CASE REPORT

Paediatric non-ketotic hyperglycaemic hemichorea–hemiballismus

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Accepted 16 March 2018

SUMMARY

Non-ketotic hyperglycaemic hemichorea–hemiballismus (NHHH) is commonly seen among elderly Asian women with type 2 diabetes mellitus. Here, we present a case of a 16-year-old Filipina with type 1 diabetes mellitus who is poorly compliant to her medications and subsequently developed right hemichorea–hemiballismus (HH). She was initially admitted with hyperglycaemia but was negative for ketonuria or metabolic acidosis. Neuroimaging showed bilateral lentiform nuclei and left caudate hyperdensities on CT and T1-weighted hyperintensity on MRI. Blood glucose was controlled with insulin. Haloperidol and clonazepam were started for the HH with gradual resolution of symptoms in 6 weeks. This is the fifth reported case of NHHH seen among the paediatric age group. NHHH in the paediatric population is clinically and radiographically similar to NHHH seen among adults. Correction of hyperglycaemia results in clinical improvement and radiographic resolution of lesions but persistent cases may necessitate specific treatment targeted towards the abnormal movements.

BACKGROUND

Chorea is characterised by random rapid irregular involuntary movements of the distal limbs, trunk and face that move from one region to the next. It may be due to a large number of factors including structural, metabolic, pharmacological and genetic causes.¹ Ballism is part of the spectrum of chorea and refers to movements that are more proximal in location and with a larger amplitude.^{2,3} In childhood, the common causes of chorea are Sydenham chorea and cerebral palsy.¹

Non-ketotic hyperglycaemic hemichorea–hemiballismus (NHHH) is an uncommon but well-known disease entity seen among adult type 2 diabetes mellitus patients. It has a distinct clinical profile with specific neuroimaging findings.⁴ The occurrence of NHHH among paediatric patients is rare and to our knowledge, only four cases have been reported so far.^{4–7} Here, we discuss the case of a 16-year-old Filipina with poorly controlled type 1 diabetes mellitus who presented subacutely with hemichorea–hemiballismus (HH) with distinct neuroimaging findings.

CASE PRESENTATION

A 16-year-old Filipina was admitted at our institution due to involuntary movements of the right extremities. She was diagnosed with type 1 diabetes

mellitus at 8 years old after initially presenting with polyuria and weight loss. She was regularly seen at the paediatric endocrinology clinic but was lost to follow-up starting 2015. The most recent insulin dose prior to admission was a split-mixed regimen of isophane insulin (HN) 8 units + regular human insulin (HR) 17 units in the morning and HN 6 units + HR 10 units at night. She claimed that capillary blood glucose (CBG) monitoring at home revealed levels ranging from 80 to 400 mg/dL. Despite elevated CBG levels, insulin dose was decreased to insulin HN 8 + HR 17 units once a day 7 weeks prior to admission due to financial constraints.

Four weeks prior to admission, she started to have random involuntary uncoordinated non-purposeful movements of the right upper extremity with no other associated signs and symptoms. Symptoms progressed and involved the right lower extremity and the right side of the face. The movements were notably absent during sleep. At this time, there was no fever, cough, colds, chest pain, dyspnoea, orthopnoea, bowel movement changes, abdominal pain or changes in sensorium. Insulin was resumed to twice a day dosing but the involuntary movements persisted. Determination of CBG was greater than 300 mg/dL on daily monitoring. Due to the persistence of the involuntary movements, she was brought to our institution and was subsequently admitted.

