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Elucidation of the clinical traits of diabetic chorea through a questionnaire survey of people with diabetic chorea from 59 Japanese hospitals

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ABSTRACT

Aims: Diabetic chorea refers to sudden involuntary movements developing in people with diabetes mellitus and is known to occur mainly in those with severe hyperglycemia. We conducted a questionnaire survey of case-reporting facilities in Japan to elucidate their clinical characteristics.

Methods: We searched the PubMed and Ichushi databases for case reports published from January 1, 2012, to December 31, 2017, using "diabetes" and "chorea" as keywords, and sent a questionnaire to the reporting institutions.

Results: Data from a total of 64 cases were included in this study. While most cases had severe hyperglycemia at the onset of diabetic chorea, hypoglycemia/improvement of the plasma glucose served as the trigger for the symptom in 14 cases (21.9%). The Early Remission Group (≤6 months) consisted of 39 cases (60.9%), while the Prolonged Partial Remission Group (>6 months) included 25 cases (39.1%). In the Prolonged Partial Remission Group (>6 months), there were more cases with widespread involuntary movement symptoms, a higher number of cases exhibiting typical imaging findings, and a greater incidence of chorea onset after the initiation of antidiabetic treatment, including hypoglycemia.

Conclusions: Most reported cases of diabetic chorea in Japan were elderly persons with type 2 diabetes mellitus and severe hyperglycemia, although there were also some cases in which the symptom developed in the setting of hypoglycemia. It has been suggested that rapid plasma glucose correction and hypoglycemia might be associated with the risk of development and prognosis of diabetic chorea.

INTRODUCTION

Diabetic chorea is characterized by the development of sudden involuntary movements, mainly in the presence of severe hyperglycemia. Diabetic chorea is sometimes referred to as diabetic hemiballism/hemichorea or diabetic striatopathy. In this study, we have standardized the terminology to diabetic chorea[1,2]. Bedwell was the first to report diabetic chorea[3]. Yahikozawa *et al.* reported cases of hemiballism in diabetic people with severe hyperglycemia, with evidence on head magnetic resonance imaging (MRI) of hyperintensity in the putamen[4]. With advances in imaging techniques, reports of cases with the typical findings of diabetic chorea on MRI and computed

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tomography (CT) are also increasing. T1-weighted MR images typically show hyperintensity in the basal ganglia, while CT images show hyperdensity in the basal ganglia[5–7].

Epidemiologically, diabetic chorea is reported as being more common in people over the age of 70 years, Asians, and women[8,9]. A systematic review by Chua *et al.* revealed that 71.6% of the reports were from Asia, with 1.65% originating from Japan[2]. The relatively low number of reports from Europe and the United States may be due to a lack of awareness and underdiagnosis of diabetic chorea in these regions[9]. While the reported prevalence of diabetic chorea is 1 in 100,000, the actual number of cases may be much higher[10]. Sex and racial differences in the development of diabetic chorea may be related to the genetic background, but the details remain unknown.

Although the clinical course of diabetic chorea has been reported to be favorable in most cases[8,11,12], it varies from case to case, and some patients have persistent or recurrent symptoms[13]. Because the condition is rare, many aspects of diabetic chorea remain poorly understood. In this study, we conducted a comprehensive questionnaire survey targeting case-reporting facilities across Japan to elucidate the clinical characteristics of diabetic chorea.

