an insulinoma from 7 series in the literature were reviewed. The high incidence of neurological features was confirmed, with confusion (152 cases), coma (82 cases) and convulsions (58 cases) predominating. Visual disturbances were common, though not accurately quantified in some series. Objective evidence of weakness on the other hand was reported in only 6 of the 222 patients. Other less common symptoms included headache (18 instances) and peripheral paraesthesiae (14 instances). In the 7 series reviewed, as in our own, it was found that in any one patient, each episode of hypoglycaemia was accompanied by the same symptom complex.

The presence of an insulinoma should be considered in any patient with unusual, or inexplicable neurological features, particularly when they are intermittent. The diagnosis can be confirmed by demonstrating an inappropriately high circulating insulin level, for the ambient blood glucose concentration.

KEY WORDS: coma, confusion, peripheral neuropathy, hypoglycaemia.

Introduction

Neuropsychiatric manifestations are common in

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patients with an insulin-secreting, islet cell tumour of the pancreas (insulinoma), but not infrequently they are misinterpreted and correct diagnosis of their cause is delayed. Failure to recognize the presence of an insulinoma may result in permanent neurological damage, or even death, and the purpose of this communication is to highlight some of the more unusual clinical features which may be associated with the disorder. We shall not elaborate upon the better known modes of presentation (Marks and Samols, 1974; Service *et al.*, 1976), except to emphasize that symptoms are maximal before breakfast, late in the afternoon and after exercise (British Medical Journal, 1981) and that they are relieved by carbohydrate. During the past 20 years at the Middlesex Hospital, there have been 30 patients in whom a diagnosis of insulinoma has been made, based upon the demonstration of an inappropriately high insulin level during hypoglycaemia (British Medical Journal, 1981) and in 27 instances, upon subsequent surgical removal of a tumour. We report here an analysis of their neurological features, together with those of a further 222 patients from the literature.

Patients and methods

We have reviewed the case records of 30 patients with an insulinoma seen at the Middlesex Hospital between 1954 and 1981 and analysed their presenting symptoms, length of history and types of neurological disturbance. Twelve patients had been seen initially by neurologists (group 1), on account of obscure neuropsychiatric illnesses; the other eighteen had been seen first by general physicians (group 2) but in every one of these cases, there had also been some features referable to the nervous system. A survey of the literature disclosed 7 large series of patients with an insulinoma, in which neurological symptoms and signs were described (Service *et al.*, 1976; Kavlie and White, 1972; Clarke *et al.*, 1972; Frerichs and Creutzfeldt, 1976; Best, Chisholm and Alford, 1978; Galbut and Markowitz, 1980; Glickman, Hart and White, 1980), but the emphasis attached to these

features varied. It was nevertheless possible to identify common problems and to define the spectrum of clinical involvement.

Results

Middlesex Hospital Series

We have analysed the clinical features of our series as a whole and in two sub-groups, in which patients presented first to either neurologists (group 1) or to general physicians (group 2).

In view of the importance of the modes of presentation, we shall illustrate our results with case reports.

Group 1. Symptoms had been present in these 12 patients for periods of 1 month to 20 years (mean 3.5 years). Six patients had been referred to neurologists because of episodic confusion, usually occurring early in the morning, or before the evening meal. A further 6 had had more concrete neurological problems, including 3 instances of hemiparesis and one instance each of monoparesis, dysarthria and coma (case 1). Four patients in this group had at some time been described as hysterical and one of these is described below (case 2).

Group 2. The length of the history in these 18 patients was generally shorter than in group 1, with a mean of 1.5 years and a range of 1 month to 9 years. Confusion was the commonest presenting problem and in one such patient (case 3), there was rapid progression to major intellectual impairment. One patient in group 2 (case 4) presented in coma, one (case 5) with ataxia and 2 with convulsions.

