Hyperglycemic Chorea-Ballism or Acute Exacerbation of Huntington’s Chorea? Huntington’s Disease Unmasked by Diabetic Ketoacidosis in Type 1 Diabetes Mellitus

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Content: Hyperglycemic chorea-ballism is predominantly observed in older type 2 diabetic patients, and it is rare in type 1 diabetes and diabetic ketoacidosis (DKA). Huntington’s disease (HD) is one of several genetic syndromes associated with diabetes, although the reported prevalence of the association varies. There are few opportunities for most physicians to diagnose early-stage HD.

Objective: We describe bilateral hyperglycemic chorea-ballism in a 40-yr-old female type 1 diabetes patient with DKA and HD.

Setting: The study was conducted in a tertiary care referral hospital.

Results: On admission, the patient exhibited severe involuntary movement of bilateral extremities with DKA, and hyperglycemic chorea-ballism was diagnosed. She recovered from chorea-ballism with admission of fluids and insulin, but mild choreatic movement persisted in the upper extremities. Brain magnetic resonance imaging and DNA analysis revealed HD. Although it has been considered that depletion of striatal $\gamma$-aminobutyric acid (GABA) content is rare in DKA, it is largely decreased in HD. Therefore, it is probable that hyperglycemic chorea-ballism or exacerbation of Huntington’s chorea resulted from transient depletion of GABA.

Conclusion: The present case provides important insights on the role of GABA in hyperglycemic chorea-ballism and on the clinical issues associated with HD diagnosis. (J Clin Endocrinol Metab 97: 3016–3020, 2012)
2003 because of drowsiness (Glasgow Coma Scale E3, V4, M4 = 11) with fever and vomiting. She had injected a total dose of 46 U of insulin with self-monitoring of blood glucose. She had no family history of diabetes mellitus. On admission, large amplitude involuntary movements involving her bilateral extremities were noted. Results of the remaining neurological examination were normal. Laboratory data on admission were as follows: plasma glucose, 791 mg/dl (43.9 mmol/liter); glycosylated hemoglobin, 9.5%; serum Na, 142 mmol/liter; Cl, 95 mmol/liter; and serum total ketones, 20.3 mmol/liter (3-hydroxybutyric acid, 15.6 mmol/liter; and acetoacetic acid, 4.7 mmol/liter). Her estimated plasma osmolarity was 356 mOsm/kg. Results of arterial blood gas analysis were as follows: arterial pH, 6.930; serum bicarbonate, 1.8 mmol/liter; and PaCO₂, 8.4 mm Hg. DKA with hyperglycemic chorea-ballism was diagnosed. Computed tomography (CT) scanning of the brain indicated mild atrophy of the bilateral nucleus caudatus and corpus striatum relative to normal features for her age (Fig. 1A). She made an uneventful recovery from DKA with fluid and insulin administration within 24 h, and the severe involuntary movements also resolved within 48 h. However, despite the disappearance of the initial abnormal involuntary movements, persistence of very mild choreatic movements of the bilateral upper extremities at rest was observed. Brain T1-weighted magnetic resonance imaging (MRI) on d 17 (Fig. 1B) revealed the bilateral atrophy of the caudate nucleus with enlargement of the frontal horns, which are characteristic findings of HD. However, no increased intensity was observed in the caudate nucleus and putamen, which are characteristic findings of hyperglycemic chorea-ballism (7, 8).

Further neurological examination revealed mild slow eye movements but no dysarthria and gait disturbance. Although psychiatric examination was not performed, her intelligence was normal. Additional history was noted carefully. Her mother had HD, symptoms of which appeared at the age of approximately 35. Her elder brother, who was her only sibling, also had HD. She had been living alone far away from her hometown for over 25 yr since the HD diagnosis in her mother. She had noticed choreatic movements and slowness approximately 2 yr before admission, and her skills related to insulin injection and blood glucose monitoring had gradually become poor approximately 6 months before admission. However, she had intentionally concealed these facts, including her family history, from her home doctor. A week before admission, she had moderate fever and cough followed by anorexia, and insulin injection was omitted 2 d before admission because of further skill impairment. Informed consent was obtained from the patient before DNA analysis, which confirmed the presence of 55 CAG trinucleotide repeats on chromosome 4. After discharge, she had been followed as an outpatient of our hospital for 5 subsequent years. Her chorea became severe gradually, and it became difficult for her to inject insulin and monitor blood glucose. For the last 3 yr she has been living in a nursing care facility.