MATERIALS AND METHODS

We searched the Ichushi (https://search.jamas.or.jp/) and PubMed (https://pubmed.ncbi.nlm. nih.gov/) databases using the keywords "diabetes" and "chorea." There were 113 case reports from Japan, and a questionnaire was sent to each institution that reported these cases. The details are shown in Figure 1. The questionnaire items pertained to the age, sex, height, weight, type of diabetes, plasma glucose level, hemoglobin A1c (HbA1c), diabetes duration, symptoms, imaging findings, treatment, and clinical course. In the clinical course section of the questionnaire, respondents were asked to select whether they used treatment for involuntary movements and to select from the following four options: resolved, improved but not completely resolved, unchanged, or worsened. The duration of symptom resolution was also asked. The University of Tokyo Graduate School of Medicine Ethics Review Board approved the conduct of this study (Ethics review number: 11866-(4)). All statistical analyses were performed using JMP Pro 18.01. Non-normally distributed variables are presented as medians and interquartile ranges (IQR). Comparisons among groups were conducted using Fisher's exact test and the Wilcoxon test for continuous variables with non-normal distribution; a probability value of less than 0.05 was considered to denote statistical significance.

RESULTS

Number of survey responses

Responses were obtained from 69 case-reporting facilities. In six cases, the doctors at the reporting facility did not agree to participate in the survey. In addition, two cases were duplicates, and the final diagnosis differed in three cases. Five facilities also shared information about another case of diabetic chorea experienced at the facility. Finally, the data of 64 cases were included in this study, including those of one case seen at our institution (Figure 1).

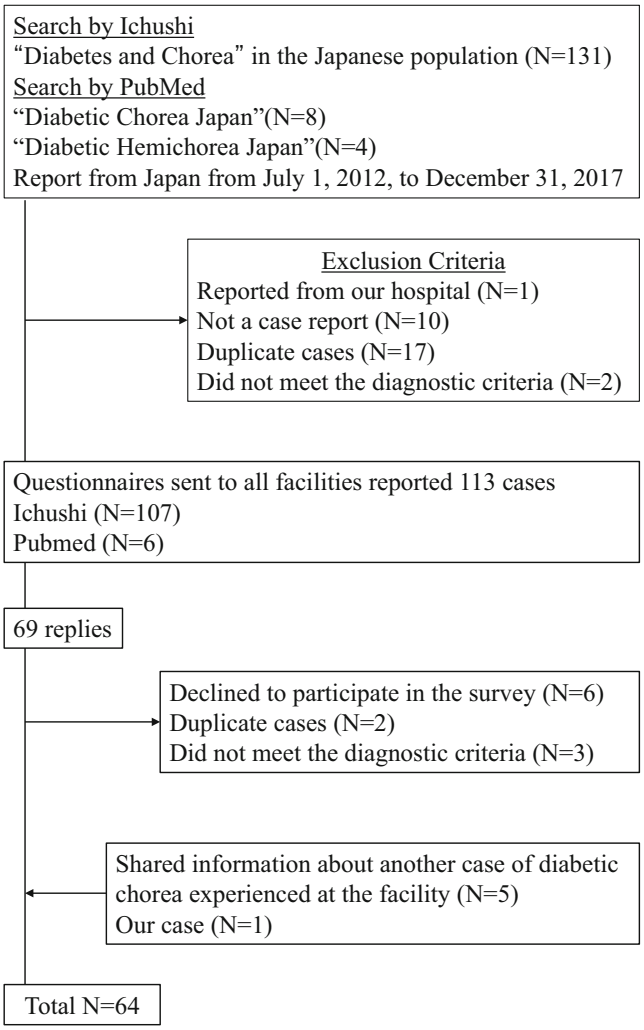

Figure 1 | A flowchart of selection of study cases.

Demographic data

The median age of the individuals was 73 years (IQR: 63–78.8). There were 31 males and 33 females, with no gender difference in the incidence of diabetic chorea. The median body mass index was 22 kg/m^2 (IQR: 20–25.6). Of the 64 cases, 59 (92.2%) had type 2 diabetes mellitus, and 5 (7.8%) had type 1 diabetes mellitus. The median duration of diabetes mellitus was 12.5 years (IQR: 8–20; Table 1). Of all the cases, 26 (40.6%) had no history of hospital visits, and 22 (34.4%) had received self-interrupted treatment.

