



An Unusual Case of Diabetes Mellitus: Ketone-Positive Hyperglycaemia Induced Hemichorea-Hemiballism

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Abstract

Hyperglycaemic Induced Hemichorea-Hemiballism (HIHH) is a complication of poorly controlled diabetes. This condition is characterised by an acute onset of involuntary movements in the context of hyperglycaemia. From our knowledge, we report the first case of ketone-positive HIHH in a Caucasian patient who had been on a Sodium Glucose Transporter 2 (SGLT-2) inhibitor. She was demonstrated to have the typical findings of increased attenuation on CT and MRI imaging in the basal ganglia. In our case, we also postulated whether there was a relationship between her basal ganglia injuries and possible cognitive decline which may have affected her adherence to blood glucose lowering therapy.

Introduction

Movement disorders are known to arise from pathology within the basal ganglia or extrapyramidal tracts. These disorders can arise from a multitude of mechanisms including cerebrovascular accidents (ischaemic and haemorrhagic), metabolic, toxic, neurodegenerative and infectious causes. Hyperglycaemia is a metabolic cause of hemiballism-hemichorea movement disorders which is characterised by a distinct, hyper attenuated lesion in the basal ganglia of an affected individual. In most cases, optimisation of glycaemic control should result in resolution of involuntary movements with time.

Case Presentation

A 60-year-old Caucasian woman presented to our hospital with a one week history of uncontrollable left sided movements. Initially, she had intermittent left arm movements which had progressed to continuous involuntary movements and involvement of her leg by the time of presentation. She was a retired librarian who lived alone in a retirement village. She had a background of type 2 diabetes mellitus, diagnosed 20 years ago, which required insulin therapy. Her other comorbidities included proliferative diabetic retinopathy, diabetic nephropathy, hypercholesterolaemia, depression, hypertension, asthma and gastro-oesophageal reflux disease. She had never smoked and consumed alcohol occasionally.

Her diabetes management comprised of metformin 500 mg TDS, empagliflozin 10 mg mane, insulin glargine 32 units nocte and insulin aspart 10 units with lunch and 18 units with dinner – the patient did not routinely eat breakfast. She did not monitor her blood glucose levels. In the past, her glycaemic control paralleled her mental well-being. Up until October 2014, her HbA1c had been sub-optimally controlled with readings in the 8% to 10% (85 mmol/mol) range, and after being lost to follow up for one year, her HbA1c peaked at 17.5% (167.8 mmol/mol) in October 2015 (Figure 1). During this time, her depression had been exacerbated by the loss of her mother.

She had been reviewed by her ophthalmologist four weeks prior to her presentation, for her annual eye review. She was noted to have marked deterioration of her vision with her right-sided visual acuity <6/60 and left eye 6/36, which improved to 6/24 with pinhole. She had chorioretinal scars due to previous pan-retinal photocoagulation, but there was no new diabetic retinopathy. Due to her marked visual deterioration, her driving licence was not renewed. Her loss of independence

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Received Date: 17 May 2017

Accepted Date: 25 Sep 2017

Published Date: 01 Oct 2017

Citation:

Lai J, Lee BH, Duggins A, Gunton JE, Hng T-M, Cheung WN. An Unusual Case of Diabetes Mellitus: Ketone-Positive Hyperglycaemia Induced Hemichorea-Hemiballism. *Ann Diabetes Res.* 2017; 1(1): 1004.

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Figure 1: HbA1c trends over the past decade as a marker of overall glycaemic control.

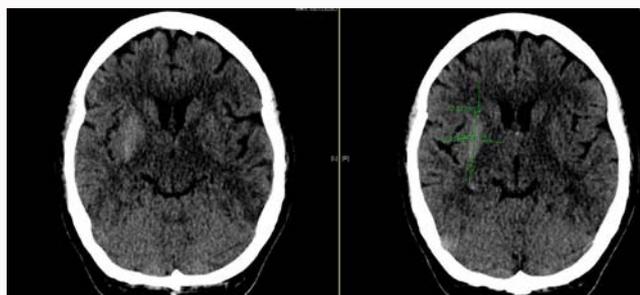


Figure 2: CT brain image demonstrating a 32.3 mm x 10.3 mm hyperdense right lesion involving the right lentiform nucleus.

contributed to her stopping her insulin therapy, upon receiving this news.

