케톤성 당뇨와 모야모야병으로 인한 허혈성 뇌졸중 동시 발생

제주대학교병원 소아청소년과

이현주 · 이주연 · 김소리나 · 오민수 · 한경희 · 강기수 · 김승효

Concurrence of Diabetic Ketoacidosis and Acute Ischemic Stroke due to Moyamoya Disease

Although the etiology of moyamoya disease (MMD) remains unknown, autoimmunity is one of the proposed pathogeneses. Unlike other autoimmune disorders that are associated with cerebral arteritis, concurrence of MMD and diabetes mellitus (DM) is rare. However, we encountered a patient with concurrent diabetic ketoacidosis (DKA) and acute ischemic stroke due to MMD. Our patient was diagnosed with glutamic acid decarboxylase antibody-positive type 2 DM (T2DM) based on laboratory and physical examination findings. Brain magnetic resonance images revealed an acute ischemic stroke in the left cerebral hemisphere and bilateral diffuse stenosis/occlusion in the middle cerebral artery and multiple collaterals. Thus, here, we report a patient with both T2DM and MMD who developed an acute ischemic stroke that was complicated by DKA.

Key Words: Diabetic ketoacidosis, Type 2 diabetes mellitus, Moyamoya disease

Hyeonju Lee, MD, Juyeon Lee, MD, Sorina Kim, MD, Min-su Oh, MD, Kyoung Hee Han, MD, Ki-Soo Kang, MD, PhD, Seunghyo Kim, MD

Department of Pediatrics, Jeju National University Hospital, Jeju, Korea

Introduction

Moyamoya disease (MMD) has diverse presentations. Although the etiology of MMD remains unknown, viral or bacterial infections, genetic factors, and autoimmune mechanisms have been implicated in disease development. Several studies have reported an increased prevalence of autoimmune diseases in patients with MMD and hypothesized that an autoimmune component contributes to MMD pathogenesis^{1,2)}.

In contrast to Graves' disease (GD) and other autoimmune diseases having well-established mechanisms of pathogenesis associated with cerebral arteritis^{3,4)}, concurrence of MMD with diabetes mellitus (DM) is very rare⁵⁻⁷⁾. The etiologies of DM and MMD are variable and have not been completely delineated with any causality⁸⁾. However, recent Asian and Western studies have reported a positive correlation between DM and MMD^{1,2)}.

To our knowledge, there have been no reports of concurrent glutamic acid decarboxylase antibody (GAD Ab)-positive type 2 DM (T2DM) and MMD in Korea. Here, we describe a 10-year old boy who simultaneously exhibited diabetic ketoacidosis (DKA) and ischemic stroke, which was induced by MMD.

We announced this report as a poster presentation in the 45th, 2017 Annual symposium of Korean Child Neurology Society

Submitted: 20 December, 2017

Revised: 22 February, 2018

Accepted: 22 February, 2018

Correspondence to Seunghyo Kim, MD
Department of Pediatrics, Jeju National University Hospital 15, Aran 13-gil, Jeju-si, Jeju-do 63241, Korea
Tel: +82-64-754-8141, Fax: +82-64-727-3114
E-mail: shped@jejunu.ac.kr

Case report

A 10-year-old boy was referred to our hospital for presentations of altered mentality. He was born at 38 weeks of gestational age, without complication, by cesarean section. Barring his father's hyperlipidemia, both parents denied family history of hypertension, DM, and cerebrovascular diseases, including MMD. Except recently consuming larger amounts of water, the patient denied history of headache, transient weakness of the extremities, and loss of body weight.

The patient had been complaining of abdominal pain and lethargy two days prior to visiting the emergency room (ER) and had become drowsy on the day of admission. His vital signs were pulse 145 beats/min, blood pressure 141/65 mmHg, body temperature 36.8°C, and respiratory rate 30/min. He also declared no underlying disease or medication.

Upon neurologic examination at the ER, the patient tried to open his eyes to the physician's speech and showed a withdrawal response when he was given a pain stimulus. The patient spoke incomprehensible sounds, and his pupils were isocoric with prompt reflexes. The motor power of the four extremities was determined as grade 3, on both sides. On physical examination, moderate-to-severe acanthosis nigricans was observed on both axilla and the abdomen. He weighed 64.8 kg (>97 percentile), was 161.7 cm tall (>97 percentile), and had a body mass index of 24.8 kg/m² (>97 percentile).

