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Hypoglycemic Encephalopathy Manifesting with Cortical Hemichorea-Hemiballismus Syndrome: A Case Report

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Abstract
Hyper-/hypoglycemic states are rare but well-established causes of hyperkinetic movements, including chorea and ballismus, usually associated with brain lesions in the basal ganglia. We report a case of hemichorea-hemiballismus (HCHB) syndrome that developed after a severe hypoglycemic episode in a 71-year-old man with poorly controlled type 2 diabetes mellitus. Uncommonly, brain MRI showed contralateral cortical-subcortical T2 and T2-FLAIR-hyperintense frontoparietal lesions, with cingulate gyrus involved, while the basal ganglia were unaffected. In patients with hypoglycemic encephalopathy associated with cortical lesions, the long-term prognosis is usually poor. Nevertheless, in our patient, the dyskinesias and the cerebral lesions progressively regressed by achieving good glycemic control. After four and 12 months, the patient's neurological examination was normal. To our knowledge, this is the first evidence of hypoglycemic etiology of cortical HCHB syndrome, supporting recent theories that cortical circuitries may independently contribute to the pathogenesis of chorea and ballismus. This is also the first report of cingulate gyrus involvement in hypoglycemic encephalopathy. Finally, this case may indicate that a subset of patients with cortical lesions due to hypoglycemia

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could present a good clinical outcome, likely depending on the size of the lesions and the duration and severity of the hypoglycemic episode.

Introduction

Hyperglycemic states are a well-established cause of hyperkinetic movements, including hemichorea and hemiballismus. Although it occurs more rarely, hypoglycemia can cause similar clinical conditions. Only a few cases of hypoglycemic hemichorea are reported in the literature, mainly presenting with negative brain MRI imaging. When detected in this condition, brain lesions are usually located in the contralateral basal ganglia, showing T2, T2-FLAIR, and DWI hyperintensities, and T1 hypointensities [1]. However, hyperkinetic movements have also been associated with isolated cortical lesions, mainly of cerebrovascular etiology, probably as the result of the functional connection between the cerebral cortex and the basal ganglia [2].

Cortical brain lesions can occur as well in hypoglycemic encephalopathy, typically being confluent and multilobar. Long-term outcomes associated with this condition are usually poor, resulting in severe disability, coma, or death [3].

Here, we report a unique single case of a patient with a hemichorea-hemiballismus (HCHB) syndrome induced by severe hypoglycemia and associated with detectable cortical contralateral brain lesions in unusual locations. Surprisingly, his clinical course was extremely benign, with rapid remission of the symptoms and a complete neurological recovery at 4- and 12-month follow-ups.

Case Presentation

A 71-year-old man was admitted to the emergency room of our hospital after being found unconscious by his relatives. At arrival, his blood glucose level was too low and not measurable. No signs of trauma, vomiting, or tongue biting were noticed. In the emergency unit, he was administered an intravenous infusion of 33% glucose solution which restored his blood sugar level to 200 mg/dL. Three hours after the admission, he regained consciousness. The cerebral CT scan was negative for acute lesions, whereas all other tests performed in the emergency unit (routine blood tests, EKG, chest X-ray, and abdomen X-ray) were unremarkable. He tested negative for SARS-CoV-2 with a PCR test.

The patient was diagnosed with type 2 diabetes mellitus at age 58 and had no history of diabetic ketoacidosis, diabetic coma, or severe hypoglycemic episodes as well as of other systemic diabetes-related complications. His hypoglycemic therapy had been recently modified by a diabetologist who had introduced a regimen of fast-release insulin three times a day plus slow-release insulin once a day as a replacement for metformin, which was poorly tolerated due to gastrointestinal side effects. He was also on low-dose aspirin for mild supra-aortic trunk vasculopathy. He had no previous history of movement disorders, seizures, or neurodegenerative diseases. Autoimmune and thrombotic markers were within range. At age 61 (in 2010), he underwent lobectomy for a lung carcinoma and received coronary angioplasty with stent implantation to treat his ischemic heart disease. Tumor follow-up was negative for recurrence, and after lung surgery, he stopped smoking.

On the second day of hospitalization, hyperkinesias of the right side of the body occurred, described by clinicians as intermittent, ballistic movements of his right limbs (prominent on

the lower limb), intermixed with rare distal choreic movements. They were almost continuous, exacerbated by stress and tasks, and receded during sleep. The patient was always conscious and distressed by them. Neurological examination, including cortical sensory examination and cognitive testing, was otherwise normal. On the suspicion of epileptic focal seizures, an EEG was registered shortly after, showing only left-hemispheric background slowing but no epileptiform discharges.