When she presented to the Emergency Department, she was mildly dehydrated, with reduced skin turgor and dry oral mucosa. She had involuntary movements in her left upper and lower limbs which were consistent with hemichorea. Furthermore, there were some truncal and neck movements.

She had involuntary, irregular and small rapid movements in her left arm, most consistent with hemichorea; rather than the higher amplitude, flinging and irregular movements described with hemiballism. Tone was normal bilaterally, with 5/5 power bilaterally in all muscle groups of the upper and lower limbs. Her reflexes were symmetrical and normal.

Her blood glucose level was 30.1 mmol/L with ketones of 1.5 mmol/L. Her calculated serum osmolality was 304 mmol/kg. There were no clinical symptoms or signs of infection, and her CRP measured 5 mg/L. Her serum bicarbonate was normal at 23 mmol/L. Her HbA1c was reported as >16% (>151 mmol/mol). In view of the ketosis, her Glutamic Acid Decarboxylase antibodies were assessed and these were negative.

A Computed Tomography (CT) of her brain revealed increased attenuation (42 Hounsfield Units) in the right lentiform nucleus of the basal ganglia (Figure 2). A subsequent Magnetic Resonance Imaging (MRI) further characterised this right lentiform nucleus lesion as having faintly increased signal on T1 weighted imaging and T2 FLAIR sequences (Figure 3). There was no evidence of basal ganglia haemorrhage or areas of diffusion restriction on diffusion weighted imaging to suggest an acute infarction. There were coincidental findings of gliotic foci in the pons and right corona radiata which were consistent with foci of old sub-clinical infarction.

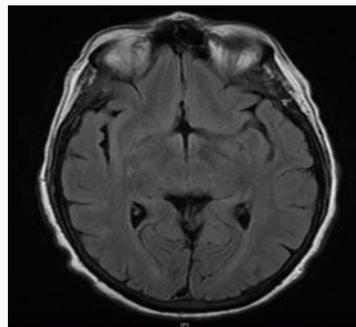


Figure 3: T2 FLAIR images demonstrating an area of attenuation in the right lentiform nucleus.

Based on the clinical presentation and radiological findings, a diagnosis of Hyperglycaemic Induced Hemichorea-Hemiballism (HIHH) was made. Her blood glucose levels dramatically improved with regular subcutaneous insulin therapy. Due to the presence of ketones, hyperglycaemia, dehydration and the risk of developing ketoacidosis, empagliflozin, a sodium-glucose transport-2 inhibitor was ceased. Her hemichorea movements were treated with topiramate and clonazepam.

Two months after initial presentation with her movement disorder, progress neuroimaging with CT and MRI demonstrated minimal radiological change. She had persistent hyperkinetic involuntary movements, which have contributed to the development of excoriated wounds to the skin of her left upper and lower limbs. She has also subsequently declined in her mental health, which has potentially hampered her recovery and ability to live independently.

Discussion

Hyperglycaemia Induced Hemichorea-Hemiballism (HIHH) is rare but recognised complication of diabetes. It is more common in elderly women with type 2 diabetes [1]. This is thought to be due to increased dopamine sensitivity secondary to oestrogen deficiency post menopause. A reported increased incidence in Asians may reflect either a genetic predisposition to HIHH to less adequate diabetic control in underdeveloped Asian countries [1,2]. Review of the literature demonstrates that the consistent factors in all cases of HIHH are persistently elevated blood glucose levels, which is reflected in a high HbA1c result.

In an analysis of 53 patients, mean HbA1c was 14.4%. HIHH is classically described in the setting of non-ketotic hyperglycaemia, thus its predominance in type 2 diabetics, but ketotic acidosis has even been postulated to be protective [3,4]. HIHH can be a presenting symptom of undiagnosed diabetes mellitus as well as a complication of poor glycaemic control in longstanding diabetes [5,6]. In our patient, Figure 1 depicts changes in HbA1c in our patient, while taking various blood glucose lowering agents, over a 10-year period.

Typically, HIHH has a favourable clinical prognosis. The majority of patients make a full recovery within six months, with control of hyperglycaemia [1]. However, some may only have partial improvement or persistent symptoms. Moreover, even after apparent clinical recovery, a recurrence of hyperglycaemia sometimes precipitates clinical relapse [1]. In addition to insulin therapy, neuroleptic and anti-epileptic agents can be used to control symptoms. Haloperidol has shown to be efficacious, and other medications including risperidone, clonazepam, topiramate and

tetrabenazine have shown variable efficacy [1,5-12].

