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Focal Neurological Symptoms as the Presenting Manifestations of Nonketotic Hyperglycemia ： Report of Two Cases

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Abstract

Focal neurological symptoms may provide the first clinical clue to the presence of nonketotic hyperglycemia (NKH) and sometimes unveil previously undiagnosed diabetes. We report two patients with hemichorea-hemiballism (HC-HB) or partial motor seizures as the first manifestation of NKH. These disorders are best treated with insulin and rehydration. The neurological symptoms generally resolve with the correction of hyperglycemia. Antiepileptic treatment, especially phenytoin, is usually futile and even aggravates hyperglycemia. The exact mechanisms of how NKH causes focal neurological symptoms are unknown. One hypothesis is related to the depletion of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), which is metabolized in the brain as an energy source in NKH. The deficiency of GABA in the basal ganglia may lead to HC-HB, while in the cerebral cortex it may lower the seizure threshold. Another hypothesis involves transient focal cerebral ischemia caused by hyperglycemia. Therefore we should not overlook NKH as a cause of focal neurological symptoms. Rapid recognition of their association will allow for prompt and correct treatment. (J Intern Med Taiwan 2007; 18: 206-211)

Key Words ：Hemichorea-hemiballism, Nonketotic hyperglycemia, Partial seizures

Introduction

In nonketotic hyperglycemia (NKH), hyperglycemia, hyperosmolality, and intracellular dehydration occur without significant accumulation of ketoacids. It is usually observed in patients over age 50 with type 2 diabetes mellitus (type 2 DM). Patients receiving certain drugs including diuretics, corticosteroids, beta-blockers, phenytoin, and diazoxide are at increased risk of developing this syndrome[1].

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Treatment requires rehydration, low dose insulin, and reversal of any precipitating cause identified.

The severity of NKH can vary widely, ranging from asymptomatic to severely symptomatic, such as coma and even death. It frequently presents with neurological manifestations including delirium, partial or generalized seizures, hemichorea-hemiballism, dysphagia, hemianopsia, hemiparesis, and hemisensory loss[2-4]. Recognition of the association of these neurological abnormalities and NKH is important because correction of the underlying hyperglycemia will lead to rapid improvement.

Case Reports

Patient 1

A 75-year-old, previously neurologically normal, woman was admitted because of jerky and irregular movements in her left limbs for one week. She had difficulty carrying objects with her left hand. She could not control the movements but she attempted to disguise the movements by incorporating them into purposeful activities. The jerks in her left leg were not as severe as in her left hand. She had suffered from type 2 DM for more than 20 years, which had been controlled with oral hypoglycemic agents. She denied history of cerebrovascular disease, hypertension, trauma, infection, or exposure to neuroleptic drugs. There was no family history of movement disorders.

On admission, she had choreiform movements involving the left face, left arm, and left leg. The chorea was continuous and could not be suppressed with voluntary effort, although it disappeared during sleep. The neurological examination was not remarkable except the involuntary movements. Initial biochemical data included serum glucose 584 mg/dl without ketonuria; serum sodium concentration 144 mEq/l; serum potassium 3.72 mEq/l and serum blood urea nitrogen (BUN) 26.2 mg/dl. The calculated serum osmolality (2 x Na + glucose/18 + BUN/2.8) was 330 mOsm/l (285-295). The glycosylated hemoglobin A_{1C} was 15%.

A brain computed tomography (CT) performed 7 days after symptom onset showed high densities in the right putamen (Fig. 1A). The brain magnetic resonance imaging (MRI) showed a lesion in the right putamen with a high signal intensity on the T1-weighted images and a low signal intensity on the T2-weighted images (Figs 1B and C). The magnetic resonance angiography did not disclose stenosis or occlusion of the major intracranial arteries.