Nevertheless, the patient was treated with diazepam 10 mg i.v. bolus, subsequently with diazepam 20 mg continuous 24 h infusion and levetiracetam 1,500 mg i.v. bolus, followed by levetiracetam 1,000 mg three times a day. As no improvement of the movements was obtained, on the third day, levetiracetam was switched to valproate 400 mg three times a day, and diazepam was discontinued, still with no subsequent benefit.

In the following days, two more EEGs were registered – the second during a hypoglycemic episode (glycemia 42 mg/dL) – resulting in nonspecific and the antiepileptic treatment was progressively discontinued. On the second and third days of hospitalization, other two CT brain scans were obtained, showing again no acute lesions.

During the hospital stay, the patient's glycemic level was strictly monitored, and the lowest serum glucose level detected was 42 mg/dL, which was promptly restored in 1 h. Glycosylated hemoglobin was 7.6%. The diabetologist modified the daily insulin intake and initiated repaglinide (starting with 1.5 mg/day, then progressively increasing to 3.5 mg/day) to adjust glucose serum levels. In the days following the hospitalization, the patient's glycemic control improved.

Three days after the start of the hyperkinesias, a brain MRI scan was performed, showing a cortical-subcortical T2 and T2-FLAIR-hyperintense left frontal lesion, extending from the precentral gyrus to the cingulate gyrus. An ipsilateral paramedian cortical lesion in the superior parietal lobule was detected too. Both lesions showed restricted diffusion on the DWI sequence, whereas the ADC sequence was mildly decreased; the T1 sequence was slightly hypointense. The basal ganglia were unaffected. Diffuse chronic cerebrovascular disease and a previous lacunar infarct in the superior cerebellar vermis were also noticed.

A second MRI performed 11 days after admission showed a reduction of the cortical T2-FLAIR left parietal lesion extension, while the frontal one – especially in its cingulate portion – was unchanged. DWI hyperintensity in both areas was markedly reduced (shown in Fig. 1). In parallel, the clinical conditions of the patient had progressively improved: 12 days after the admission, the choreic-hemiballistic involuntary movements had markedly reduced, while his glycemic control improved. Given these findings, a lumbar puncture was not considered necessary, as the clinical suspicion of a hypoglycemic encephalopathy was consistent. Eventually, 15 days after the admission, the patient was discharged to a rehabilitation facility, where the choreic-hemiballistic involuntary movements completely subsided within 20 days after their onset, in parallel with the improvement of the patient's glycemic control (shown in Fig. 2).

Four and 12 months later, respectively, his neurological examination, including cognitive testing, was normal, and two brain MRIs confirmed the complete regression of the cerebral lesions. The patient's glycemic control was good, and he denied any recurrence of the hyperkinesias, thus confirming that the abnormal movements were directly linked to the hypoglycemic episode.

Discussion

We present a case of promptly resolved hypoglycemic coma complicated by the development of HCHB syndrome. Only a few cases of hemichoreic or choreoathetotic