The pathogenesis of HHH is poorly understood. Proposed mechanisms include: hyperglycaemia induced hyperviscosity causing hypoperfusion to the basal ganglia, focal cerebral metabolic disturbances and depletion of Gamma-Aminobutyric Acid (GABA) neurotransmitter in the basal ganglia with reduced inhibitory signal [7,13]. ¹⁸F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) studies carried out on patients with HHH demonstrate a marked reduction in the glucose uptake in the corresponding basal ganglion of the affected individual. This provides evidence for cerebral glucose metabolism failure as an underlying cause of the focal neurology [14,15]. Furthermore, in the hyperglycaemic state, where aerobic metabolism via the citric acid cycle is suppressed, GABA becomes the substrate for anaerobic metabolism to succinic acid, in order to meet ongoing cerebral energy demand [1,16]. In the ketoacidotic state, acetoacetate can be used to replenish GABA and this may explain the rarity of HHH in diabetic ketoacidosis or type 1 diabetes [17]. Whilst our patient was non acidotic, she is the first reported case of HHH in a patient with ketosis possibly related to the use of a Sodium Glucose Transporter-2 (SGLT-2) inhibitor.

Typical MRI brain findings feature a high intensity, unilateral basal ganglia lesion on the T1-weighted imaging [1,13]. The putamen is almost always involved, but sometimes the caudate and globus pallidus are involved in addition. The aetiology of the MRI hyperintensity lesion on the T1-weighted images is controversial. Several hypotheses have been proposed to explain the radiological findings in HHH, these include: 1) putaminal haemorrhage, 2) central pontine myelinolysis, 3) Wallerian degeneration of neurones, and 4) cytoplasmic oedema of the gemitocytic astrocytes in response to acute cerebral injury [7,18-20].

Other metabolic and systemic conditions are also associated with MRI brain findings of a hyperintense basal ganglia lesion on T1 weighted imaging. These include manganese toxicity in long term parenteral nutrition, hepatolenticular degeneration due to chronic liver disease, chronic use of potassium permanganate by intravenous drug users, hypoxic ischaemic changes, disorders of calcium metabolism, Fahr disease, lupus, neurofibromatosis and Wilson disease [18,21-24]. These conditions tend to present with bilateral T1 hyperintense lesions. It is uncertain why HHH usually presents with unilateral features, while other metabolic disorders present with bilateral changes, but this feature is a distinguishing characteristic. In other MRI sequences, contrasting with the consistently elevated T1 signal in HHH, putaminal T2 signal is variable [1]. The T1 weighted imaging findings are usually reversible, but lag behind clinical improvement [13].

In our patient, we postulated whether the hyperglycaemic basal ganglia injuries impacted her cognitive and executive function. It is known that in other hyperkinetic movement disorders such as antiphospholipid syndrome and Sydenham's chorea, that these patients demonstrate cognitive deficits [25,26]. Due the decline in our patient's mental health and her initial acute presentation we did not formally assess cognition. We hypothesize that interruption of the prefrontal basal ganglia, as demonstrated by the T1 weighted lesions on MRI brain in HHH, may be related to a potential a motivational cognitive syndrome; and our patient's subsequent incapacity to maintain reasonable glycaemic control. The question is then whether the initiating hyperglycaemia was due to an apathetic cognitive syndrome which caused the basal ganglia changes or whether the

physical manifestations of a basal ganglia injury caused our patient's apathy towards her glycaemic control.

Conclusion

HHH presents in the context of non-ketotic hyperglycaemia, but can also present with ketosis as in our patient. In an elderly woman presenting with the subacute onset of hemichorea in the context of hyperglycaemia, HHH is overwhelmingly likely. Confirmation depends upon typical CT or MR imaging findings. HHH is known to have a favourable prognosis with improvement in glycaemic control; however in our patient, despite better glycaemic control, there was minimal clinical improvement. Her long-term outcome remains guarded. HHH is a rare condition, but with hyperglycaemia and classical MRI changes, clinicians should recognise it as a differential diagnosis of hemichorea-hemiballismus.

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