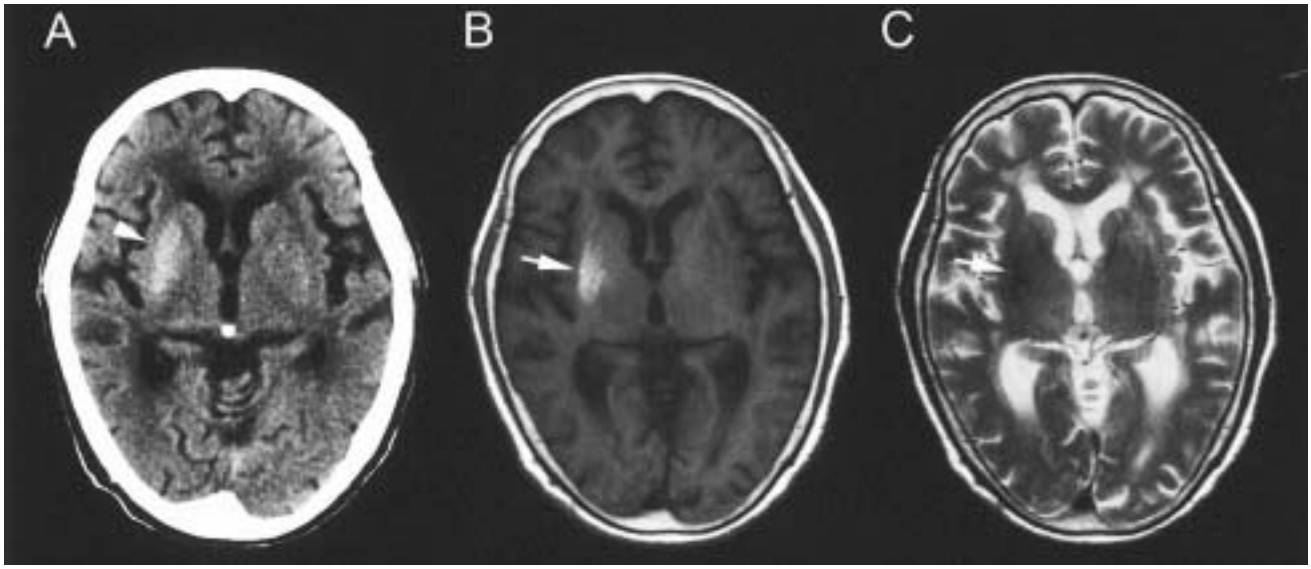

Fig.1.Neuroimaging studies of patient 1. The right putamen (arrowhead) was hyperdense on noncontrast CT (A). Transaxial T1-weighted MRI (B) demonstrated increased signal intensity in the right putamen (arrows), which was hypointense on T2-weighted images (C).

Hyperglycemia was corrected by insulin therapy followed by treatment with oral hypoglycemic agents. The chorea was continuously present although the frequency and the amplitude of choreiform movements decreased as the serum glucose approached normal levels. She was discharged on oral hypoglycemics. A trial of haloperidol at doses of 0.5 mg three times per day diminished the severity of chorea over the next 2 months. Then the chorea disappeared.

Patient 2

A 59-year-old man presented with a 4-day history of episodic uncontrollable clonic jerks of the left limbs. The movements began suddenly and ended in 5 to 10 minutes, followed by partial paralysis in his left limbs. The muscle strength improved gradually until another attack happened. There were at least 5 attacks before admission. He had a 4-year history of type 2 DM but he had not received treatment in recent months. He also had hypertension. He did not have a history of cerebrovascular disease, head trauma, infection, or brain tumors. He denied being alcoholic.

On the day of entry, he fell down the stairs when jerks of the left limbs occurred again. In the emergency room, he was clear and had partial motor seizures affecting his left arm and leg. Seizures stopped following intravenous administration of 10 mg of diazepam. Intravenous phenytoin at 20 mg/kg was given as loading dose, followed by 100 mg every 8 hours. On admission, neurological examination showed left hemiparesis with decreased tone in the left extremities. A right hemisphere lesion was suspected but CT and MRI studies of head were not remarkable (Fig. 2). The level of blood glucose was 387 mg/dl and glycosylated hemoglobin A_{1C} was 13.9%. No ketones were detected in his urine or blood. The serum sodium concentration was 137 mEq/l; serum potassium 4.09 mEq/l; serum calcium 10.2 mg/dl and serum blood urea nitrogen 11.4 mg/dl. The measured serum osmolality was 306 mOsm/l.

Insulin therapy was started to correct hyperglycemia and the level of blood glucose was between 399 mg/dl and 249 mg/dl in the first two days. Even though the serum level of phenytoin (19.03 μg/ml) was maintained in the therapeutic range (10-20 μg/ml), the partial motor seizures still occurred 3 and 5 times on the first and second hospital day, respectively. Each episode lasted from about 30 seconds to 2 minutes. As blood glucose fell below 200 mg/dl on the third day, the seizures resolved. Neurological examination returned normal 4 days after admission. Then phenytoin was discontinued.