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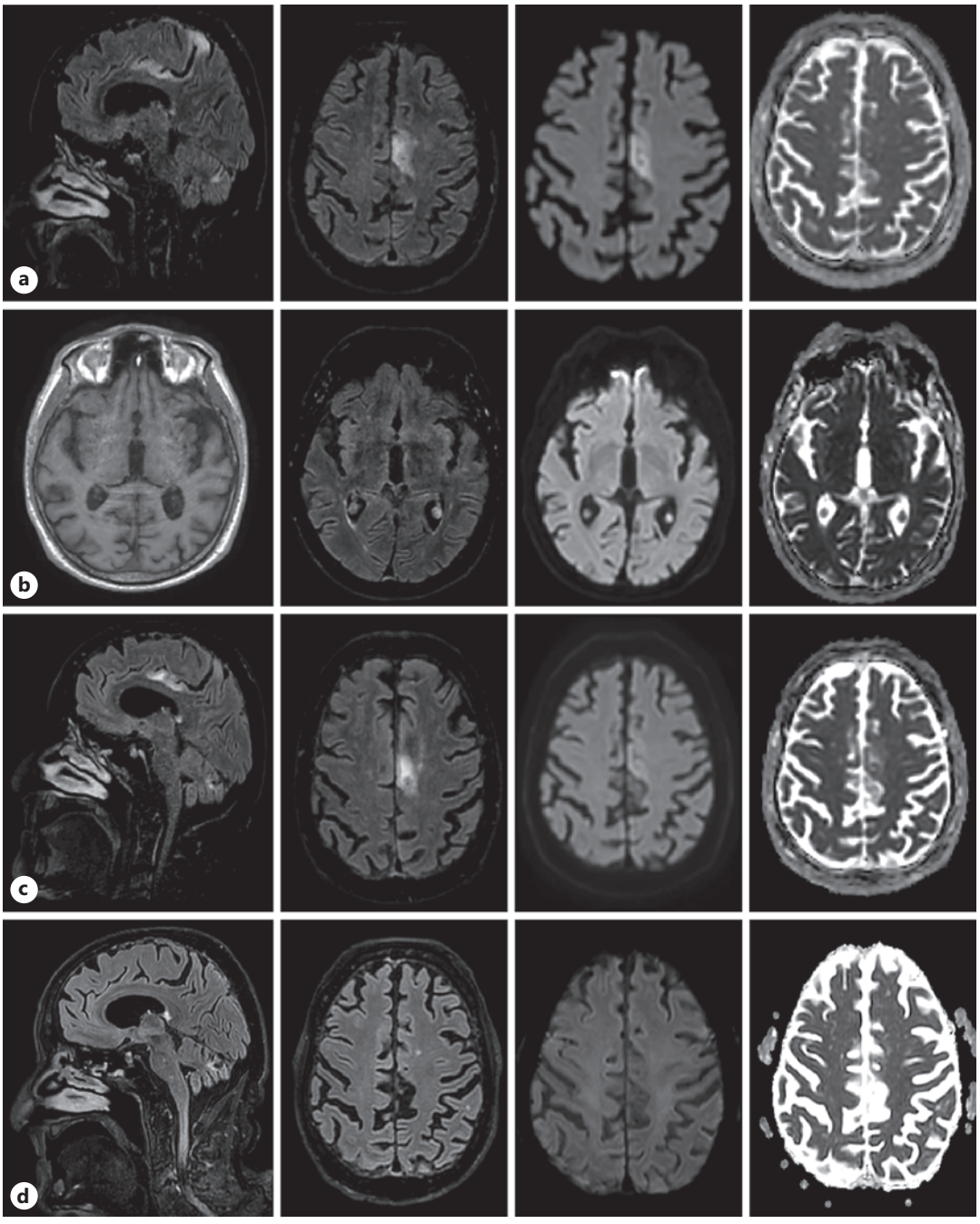

Fig. 1. Serial patient's brain MRIs are shown in the picture. Respectively, T2-FLAIR (first two pictures), DWI, and ADC sequences are reported. In the first MRI (**a**), a cortical-subcortical left frontal lesion, involving the cingulate gyrus, and an ipsilateral paramedian, parietal cortical lesion are evident. Both lesions are hyperintense on T2, T2-FLAIR, and DWI sequences, while ADC is mildly decreased. No lesions were detected in the basal ganglia on T1, T2-FLAIR, DWI, and ADC sequences (**b**). After 6 days (**c**), the left parietal T2-FLAIR hyperintensity was clearly reduced, while the frontal one was just slightly diminished. DWI restrictions in both areas were decreased, especially in the parietal location. ADC was normal. T1 sequences were slightly hypointense. The follow-up MRI imaging at 4 months (**d**) showed complete regression of the abnormalities.