Table 1 | Clinical features of the cases

Background (n = 64)	
Age (years), median (IQR)	73 (63–78.8)
Male (%)	48.4
Body mass index (kg/m^2), median (IQR)	22 (20–25.6)
Type of diabetes	
Type 1 diabetes (%)	7.8
Type 2 diabetes (%)	92.2
Duration of diabetes (years), median (IQR)	12.5 (8–20)
Plasma glucose level (mg/dL), median (IQR)	475 (325–678.3)
HbA1c (%), median (IQR)	14.3 (12.7–15.7)
Symptom of chorea (%)	
Unilateral	82.8
Bilateral	17.2
Typical MRI findings (%)	73
Typical CT findings (%)	61.4
Treatment (%)	
Glycemic control	35.9
Medication for involuntary movements	64.1
Clinical course	
Symptom remission rate (%)	
Resolved	67.5
Improved but not completely resolved	32.5
Unchanged	0
Worsened	0
Days to symptoms remission (days), median (IQR)	7 (IQR: 3–14)

The typical finding on MRI is a high signal intensity in the basal ganglia on T1-weighted images. The typical finding on CT scans is hyperabsorption in the basal ganglia. Glycemic control refers to treatment for control of plasma glucose only. Medication for involuntary movements refers to administration of drugs for involuntary movements in addition to that for achieving glycemic control. Continuous variables are presented as median values (IQR). CT, computed tomography; HbA1c, hemoglobin A1c; IQR, interquartile range; MRI, magnetic resonance imaging.

Laboratory findings

The median plasma glucose level and median HbA1c level at the onset of diabetic chorea were 475 mg/dL (IQR: 325–678.3) and 14.3% (IQR: 12.7–15.7), respectively (Table 1). Although the condition was associated with hyperglycemia in most cases, 14 cases (21.9%) showed the onset of the diabetic chorea in a state of hypoglycemia or following improvement of the plasma glucose levels after treatment. Of these 14 cases, three showed onset of diabetic chorea during a period of apparent hypoglycemia, eight showed onset of chorea following improvement of the plasma glucose level after hospitalization, including hospitalization for education, and three showed onset of the condition after intensification of the treatment at the outpatient clinic; 13 of the 14 cases were receiving treatment with insulin, and the remaining one case was receiving a sulfonylurea.

The survey also revealed 12 cases with apparent ketotic hyperglycemia at the onset of diabetic chorea. Three of the 12 cases (25%) with ketotic hyperglycemia in this study had type 1 diabetes mellitus, and all presented with diabetic ketoacidosis. The remaining nine cases of ketotic hyperglycemia had type 2 diabetes mellitus, comprising four cases of soft drink ketosis, four cases of self-interruption of treatment (three on insulin and one on oral medication), and one case of type 2 diabetes mellitus with drug-induced hyperglycemia (due to Leuprorelin).

In contrast, two of the 52 cases (3.8%) with non-ketotic hyperglycemia had type 1 diabetes mellitus. The remaining 50 cases with non-ketotic type 2 diabetes mellitus included 19 untreated, 16 self-interrupted (five on insulin, nine on oral medication, and two with unknown treatment history), seven cases were receiving oral treatment, four cases were receiving insulin therapy, and four cases involved type 2 diabetes mellitus with steroid use. The proportion of type 1 diabetes mellitus in ketotic and non-ketotic hyperglycemia was significantly higher (25% vs 3.9%, $P = 0.042$). One case of ketotic hyperglycemia and one case of non-ketotic hyperglycemia led to the diagnosis of type 1 diabetes mellitus at the onset of diabetic chorea.