Initial laboratory findings confirmed severe DKA that was accompanied by acute pancreatitis with the following values: pH 6.92, pCO₂ 10 mmHg, HCO₃ 5.2 mmol/L, tCO₂ 2 mmol/L, serum glucose 779 mg/dL, amylase 623 (normal, 35-110) IU/L, and lipase 2,403 (normal, 13-60) IU/L. On the lipid profile of the patient, triglyceride and total cholesterol were 239 (normal, 50-130) mg/dL and 173 (130-250) mg/dL, respectively. Thyroid function tests showed low triiodothyronine 3 levels (0.41; normal, 0.8-2.0 ng/dL), lower-than-normal thyroid stimulating hormone levels (0.28; normal, 0.27-4.20 μ IU/ml), and low free triiodothyronine 4 levels

(0.65; normal, 0.93-1.70 ng/dL). Thyroid autoantibodies were within the normal range: Thyroglobulin Ab 14.64 (normal, 0-115) IU/mL, anti-thyroperoxidase Ab 7.59 (normal, 0-34) IU/mL, and TSH-receptor Ab 0.3 (normal range, 0-1.75) IU/L. The patient showed elevated HbA1c (9.5%; normal, 4.0-6.0%), normal insulin (6.56; normal, 2.6-24.9 μ U/mL), and normal C-peptide levels (1.18; normal, 1.1-4.4 ng/mL). However, elevated levels of GAD Ab (9.28; normal, <1.0 U/mL) and insulin Ab (6.39%; normal, <5.4%) were detected. An abdominal CT was revealed swelling of the pancreas, with peripancreatic fatty infiltration and a diffuse fatty liver. Brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) indicated that the patient experienced an acute ischemic stroke in the left cerebral hemisphere (Fig. 1A-D) and showed bilateral diffuse stenosis/occlusion of the middle cerebral artery and multiple collaterals (Fig. 2A-C). We did not further evaluate the patient for etiologies of acute pancreatitis, hypertension, and moyamoya vessels.

Continuous renal replacement therapy was performed to correct the severe metabolic acidosis and insulin treatment was performed to control the patient's high blood glucose levels. The patient began to regain his mentality on the third day of hospitalization and complained of right hemiplegia. On the fourth day, his mentality returned to a normal state.

The patient initially received intravenous insulin treatment, which changed to subcutaneous treatment on the fourth day of hospitalization, along with metformin. His blood glucose levels stabilized with metformin alone and remained stable after the discontinuation of insulin treatment. The right hemiplegia receded, and he received surgical treatment for MMD on the 37th day after admission.

Discussion

Here, we present the case of a patient who was reported to be previously healthy and had not recently seen physicians due to

Fig. 1. A-C. Brain magnetic resonance (MR) diffusion-weighted images show multiple foci or diffusion restriction in the left frontal lobes and bilateral periventricular and subcortical white matter in the fronto-parietal lobes (white circle). D. The brain MR T2-weighted image demonstrates loss of normal signal and a void of absence in the bilateral middle cerebral arteries (white arrow).

diabetic symptoms or headaches. Two days prior to the ER visit, he complained of abdominal pain and lethargy, followed by drowsiness on the day of admission. The second day after admission, the patient did not open eyes, in spite of pain stimulus, and could not even utter incomprehensible words. The same day, we performed brain MRI and MRA to evaluate the aggravated altered mentality. The imaging studies showed an acute ischemic stroke, which was due to MMD. Neurologic examination was partially limited, due to the altered mentality of the patient. It was not until the third day of hospitalization, when the patient complained of not being able to move his right hand and leg, that medical team detected right-sided hemiplegia.

The patient was finally diagnosed with GAD Ab-positive T2DM and MMD. Both diseases induced two acute manifestations, DKA and acute ischemic stroke. The hyperosmotic disturbance of neuronal activities that is induced by DKA might cause altered mentality. Right hemiplegia was mainly thought to be due to compromised moyamoya vessels.

Ketoacidosis seldom occurs spontaneously in patients with T2DM. When ketoacidosis appears, it can develop due to acute stress from infection or other illnesses⁹. Considering this sequence, in this case, acute stress may have developed from acute pancreatitis, which caused the acute disturbance of blood glucose and resulted in DKA. Metabolic acidosis likely occurred by DKA triggered hyperventilation as compensating mechanism, which resulted in an acute ischemic stroke in the moyamoya vasculopathy. Moreover, hyperglycemia aggravates cerebral ischemia⁶.

