SHORT REPORT

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

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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.

Hemichorea-hemiballism (HCHB) is a clinical syndrome characterised by continuous, involuntary movements involving one side of the body. Non-ketotic hyperglycaemia has been associated with various neurological abnormalities, and among these, HCHB is one of the most frequently observed syndromes.[1–3] In most previously described cases, the involuntary movements were typically unilateral, with characteristic magnetic resonance imaging (MRI) findings in the contralateral striatum, consisting of high signal intensity on T1 weighted scans.[2] Moreover, both the clinical syndrome and MRI signs were reversible within days or weeks after the normalisation of blood glucose. Thus, a transient, reversible metabolic impairment within the basal ganglia has been considered as a possible cause of this disorder. The number of cases reported so far does not allow an unequivocal interpretation of the underlying pathogenic mechanisms. Here, we describe three patients who developed a persistent[3] and generalised chorea-ballism, despite the correction of hyperglycaemia and the regression of MRI alterations. Interestingly, a high degree of red blood cell acanthocytosis was found on peripheral blood examination, suggesting that the search for acanthocytes should be performed in these patients, and might contribute to understanding the pathogenic mechanisms underlying cases of hyperglycaemia induced chorea-ballism.

CASE 1

A 72 year old woman with no familial or personal history of neurological illness or drug abuse, being treated for hypertension and diabetes mellitus, was admitted to the emergency department after developing right HCHB. Laboratory studies demonstrated high glucose values (5070 mg/litre; normal values, 700–1100), although she was being treated with sulfanylureas (metphormine, 500 mg twice daily), whereas the metabolic investigation was normal and there was no evidence of ketosis. The symptoms developed subacutely over two days, unilaterally, initially with choreiform movements involving right hemisoma, subsequently assuming ballistic proportions. On admission, the neurological examination revealed no abnormal pyramidal or sensory signs. Cognitive impairment, personality, and behavioural changes were not found. During hospitalisation, the involuntary movements became bilateral, also involving orofaciolingual muscles. The laboratory studies during the acute phase identified a peak of red blood cell acanthocytosis (> 70%; fig 1), observed by two independent haematologists in peripheral fresh blood smears, and confirmed by re-testing. Routine analyses, including hepatic and renal function, were normal. The expression of Kell blood group antigens was normal, ruling out McLeod syndrome.[4] Serum apolipoprotein B (apoB) was present. A genetic search for chorea-acanthocytosis was negative. MRI showed high signal intensity in the putamen bilaterally (right > left) in T1 weighted images (fig 2 A, B), and hypointensity in T2 weighted images. Single photon emission computed tomography investigation confirmed hypoperfusion in the subcortical regions bilaterally (data not shown). Haloperidol treatment (up to 6 mg/day) was initiated, after performing all blood investigations, for the persistence of the involuntary movements, and a moderate benefit was seen. Six weeks later, a blood test confirmed the presence of 5% acanthocytes—the proportion regarded as significant for acanthocytosis is set at 3% of altered blood cells.[4] Six months after
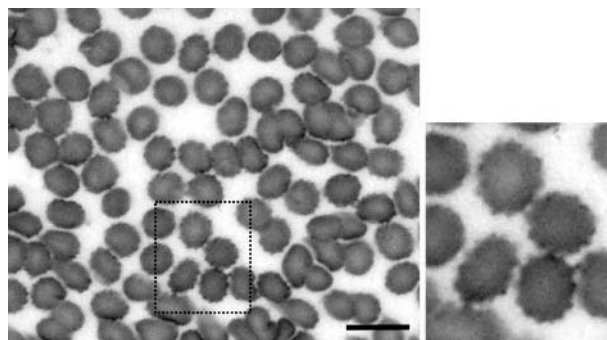
Figure 1 Light microscopy of a peripheral blood film from patient 1. Red blood cells show the typical spiculae around the membrane. The image on the right is a higher power image of the section shown in the box on the left. Bar, 17 μM.