Examination of the differences in the clinical characteristics of diabetic chorea between people with apparent ketotic hyperglycemia and non-ketotic hyperglycemia revealed that those with ketotic hyperglycemia were significantly younger than those with non-ketotic hyperglycemia (53 years (IQR: 35.3–69) vs 74 years (IQR: 65.3–79), $P < 0.001$). The median plasma glucose level was 836 mg/dL (IQR: 678.3–1,098.8) in people with ketotic hyperglycemia and 384 mg/dL (IQR: 307–536.3) in those with non-ketotic hyperglycemia. Plasma glucose levels were significantly higher in cases of ketotic hyperglycemia than nonketotic hyperglycemia ($P < 0.001$). The median HbA1c in the people with ketotic hyperglycemia was 16.3% (IQR: 15–19.3), which was significantly higher than that in the people with non-ketotic hyperglycemia (14.1% (IQR: 12.6–14.8), $P < 0.001$). There were fewer cases with the typical imaging (CT/MRI) findings associated with diabetic chorea among people with ketotic hyperglycemia than among those with non-ketotic hyperglycemia (50% vs 84.6%, $P = 0.017$; Table S1).

Characteristics of the symptoms in diabetic chorea

The involuntary movements were unilateral in 53 cases (82.8%) and bilateral in 11 cases (17.2%; Table 1). The involuntary movements involved the upper and lower limbs in 35 cases, only the upper limbs in 15 cases, and the face and the upper and lower limbs in 8 cases. Please refer to Table S2 for details.

The involuntary movements included chorea in 29 cases (45.3%), chorea and ballism in 18 cases (28.1%), and ballism alone in 7 cases (10.9%). Choreoathetosis was noted in five cases (7.8%), and the involuntary movements were unclassifiable in five cases (7.8%).

Imaging findings

The typical finding of diabetic chorea on head MRI is a high signal intensity in the basal ganglia on T1-weighted images. Head MRI was performed in 63 patients; it was omitted in the

remaining one person as he/she had an implanted pacemaker. Of the 63 cases, 46 (73%) showed a high signal intensity in the basal ganglia on T1-weighted MR images, which is a typical finding associated with diabetic chorea; 10 cases (15.9%) did not show the typical findings of diabetic chorea on T1-weighted MRI, and the remaining seven cases (11.1%) showed atypical findings, including old cerebral infarction, hemorrhage, and calcification of the basal ganglia.

The typical finding associated with diabetic chorea on CT images is hyperdensity in the basal ganglia. CT was performed in 44 of the 64 cases. Of the 44, twenty-seven cases (61.4%) showed hyperdensity of the basal ganglia. Thirteen cases (29.5%) did not show the typical CT findings of diabetic chorea, and four cases (9.1%) showed atypical imaging findings, including old hemorrhage, hypodense areas, and calcification.

In 50 cases (78.1%), typical findings of diabetic chorea were found on CT and/or MRI. Both MRI and CT were performed in 43 cases. Then, we examined the degree to which the typical findings were matched on MRI and CT in 35 cases after excluding eight cases with atypical findings. Both MRI and CT showed typical findings in 23 cases (65.7%), only CT showed typical findings in one case (2.9%), and only MRI showed typical findings in seven cases (20%). Furthermore, four cases (11.4%) did not show the typical findings associated with diabetic chorea on either CT or MRI.

Among the cases that occurred following hypoglycemia or rapid glycemic improvement, MRI revealed typical findings in 10 of the 12 cases, while the remaining two cases did not exhibit these typical features.

Treatment and prognosis

The treatment for diabetic chorea is control of the plasma glucose; however, many people with diabetic chorea also received medication for involuntary movements; 23 cases (35.9%) received antidiabetic treatment only, and 41 cases (64.1%) received medication for both involuntary movements and glycemic control; the most commonly used drug was haloperidol (33 cases).

Regarding changes in symptoms after the initiation of treatment, respondents were asked to select from the following four options: resolved, improved but not completely resolved, unchanged, or worsened. As a result, 40 cases (67.5%) reported symptom resolution, and 24 cases (37.5%) reported persistent symptoms. There were no cases of "unchanged" or "worsened" symptoms. The median duration of symptom resolution was 7 days (IQR: 3–14), and the median observation period for persistent symptoms was 180 days (IQR: 90–360). In a systematic review by Chua *et al.*, the median treatment duration with plasma glucose control was 2 days, and the median treatment duration for those using medication for involuntary movements was 14 days[2]. Additionally, Oh *et al.* reported that 97.4% of cases fully recovered within 6 months[8].

