

# A case of hemichorea-hemiballism presenting in association with diabetic ketoacidosis

## Hibba Kurdi<sup>1</sup>

BSc, MBBS, MRCP(UK), Core Medical Trainee

## Dana Ershaid<sup>1</sup>

MBBCh, MRCP(UK), Specialist Registrar in Diabetes and Endocrinology

## Peter Evans<sup>1</sup>

MBBS, MD, FRCP(UK), Professor of Diabetes and Endocrinology

<sup>1</sup>The Royal Gwent Hospital, Newport, South Wales, UK

### Correspondence to:

Hibba Kurdi, BSc, MBBS, MRCP(UK), Core Medical Trainee, The Royal Gwent Hospital, Cardiff Road, Newport NP20 2UB, UK; email: hibba.kurdi@doctors.org.uk

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## Abstract

Movement disorders are a rare but recognised manifestation of non-ketotic hyperglycaemic episodes on a background of poorly-controlled diabetes mellitus. The literature is otherwise sparse when it comes to an association between hemichorea-hemiballism and diabetic ketoacidosis (DKA).

A patient with no past medical history of note was admitted with a sudden-onset involuntary movement disorder and was found to be in DKA during her inpatient stay. There was a delay in diagnosis and management as all efforts pointed in the direction of diagnosing the cause of the sudden-onset hemichorea-hemiballism as a potential cerebrovascular event. The movements subsided with treatment of the ketoacidosis and with the addition of tetrabenazine. Imaging revealed a hyperdensity of the left basal ganglia consistent with a metabolic cause and not an ischaemic event.

Although the pathophysiology of movement disorders in diabetes is still unclear, this case highlights the importance in maintaining a wide list of differentials when faced with an atypical presentation of hemichorea-hemiballism, especially as DKA is a reversible emergency with high mortality rates if left untreated. Hemichorea-hemiballism as a consequence of DKA seems to be a multifactorial phenomenon. In this case, it began with non-ketotic hyperglycaemia and evolved into ketoacidosis. Confounding factors precipitating this included infection, and delayed diagnosis and management. Copyright © 2017 John Wiley & Sons.

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## Key words

movement disorder; diabetic ketoacidosis; hemichorea-hemiballism; diabetic striatopathy; non-ketotic hyperglycaemia

## Introduction

Movement disorders can be a presentation of both hyperglycaemia and hypoglycaemia. The most commonly recognised is an entity referred to as hemichorea-hemiballism (reported most commonly in the elderly population aged over 65 years with diabetes).<sup>1</sup> It is often difficult to distinguish hemichorea from hemiballism and the terms are frequently used interchangeably. Currently, it is thought that they form opposite sides of the same spectrum with ballism being considered a severe form of chorea. The term chorea is used to describe continuous random involuntary muscle contractions that have a wide list of differential diagnoses and represent a dysfunction of neuronal connections between the basal ganglia and motor cortex.<sup>2</sup>

The usual approach on diagnosis of the movement disorder is to screen for the most common causes including ischaemia and the less common including autoimmune and genetic causes. Diabetic ketoacidosis (DKA) is now a well-recognised diabetic emergency but is rarely associated with movement disorders.

The management and diagnosis of metabolic causes of movement disorders are often delayed as other more common diagnoses are pursued. This often leads to clinical deterioration in symptoms, such as the development of DKA in this case.

In this case study, we explore the relationship between diabetes and hemichorea-hemiballism.

## Case history

We present a 70-year-old, fully independent female of Caucasian origin who was admitted on a Friday evening with a sudden-onset involuntary movement disorder spanning three days and involving the right upper and lower limbs.

She sought medical attention from her GP one week prior to her hospital admission, due to right thumb pain. Non-steroidal anti-inflammatory medication was prescribed and, together with that, she had controlled the pain with over-the-counter herbal remedies which she was taking on a regular basis. These included extracts of *Rhodiola rosea* to combat fatigue and

stress, as well as French pine bark for antioxidant effects. A set of routine investigations including uric acid levels were negative and there was no obvious history of trauma.

It is unclear whether any blood glucose measurements were taken at the time, but in retrospect there was a subacute onset of osmotic symptoms following the same timeframe. She described herself as 'stoic' and usually declined any interaction with her GP.

The past medical history is limited to a previous traumatic head injury resulting in no neurological deficit. The social history is equally sparse being a lifelong non-smoker and tee-total. Family history includes type 2 diabetes (late presentation at over 65 years of age) and one generation of maternal breast cancer.

