

Focal seizures and non-ketotic hyperglycaemia

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Abstract

The clinical features of seven patients with non-ketotic hyperglycaemia who developed focal seizures are presented. All patients were alert except one who was mildly confused. Glucose values varied from 17.8 to 55.1 mmol/l, while calculated osmolarity values were elevated in all cases to a mild or moderate extent (299.1 to 346.5 mmol/l). In three cases diabetes mellitus was a new diagnosis. Four patients had recurrent episodes of focal seizures when glycaemic control was lost. Movement induced or kinesigenic seizures were seen in three cases and epilepsy partialis continua in one case. Seizures associated with hyperglycaemia are resistant to anticonvulsant treatment and respond best to insulin and rehydration. Focal seizures in adults may indicate diabetes mellitus.

The link between focal seizures and hyperglycaemia was first reported in 1965¹ yet in one well known textbook of epilepsy, hyperglycaemia-associated seizures are not mentioned at all.² The phenomenon may not be rare; in a review of 158 cases of non-ketotic hyperglycaemia 19% had focal motor seizures.³

We report seven patients, including three previously undiagnosed diabetics, who presented with focal seizures and non-ketotic hyperglycaemia. We suggest that once clinicians are made aware of the association between focal seizures and hyperglycaemia, as happened early in 1989 at this hospital, further cases are readily identified and managed more appropriately.

Patients and methods

Six of the patients were seen by at least one of the authors and five (cases 1, 2, 3, 4, 5) were diagnosed in 1989. We also carried out a search of discharge diagnoses from this hospital for

the preceding 10 years looking for the combined international disease coding for diabetes mellitus (DM) and focal seizures. Only one patient (case 6) was identified in this way, and the significance of the association had not been appreciated by the attending physicians. The seventh case was an outpatient. The admission data on all patients is summarised in table 1. Table 2 gives details of the patterns of seizure.

CASE REPORTS

Case 1—A 39 year old carpenter was admitted in January 1989 with intermittent muscle spasms affecting the right arm for three weeks. His intake of alcohol had been high in the past, but he had been teetotal for six months. The onset was abrupt with episodes of painful tonic flexion of the right thumb and fingers. Progressively more proximal parts of the arm became affected until a full Jacksonian sequence was seen: tonic flexion of the wrist followed by flexion at the elbow and abduction at the shoulder as the whole arm was twisted into a bizarre posture. A brief period of jerking of the arm was then followed by postictal weakness. Dozens of attacks occurred daily without obvious trigger and jerking of the arm was observed during sleep. After one week in hospital the seizures also affected the face with speech arrest. Blood glucose on admission was 55.1 mmol/l without ketonuria; serum calcium and magnesium concentrations were within normal limits. There was no past history of

Table 2 Summary of seizure patterns

Case	Tonic	Clonic	Kinesigenic	Sites			Postictal weakness
				Face	Arm	Leg	
1	+	+	-	+	+	-	+
2	+	-	+	-	+	-	-
3	-	+	+	-	+	+	-
4	-	+	+	-	+	+	-
5	-	+	-	-	+	-	-
6	+	+	-	+	+	+	+
7	-	+	-	+	-	-	?

Table 1 Patients presenting with hyperglycaemia and focal seizures: summary of admission data

Case No	Age (years)/ Sex	Previous diabetes mellitus	Glucose (mmol/l)	Sodium (mmol/l)	Osmolarity (mosmoles/l)*	CO ₂ (mmol/l)	Urinary ketones
1	39/M	No	55.1	136.0	346.5	14.0	0
2	62/F	No	17.8	136.0	301.5	25.0	NA
3	54/F	NIDDM	34.5	144.0	341.6	11.0	1+
4	75/F	NIDDM	34.3	131.0	317.2	25.0	0
5	70/F	NIDDM	42.1	132.0	320.6	17.0	0
6	60/F	No	28.2	137.0	342.2	25.0	3+
7	34/M	NIDDM	13.0	136.0	299.1	22.0	0

*Osmolarity = (Na + K) × 2 + urea + glucose where urea and glucose are in mmol/l.³ All osmolarity values were elevated above normal range (285 to 295 mosmoles/l).
NIDDM = non-insulin dependent diabetes mellitus.

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Received 14 September 1990 and in revised form 13 May 1991.
Accepted 25 June 1991

DM. Treatment was with insulin and intravenous fluids until satisfactory glycaemic control was achieved. Carbamazepine, which had initially been prescribed, was discontinued after one week. CT brain scan was normal. No further episodes of focal seizures occurred during 24 months' follow up.