In this study, to examine factors associated with the prognosis of diabetic chorea, we defined two groups: the Early Remission Group (≤6 months), in which symptoms resolved within 6 months, and the Prolonged Partial Remission Group (>6 months), in which symptoms improved but persisted for more than 6 months. We then examined the association between factors such as age, sex, HbA1c, symptom severity, medication use for involuntary movements, typical imaging findings, and the onset of symptoms after the initiation of antidiabetic treatment, including hypoglycemia, between the two groups. The potential use of involuntary movement medications at the time of symptom resolution was not considered.

The Early Remission Group (≤6 months) included 39 cases (60.9%), while the Prolonged Partial Remission Group (>6 months) included 25 cases (39.1%). In the Prolonged Partial Remission Group (>6 months), there were more cases with widespread lesions throughout the body (96% vs 65.8%, $P = 0.005$), more cases with typical imaging findings (92% vs 69.2%, $P = 0.036$), and a higher incidence of symptoms developing after the initiation of antidiabetic therapy, including hypoglycemia (44% vs 7.7%, $P = 0.001$). In the Prolonged Partial Remission Group (>6 months), there was a tendency for a higher rate of medication use for involuntary movements (80% vs 53.9%, $P = 0.060$; Table 2).

The symptom remission rate did not differ significantly between the individual groups with ketotic and non-ketotic hyperglycemia, but the interval to symptom remission from the onset was 4 days (IQR: 0.8–6.5) in the group with ketotic hyperglycemia, significantly shorter than the interval of 7 days (IQR: 3–30) in the group with non-ketotic hyperglycemia ($P = 0.035$; Table S1).

DISCUSSION

Diabetic chorea is a rare complication of diabetes, but much about this complication remains unknown. In this study, we conducted a questionnaire survey of facilities in Japan that have reported cases of diabetic chorea to clarify the clinical characteristics of individuals with this condition. People with diabetic chorea in Japan are mostly elderly people with type 2 diabetes mellitus and severe hyperglycemia.

The median age of the reported people with diabetic chorea was 73 years (IQR: 63–78.8), with most people being elderly. The high prevalence of diabetic chorea in the elderly is consistent with previous reports[2,14]. However, there were also reports of the condition in younger people in their 30s and children with type 1 diabetes mellitus[12,15–17]. No gender difference in the incidence was found in this survey, although most previous reports have suggested that diabetic chorea is more common in women[1,2,9,18]. The median plasma glucose level at the onset of diabetic chorea was 475 mg/dL (IQR: 325–678.3), and the median HbA1c level was 14.3% (IQR: 12.7–15.7). The high median plasma glucose and HbA1c levels were consistent with previous reports[2,14].

According to the results of this questionnaire survey, 14 cases developed chorea after the initiation of antidiabetic treatment and during periods of hypoglycemia. Furthermore, the

Table 2 | Factors associated with symptom remission

	Early remission group ≦6 months	Prolonged partial remission >6 months	*P* value
Number of cases (%)	39 (60.9)	25 (39.1)	–
Male (%)	51.3	44	0.616
Age, median (IQR)	74 (63–80)	72 (62–77.5)	0.453
HbA1c (%), median (IQR)	14.2 (12.7–15.9)	14.4 (13.2–15.6)	0.977
Extensive symptoms (%)	65.8	96	0.005†
Typical imaging findings (%)	69.2	92	0.036†
Treatment with drugs for involuntary movements (%)	53.9	80	0.060
Cases of onset after initiation of antidiabetic treatments, including in the setting of hypoglycemia (%)	7.7	44	0.001†