**Initial assessment.** On examination at the bedside, proximal uncontrolled and irregular movements of the right upper and lower limbs were observed, most consistent with hemichorea-hemiballism (HC-HB). No involvement of the face or speech was noted, and she had no other focal neurological deficit.

Other systems examinations were unremarkable. The movements were continuous and unrelenting since initial presentation. The initial clerking reports a mild 'erythema' to the right thumb and wrist. This was not revisited until post weekend when intravenous (IV) antibiotics were started for a cellulitis that had now spread to the forearm.

Her bloods showed a random blood glucose of 28.1mmol/L with blood ketones of 3mmol/L. Venous blood gas showed a pH of 7.38, HCO<sub>3</sub> 20.7mEq/L, PCO<sub>2</sub> 4.7kPa, and lactate of 1.4mmol/L. She had negative inflammatory markers with a full blood count in the normal range.

**Subsequent measures.** Despite an initial elevated lab glucose reading, including a ketosis and HbA<sub>1c</sub> of 148mmol/mol on admission, no other bedside capillary blood glucose monitoring was undertaken after the initial assessment (clinical judgement was distracted by the ongoing movement disorder and ignoring the evolving right arm cellulitis).

A CT brain on admission revealed a unilateral increased density of the left

basal ganglia with mild periventricular small vessel ischaemic changes that appeared chronic in nature. There were no other intracranial pathologies identified on review with a neuro-radiologist. This hyperdensity of the left basal ganglia was initially interpreted as ischaemic; antiplatelet therapy was therefore commenced, awaiting an inpatient stroke team review.

**Review.** Review by the medical oncology team two days later for increasing drowsiness found her to have a blood glucose reading of 24mmol/L with ketones of 5.4mmol/L and metabolic acidosis. The triggering factor was a cellulitis that she had developed in her right hand and she was started on IV antibiotics as per local guidelines. She was started on the DKA protocol and was thereafter reviewed by our diabetes specialist nurses post weekend who switched her over to a twice-daily mixed regimen of insulin post resolution of the DKA.

Trace elements including magnesium, thyroid function tests, antibodies such as anticardiolipin and anti-β-2 glycoprotein-1 were found to be within the normal range. These were tested to exclude autoimmune disease that can present with chorea-like symptoms. The lipid profile showed normal total cholesterol with a slightly low HDL of 0.7mmol/L.

She was reviewed by neurology three days into her admission, who suspected a metabolic diabetes-related left basal ganglia or thalamic lesion. The hemichorea-hemiballism movements had already markedly improved as she was now able to use semi-purposeful movements in order to disguise them, but a trial of tetrabenazine was initiated as the patient was becoming very distressed by the fact that they were still continuous.

The patient was reviewed by a stroke physician who recommended an MRI brain but the patient declined.

**Outcome.** The movement disorder secondary to a new diagnosis of diabetes resolved completely after eight days. Discharge was achieved in a total of 10 days. The tetrabenazine was continued for a total of four weeks. Antislet cell and anti-GAD antibodies were also within normal range, although this does not necessarily exclude a diagnosis of type 1 diabetes mellitus.

## Discussion

In retrospect, early cellulitis of the right arm was missed, with the healing process being impaired due to the persistent hyperglycaemia. The movement disorder resolved with treatment of the DKA and did not return even up to six weeks post-acute admission on review in medical outpatients. The diagnosis of a common cerebrovascular accident as opposed to a rare HC-HB secondary to hyperglycaemia led to a diagnostic bias that is termed an 'availability' bias.<sup>3</sup> This bias leads clinicians to make diagnoses based on similar experiences that they have previously encountered as they are 'common'.

Movement disorders related to hyperglycaemia are more prevalent in non-ketotic hyperglycaemia (NKH). This was first reported by Bedwell as early as the 1960s.<sup>4</sup> Since that time there have been other reports of hemichorea-hemiballism manifesting as the initial presenting complaint in diabetes mellitus but is usually seen in the elderly population over 65 years of age.<sup>5</sup> In NKH, gamma amino-butyric acid (GABA) and acetylcholine are used as an alternative source of energy. Depletion of these neurotransmitters leads to a disinhibition of the thalamus, resulting in hyperkinetic disorders. However, in DKA acetoacetate produced in the liver as a by-product can be used to produce GABA and it would therefore seem counterintuitive for this to result in a movement disorder. Therefore, movement disorders in DKA may be multifactorial and not dependent on one cause.<sup>6</sup>

The myriad of factors contributing to the complex relationship between DKA and movement disorders is illustrated by the case of a 37-year-old with type 1 diabetes mellitus who developed HC-HB after a central pontine myelinolysis secondary to huge osmotic shifts during the DKA episode. However, the abnormal movements presented three weeks after the DKA episode was treated. Despite symptomatic resolution, the hyperintensity seen in the putamen persisted on repeat imaging.<sup>7</sup> Resolution of imaging findings is often reported to lag behind clinical recovery.