Case 2—A 62 year old woman was referred to a psychiatrist in June 1989 because of bizarre posturing of the body. While walking, she would develop uncontrolled elevation of the left arm with turning of the neck to the left and retro-collis. Each episode lasted five minutes and was associated with distinct diaphoresis. Four episodes occurred before they were recognised as seizures and not hysterical behaviour. Blood glucose was 17.8 mmol/l without ketonuria; there was no past history of DM. She was given glibenclamide 5 mg daily. Phenytoin was discontinued after 19 days with no recurrence of seizures over 18 months' follow up on glibenclamide and controlled diet. CT brain scan showed perisylvian atrophy on the right side.

Case 3—A 54 year old woman with DM was admitted in August 1989 with hyperglycaemia and jerking of the right arm and leg induced by movement of the same side. During a seizure, typical Jacksonian progression from wrist to elbow to shoulder was noted with postictal weakness of the limb. Blood glucose was 34.6 mmol/l on day 1 and after insulin treatment, 18.1 mmol/l on day 2 when the last seizure occurred. Phenytoin treatment was started on day 1 and stopped after one month with no recurrence of seizures during 16 months of follow up.

Case 4—A 75 year old woman with hypertension and DM was admitted in January 1987 with a five day history of jerking of the right arm and leg and symptoms suggestive of a urinary tract infection. Blood glucose was 34.3 mmol/l. She was treated with intravenous fluids, insulin, cotrimoxazole, and carbamazepine. The seizures stopped after six days, and she was discharged on insulin treatment. A CT brain scan showed a small infarct in the right parieto-frontal region. In April 1988, she was admitted with a diagnosis of congestive cardiac failure and hypoglycaemic treatment was changed to glucophage and glibenclamide. In March 1989, there was a recurrence of jerking of the right arm reproducibly induced by movement of the same limb. Blood glucose was 37.7 mmol/l, probably related to a dental abscess. The seizures and postictal weakness of the right leg settled within a day on insulin treatment. Carbamazepine was discontinued in December 1989, and she remained seizure free with good glycaemic control on insulin treatment during the following 12 months.

Case 5—A 70 year old woman with DM was taking chlorpropamide and metformin when she became hypoglycaemic. Chlorpropamide alone was restarted after one week. Two weeks later (September 1989) she was seen in the

medical clinic with global confusion and episodes of spontaneous jerking of the right arm lasting about two minutes. Her blood pressure was 204/108 mm Hg and glucose was 42.1 mmol/l. The following day, after rehydration and insulin treatment, both the seizures and confusion resolved. She was discharged on gliclazide and methyl dopa but subsequently changed to insulin treatment as glycaemic control was not optimal. In April 1990, she was admitted to hospital with focal seizures of the left arm. Blood glucose on admission was 48 mmol/l; she admitted poor compliance with insulin treatment. Intravenous fluids and insulin were given with reduction in blood glucose and cessation of seizures within a day. No further focal seizures occurred during eight months' follow up.

Case 6—A 60 year old obese woman with hypertension was admitted in 1981 with repeated left-sided partial motor seizures affecting her face and upper and lower limbs. There was a tonic phase lasting 10 seconds followed by clonic jerking lasting about 30 seconds. Residual flaccid weakness of the left arm was noted. Initial blood glucose was 28.2 mmol/l with 3+ ketonuria but normal plasma CO₂. She had no history of diabetes mellitus. Blood pressure was 200/110 mm Hg. A right hemisphere lesion was suspected. The seizures proved difficult to control initially despite treatment with diazepam, dexamethasone, sodium valproate, and phenytoin but settled when blood glucose reached normal values. She was discharged taking chlorpropamide, metformin, phenobarbitone, and phenytoin. She remained free of seizures until April 1984 when she was readmitted with episodes of left arm jerking and a blood glucose of 31.1 mmol/l, possibly due to non-compliance with hypoglycaemic drug treatment. The jerking stopped the following day when her blood glucose was 16.3 mmol/l. Ten days later she became hyperglycaemic (33.1 mmol/l) and was re-admitted with continuous left arm jerking which persisted despite phenytoin, carbamazepine, paraldehyde, diazepam, and dexamethasone treatment for 11 days when a urinary tract infection was discovered and treated. Isotope brain scan and carotid angiography were both normal. (CT scanning was not available in the hospital at this time.) The patient remained free of seizures on insulin and carbamazepine treatment until her death at home in September 1985. A necropsy was not performed.