The Early Remission Group (≦6 months) includes individuals whose symptoms disappeared within 6 months. The Prolonged Partial Remission Group (>6 months) includes individuals whose symptoms improved but lasted for more than 6 months. The extent of symptoms (number of body regions involved) was compared between cases in which symptoms were bilateral and/or involved both the upper and lower extremities and those in which it was unilateral and confined to the upper and lower extremities. Typical imaging findings were defined based on the findings of MRI or CT. Treatment with drugs for involuntary movements refers to the administration of drugs for the involuntary movements in addition to that for achieving glycemic control. Cases of onset after initiation of treatment for glycemic control, including in the setting of hypoglycemia, include those who developed the symptom during periods of apparent hypoglycemia, at the time of improvement of the plasma glucose levels after hospitalization, or after intensified treatment in the outpatient setting. Continuous variables are presented as median values (IQR). †Statistical significance was set at $P < 0.05$ and assessed by Fisher's exact test. CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging.

remission rate was lower in these 14 cases (Table 2). While there have been reports of diabetic chorea developing after the initiation of antidiabetic treatment[6,19] or during periods of hypoglycemia[20–33], no relationship between these factors and the prognosis has been reported. It has long been known that rapid glycemic control exacerbates diabetic neuropathy[34–36], and the low symptom remission rate in people developing diabetic chorea after the initiation of antidiabetic treatment and in the setting of hypoglycemia also suggests that slow glycemic control is important. Although people with diabetic chorea are generally considered to have a good prognosis, 64.1% of cases in this study required medications, such as haloperidol, for the treatment of involuntary movements, and symptoms did not resolve in 37.5% of people with diabetic chorea. Even from the point of view of the quality of life, the clinical course was poor.

The pathophysiology of diabetic chorea remains unclear. Some proposed mechanisms for the degeneration of the basal ganglia as the cause of diabetic chorea include infarction, ischemia, hemorrhage, osmotic changes, calcium deposition, etc.[2,5,8] Due to degeneration of the basal ganglia, inhibition of the thalamus from the internal part of the globus pallidum is suppressed, decreasing activity of the "indirect pathway" in the classical basal ganglia circuit, resulting in involuntary movements[37]. In hyperglycemia, the brain uses gamma-aminobutyric acid (GABA) as an alternative source of energy[8]. These mechanisms may also be responsible for the depletion of GABA in hyperglycemia and inhibition of the basal ganglia output from the globus pallidum inner node to the thalamus, resulting in involuntary movements. The theory of transient ischemia is widely accepted because, in many cases, diabetic chorea is unilateral, the symptom is reversible, and the course of the CT findings differs from that of hemorrhage[2]. The hypothesis that the cerebral blood flow decreases in hyperglycemia is also consistent with this theory[38].

In ketotic hyperglycemia, GABA is produced and is less likely to be deficient; however, in non-ketotic hyperglycemia, GABA and acetic acid are thought to be depleted[8]. Consequently, most cases of diabetic chorea are considered to occur in the setting of non-ketotic hyperglycemia.

However, it remains a challenge to explain the pathophysiology of diabetic chorea that develops during periods of hypoglycemia and in the setting of rapid correction of plasma glucose levels. People who develop diabetic chorea in the setting of hypoglycemia and rapid correction of the blood glucose levels exhibit a low rate of symptom remission, suggesting that additional mechanisms may be involved. At the cellular level, glucose deficiency, ischemia, and hypoxia can induce cell stress[30]. It has been reported from MRI studies of the brain that the basal ganglia, cortex, substantia nigra, and hippocampus may be vulnerable to hypoglycemia[39]. There is a case report of a person in whom the MRI changes due to hypoglycemia were not in the basal ganglia or thalamus but in the cortical region, and the symptoms disappeared with improvement in glycemic control[27]. In 17 previously reported cases[6,19–33] of diabetic chorea following hypoglycemia or rapid glycemic improvement, seven cases exhibited typical findings on T1-weighted MRI, while four cases showed no MRI abnormalities. Three cases presented atypical findings: in two cases, the basal ganglia showed a low signal on T1-weighted images and a high signal on T2-weighted images; in one case, the cortex showed a high signal on T2-weighted images. In the remaining three cases, MRI findings were not available. It has been reported that the injury sites in hypoglycemic encephalopathy typically include the cortex, white matter, entorhinal cortex, and caudate nuclei, with low signal on T1-weighted images and high signal on T2-weighted images[39]. However, it remains unclear whether the atypical MRI findings observed in some cases are attributable to hypoglycemia or whether specific imaging features can be identified following hypoglycemia correction or rapid plasma

