Acanthocytosis as a predisposing factor for non-ketotic hyperglycaemia induced chorea-ballism

A Pisani, M Diomedi, A Rum, P Cianciulli, R Floris, A Orlacchio, G Bernardi, P Calabresi

**Background:** Episodic non-ketotic hyperglycaemia in patients with diabetes may be responsible for a syndrome characterised by hemichorea-hemiballism associated with unique radiological features.

**Objective:** To investigate whether factors other than hyperglycaemia may be responsible for the neurological involvement.

**Methods:** Three patients who developed a persistent chorea-ballism syndrome triggered by a hyperglycaemic crisis were investigated. In these patients, the persistence of the involuntary movements required neuroleptic medication.

**Results:** T1 weighted magnetic resonance imaging revealed bilateral hyperintense lesions involving the striatum. Surprisingly, in these patients, the laboratory investigations revealed peripheral red blood cell acanthocytosis in a significant proportion of cells.

**Conclusion:** Compared with the large population of patients with diabetes who do not show abnormal involuntary movements, unrecognised acanthocytosis in diabetes might render patients prone to develop hemichorea-hemiballism.

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hospital discharge, choreic movements were still present, requiring a low dose of haloperidol (0.5 mg/day). Interestingly, at that time, MRI showed an almost complete resolution of the striatal hyperintensity (fig 2C, D).

**CASE 2**

An 81 year old man was admitted to the emergency department because of a hyperglycaemic crisis (glucose value, 5800 mg/litre) associated with a confusional state, despite a regular intake of gliclazide (40 mg twice daily). After correction of the metabolic disequilibrium, a complete resolution of the confusional state was achieved. Eight days after the acute episode the patient developed a left HCHB, which progressively diffused contralaterally. Abnormal pyramidal or sensory signs were not found. A peripheral blood investigation, performed four weeks later, showed the presence of acanthocytes (5%), observed independently by two haematologists. The expression of Kell blood group antigens and serum apoB were normal; genetic analysis for chorea-acanthocytosis was negative. MRI showed signal hyperintensity in the putaminal regions, with a predominance of the right side in T1 weighted images. Pharmacological treatment with haloperidol produced only a modest benefit. Nearly six months after discharge a left HCHB was still present, whereas MRI images showed a resolution of the previously documented putaminal hyperintensity.

**CASE 3**

A 64 year old man came to our attention in the outpatient clinic. He complained of the acute appearance, nearly 30 days before, of involuntary movements in his left hemisoma. There was no personal history of neurological illness or drug abuse. He presented choreic-ballistic movements involving both his left arm and leg. No sign of pyramidal or sensory abnormalities was found. Routine laboratory investigations demonstrated hyperglycaemia (3900 mg/litre), confirmed by subsequent analyses, whereas there was no evidence of ketosis. The patient was unaware of suffering from diabetes. Therefore, pharmacological treatment with sulfanylureas was started (a combination of glibenclamide 200 mg and metformine 2.5 mg twice daily), with a satisfactory control of glycaemia. He underwent MRI, which showed a right putaminal hyperintensity in T1 weighted images. Peripheral blood investigations, performed nearly six weeks after the onset of HCHB, showed the presence of acanthocytes (~98%), confirmed independently by two haematologists. Treatment with haloperidol up to 6 mg/day had only a modest effect.

**DISCUSSION**

HCHB has been associated with stroke, neurodegenerative disorders, tumours, infectious diseases, drug abuse, and metabolic derangement. Recent reports have described the appearance of HCHB in the course of hyperglycaemic crises in
patients with diabetes, accompanied by hyperintense signals in the caudate and putamen on T1 weighted MRI images. Most of these patients have shown reversible clinical and MRI signs after adjustment of blood glucose concentrations. In a few cases, a persistent choreic syndrome has been described, despite the normalisation of glucose concentrations.

The neuropathological nature of the characteristic MRI alterations is still controversial. A biopic specimen from the hyperintense putamen revealed the presence of gliosis with abundant reactive astrocytes, also named gemistocytes, but without deposition of hemosiderin. A necropsy report from a patient with HCHB showed similar findings. Interestingly, proton MRI spectroscopy and diffusion weighted MRI studies in HCHB suggest that both a hyperviscosity syndrome, possibly caused by hyperglycaemia, and concomitant cytotoxic oedema could be the cause of the MRI changes. These studies converge towards a common hypothesis of a metabolic alteration of striatal neurones, as supported by a single photon emission computed tomography study showing the presence of pronounced energy metabolism impairment in the striatum. This interpretation is not surprising considering that, among neuronal subtypes, striatal medium spiny neurones are highly vulnerable to energy depletion. The hypothesis of a reversible metabolic impairment may explain those cases where transient MRI and clinical alterations occurred. Conversely, the pathogenic mechanisms at the basis of a persistent syndrome, as in our patients, remain uncertain.

Recent experimental evidence shows that red blood cell membrane alterations are shared by three distinct hereditary neurological disorders, referred to as “neuroacanthocytosis”, including abetalipoproteinaemia, which is characterised by an inherited absence of apoB, leading to a progressive spinocerebellar ataxia, neuropathy, and retinitis pigmentosa. Chorea-acanthocytosis is characterised by a choreic syndrome with orofacial dyskinesia, dysphagia, dysarthria, seizures, and dementia. The third disease is McLeod syndrome, characterised by chorea, myopathy, neuropathy, and abnormal expression of Kell blood group antigens. Therefore, the clinical and laboratory findings obtained from our patients seem to exclude a typical “neuroacanthocytosis”.

Our present results provide the first evidence that an unrecognised acanthocytosis in diabetes might render patients susceptible to develop HCHB. However, the presence of acanthocytes appears to be unique to those patients with diabetes who develop HCHB, rather than being present in all patients suffering from diabetes. Of note, the HCHB syndrome reported in the literature appears to differ from our cases in several respects, namely: (1) two of the three patients developed choreic-ballistic movements not confined to a single hemisoma, (2) despite the reduction of both the radiological signs and the metabolic derangement, the clinical symptoms persisted; and (3) the presence of acanthocytosis, with dynamic changes of its percentage during the different phases of the disease (in case 1).

Several indications suggest a functional modification of erythrocyte membrane proteins, which might induce the morphological changes leading to acanthocyte formation, supporting the hypothesis that the percentage of acanthocytes may fluctuate in relation to a particular metabolic state. In our patients, the hyperviscosity induced by hyperglycaemia might result in a transient dysfunction of vulnerable striatal neurones in predisposed individuals. This hypothesis is in agreement with the notion that hyperglycaemia worsens the outcome in human stroke. Alternatively, another possibility could be that the same metabolic and osmotic process that deforms the red blood cells affects neuronal membranes, thus impairing neuronal function.

In conclusion, the presence of acanthocytes in circulating peripheral blood might be indicative of a predisposition to HCHB. Further studies, investigating a larger cohort of patients, are required to address the intimate relation between haematological and neuronal dysfunction.

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Authors’ affiliations

A Pisani, M Diomedì, A Rum, A Orlacchio, G Bernardi, Clinica Neurologica, Università di Roma Tor Vergata and Fondazione Santa Lucia, Rome I-00133, Italy

P Gianculli, Day Hospital Talassemie, Ospedale S. Eugenio, Rome I-00144, Italy

R Floris, Istituto di Radiologia, Università di Roma Tor Vergata, Italy

P Calabresi, Clinica Neurologica, Università di Perugia, Perugia I-06516, Italy

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