Discussion

Hyperglycemic chorea-ballism, hemilateral or bilateral, has been predominantly reported in older nonketotic hyperglycemic patients with type 2 diabetes and is very rare in patients with DKA and type 1 diabetes. Only three cases of DKA with hyperglycemic chorea-ballism in patients with type 2 diabetes exist in the English literature (9–11). In addition, as shown in Table 1, a review of the literature revealed eight cases of type 1 diabetes with hyperglycemia-induced chorea-ballism, including the present case (12–17). Of these, five cases (62.5%) were associated with DKA. We analyzed the data from a total of 83 cases with type 2 diabetes and hyperglycemic chorea-ballism, including a review of 53 cases from 1985 to 2001 (8), and two reports of 25 cases (11) and five cases (7) from a single institution. The mean age (±SD) of patients with type 1 diabetes (31.8 ± 17.9 yr; n = 8) was significantly lower than that of patients with type 2 diabetes (71.3 ± 11.2 yr; n = 83) (P = 0.000; Mann-Whitney U test). The number of negative brain CT- and/or MRI-specific findings was higher in patients with type 1 diabetes (50.0%) than in those with type 2 diabetes (13.3%) (P = 0.023, χ² test). Chorea-ballism improved in patients with type 1 diabetes as well as in those with type 2 diabetes (Table 1). Our case is the first to show type 1 diabetes with HD with possible exacerbation of chorea or hyperglycemic chorea-ballism in HD due to DKA.
Although the pathogenesis of chorea provoked by non-ketotic hyperglycemia remains uncertain, various hypotheses have been proposed, including metabolic, cerebrovascular, or dopaminergic activity changes. Hyperglycemia and/or metabolic acidosis produce a decrease in blood flow in the basal ganglia (18, 19). Hyperglycemia leads to an anaerobic metabolic pathway, which causes increased metabolism of γ-aminobutyric acid (GABA) in the brain as an alternate energy substrate, and consequently results in depletion of GABA content in the basal ganglia, decreased inhibitory signal, and hyperactive movement (7, 11, 20). In patients with ketoacidosis, acetoacetate can be used as a source of GABA (20), which is considered to be one of the causes of chorea-ballism. Especially massive hyperviscosity due to hyperosmolarity may also be included as one of the causes of chorea-ballism. GABA deficiency. That is, the basal ganglia may be susceptible to autoimmune attack via opening of the blood–brain barrier by hyperglycemia-related hyperviscosity and that anti-GAD antibody may be an etiopathological agent because GAD is a marker for GABAergic neurons, which are abundant within the striatum. Thereafter, Mihai et al. (15) reported a case of ketoacidotic hyperglycemic chorea-ballism in a 15-yr-old female with type 1 diabetes who had 9000 U/ml of anti-GAD antibody (Table 1 (13). A delicate internal metabolic milieu during hyperglycemia with ketoacidosis could have played a critical role in the development of chorea-ballism.

Ahlskog et al. (7) hypothesized the participation of anti-glutamic acid decarboxylase (GAD) antibody, which is one of the markers of autoimmune type 1 diabetes, in GABA deficiency. That is, the basal ganglia may be susceptible to autoimmune attack via opening of the blood–brain barrier by hyperglycemia-related hyperviscosity and that anti-GAD antibody may be an etiopathological agent because GAD is a marker for GABAergic neurons, which are abundant within the striatum. Therefore, it is believed that patients with HD are susceptible to a slight decrease in GABA content due to hyperglycemia, hyperosmolarity, and/or ketoacidosis, which leads to chorea-ballism or exacerbation of Huntington’s chorea in DKA. The present case could be a model of the GABA theory in hyperglycemic chorea and provides an important insight into the mechanism(s) of hyperglycemic chorea-ballism.

On the other hand, no abnormal involuntary movements were observed in the other three DKA episodes that were experienced for the subsequent 5 yr. Plasma glucose and acid-base disturbances were similar to those in the present episode [plasma glucose ranged from 980 mg/dl (54.4 mmol/liter) to 1114 mg/dl (61.9 mmol/liter); estimated plasma osmolality ranged from 345 to 382 mOsm/kg; serum total ketone ranged from 20.8 to 22.4 mmol/liter; and arterial pH ranged from 6.905 to 7.105]. A similar case of type 1 diabetes with Moyamoya disease has also been reported in which hyperglycemic chorea-ballism was observed in only one of four DKA episodes (Table 1 (13). A delicate internal metabolic milieu during hyperglycemia with ketoacidosis could have played a critical role in the development of chorea-ballism.