glucose improvement in diabetic chorea. Further studies are required to clarify these findings.

Hypoglycemia is believed to induce cytokine production, resulting in vascular endothelial damage and abnormal coagulation due to platelet dysfunction. Thus, in the setting of hypoglycemia and rapid correction of the plasma glucose, such additional mechanisms may also contribute to transient ischemia of the basal ganglia[40].

Furthermore, it is unclear whether the blood pressure and lipid profile might also be involved in the pathogenesis of diabetic chorea, as in macrovascular diseases[1]. Thus, further research is required to elucidate the pathogenesis of diabetic chorea.

Previous reports have suggested that in most cases, diabetic chorea occurs in the setting of non-ketotic hyperglycemia[18,41]. However, a certain percentage of cases of diabetic chorea are also known to arise in the setting of ketotic hyperglycemia[2,14]. Previous reports have reported that in 18.3% of people, diabetic chorea occurred in the setting of ketotic hyperglycemia[2]. In this study, 12 cases (18.8%) developed chorea in the presence of ketotic hyperglycemia. The median plasma glucose levels were 836 mg/dL (IQR: 678.3–1,098.8) in people with ketotic hyperglycemia and 384 mg/dL (IQR: 307–536.3) in those with non-ketotic hyperglycemia. Plasma glucose levels were significantly higher in the ketotic hyperglycemia group compared to the non-ketotic hyperglycemia group ($P < 0.001$).

A comparison of plasma glucose levels between ketotic ($n = 20$) and non-ketotic ($n = 108$) hyperglycemia based on previously published data[1,8,13,18,42,43] showed median plasma glucose levels of 576.5 mg/dL (IQR: 385.3–784) and 370 mg/dL (IQR: 270.3–502.3), respectively. The median plasma glucose levels were significantly higher in the ketotic hyperglycemia group, which is consistent with the results of our study ($P < 0.001$).

With respect to the development of diabetic chorea, ketotic hyperglycemia is less likely to cause GABA depletion compared to non-ketotic hyperglycemia. Furthermore, due to the neuroprotective effects of ketones[44,45], it is suggested that diabetic chorea may develop at higher plasma glucose levels in ketotic hyperglycemia than in non-ketotic hyperglycemia.

Individuals with ketotic hyperglycemia who develop diabetic chorea have also been reported to be relatively young and less likely to show typical imaging findings associated with chorea[43]. Consistent with the above, in this study, people with diabetic chorea in the setting of ketotic hyperglycemia were younger and often did not exhibit typical imaging findings.

Ketones are thought to act as central nervous system protectors, and their usefulness in treating epilepsy and Parkinson's disease has been previously reported[44,45]. Age, sex, race, and other genetic factors have been reported to affect the ketone-producing capacity of the body[46–49]. These findings suggest that diabetic chorea may be related to the body's ketone production capacity, as some individuals with poor glycemic control develop diabetic chorea while others do not, and further verification is required. In addition, SGLT2 inhibitors have been reported to enhance the production of ketone bodies[50], and dapagliflozin has been reported to improve the symptoms of Huntington's disease[51]. Ketone diets have also been reported to be useful in treating epilepsy and neurodegenerative disorders[52]. Ketone diets and SGLT2 inhibitors, which promote ketone production, are expected to be beneficial for suppressing the development and recurrence of diabetic chorea; however, further validation is needed.