At the emergency room, she was received alert, communicative, afebrile and not in respiratory distress. She was normotensive at 120/80 mm Hg and had a normal cardiac examination. Her standing height is 126 cm (z score < -3) with a weight of 31.4 kg and a body mass index of 19.7 kg/m². Midparental height was computed and was 144 cm. With the presence of axillary hair, absence of facial hair, breast Tanner 2 and pubic hair pattern grade 3, she was given a sexual maturity rating of 3. At this time, she has not had her menarche. The rest of the systemic physical examination was unremarkable. She had involuntary random jerk-like uncoordinated non-purposeful movements of the right upper and lower extremities with associated twitching of the right face. There were no other associated pyramidal tract signs, weakness or hypotonia. There was no milkmaid's grip, tongue darting or pronator's drift. She was oriented to three spheres with intact higher cortical functions. She had 20/50 visual

To cite: Suratos CTR, Benitez JAE, Urquiza SC, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-223429

Figure 1 Unenhanced cranial CT scan on axial sections showing asymmetric hyperdensities in the bilateral lentiform nuclei (L) and left caudate nucleus (C), with prominence of the cortical sulci and lateral fissures on the right hemisphere (red asterisks).

acuity and on funduscopy, there were no papilloedema on both eyes, no haemorrhages and no of signs of diabetic retinopathy. There were also no Kayser-Fleischer rings around the corneal-scleral junction. The rest of the neurological examination was unremarkable.

INVESTIGATIONS

Laboratory examinations showed an elevated CBG of 317 mg/dL, normal antistreptolysin O titre of <200 and haemoglobin A1c of 12%. Serum creatinine and serum electrolytes (sodium, potassium, chloride, calcium, phosphorus and magnesium) were all normal and effective serum osmolality was calculated at 305 mOsm/kg. Complete blood count showed mild leucocytosis at $12.1 \times 10^9/L$, but haemoglobin, haematocrit, platelet count and differential counts were normal. Urinalysis showed glucosuria, albuminuria but absent ketonuria. Arterial blood gas was interpreted as compensated respiratory alkalosis (blood pH 7.506, pCO_2 30.7 mm Hg, pO_2 104.9 mm Hg, HCO_3^- 24.6 mmol/L). The serum C reactive protein, intact parathyroid hormone and thyroid function tests were also within normal limits. Further workup revealed an elevated total urine protein of 4.029 g/24 hours and bilateral renal parenchymal disease on ultrasound of the kidneys. Based on the Greulich-Pyle method, bone age was compatible with a 16–17-year-old female.

Initial cranial CT scan showed asymmetric hyperdensities (80–98 HU) involving the bilateral lentiform nuclei and the left caudate nucleus (figure 1). The cortical sulci and lateral fissures on the right appear prominent on the scan.

Figure 2 Gadolinium contrast-enhanced cranial MRI on axial sections showing hyperintense signals in the bilateral lentiform nucleus (L) and left caudate nucleus (C) on T1-weighted and T2/FLAIR and mild hyperintensity on T2-weighted imaging. Volume loss is seen particularly in the right cerebral hemisphere (red asterisks). FLAIR, fluid-attenuated inversion recovery.

TREATMENT

Insulin HR was initially increased to 10 units every 6 hours (1.27 units/kg/day). Enalapril at 5 mg/day and furosemide at 40 mg/day were started for diabetic nephropathy. On the third day of hospitalisation, CBG levels started to go below 200 mg/dL, but she still had right hemichorea, which eventually progressed to higher amplitude ballism. Haloperidol was initially started at 0.5 mg/day then increased to 0.75 mg/day after 4 days without response.

OUTCOME AND FOLLOW-UP

She was discharged after 10 days with controlled blood sugars but still with right HH. She was maintained on insulin premixed 30/70 at 1.5 units/kg/day (30 units in the morning and 18 units at night) and haloperidol at 1 mg/day.

Follow-up cranial MRI with gadolinium contrast done 1 month after the cranial CT showed hyperintense signal of the left caudate and bilateral lentiform nuclei on T1-weighted imaging (T1WI) and T2/fluid-attenuated inversion recovery (T2/FLAIR) and mild hyperintensity on T2-weighted imaging (T2WI). The right lentiform nucleus also shows minimal T1WI and T2/FLAIR hyperintensity and smaller focus of hyperintensity on T2WI (figure 2). Volume loss is again apparent particularly involving the right cerebral hemisphere especially its temporal lobe. Ex vacuo dilatation of the right lateral ventricle was observed.