<table>
<thead>
<tr>
<th>Case no. (Ref.)</th>
<th>Age (yr)/sex</th>
<th>DKA</th>
<th>Age at DM onset (yr)</th>
<th>Involved side</th>
<th>Image findings (CT and/or T1 MRI)</th>
<th>BS (mg/dl)</th>
<th>Plasma osmolality (mOsm/kg)</th>
<th>Outcome</th>
<th>Recovery</th>
<th>Neuroleptics</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (12)</td>
<td>26/M</td>
<td>–</td>
<td>13</td>
<td>Rt ULE</td>
<td>T1 MRI; Lt Caud and Put infarction</td>
<td>270</td>
<td>Improve</td>
<td>nd</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (13)</td>
<td>20/F</td>
<td>+</td>
<td>18</td>
<td>Lt ULE</td>
<td>T1 MRI; high in Rt Caud and low in Put</td>
<td>842</td>
<td>Improve</td>
<td>3 d</td>
<td>Moyamoya disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (14)</td>
<td>17/M</td>
<td>+</td>
<td>17</td>
<td>Lt FS</td>
<td>No lesion</td>
<td>766</td>
<td>Improve</td>
<td>A few hours</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (14)</td>
<td>29/F</td>
<td>+</td>
<td>19</td>
<td>Rt FS</td>
<td>No lesion</td>
<td>367</td>
<td>Improve</td>
<td>nd</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (15)</td>
<td>15/F</td>
<td>–</td>
<td>nd</td>
<td>Rt ULE</td>
<td>No lesion</td>
<td>(e)294</td>
<td>Improve</td>
<td>1 d</td>
<td>+ Anti-GAD Ab 9000 U/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 (16)</td>
<td>70/F</td>
<td>–</td>
<td>70</td>
<td>Bil ULE</td>
<td>CT, high in Bil Put; T1 MRI, high in Bil Caud</td>
<td>630</td>
<td>Improve</td>
<td>4 months</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 (17)</td>
<td>37/M</td>
<td>+</td>
<td>nd</td>
<td>nd</td>
<td>T1 MRI, high in Lt Put</td>
<td>528</td>
<td>Improve</td>
<td>nd</td>
<td>Kid Transpl; Cent Pont Myel HD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 (present case)</td>
<td>40/F</td>
<td>+</td>
<td>10</td>
<td>Bil ULE</td>
<td>No lesion</td>
<td>791</td>
<td>Improve</td>
<td>2 d</td>
<td>–</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ab, Antibody; Bil, bilateral; BS, blood sugar; Caud, caudate; Cent Pont Myel, central pontine myelinolysis; DM, diabetes mellitus; (e), estimated; F, female; FS, facial spasm; Kid Transpl, kidney transplantation; Lt, left; M, male; nd, not described; Put, putamen; Rt, right; ULE, upper and lower extremities.
normal range, <1.5 U/ml). In two of the other three DKA episodes, anti-GAD antibody titers were measured. The titers had slightly increased to 1.9 and 3.6 U/ml. It seems unlikely that anti-GAD antibody titers played any role in the presenting episode. Further studies are needed for the development of the theory.

On admission, our diagnosis was hyperglycemia-induced chorea-ballism in type 1 diabetes mellitus with DKA. Although causes of chorea include many disorders, it is commonly believed to be a manifestation of HD. In the present case, the fact that observed involuntary movements were caused by acute onset chorea-ballism in type 1 diabetes and the erroneous belief that HD should not be suspected if there is no apparent family history delayed the HD diagnosis. Rapid recovery from severe involuntary movements also supported our diagnosis.

There have been a few reports of acute and transient exacerbation of chorea in HD caused by drugs or during pregnancy (22–25). Although, such cases due to metabolic derangement have not been reported, it could be possible that the present episode resulted from transient acute exacerbation of Huntington’s chorea by hyperglycemia, hyperosmolarity, and/or ketoacidosis that previously had been subclinical.

HD is classified into a group of genetic syndromes sometimes associated with diabetes (2). An increased incidence of diabetes has been reported in studies conducted before the identification of the HD gene (3, 4). In animal studies, insulin deficiency was found to have a toxic effect on pancreatic β-cells. This was confirmed on the basis of expression and accumulation of mutant huntingtin, which is the most likely cause of the association (6, 26). However, a recent pathological examination with pancreatic tissue sections at different disease states showed that the pattern of insulin immunostaining, insulin transcript levels, and islet β-cell areas were similar in patients with HD and the controls (27). Moreover, clinical investigation using the oral glucose tolerance test did not support the increased risk of diabetes mellitus (5), and also the association of type 1 diabetes with HD has not been reported. These recent findings have raised a question about the extent to which transgenic mice models reflect the pathology of human HD (5). Large-scale studies on diabetes in HD and additional case reports of type 1 diabetes could provide further insights into the association of HD with diabetes.

Another important issue involves social and clinical problems. Although diagnosis of HD with typical symptoms and family history is straightforward, diagnosis of early-stage HD must be difficult for non-neurologists, including endocrinologists and diabetologists, especially under the condition of concealed medical histories. Although discontinuation of insulin is a common cause of DKA, the actual cause presented here was unique and highly suggestive. We should keep in mind that most of the patients with HD and their relatives never mention their inheritance (28–30). The patient had been living alone apart from her hometown since the age of 15 yr, which was soon after the diagnosis of HD in her mother. She never returned to her hometown. She went to university and became a member of the co-medical staff of a hospital after graduation. She must understand the meaning and significance of hereditary risk throughout the course of her life as a function of life choices made at any given times (30). And she has gone on living preferably with passion for life despite the number of the risks and prejudice (28–30). Insulin injections and blood glucose monitoring must be a sign of competence and a way of independence for the patient. This case illustrates that establishment of a reliable patient–physician relationship with sharing and/or discovery of all aspects of medical histories cannot be too strongly emphasized.

Acknowledgments

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