Lesson of the Week

Focal epilepsy in diabetic non-ketotic hyperglycaemia

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In non-insulin-dependent diabetes mellitus hyperglycaemia without ketosis may be present for months or years before the disease becomes overt. We report five patients, four of whom were not previously known to have diabetes, who presented with focal epilepsy resistant to anticonvulsants. Unsuspected hyperglycaemia was discovered during investigation. Treatment of the diabetes with insulin or sulphonylurea drugs abolished the focal convulsions, for which no other cause was identified. None of the patients was ketotic, and we suggest that seizures such as these may signal the gradual approach of hyperosmolar coma when treatment is still comparatively straightforward. The danger is that the diagnosis of diabetes may be missed in a patient presenting with newly acquired focal epilepsy.

Diabetes mellitus may present with focal convulsions which respond only to treatment of the diabetes and not to antiepileptic drugs

Case reports

Case 1—A 78 year old shepherd presented with focal motor seizures of the left arm which had increased in frequency and severity over three days. He remained alert during the seizures, each of which lasted about a minute and left a transient flaccid weakness and sensory loss in the arm. Examination showed nothing else of note. On admission he had a blood glucose concentration of 46·5 mmol/l (838 mg/100 ml) but no ketonuria. Rehydration, insulin, and phenytoin were started and within 24 hours the seizures had stopped. In retrospect he recalled having polyuria and polydipsia. Computed tomography (CT) of the head showed normal appearances; electroencephalography was not performed. His diabetes was controlled with chlorpropamide alone. The phenytoin was withdrawn after 11 days, and when last seen he had been free of seizures for five years.

Case 2—A 66 year old housewife presented after four days of episodic jerking of her left arm, having suffered headaches, diplopia, and clumsiness of the left hand for a week. She also reported a weight loss of 9 kg over 18 months. On admission she was having repeated focal motor seizures of the left arm and left side of the face lasting two or three minutes with no loss of awareness. Between seizures there was flaccid weakness, pronounced ataxia, and sensory loss in the left arm and left facial weakness. General examination findings were normal. Her blood glucose concentration reached 33 mmol/l (595 mg/100 ml) but there was no ketonuria. Cerebrospinal fluid, electroencephalogram, and CT scan were normal. The diabetes was treated and she was given phenytoin, but the seizures stopped only when the hyperglycaemia had responded to insulin. All her neurological signs disappeared in a few days and the phenytoin was withdrawn after a month. Four years later there had been no further seizures and her diabetes was well controlled with insulin.

Case 3—A 54 year old housewife with enormous obesity was taking chlorpropamide for diabetes and diuretics for mild hypertension. One month before admission she had had pleurisy which resolved with antibiotics, and continuing thirst and polyuria. Nine days before admission she began to have motor seizures affecting her left arm, and in hospital Jacksonian march fits were observed spreading from thumb and fingers up her left arm, interspersed with global flaccid weakness and incoordination of the arm. She was also feverish and had atrial fibrillation, foot ulcers, and a urinary tract infection. Blood glucose concentration was 24·5 mmol/l (441 mg/100 ml) on admission; ketonuria was not detected. She was managed with intravenous fluids, antibiotics, and insulin, but no anticonvulsants (in the light of experience with the other two patients). After 48 hours the seizures and neurological signs had disappeared. CT showed some cortical atrophy but no focal lesion; the electroencephalogram was normal. She continued to inject insulin and had suffered no further seizures for two years.

Case 4—A remarkably fit 86 year old woman was referred to the neurological outpatient department with one week of increasingly frequent attacks of "going vacant" for a few minutes, later accompanied by twitching of the right side of the face. Between seizures she showed mild dysphasia and dysarthria but was otherwise well. CT scan was normal and electroencephalography showed slight left temporal slow wave activity during seizures. Phenytoin was prescribed without effect; the blood glucose concentration was then found to be 24 mmol/l (432 mg/100 ml). When her diabetes was brought under control with glibenclamide the seizures disappeared. In retrospect she recalled that she had had thirst and polyuria for three months. The phenytoin was stopped after one month, and 14 months later she had remained seizure free.

Case 5—A 63 year old man was admitted complaining of weakness in his right hand and four attacks of jerking of the right arm the day before. He was otherwise well and examination showed only distal weakness with hyperreflexia of the right arm and grade 1 vascular changes in the fundi. Blood glucose concentration was 14·3 mmol/l (258 mg/100 ml) on admission and there was no ketonuria. Over the next two days in hospital he had focal motor seizures of the right side lasting up to 30 minutes, which failed to respond to increasing doses of phenytoin, phenobarbitone, and diazepam; meanwhile little attention was paid to his moderate hyperglycaemia. Eventually insulin was begun when the blood glucose value reached 23 mmol/l (414 mg/100 ml), with control of the hyperglycaemia and disappearance of fits. CT scan and electroencephalogram were normal; over the next six months he had had no further fits and had taken no anticonvulsants.

None of these patients gave any history of past epilepsy, stroke, or head injury and no focal lesion of the brain could be detected radiologically in any of them; indeed, none had any neurological symptoms or signs once the epilepsy was controlled. All presented with focal motor epilepsy as the first clinical manifestation of hyperglycaemia without ketoacidosis. All were alert and outwardly seemed well but for their seizures. Urea and electrolyte values were within normal limits. Plasma osmolarity was calculated in four cases according to Loeb's formula[1] and was normal or slightly increased—case 1, 317 mmol (mosmol)/l; case 2, 312 mmol/l; case 3, 285 mmol/l; case 5, 274 mmol/l. The normal range is 285-295 mmol/l.