On follow-up, she still had HH and was complaining of difficulty sleeping due to the involuntary movements. Haloperidol was increased to 2 mg/day and clonazepam was added at 1 mg/day. HH decreased in intensity after 3 weeks and eventually disappeared on the sixth week. Haloperidol and clonazepam were tapered and discontinued with resolution of HH.

DISCUSSION

Our patient developed NHHH 3 weeks after decreasing her insulin dose. She presented at the emergency room with elevated blood sugars and absence of urinary ketones. Abnormal movements complicating hyperglycaemia in diabetes mellitus is well reported in literature, and the most common and best recognised is HH.^{3 8}

In NHHH, the abnormal movements occur acutely and unilaterally, such as in our patient, but it can also be insidious and generalised. Like most movement disorders, the abnormal involuntary movements disappear during sleep.⁸

In a review of 53 cases, most patients were elderly women, with a mean age of 71.1 years. In the same review, 91% of the patients were of Asian origin, suggesting a genetic predisposition or inadequacy of blood sugar control among patients in developing countries.⁹

NHHH is rarely seen in children with only four reported cases to date (see table 1).^{4–7} Interestingly, NHHH is the presenting manifestation of diabetes mellitus in three cases.^{5–7}

The exact mechanism underlying NHHH is not yet well understood but the current hypothesis invoked is the depletion of gamma-aminobutyric acid (GABA) and acetylcholine receptors in the basal ganglia, particularly the putamen.⁸ In hyperglycaemic episodes, the Krebs's cycle is inactivated and glucose metabolism is shifted to the anaerobic pathway, depleting acetate production, eventually reducing acetylcholine.^{8 9} During anaerobic metabolism, the brain then uses GABA to produce energy, depleting GABA in the process causing metabolic acidosis. Notably, there is paucity of abnormal movements in diabetic ketoacidosis (DKA). In DKA, ketones are used as energy source, producing GABA in the process.⁸ Finally, the combination

Table 1 Summary of reported cases of NHHH in children

	Mihai <i>et al</i> ⁵	Alves <i>et al</i> ⁴	Faundez <i>et al</i> ⁶	Aquino <i>et al</i> ⁷
Age/Sex	15/F	8/M	13/M	14/F
Movement type	Hemichorea–hemiballismus right foot, arm and face	Chorea right upper extremity	Hemichorea–hemiballismus left arm and leg	Hemichorea–hemiballismus left arm and leg
Duration of symptoms	1 day	15 days	10 days	3 days
Blood glucose	367 mg%	149 mg/dL	29 mmol/L (522 mg/dL)	349 mg/dL
MRI lesion	None	T1 hyperintense, T2 isointense bilateral caudate and putamen, T2 hyperintense signal in the right putamen with atrophy	T1 hyperintense, T2 and FLAIR hypointense, restricted ADC right caudate nucleus and putamen	T1 and T2- hyperintense signal on the right striatum
Follow-up MRI time	Not done	2 months	3 months	3 & 4 years
Follow-up imaging lesion	Not applicable	CT scan: hyperdensities in the caudate-putamen bilateral frontal linear hyperdensities corticomedullary junction	MRI: T1 hyperintense hemosiderin deposits and atrophy of the right basal ganglia	MRI: persistent signal abnormalities on the right basal ganglia and reduced volume of the right putamen and caudate nucleus
Course	Complete resolution	Complete resolution	Complete resolution	No resolution
Duration of abnormal movement	1 day	2 days	4 weeks	4 years
Treatment	Haloperidol, phenobarbital, clonazepam, diazepam	Valproic acid	Tetrabenazine	Haloperidol (maximum 10 mg/day), valproic acid (maximum 1500 mg/day)

ADC, apparent diffusion coefficient; FLAIR, fluid-attenuated inversion recovery; NHHH, non-ketotic hyperglycaemic hemichorea–hemiballismus.

