



# Encephalopathy following diabetic ketoacidosis in a type 1 diabetes patient

AD Miras\*, H Ward

## Introduction

Hyperglycaemic emergencies and specifically diabetic ketoacidosis are common and treated, at least initially, by physicians who are not necessarily specialised in the field of diabetes. Various clinical protocols are utilised with variable success. Many metabolic derangements occur simultaneously and, together with patient factors, make the restoration of metabolic balance challenging. Complications can surface rapidly and in mysterious ways, requiring astuteness on behalf of the acute physician in order to avoid long-term irreversible damage.

## Case history

A 44-year-old gentleman with type 1 diabetes mellitus was transferred to our Emergency Department after having been found collapsed in his home with a Glasgow Coma Score (GCS) of 11/15. His sister alerted the authorities after not having heard from him in three days. The police and ambulance service found him semi-comatose in his flat. There was no evidence of alcohol or drugs at the scene.

Collateral history from his sister and family doctor revealed that the patient had had diabetes for 16 years with a most recent HbA<sub>1c</sub> of 7.6%. He was on a basal bolus regimen of insulin and did not have any other co-morbidities. He had suffered from recurrent hypoglycaemic episodes including two emergency hospital admissions in the previous three years for severe hypoglycaemia precipitated by alcohol binges. Due to depression he had recently lost his job as a computer analyst. He lived alone, there was no history of any aggressive

## ABSTRACT

A 44-year-old gentleman with type 1 diabetes mellitus was found collapsed with diabetic ketoacidosis. Following correction of the metabolic derangements his level of consciousness improved but he became encephalopathic, exhibiting unprecedented aggression with non-specific neurological signs. This profound neurological state persisted for one month. Reversible causes of encephalopathy were investigated and excluded. The patient made a slow and almost complete recovery over a period of six months.

Encephalopathy is an unusual complication of hyperglycaemic emergencies with poorly understood underlying mechanisms. This case demonstrates the importance of considering and treating the numerous reversible causes of an encephalopathic state before attributing altered levels of consciousness to the acute metabolic disturbances only. Copyright © 2010 John Wiley & Sons.

*Practical Diabetes Int* 2010; 27(2): 76–78

## KEY WORDS

type 1 diabetes; encephalopathy; hypophosphataemia; thiamine deficiency; hypoglycaemia

behaviour and he was known to be always very polite and pleasant.

On arrival he was unwell with Kussmaul's breathing, tachycardic at 115bpm, BP 134/76mmHg, with signs of dehydration. Systemic examination did not reveal signs of sepsis and there were no focal neurological findings. Initial investigations revealed acute renal failure and a metabolic acidosis with a pH of 7.07, PCO<sub>2</sub> 1.6, PO<sub>2</sub> 20.1, HCO<sub>3</sub> 3.5, lactate 4.5. Serum sodium ranged between 143 and 146mmol/L, and serum phosphate between 0.80 and 0.86mmol/L during his acute illness. Liver and bone profiles were normal. Urine dipstick was strongly positive for ketones and the serum glucose was 36mmol/L. Initial treatment was with intravenous 0.9% saline, soluble insulin and potassium replacement as per hospital protocol for the treatment of diabetic ketoacidosis. Within 36 hours he received 5L of 0.9% saline followed by 4L of 5% dextrose, all bags containing potassium. He was transferred to the High Dependency Unit where his

fluid and acid-base balance was monitored closely.

Within 24 hours into his admission the initial metabolic derangement was reversed but his GCS remained low at 11/15. CT scan of the head performed 16 hours after admission was completely normal and a lumbar puncture did not reveal any evidence of meningitis (opening pressure 21cm H<sub>2</sub>O, no red or white blood cells, glucose 12.1mmol/L and protein 51mg/dl). Microbiology cultures and toxicology for recreational drugs, alcohol, paracetamol and salicylate were all negative. In view of his previous hospital admissions, intravenous thiamine was administered for three days followed by an oral course.