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Abbreviations: apoB, apolipoprotein B; HCHB, hemichorea-hemiballism; MRI, magnetic resonance imaging
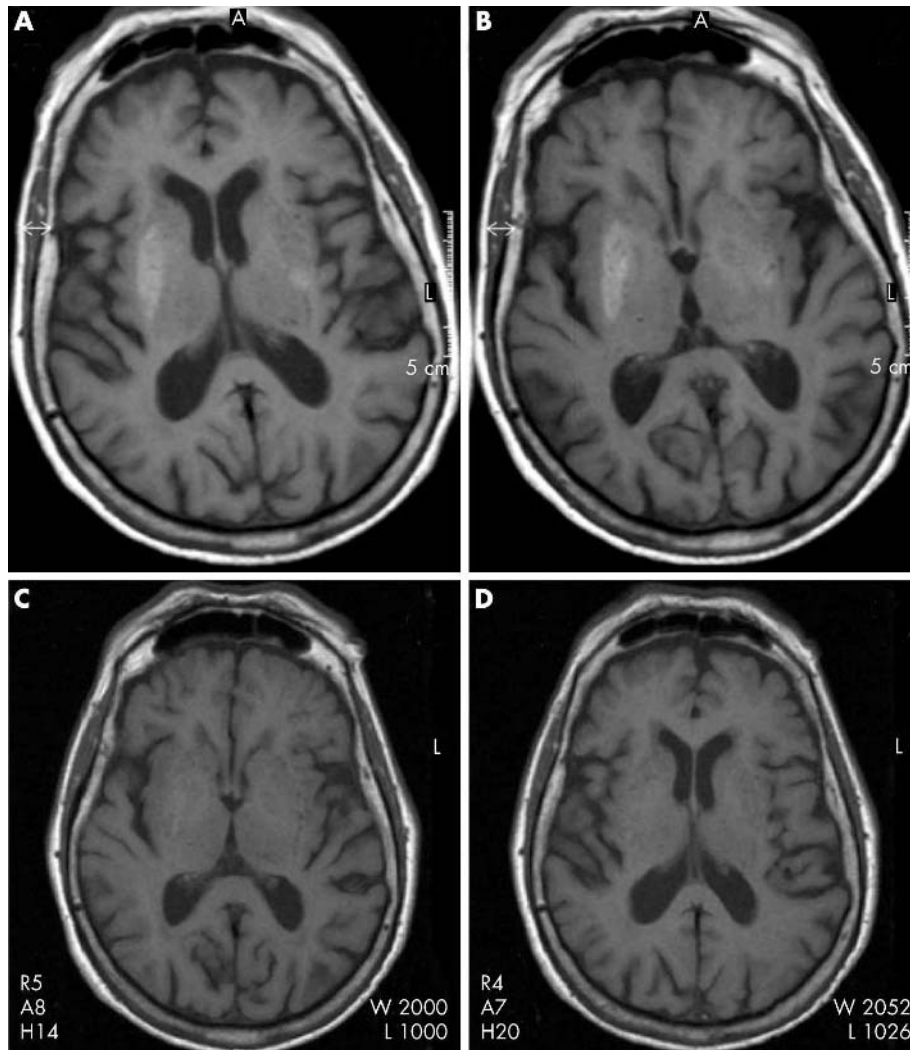
Figure 2 (A, B) Axial T1 weighted magnetic resonance imaging (MRI) showing pronounced hyperintensity of signal bilaterally in the putamen (right > left) in patient 1. (C, D) A follow up MRI study revealed that the abnormal hyperintense putaminal lesions were significantly reduced six months later, as noted on T1 weighted images.

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 metphormine 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.[1] 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.[2 5–8] 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.[3]

The neuropathological nature of the characteristic MRI alterations is still controversial. A bioptic specimen from the hyperintense putamen revealed the presence of gliosis with abundant reactive astrocytes, also named gemistocytes, but without deposition of hemosiderin.[5] A necropsy report from a patient with HCHB showed similar findings.[6] 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.[7] 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.[8] This interpretation is not surprising considering that, among neuronal subtypes, striatal medium spiny neurones are highly vulnerable to energy depletion.[9] 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[4] 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.[4] 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.[4] 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.[10] 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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