in the series as a whole are summarized in Table 1. Confusion was the commonest presenting problem, being recorded on direct questioning in 20 patients. Other features were uncommon as the initial presentation, but occurred with increasing frequency as the illness evolved. Thus, coma occurred at some point in 16 patients, but was the presenting feature in only 2. The period of unconsciousness was generally short, but in 2 instances (cases 1 and 4) was prolonged and associated with decerebrate rigidity. Convulsions were seen in 8 patients, although they occurred at presentation in only 2; they were generalized and there were no examples of post-ictal paralysis. When fits occurred, they were preceded in every case by a period of strange behaviour. Weakness was an uncommon finding, but when there were episodes of paralysis, it is noteworthy that the pattern of involvement in any one patient was remarkably similar. The shortest period of paralysis was 1 hr and the longest 3 days, but in all patients affected, recovery was eventually complete. Sensory abnormalities were also uncommon and only 2 out of 30 subjects volunteered the occurrence of paraesthesiae during attacks of hypoglycaemia, although this symptom could be elicited from a further 12, upon direct questioning. In only one patient (case 4), was there evidence of a hypoglycaemic peripheral neuropathy. Interestingly, this only became apparent after removal of the insulinoma, when this patient's more serious neurological problems began to improve. The neuropathy remitted rather slowly, but the muscular wasting of the hands, which was its most prominent feature, eventually resolved completely (Figs 1 and 2).

TABLE 1. Analysis of neurological features in the present series

Feature	Numbers of patients affected	Number of instances as presenting symptom
Confusion	20	20
Coma	16	2
Convulsions	8	2
Diplopia	5	2
Blurred vision	5	
Headache	5	
Dysarthria	3	1
Hemiparesis	3	3
Generalized weakness	3	
Paraparesis	2	
Monoparesis	2	
Paraesthesiae	2	
Personality change	2	
Dizziness or ataxia	2	1
Cramps in legs	1	
Amnesia	1	

Total numbers: 30. Duration of history 1 month to 20 years, with mean of 3.09 years.

The neuropsychiatric manifestations encountered

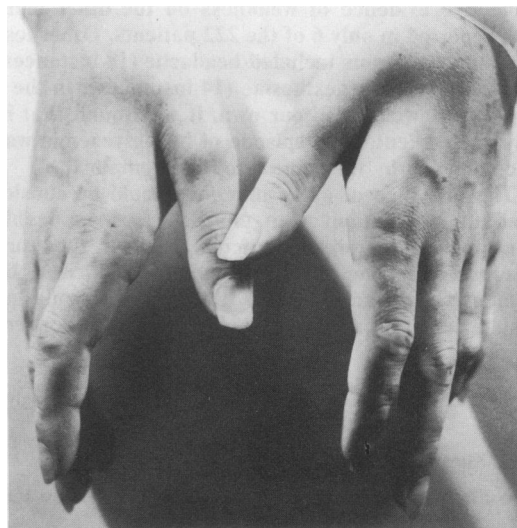


FIG. 1. The hands of case 4 before treatment.

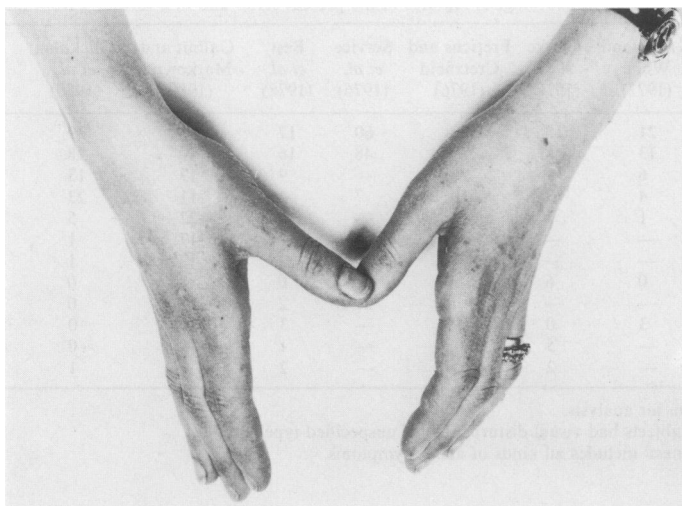


FIG. 2. The hands of case 4, 2 years after removal of an insulinoma.

Case reports

Case 1. A 34-year-old woman had episodes of confusion before breakfast for 1 year, before being admitted unconscious to another hospital. Despite rapid diagnosis and treatment of her hypoglycaemia, she was within 48 hr in a state of decerebrate rigidity. Following removal of the tumour however, her condition improved considerably and within 2 years, her only major residual disability was palatal paralysis.