As previously mentioned, ketone bodies increase GABA synthesis and are therefore thought to be protective against movement disorders. There

has been one report of a ketogenic diet used as treatment for intractable epilepsy, leading to bilateral putamen lesions with associated movement disorder not present on imaging prior to initiation of the diet. It is hypothesised that there may have been an adverse reaction between ketogenic diet and sodium valproate causing an increase in lactate as a by-product of anaerobic energy, therefore adding more weight to the 'multifactorial' link between ketoacidosis and movement disorders.<sup>8</sup>

There are not many cases of movement disorders in the context of DKA; however, there were two cases of hemifacial spasm that occurred with DKA and resolved with tight glycaemic control. Symptoms lasted for a few hours; no abnormalities were detected on imaging, including MRI and CT.<sup>9</sup>

The exact pathology underlying the relationship between diabetes and hemichorea-hemiballism is unknown and includes theories involving petechial haemorrhage and hyperviscosity. Most patients with hyperglycaemic-related HC-HB are found to have a high serum osmolarity. This is thought to potentially cause a reduction in cerebral blood flow, leading to a transient ischaemic event but not infarction – which in turn results in basal ganglia dysfunction.<sup>10</sup> There are some studies that have demonstrated a reduction in blood flow that has persisted as late as four months after the initial presentation. This is not reliably reproduced for each individual case.<sup>11</sup>

Other theories involve the role of the depression of the Krebs cycle in DKA and the take-over of anaerobic pathways and an upsurge in lactate. Magnetic resonance angiography studies have shown an increase in lactate in the region of the basal ganglia, and other studies include the depletion of GABA and acetylcholine neurotransmitters. Many of these studies looking into the pathogenesis of the hyperglycaemia-related HC-HB phenomenon are inadequate due to the multiple coexistent comorbidities and differences in timings of the post-mortems.

Abe *et al.* describe a study of six patients with hyperglycaemia-induced HC-HB who had biopsies of the striatum. Results revealed patchy necrotic tissue, severe thickening of

### Key points

- Although hyperglycaemia-associated movement disorders are rare, any new presentation of chorea should prompt full investigation for all possible causes including those considered to be less common
- Diabetic ketoacidosis is a reversible medical emergency that should be treated if all criteria are met, regardless of whether the diabetes is labelled as type 1 or type 2 diabetes
- A high index of suspicion is needed for potential underlying undiagnosed chronic medical problems in patients who are reluctant in engaging with medical services

all layers of the arterioles, narrowing of vessel lumens, as well as hyaline destruction. They went on to coin the term 'diabetic striatopathy'. However, it is still unclear whether a relationship between ischaemic insult and changes on MRI is associated with striatal vasculopathy.<sup>12</sup>

The diagnostic conundrum is not limited to pathophysiology alone as CT and MRI changes are often variable. The most consistent and common feature on MRI is a hyperintense signal of the contralateral putamen.<sup>10</sup> In the minority of patients, HC-HB can occur with ipsilateral basal ganglia lesions, as seen in this case, or lesions expanding beyond the basal ganglia to the internal capsule and midbrain.<sup>13</sup>

There is no consensus on whether CT or MRI imaging is superior in picking up this diabetic striatopathy or striatal disease. Occasionally, imaging abnormalities may precede the onset of symptoms and, although most resolve with resolution of symptoms, others persist – the longest reported is six years. Accuracy is difficult as repeat imaging for academic purposes if asymptomatic cannot be justified.<sup>12</sup>

HC-HB has also been reported with hypoglycaemic episodes, but has shown on MRI to have a different topographical predilection on imaging – preferring hippocampus, basal ganglia and temporal lobe. The pathophysiology of this is again unclear and may be related to temporary striatal dysfunction, with decreased blood flow in the basal ganglia and increased perfusion of the thalamus.<sup>14</sup>

Control of blood glucose levels is the mainstay of treatment, as described in this case whereby treatment of the DKA led to an improvement in symptoms. Other treatment options include typical and atypical antipsychotics, benzodiazepines and

some anticonvulsants, including sodium valproate and topiramate.