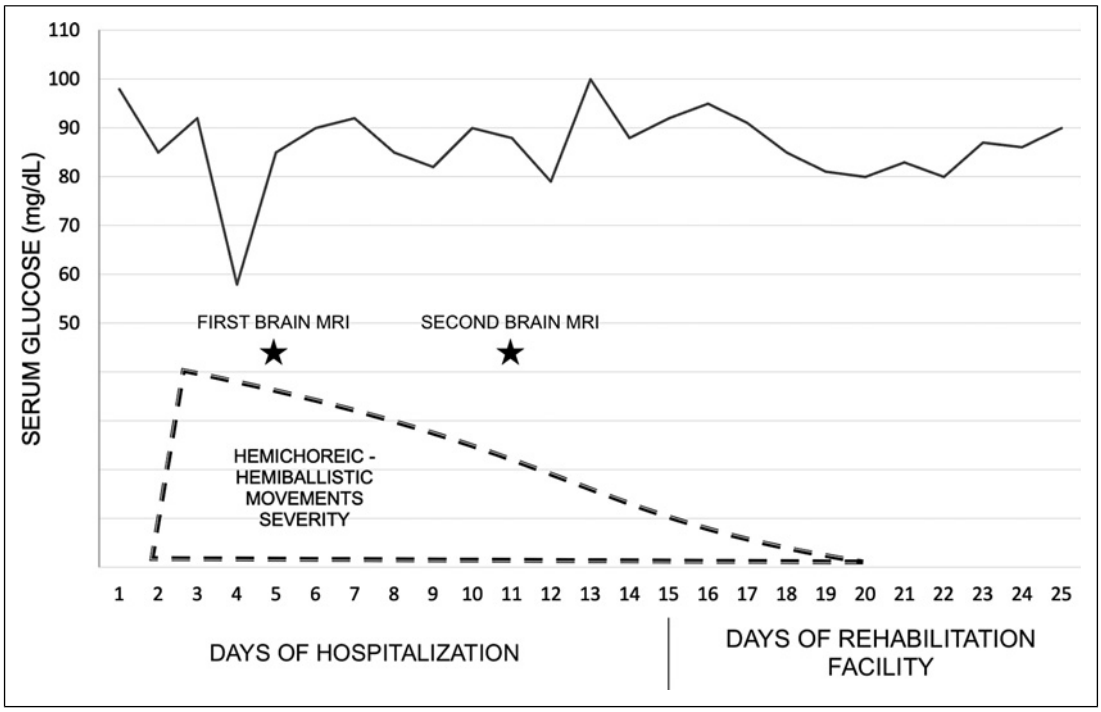

Fig. 2. Patient's clinical course during the hospitalization and the rehabilitation facility.

involuntary movements induced by hypoglycemia are described in the literature [1, 4–10], mainly associated with negative brain MRI imaging or with hyperintense lesions in the basal ganglia on T2-, FLAIR-, and diffusion-weighted sequences and hypointense lesions on T1 sequence. In our case, the patient's brain MRI showed two cortical-subcortical, unilateral, frontal, and parietal lesions in the left hemisphere, with cingulate cortex involvement, while the basal ganglia were free from lesions.

Symptomatic unilateral chorea/ballism has prior been reported in the setting of acute stroke affecting the basal ganglia (mostly subthalamic and lentiform nuclei), with the suggested pathophysiology being a diminished activity of the "indirect pathway" in the classic basal ganglia circuitry scheme [11]. However, in the past few years, a growing literature has been published reporting cases of such hyperkinetic movements as arising from ischemic strokes affecting the frontoparietal cortex [12–14], thus questioning this model centered on the classic basal ganglia circuitry dysfunction as the only cause of hemichorea and hemiballismus. The mechanism by which cortical lesions result in hemichorea is not well understood. It has been hypothesized that the impairment of the "hyperdirect pathway," a circuit inhibiting movement in which cortical neurons' axons activate directly the subthalamic nucleus, may cause hemichorea through disinhibition of the thalamus, normally inhibited by the subthalamic nucleus [15]. Moreover, a study using lesion network mapping techniques indicated hemiballismus and hemichorea networks as centered on the postero-lateral putamen and functionally connected to several nodes including motor, premotor, and supplementary motor cortical areas [2].

This is, to our knowledge, the first evidence of hypoglycemic etiology of cortical HCHB syndrome and supports the recent theories that there may be an independent contribution of the cortical areas to the pathogenesis of HCHB, even without significant involvement of the basal ganglia and the thalamus. Derangement of the wiring between the frontal and parietal cortex may be a possible mechanism of the cortical HCHB syndrome here observed [16]. Our

case reinforces the view that HCHB motor pathways are widely distributed throughout the brain and reminds clinicians that cortical brain lesions are not only associated with epileptic alterations and symptoms, thus avoiding inadequate therapies. The cerebral lesions observed in hypoglycemic encephalopathy are usually bilateral and typically located in the basal ganglia or the hippocampi. When present, the involvement of the cerebral cortex in most cases is usually bilateral, does not match typical arterial territories, and is associated with a poor prognosis. However, on rare occasions, unilateral cortical, confluent, and multilobar lesions are observed [3, 17]. To our knowledge, this is the first evidence that the cingulate gyrus can also be damaged in hypoglycemic encephalopathy and that focal, unilateral cortical lesions can occur too. Like other cases [17, 18], the unilateral cortical involvement of our patient could be explained by a generalized asymmetry of cerebral vascularization.

About 20 days after the onset of the movements, our case was completely asymptomatic, in line with the complete regression of the cerebral lesions shown by follow-up MRI imaging. Although this outcome is unusual in patients with cortical involvement, who usually have a worse prognosis [3], this case suggests that in hypoglycemic encephalopathy a good clinical outcome is also possible, likely depending on the size of the lesions and the duration and severity of the hypoglycemic episode. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000528880).

Statement of Ethics

The patient involved in this study has given his written informed consent to publish his case (including publication of images and videos). Ethical approval is not required for this study in accordance with national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

F. Pasini: original idea, first draft, final manuscript writing. L. Brighina: draft correction and supervision of the project. A. Karantzoulis, G. Fanella, F. Brovelli, and C. Ferrarese: draft revision. D. Iacobucci, V. Aprea, B. Storti, F. Santangelo, F. Canonico, and P. Remida: data providing.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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