Case 2. A 63-year-old woman had been investigated for blackouts and headache over a year period at many different hospitals. Each had concluded that the symptoms were epileptic and the diagnosis of insulinoma was only made when she volunteered a craving for sweet foods and intense hunger after attacks. The symptoms were eliminated after removal of the tumour.

Case 3. A 30-year-old man was found in a trance-like state in December 1976, but he recovered spontaneously. He worked as an electronics engineer and had no further trouble until April 1977, when he canvassed vigorously in a local election. Strange behaviour then caused his referral to a psychiatrist, but soon after this, he was found unconscious in bed. Despite treatment for hypoglycaemia, he remained in this state for 2 days and thereafter was severely obtunded. Following removal of the insulinoma, he improved gradually, but was left with marked intellectual impairment, which persisted for 6 months. His wife now reports that he has returned completely to normal.

Case 4. A 32-year-old woman had a short history of episodic, uncharacteristic behaviour, with head-

ache and diplopia. Following one such attack, she took to her bed at 11.00 a.m. and by 10.00 p.m. was deeply unconscious. Despite treatment for hypoglycaemia, she developed decerebrate rigidity, which lasted for 10 days. Neurological features then showed marked fluctuation, despite maintaining normoglycaemia; they included cerebellar ataxia, expressive dysphasia and left homonymous hemianopia. She improved only very slowly after removal of the insulinoma and during her recovery was found to have a peripheral neuropathy. This affected the small hand muscles (Fig. 1) and resolved over a 2-year period (Fig. 2). She was eventually left only with residual spastic dysarthria and cerebellar ataxia.

Case 5. A 62-year-old man became acutely ataxic during his daughter's wedding, a problem which was, not unreasonably, ascribed to alcohol. There were further episodes over the next few months, usually late in the afternoon, in which he developed a truncal ataxia and slurring dysarthria. Hypoglycaemia was shown during such an attack and improvement eventually brought about with large doses of diazoxide and subsequently, by the removal of a small insulinoma.

Case 6. A 56-year-old woman gave a 5-year history of episodes of hemiparesis. The first attack had affected her left arm and leg, while gardening late in the afternoon; it resolved over a 2-hr period, following her evening meal. Over the next 4 years, she experienced short-lived attacks of hemiparesis, involving alternately the right and left sides of the body; these occurred while in bed in the mornings and improved after breakfast. They were thought at first to be hysterical, but the diagnosis was revised

TABLE 2. Analysis of neurological features in the present series and in a further 7 from the literature

	Kavlie and White (1972)	Clarke <i>et al.</i> (1972)	Frerichs and Cretzfeld (1976)	Service <i>et al.</i> (1976)	Best <i>et al.</i> (1978)	Galbut and Markowitz (1980)	Glickman <i>et al.</i> (1980)	Present series	All groups
Total	21	15	29	60	17	41	39	30	252
Confusion	13	8	9	48	16	40	18	20	172
Coma	6	11	26	—	9	17	13	16	98
Convulsions	4	3	10	7	—	11	23	8	66
Weakness	1	5	17	—	0	22	5	3	53
Headache	—	—	—	—	—	17	1	5	23
Blurred vision	—	—	—	51*	3	12	1	5	—
Paraesthesiae	0	6	0	—	0	8	0	2	16
Diplopia	—	—	7	51*	2	—	0	5	—
Paralyses	3	0	0	—	3	0	0	7	13
Dizziness	—	5	1	—	1	—	0	2	9
Dysarthria	—	2	—	—	2	1	1	3	9

— = insufficient data for analysis.

*In this report 51 subjects had visual disturbances of unspecified type.

The category 'dizziness' includes all kinds of ataxic symptoms.

eventually to transient ischaemic attacks. During the investigation of this possibility, she was found one morning to have fasting hypoglycaemia. Her symptoms were abolished completely by the removal of a small insulinoma.