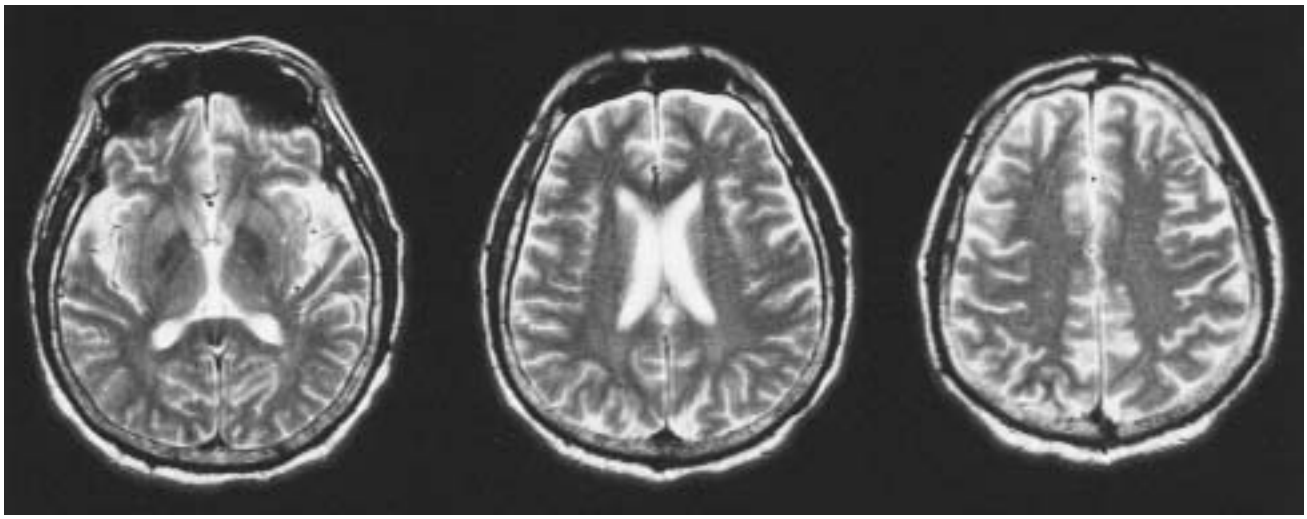

Fig.2. Brain MRI of patient 2 performed one week after the onset of symptoms revealed symmetric periventricular high signal areas and several small hyperintense lesions in the deep white matter of bilateral cerebral hemispheres, which might reflect nonspecific ischemic changes.

Subsequently, he was discharged on oral hypoglycemic agents.

Discussion

Ballism means irregular, coarse, jerky, flinging movements due to contraction of proximal limb muscles. Chorea consists of similar but more continuous, random, jerking movements restricted to distal muscles. When these movements are confined to one side of the body, i.e. hemichorea-hemiballism (HC-HB), lesions in the contralateral subthalamic nucleus and pallidosubthalamic pathways are usually present. Stroke is the commonest pathologic process. The differential diagnosis includes any focal lesion located generally in basal-ganglia structures, such as neoplasms, vascular malformations, tuberculomas, and demyelinating plaques. Occasionally, a systemic disorder such as thyrotoxicosis, systemic lupus erythematosus, human immunodeficiency virus infection, and NKH causes HC-HB [5,6].

HC-HB with NKH tends to occur in elderly people with a female predominance. Most reported cases are in people of East Asian origin, which suggest a possible genetic disposition to the disorder [6]. There have been a few reports regarding cases of HC-HB with NKH in Taiwan, with the similar clinical and neuroimaging characteristics [7-10]. HC-HB generally disappears within hours after correction of hyperglycemia. However, some patients have persisting involuntary movements for longer than 3 months, although these movements are much milder than at presentation [6].

Neuroimaging findings in NKH-related neurological disorders are varied. In those with HC-HB, the imaging abnormalities include increased densities on CT and hyperintense lesions on T1-weighted MRI in the contralateral basal ganglia [5,8,9,11]. These lesions generally resolve within a few months, although there has been a case of persistent striatal hyperintensity on T1-weighted MRI for up to 6 years [8]. In patients with seizures and NKH, the cerebral imaging is usually normal [12,13]. However, partial seizures per se may occasionally result in transient gray and white matter MRI signal changes, thereby complicating image interpretation. The imaging findings of patient 1 were consistent with those in the previous reports of HC-HB with NKH. In patient 2, the CT and MRI findings were not remarkable and thus ruled out other possibilities that might provoke partial seizures.