MRI, essential for confirmation of the diagnosis, was performed in almost all cases in the study (98.4%), and CT was performed in 44 cases (68.8%). Imaging studies of diabetic chorea have revealed that MRI is more sensitive than CT to confirm the diagnosis of diabetic chorea[2]. In this study, one case showed typical imaging findings on only CT, while seven cases showed typical imaging findings on only MRI. Typical imaging findings are reported to disappear earlier on CT than on MRI[2]. Among the observed cases in this survey, CT findings appeared before the onset of symptoms, suggesting that the findings on CT may appear as well as disappear earlier. Based on our survey results, it seems advisable to perform CT and MRI in people with diabetic chorea. The presence or absence of imaging findings and the timing of the appearance of the findings may vary from case to case[53].

In some cases, diabetic chorea was not immediately diagnosed. One case of diabetic chorea was misdiagnosed as cerebral hemorrhage due to hyperabsorption of the basal ganglia on CT, and the person was sent to the emergency department. At first glance, it may be difficult to distinguish diabetic chorea from cerebral hemorrhage on CT images. The time course of changes in the CT findings differs between diabetic chorea and cerebral hemorrhage, which may be useful in distinguishing between the two conditions[54–56]. In another case, the person was initiated on antiplatelet agents for suspected cerebral infarction based on the clinical symptoms without performing any imaging studies or plasma glucose level measurements. It is important for diabetic chorea to be widely recognized because the diagnosis was not made promptly in some of the reported cases, leading to potential misdiagnosis or delayed treatment. Other tests, such as single-photon emission computed tomography (SPECT), electroencephalography (EEG), and positron emission tomography (PET), have been performed, but no consensus has been reached yet on their usefulness[6].

This study had some limitations. The 64 cases in this study were aggregated from the responses to the questionnaire survey and may not reflect the general population. Responses to the questionnaire were not obtained for all the reported cases. In addition, it is considered that there could have been an element of publication bias because only case reports are targeted. Another limitation is that, regarding the use of medications for involuntary movements, it is difficult to determine the duration of involuntary movement medication use based on the responses, and it is also challenging to ascertain whether involuntary movement medications were still used at the time of symptom resolution.

In summary, most people with diabetic chorea in Japan are elderly individuals with type 2 diabetes mellitus and severe hyperglycemia, although there were also some reports of cases with the onset of diabetic chorea after the initiation of antidiabetic treatment and in the setting of hypoglycemia. Rapid changes in the plasma glucose levels, especially during the initiation of antidiabetic treatment or episodes of hypoglycemia, have been suggested as exerting an influence on the risk of development and prognosis of diabetic chorea. Careful glycemic control is essential to prevent the development of diabetic chorea. It is also crucial for diabetic chorea to be widely recognized so that it can be diagnosed promptly and treated early.

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DISCLOSURE

The authors have no conflicts of interests to declare. Takashi Kadowaki and Toshimasa Yamauchi are an Editorial Board member of Journal of Diabetes Investigation and a co-author of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication.

Approval of the research protocol: This study was approved by the Ethics Review Committee of the University of Tokyo Graduate School of Medicine, and was conducted in conformity with the principles of the Declaration of Helsinki (Ethics review number: 11866-(4)).

Informed consent: This study was a retrospective analysis, and obtaining consent from the people with diabetic chorea at each institution was difficult, and consent was obtained from those attending or fellow physicians. To protect personal information, we asked that no personally identifiable information be included in the questionnaire responses. An option for opt-out was posted on the website of the Department of Diabetes and Metabolic Diseases at the Graduate School of Medicine, University of Tokyo, Japan.

Approval date of registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Clinical features of diabetic chorea associated with ketotic hyperglycemia.

Table S2. Symptom site.

Appendix S1. Supplementary Acknowledgments.