Published reports

There was no distinction in the series from the literature, between symptoms occurring at presentation and those occurring at any time during the illness. The commonest symptoms in the 222 patients reviewed were confusion (152 instances; 69% of cases), coma (82 instances; 37% of cases) and convulsions (58 instances; 26% of cases). The less common symptoms are summarized in Table 2, from which it will be seen that there was some variation in the reported incidence of neurological findings. Visual disturbances were surprisingly common in the experience of Service *et al.* (1976), who recorded the problem in 51 out of 60 subjects. Objective signs of paralysis, on the other hand, were uncommon and only 6 examples were found in the total 222 patients. Paraesthesiae were also rare, being present in only 14 out of the total, as were headaches, with only 18 examples.

Discussion

It is seldom difficult to diagnose the presence of an insulinoma (Glickman *et al.*, 1980), but a high index of suspicion is required in atypical cases and especially so when neurological features predominate. Generalized, subjective weakness affects about one in 5 patients, but this is a vague symptom and one which is unlikely to lead to a correct diagnosis. Objective paralyses, including hemiplegia, monoplegia and paraplegia may however, also occur; they

usually last a matter of hours and recover fully, but can recur in identical form. The differentiation of such episodes from transient ischaemic attacks can be made by inquiring for the simultaneous presence of symptoms of hypoglycaemia.

One of the rarest forms of weakness in patients with an insulinoma is associated with a hypoglycaemic peripheral neuropathy (Jaspan, Wollman and Bernstein, 1982; Jayasinghe, Nimalasuriya and Dharmasada, 1983). This is predominantly motor and affects the arms more than the legs. Weakness and wasting of the small hand muscles is a prominent feature of the disorder and was noted in our case 4.

Visual disturbance is a frequent symptom of hypoglycaemia. Disordered perception is common, though difficult to quantify (Service *et al.*, 1976); blurring of vision on the other hand was recorded in 3 of the series we surveyed (Best *et al.*, 1978; Galbut and Markowitz, 1980; Glickman *et al.*, 1980) and together with our own cases, affected a total of 21 patients (5.6%), but in none did examination between attacks show any external ocular muscle abnormality. Dizziness or sensations of clumsiness are important because they may be mistakenly ascribed to alcoholic intoxication, particularly when there is the not infrequent accompaniment of a cerebellar type of ataxia. Slurring dysarthria is common at this time, but other speech disorders, including dysphasiae seldom occur.

It is not known why hypoglycaemia produces such widely different neurological syndromes in different individuals. Presumably the final common pathway is neuronal energy deprivation (Scheinberg, 1966), but possibly the effects of this might be magnified in areas of the brain with an associated structural or biochemical abnormality. Certainly, the stereotyped form of attacks in any one individual suggests that

the hypoglycaemia may be accentuating a pre-existing, under-lying lesion, but there is no good neuropathological evidence to support this hypothesis. The wide clinical spectrum which can be associated with neuroglycopenia should be considered in the assessment of any unusual neurological syndrome (Harrington *et al.*, 1983). If the patient is seen while symptoms are occurring, a blood sample should be obtained at once to be analysed for glucose and insulin content, with the aim of demonstrating inappropriate hyperinsulinism (Marks, 1971). If attacks do not occur spontaneously, an attempt should be made to provoke one by fasting; this will be successful in 90% of cases after overnight fasting on 3 consecutive occasions and in 98% after 72 hr fasting (Marks and Rose, 1981). If the index of suspicion is still high and investigations have provided equivocal results, a suppression test should be arranged (Turner and Harris, 1974). If endogenous C-peptide levels fail to fall after the deliberate induction of hypoglycaemia, the presence of an insulinoma is strongly supported (Rubenstein *et al.*, 1972; Service *et al.*, 1977). Difficulties in diagnosis may however occur when the patient's hypoglycaemia has been procured factitiously. The deliberate injection of insulin can be detected because the circulating insulin concentration will be much higher and C-peptide much lower than in cases of insulinoma (Stellon and Townell, 1979). The ingestion of sulphonylureas however, may only be detected by catching the patient 'red-handed' or by showing the presence of the drug in a blood sample (Sved, McGilveray and Beadoin, 1976). To confirm the diagnosis of an insulinoma is usually quite straightforward, once the possibility of the presence of one of these rare tumours has been considered. Their ability to cause unusual neurological manifestations should, therefore, always be borne in mind.

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