Over the following five days his drowsiness gradually resolved but was replaced by an uncharacteristic verbally and physically aggressive behaviour towards the nursing and medical staff. The patient had to be restrained by hospital security on a number of occasions and, reluctantly, antipsychotics were administered to

Dr Alexander Dimitri Miras, MRCP, BSc, Specialist Registrar in Endocrinology and Diabetes

Dr Helen Ward, MRCP, PhD, Consultant in Endocrinology and Diabetes

St Peter's Hospital, Chertsey, UK

\*Correspondence to: Dr Alexander Dimitri Miras, MRCP, BSc, Specialist Registrar in Endocrinology and Diabetes, St Peter's

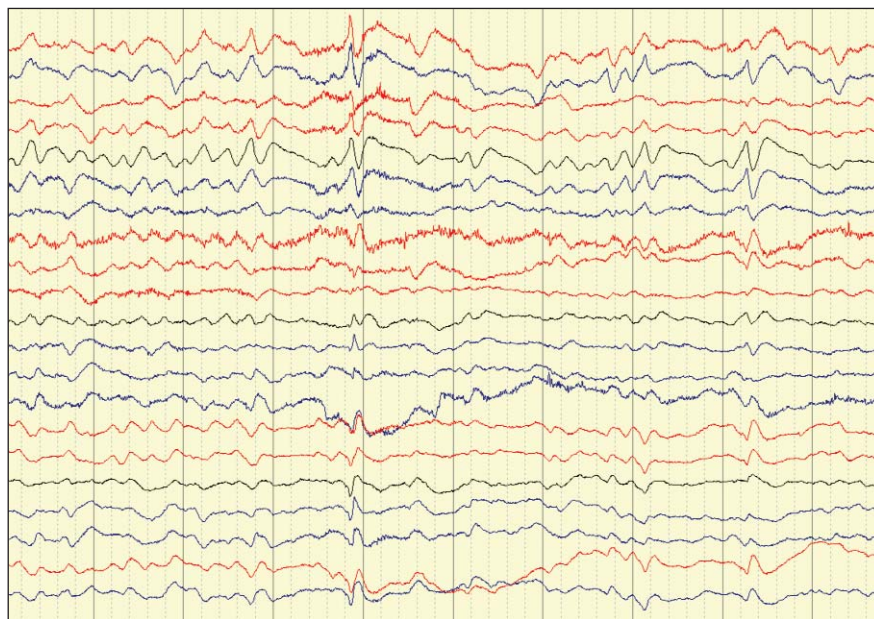
Hospital, Guildford Road, Chertsey KT16 0PZ, UK; e-mail: a.miras@boltblue.com

Received: 9 December 2008

Accepted in revised form: 2 July 2009



**Figure 1.** Electroencephalogram showing diffuse slow activity of approximately 4.5Hz (normal 8–13Hz). (Reproduced courtesy of Dr Adrian J Fowle, FRCP, BSc, Consultant Clinical Neurophysiologist, St Peter's Hospital, Chertsey, UK)



facilitate basic nursing care. His family were surprised and upset by his unprecedented and fluctuating aggression and confusion even though in their presence their intensity was ameliorated. Neurological examination at this stage revealed a slow, stuttering speech, automation, lip flickering and a persistent non-painful penile erection. No ophthalmoplegia or cerebellar signs were observed. MRI of the brain at this stage was entirely normal with no evidence of pontine myelinolysis. An electroencephalogram showed slow wave activity, generalised in the theta and delta range consistent with an encephalopathy (Figure 1). Other causes of an encephalopathic state were considered and subsequently excluded (Table 1).

A month after his admission, his aggressive behaviour gradually regressed. The patient's short- and long-term memory improved and he was eventually orientated in time, place and person. His speech and higher mental functions were still impaired. He was transferred to a local neuropsychiatric rehabilitation facility where he stayed for a month. Six months following his presentation, he has returned home and has now started to manage his finances with the help of family and social services, but remains irritable and his speech is still slow.

### Discussion

Encephalopathy precipitated by hyperglycaemic emergencies is described in the literature but the underlying mechanisms are poorly understood.<sup>1</sup> The metabolic derangements that occur during diabetic ketoacidosis/hyperosmolar hyperglycaemic state can produce a very similar clinical picture.<sup>1</sup> In addition, there are a number of potential confounding factors, such as the use of drugs and alcohol prior to presentation, variability in protocols and practice for the treatment of adult hyperglycaemic emergencies and coincidental presentation of encephalopathy due to another cause in a patient with diabetes with secondary metabolic disturbance.

Megarbane *et al.*<sup>1</sup> implicate hypophosphataemia as a precipitant for encephalopathy post diabetic ketoacidosis and treatment of this results in progressive and complete recovery. Hypophosphataemia is a very common electrolyte disturbance following treatment of diabetic ketoacidosis being caused by phosphaturia, which is a direct effect of serum acidosis and is worsened by a shift of phosphate together with glucose into the cells during treatment. Reduced levels of red blood cell 2, 3 diphosphoglycerate may reduce the amount of oxygen delivered to

**Table 1.** The following tests were either negative or the results were in the normal reference range

- HIV serology
- Syphilis serology
- Hepatitis B and C, CMV, EBV serology
- CSF viral serology
- Short synacthen test
- Serum lead
- Serum caeruloplasmin/urinary copper
- Serum ammonia

HIV = human immunodeficiency virus; CMV = cytomegalovirus; EBV = Epstein-Barr virus; CSF = cerebrospinal fluid.

the brain among other organs and precipitate encephalopathy. Our patient's phosphate levels did drop to a value of 0.26mmol/L (normal range 0.80–1.40mmol/L) two days into his admission. However, his encephalopathic state preceded this derangement despite improvements in pH and ketonuria and no clinical improvement was observed with correction of hypophosphataemia.