Case 7—A 34 year old man with DM was seen in July 1985 after two brief episodes of twisting of his mouth to the right, salivation, and "loss of speech". He gave a history of two identical events occurring one and two years previously. He was being treated with chlorpropamide and metformin and claimed good control, with aglycosuria and blood glucose around 6 mmol/l until recent months when blood glucose was up to 13 mmol/l. CT brain scan was normal. No further seizures occurred after intensified dietary and oral hypoglycaemic treatment;

blood glucose remained between 4 and 6 mmol/l. Four months later after a single recurrence, carbamazepine was started. Over the next four years, despite therapeutic carbamazepine levels, seizures recurred only when good diabetic control was lost on three occasions (glycosylated Hb 13%, normal range < 7.5%; blood glucose between 10–14 mmol/l on each occasion).

Discussion

These seven patients (all black) developed focal seizures with non-ketotic hyperglycaemia. In cases 1 and 3 there was mild acidosis not accompanied by significant ketonuria, suggesting the absence of ketonaemia. Despite the single finding of 3+ ketonuria in case 6, we do not believe this was a case of diabetic ketoacidosis as the laboratory measured CO₂ was normal. The focal seizures led to the discovery of DM in cases 1, 2, and 6. In nine of 21 reported patients with hyperglycaemia and epilepsy partialis continua, the seizure disorder was the earliest manifestation of DM,⁴ and four of the five cases with focal seizures reported by Grant and Warlow were newly diagnosed diabetics.⁵ Thus along with polydipsia and polyuria, focal seizures may be an early symptom of non-ketotic hyperglycaemia in DM.

As illustrated by four of our cases (4, 5, 6, 7) hyperglycaemia induced seizures may recur when glycaemic control is lost, even if the patient is on long term anticonvulsant drugs. As far as we are aware this observation has not been reported before. The rare phenomenon of movement induced (kinesigenic) seizures was noted in three of our patients (cases 2, 3, 4). Kinesigenesis was diagnosed in case 2 based on her vivid description of a focal seizure provoked by walking; in cases 3 and 4 focal seizures could be repeatedly induced by asking the patient to move the limb. Brick *et al*⁶ recently reported this phenomenon of reflex epilepsy in five patients (aged 54 to 66 years) with non-ketotic hyperglycaemia, and these authors point out that only eight cases have been previously recorded. They noted that after each kinesigenic seizure there is a refractory period, which may be as long as 30 minutes, during which a second seizure cannot be provoked.⁶ Gabor was able to show independence from peripheral afferent impulses by administering a brachial plexus block to a patient with kinesigenic seizures of the left arm. Seizure activity persisted in the head and neck and was recorded on an electroencephalogram when the patient, still hyperglycaemic, attempted to move her paralysed arm.⁷

The cause of the association between hyperglycaemia and focal seizures is still debated. The explanation of hypertonicity or hyper-

glycaemia alone is unsatisfactory as in diabetic ketoacidosis focal seizures are rare. Osmolarity in our patients ranged from mild to moderate values (299.1 to 346.5 mmol/l) while in the patients reported by Grant and Warlow, corresponding values were either normal or slightly raised.⁵ In the presence of hyperglycaemia GABA metabolism is increased and the levels of this important inhibitory neurotransmitter may be depressed resulting in a reduction of seizure threshold. Ketosis itself has an anti-convulsant action due to intracellular acidosis which is known to increase glutamic acid decarboxylase activity leading to increased levels of GABA.⁸ Focal reduction in blood flow may be important and is known to occur in hyperglycaemia⁹ but even when this was severe enough to cause cerebral infarction (seen on CT scanning in our cases 2 and 4) focal seizures occurred only when blood glucose was high.

Focal seizures associated with non-ketotic hyperglycaemia are refractory to anticonvulsant treatment and respond best to insulin and rehydration. All except our most recent case (case 5) received anticonvulsant drugs initially which were withdrawn without the return of seizures in the absence of hyperglycaemia. Anticonvulsant treatment was continued in cases 6 and 7, though in both of these cases focal seizures recurred when glycaemic control was lost. Furthermore, phenytoin has been shown to inhibit insulin secretion and may well aggravate hyperglycaemia.¹⁰

In conclusion, there needs to be greater awareness of the association of non-ketotic hyperglycaemia and focal epilepsy. If not recognised the diagnosis of DM may be missed and the patient subjected to unnecessary investigations and inappropriate treatment. The occurrence of focal seizures in a middle aged to elderly patient should signal the possibility of DM.

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