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Discussion

Most published reports on diabetic hyperglycaemia without ketosis are concerned with hyperosmolar coma,[2-4] a grave condition which represents one extreme of a biochemical continuum. In practice, diabetics show a spectrum of hyperglycaemia and are often detected before they develop severe hyperosmolarity. Our five patients are typical of the sort of person most likely to acquire this syndrome. Reviews find that they are usually elderly with mild non-insulin-dependent diabetes which is often making its first appearance. They tend to harbour chronic disease and to be taking medications, particularly steroids and diuretics. When a combination of infection and contributing insults precipitates hyperglycaemia the onset of polyuria and polydipsia is insidious.

Focal epilepsy may be the first indication of diabetes in some patients in this group. Seizures are frequent and repetitive and often leave a transient postictal paralysis. As a rule hyperglycaemia is not severe (less than 40 mmol/l (721 mg/100 ml))[5] and osmolarity is normal or only slightly increased. The patients are usually alert even during the seizures. If, however, their diabetes is not treated they develop hyperosmolarity with progressive impairment of consciousness and the seizures stop: a sequel which is evident from case histories of patients in coma who had earlier passed through a phase of convulsions.[6]

Thus focal epilepsy is seen, according to Singh and Strobos, "in a setting of moderate hyperglycaemia, hyponatraemia or normonatraemia, and mild hyperosmolarity."[7] As long as these biochemical disturbances remain uncorrected the seizures persist. They do not respond to anticonvulsants but disappear with insulin and rehydration. The patients then recover and remain free of epilepsy while their diabetes is controlled. In some cases on record further episodes of hyperglycaemia when control slipped were again accompanied by seizures. After recovery the electroencephalogram is normal and it is exceptional to find any structural abnormality of the brain.

The occurrence of focal epilepsy as a presenting feature of hyperglycaemia without ketosis was first emphasised by Maccario *et al* in 1965.[8] Other examples have been documented since then in American publications.[5 6 9 10] The association has not been noted in British journals or textbooks and we believe that many cases pass unrecognised. A survey of neurological manifestations in non-ketotic hyperglycaemia found that seizures, focal neurological impairment (usually postictal), myoclonic twitches, nystagmus, or meningeal signs have been recorded.[6] Another review of 158 previously published cases of non-ketotic hyperglycaemia concluded that a quarter of patients had seizures and 19% focal motor seizures.[10] Also described with this form of diabetes have been focal motor status epilepticus,[7 10] focal seizures triggered by movement,[5] tonic postural synergies ("fencing posture seizures"),[11] and choreoathetosis or ballismus.[12]

The association is difficult to explain. Focal seizures are classically symptomatic of structural lesions within the brain, and it is usually proposed that small, clinically undetectable areas of critical ischaemia are present in these patients' brains which are apt to become seizure foci in response to further insults. Generalised convulsions, however, are more usually provoked by metabolic disturbances: since elderly patients with diabetic ketoacidosis or hypoparathyroidism[13] are equally likely to have cerebrovascular disease, why do they not present with focal fits?

Theories based on cellular dehydration due to the hyperosmolarity achieved in the absence of ketosis have been explored in detail[14] and experimental studies adduced to show that hypertonic solutions will activate existing seizure foci.[15] But most of our patients presented with seizures when their hyperglycaemia was moderate and their plasma osmolarity normal or only slightly raised. This renders theories of hypertonicity unsatisfactory and makes the absence of focal seizures in diabetic ketoacidosis all the more striking. It has been suggested that ketosis has an anticonvulsant effect, since a ketogenic diet is thought to be of benefit to epileptic children (interestingly, of most benefit to those with partial seizures).[16] When a comparatively moderate biochemical disturbance results in convulsions probably several factors have a hand in the outcome. The explanation of hyperosmolarity alone is inadequate.

Although it is unusual to see diabetes masquerading as epilepsy, our experience of five patients in as many years suggests that with awareness of the association more cases would be recognised. We believe that focal epilepsy occurring in elderly patients with non-insulin-dependent diabetes may be the herald of hyperosmolar coma and must be treated by controlling the diabetes; neurological symptoms and signs will then be reversed. Anticonvulsant drugs are ineffective and phenytoin may even be harmful, since it may aggravate hyperglycaemia.[17 18] Frequent focal seizures with no obvious cause should suggest the possibility of diabetes.

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Some people have a diagonal crease in the lobes of their ears called Hadrian's sulcus. As the emperor of that name, a typical A personality, died of coronary heart disease in his 40s many physicians believe that this diagonal crease is a genuine pointer to the danger of coronary heart disease or of diabetes and hypertension. What evidence is there to support this?

There have been many reports correlating the diagonal crease in the ear lobe with coronary artery disease. I was not aware that it is called Hadrian's sulcus, or that the emperor died of coronary artery disease. There seems little doubt that the diagonal ear crease is associated with aging and that perhaps the sign identifies individuals who are aging more rapidly than normal.[1] In a most comprehensive study 1000 unselected patients were examined for the presence of the ear lobe crease and were evaluated for the presence of coronary artery disease, using both clinical and angiographic criteria.[2] A high degree of correlation between the two was found, and in this study the association was independent of age. Apparently oriental and native American Indians are exceptions.—C W H HAVARD, consultant physician and endocrinologist, London.

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