of reduced GABA and acetylcholine and metabolic acidosis produces basal ganglia dysfunction leading to chorea. However, this theory does not explain the persistence of abnormal movements even after correction of hyperglycaemia. Apart from that, chorea may also occur in hypoglycaemia and ketotic hyperglycaemia suggesting another mechanism for the development of HH.^{8–10}

Diagnosis of NHHH is made based on typical clinical, laboratory and radiological features. Neuroimaging may show variable results but the finding most commonly seen is contralateral putaminal hyperintensity in T1WI without mass effect and perilesional oedema.^{8,9,11} Additional caudate nucleus or globus pallidus involvement may also be seen.⁹ T2WI may show variable results, either isointense or hypointense to the surrounding normal basal ganglia.¹¹ Plain cranial CT images would show hyperattenuation on the same areas described above.¹² There are many hypotheses to explain the T1WI findings, but the most commonly promoted premise is the presence of a protein hydration layer in swollen gemistocytes.¹¹ Gemistocytes are reactive astrocytes that are swollen and appear during acute injury. Thereafter, they gradually decrease in size once the acute injury is resolved.¹³ Petechial haemorrhage and calcification were also postulated to explain the findings on both CT and MRI.¹² Biopsy findings, however, more strongly supports the gemistocytic theory. In the sampled putamen, abundant gemistocytes with fragments of gliotic tissue without infarction or haemorrhage were found.¹³

The mainstay of treatment for abnormal movements induced by hyperglycaemia is reduction of blood glucose levels.⁸ The clinical and radiological course of NHHH is favourable, usually resolving after blood sugar control.^{5,9} However, after correction of hyperglycaemia, abnormal movements may persist even up to 5.6 years.⁹ Persistent abnormal movements may necessitate symptomatic treatment.⁸ This includes the dopamine receptor blockers haloperidol and chlorpromazine, the cholinergic-depleting agent tetrabenazine, benzodiazepines, such as diazepam and clonazepam, and anticonvulsants including valproic acid and topiramate.⁸ Basal ganglia lesions also resolve radiographically but may take longer than the clinical improvement.¹² In a review of cases, 86% showed

resolution of high-intensity basal ganglia lesions on T1WI after a follow-up period of 2 months to 1.5 years.⁹ In a few cases, the abnormal movements may recur after an episode of hyperglycaemia.⁹

Unique to our case is the presence of cerebral volume loss seen in both cranial CT and MR images. Neuroimaging studies have shown that type 1 diabetes mellitus is associated with total and regional loss of grey and white matter volume.¹⁴ These structural brain abnormalities, such as ventricular and gyral atrophy are common and more prevalent among patients diagnosed with type 1 diabetes mellitus at an early age.¹⁵ In our review of cases, only our patient showed the described brain abnormalities seen among patients with type 1 diabetes mellitus owing to the fact that our patient has had the disease since 8 years old.

In summary, this case described NHHH seen in a Filipina with uncontrolled type 1 diabetes mellitus. The clinical profile and neuroimaging findings in NHHH are similar for adult and paediatric cases. The mainstay of treatment is correction of hyperglycaemia, but in persistent cases, drugs targeted towards the abnormal movements are necessary. Follow-up neuroimaging may be necessary to determine the extent of reversibility of the basal ganglia lesions and also to monitor the progression of brain atrophy seen in our patient.

Learning points

- Non-ketotic hyperglycaemic hemichorea–hemiballismus (NHHH), which is usually seen among elderly diabetic patients, may also be seen in the paediatric population.
- It has a similar clinical course and neuroimaging findings.
- Treatment consists of correction of hyperglycaemia and use of specific drugs targeting the abnormal movements.

Acknowledgements Special thanks to Dr. Franchesca Gabrielle Gabriel for proofreading the manuscript.

Contributors CTRS was involved in the diagnosis of the case, drafting the work and revising it. SCU was involved in the interpretation of the radiographic findings.

JAE LB was involved in revising the manuscript. CALS was involved in the diagnosis of the case and final approval of the version for submission.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Guardian consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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