Onset of partial seizures usually suggests an underlying structural lesion in the brain, such as cerebral neoplasm, cerebrovascular disease, encephalitis, or abscess. Partial seizures also occur in metabolic disorders, such as NKH with or without associated hyperosmolality [12,14]. In a review of 158 cases of NKH 19% had partial motor seizures [15]. They usually occur in patients 50 years or older and frequently reveal undiagnosed diabetes [12]. Partial seizures associated with NKH are refractory to antiepileptic drugs and respond best to insulin and rehydration [12,13,16]. Antiepileptic treatment, especially phenytoin, is likely to aggravate seizures [17]. In patient 2, there has been even more seizures after the use of phenytoin until the correction of hyperglycemia. It is probably due to the effect of phenytoin on inhibition of insulin secretion, which may well worsen hyperglycemia [18].

The pathophysiology of partial seizure or HC-HB in NKH remains speculative. It is probably multifactorial and hyperglycemia is undoubtedly one of the factors. One hypothesis is related to the lowered threshold for seizure or dysfunction of the basal ganglia due to a deficiency of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) [8,11,17,19]. During hyperglycemic crisis the activity of tircarboxylic acid cycle (Krebs cycle) and glucose utilization are depressed in the brain, so the cerebral metabolism shifts to alternative pathways. In ketoacidosis, ketones are used as an energy source and GABA can be resynthesized. As a result, HC-HB or partial seizures rarely occur with diabetic ketoacidosis. While in NKH, the brain metabolizes GABA into succinic acid via the succinic acid semialdehyde

pathway and thus depletes GABA rapidly[19]. However, the fact that the involuntary movements and the signal changes on MRI in cases of HC-HB may persist well beyond the episode of hyperglycemia speaks against this hypothesis as the only explanation.

Another hypothesis involves transient focal cerebral ischemia caused by hyperglycemia. Cerebral hypoperfusion may result from an increase in cerebrovascular resistance due to the higher brain water content during hyperglycemia or to a loss of flow regulation caused by impaired metabolism[20]. Reversible focal ischemia, which does not result in an obvious cerebral lesion, may play a role in the pathogenesis of partial seizures and hence explain the postictal deficit observed[14]. Consequently cerebral imaging is usually normal in patients with NKH-related partial seizures. On the contrary, a hyperintense putamen on T1-weighted MRI is commonly found in HC-HB with NKH and may represent an incomplete ischemic injury which is insufficient to cause infarction. The similar MRI findings have been reproduced in rats by 15-minute occlusion of the middle cerebral artery. The hyperintensity on MRI histologically corresponds to selective neuronal death and gliosis with preservation of the macroscopic structure of the brain that appear after brief ischemia[21]. These microscopic lesions may offer an explanation why HC-HB sometimes outlast the period of hyperglycemia, as seen in patient 1.

Knowing or considering that focal neurological symptoms may occur with NKH, in particular in a middle aged to elderly patient, is very important for early diagnosis and institution of appropriate therapy. It also helps avoid unnecessary etiological workup and prevent progression of NKH to a state of hyperosmolar coma with its coincident higher mortality.

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非酮性高血糖以局部神經症狀爲最初之表現：二病例報告

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摘　要

局部神經症狀可能爲非酮性高血糖患者最早出現的症狀，而且有時因此診斷出早已罹患但不自知的糖尿病。我們報告兩位非酮性高血糖患者，一位有一側肢體的舞蹈症，另一位則是有局部的運動型抽搐。這些疾患最佳的治療爲胰島素及補充體液，當血糖控制之後，症狀通常很快緩解，若使用抗癲癇藥物來治療非酮性高血糖引起之抽搐，特別是二苯妥因 (phenytoin)，常常無效，甚至使血糖更加升高。爲何非酮性高血糖會導致局部神經症狀，原因仍不明，有一假說爲當有非酮性高血糖時，腦部會以代謝伽馬氨基丁酸 (Gamma-aminobutyric acid，簡稱GABA) 來提供能量，GABA 在腦部的作用爲抑制性神經傳導物質，因GABA 被代謝掉而不足，在基底核便產生舞蹈症，在大腦皮質便產生抽搐。另外有一假說認爲高血糖會造成腦部血流灌注不足，使腦部暫時性局部缺血，因而產生症狀。所以遇到患者以局部神經症狀表現時，不可忽略掉非酮性高血糖這個原因，快速的診斷才能指引正確的治療。