A very interesting report by Clark *et al.*<sup>2</sup> highlights the importance of acute thiamine deficiency in diabetic ketoacidosis. Malnutrition, osmotic diuresis, insulin deficiency and even insulin administration can all deplete the body's thiamine stores. Neuronal damage caused by thiamine deficiency affects specific vulnerable regions in animal models including the thalamus, inferior colliculus, mammillary body, medial geniculate nucleus and medial vestibular nucleus. The pathophysiological mechanisms behind this neuronal insult include cellular endothelial dysfunction directly caused by lack of thiamine and low levels of brain neurotransmitters including GABA, glutamate and serotonin which rely on thiamine for their production. Due to the previous admissions with alcohol related hypoglycaemia our patient received early replacement with intravenous thiamine without any apparent impact on the course of his encephalopathy.

Alcohol induced hypoglycaemia is well described and a well known danger in diabetic patients. Excessive alcohol intake reduces gluconeogenesis and subsequently intestinal



## Encephalopathy following diabetic ketoacidosis

absorption and glycogenolysis.<sup>3</sup> Brain tissue is selectively vulnerable to the resultant hypoglycaemia with the cortex, basal ganglia, substantia nigra and hippocampus most commonly affected. Initial MRI changes include hyperintensity and hypointensity on T1 and T2 weighted images followed by diffuse brain oedema and atrophy in the more severe cases.<sup>4</sup> Looking retrospectively at our patient's presentation, it is possible that he suffered a hypoglycaemic episode followed by rebound hyperglycaemia with ketoacidosis due to subsequent omission of insulin. Mild hypoglycaemia induced cerebral lesions cannot be detected by MRI or CT; however, his encephalopathy was so profound and persistent that radiological changes might be expected to be observed and, interestingly, were not.

Therefore, we postulate that our patient suffered from a non-specific and reversible encephalopathy related to diabetic ketoacidosis. To this day, after careful investigation

### Key points

- Diabetic ketoacidosis is a common medical emergency causing multiple and complex metabolic derangements
- Encephalopathy following treatment of diabetic ketoacidosis is rare and its mechanisms poorly understood
- Acute physicians should consider the various causes of an acute encephalopathy – including hypoglycaemia, hypophosphataemia, thiamine deficiency, hypoadrenalism, alcohol excess, cerebral oedema and infections – and treat them when possible
- Diabetic ketoacidosis *per se* can cause an encephalopathic state without a single identifiable cause. The involvement of a multidisciplinary team and caution in avoiding hypoglycaemia are crucial for optimum long-term outcome

into the events leading to his presentation and in patient management and extensive searches of the medical literature, we have been unable to pinpoint a clear cause for encephalopathy, apart from diabetic ketoacidosis. We present this case to raise awareness among the medical profession of the early identification and treatment of reversible causes of an encephalopathic state in future patients. If this proves difficult, all

efforts during patient recovery should be focused on the avoidance of hypoglycaemia and on multidisciplinary involvement of highly skilled staff for optimum outcome.

### Conflict of interest statement

There are no conflicts of interest.

### References

References are available at [www.practicaldiabetesinternational.com](http://www.practicaldiabetesinternational.com).

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**References**

1. Megarbane B, Guerrier G, Blancher A, *et al.* A possible hypophosphataemia induced life threatening encephalopathy in diabetic ketoacidosis. *Am J Med Sci* 2006; **6**: 384–386.
2. Clark JA, Burny I, Sarnaik AP, *et al.* Acute thiamine deficiency in diabetic ketoacidosis: Diagnosis and management. *Pediatr Crit Care Med* 2006; **7**(6): 595–599.
3. Jain H, Beriwal S, Singh S. Alcohol induced ketoacidosis, severe hypoglycemia and irreversible encephalopathy. *Med Sci Monit* 2002; **8**(11): CS77–79.
4. Fujioka M, Okuchi K, Hiramatsu K-I, *et al.* Specific changes in human brain after hypoglycaemic injury. *Stroke* 1997; **28**: 584–587.