### Conclusion

The case presented here demonstrates a 'multifactorial' process linking movement disorders and DKA. An initial non-ketotic hyperglycaemic state progressed to a DKA because the hyperglycaemia and evolving cellulitis were overlooked.

Although we are taught at medical school that 'common things are common', we highlight here the importance of a high index of suspicion with regard to undiagnosed medical conditions in patients who are reluctant to engage with medical services.

Opportunistic screening for chronic disease should be considered in the event that such patients present to primary or secondary care. A thorough history should be taken, including herbal remedies; a thorough literature search conducted did not reveal any cause-and-effect relationship between herbal remedies taken and chorea.

Our patient is likely to have had a longstanding undiagnosed diabetes mellitus prior to her admission, given the grossly elevated HbA<sub>1c</sub>. Although type 1 diabetes is the most likely option, it is quite difficult in this case to label the diabetes. This emphasises the importance of treating DKA if criteria are met, regardless of whether it is thought to be a type 1 or type 2 diabetes mellitus.

This case highlights other important issues: junior doctors need to be empowered to seek out specialist advice via other means, including telephone out-of-hours. Most district general hospitals do not have in-house services such as neurology out-of-hours, but will have access to these services via their local tertiary centre. Addressing barriers

to accessing such services will lead to improved patient care due to early specialist input – which would have improved outcomes in this case and potentially lead to an early recognition of the DKA.

Capillary blood glucose monitoring on acute admission units often gets overlooked, especially if patients are not known to have a history of diabetes. This is an area that could potentially benefit from undertaking a quality-improvement project; an introduction of hyperglycaemia >14mmol/L as a formal part of early-warning scores may trigger earlier review of patients and prevent progression of non-ketotic diabetes to ketoacidosis.

In the meantime, we are actively contributing to the ‘Think Glucose’ campaign and will aim to share lessons learnt from this case

with the wider hospital network through presentation at our local medical meetings. Our diabetes specialist nurses have given important take-home messages from this case to primary care.

#### Declaration of interests

There are no conflicts of interest declared.

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## Diabetes vignette

# ‘My diabetes precipitated psychosis in my mum’

After stabilising a 10-year-old female patient diagnosed with new-onset type 1 diabetes mellitus, insulin therapy was switched to subcutaneous injections and diabetes education was started.

The mother of the patient mentioned repeatedly that this diagnosis of diabetes was very stressful to herself. The mother’s reaction was initially related to self-guilt and blame then started to become non-coherent. She stated that ‘she was not commissioned on this earth to deal with diabetes’. When her speech became completely disorganised and delusional, she was escorted to the emergency room where she was diagnosed with acute psychosis and admitted to the psychiatry unit of the same hospital in which her daughter was being treated.

The child protection services were called to take over the legal responsibility of the child. The estranged father was found and he confirmed that his ex-wife had been diagnosed previously with schizophrenia. He completed the diabetes education class and was able to assume the responsibility for his daughter.

#### Discussion

The new onset of diabetes in children carries a heavy stress burden on the parents. The diagnosis is irreversible, it interferes with feeding habits of the child, and may aggravate needle phobia in both children and parents.

The new diagnosis of type 1 diabetes has been found to cause the symptoms of post-traumatic stress disorder.<sup>1</sup> Paediatric parenting stress linked to type 1 diabetes has been related to increased responsibility and fear.<sup>2</sup> Family stress is well known to affect negatively the metabolic control of type 1 diabetes in children.<sup>3</sup> Medical outcomes of the disease such as adherence to treatment and health status of children are also affected by this stress.<sup>4</sup> Family conflict, single parent settings and adolescent age of the child may also contribute to increased stress that would lead to poor metabolic control of children with diabetes.<sup>5</sup>

Social and psychological interventions are key factors in dealing with parental stress.<sup>6</sup> Parents should always be assisted to cope with the demands of caring for children with diabetes.<sup>7</sup> Thus, the multidisciplinary

approach of adding professionals from social work and psychological health should be a standard of care in coping with childhood diabetes.

**Michael Yafi, MD**, Associate Professor and Division Director, Department of Pediatrics, Division of Pediatric Endocrinology, The University of Texas, Houston, Texas, United States; email: michael.yafi@uth.tmc.edu

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