Although MMD rarely concurs with DM⁵⁻⁷, there are several cases of both DM and MMD with or without GD. A 20-year-old woman with T1DM and MMD showed four incidences of DKA. She showed neurologic signs of hemichorea and broca aphasia on the third and fourth DKA episodes, respectively⁵. Both neurologic symptoms disappeared with the resolution of DKA. Suzuki et al. reported that two 38 and 43-year-old individuals who had untreated T2DM and GD showed neurologic symptoms of left radial nerve palsy and left hemiparesis, respectively, which resulted from MMD. The authors did not report further about the

results of the neurologic symptoms⁶. Noh et al. reported a 16-year-old girl who had been finally diagnosed with T1DM, GD, and MMD. A thyroid storm developed six hours after the start of DKA management and was followed by right hemiplegia, which completely resolved within one month⁷.

Recently, two Asian and Western studies reported an increased prevalence of autoimmune diseases, and both indicated that DM and GD were more common than other autoimmune diseases^{1,2}. The prevalence of T1DM with MMD was significantly higher in the general MMD population¹. However, the prevalence of T2DM did not statistically differ between the MMD and general populations. Both studies concluded that the unusually high prevalence of autoimmune disease, such as T1DM and thyroid disease, suggested an underlying autoimmune component of moyamoya². To date, there have been few reports regarding the relationship between T2DM and MMD, and therefore, with the current data, it is difficult to verify whether both diseases correlate.

However, several studies have reported that 9.8–30% of the population, aged 10–19 years, with T2DM were positive for GAD-65 Ab¹⁰⁻¹². GAD has multiple isoforms, and GAD-65 is expressed selectively in GABAergic neurons and pancreatic β -cells in human islets¹¹. One study has suggested that insulin autoantibodies or islet cell Ab in diabetes indicates beta cell-directed autoimmunity¹².

In addition, Klingensmith et al. mentioned that patients with T2DM who are positive for GAD-Ab showed significantly different features than patients with T2DM and who were Ab negative. The former also presented features that resembled those found in patients with T1DM¹³. Considering this evidence, we may consider our case, which had T2DM and autoantibody positivity, to more closely resemble the autoimmunity of T1DM. Since our patient has GAD Ab-positive T2DM, we can assume that autoantibodies may play a role in the pathogenesis of moyamoya vasculopathy in this individual. However, further investigations into the potential role of autoantibodies linking DM to MMD should be performed through experimental and large clinical studies.

In conclusion, to our knowledge, this is the first report of the

Fig. 2. A. A puff-of-smoke appearance is observed on magnetic resonance angiography (MRA), (white circle). B. MRA shows stenosis of supraclinoid portion of the left internal carotid arteries (white arrow). C. MRA shows stenosis of the supraclinoid portion of the right internal carotid arteries (yellow arrow).

simultaneous occurrence of acute ischemic stroke and DKA in a case with both MMD and GAD Ab-positive T2DM in Korea. Moyamoya has been reportedly to correlate with various conditions, and an analysis of the coexisting diseases that occur with moyamoya may be helpful in investigating moyamoya pathogenesis. Thus, the prevalence and clinical characteristics of autoimmune diseases that present in combination with MD in South Korea should be further investigated, as performed in other studies^{1,2)}. Furthermore, the possibility of other cerebrovascular abnormalities should be considered in cases with atypical neurologic symptoms or signs that are otherwise unexplainable by DKA alone, and in such cases, prompt CNS imaging evaluations should be performed.

요약

현재까지 모야모야병을 유발하는 원인으로 바이러스, 세균 감염, 유전, 그리고 자가면역 역 기전 등이 제시되고 있지만 정확한 원인은 밝혀져 있지 않다. 이러한 기전들 중에 전신성 홍반성 루프스, 갑상선 기능 항진증 등의 자가면역질환이 대뇌혈관질환과 흔히 동반된다. 이에 반해, 면역질환으로서의 당뇨병과 모야모야병과의 관련성에 대해서는 극히 일부에서 증례로 보고 되고 있다. 하지만, 최근 해외 연구에서 당뇨병과 모야모야 병과의 관련성에 대한 증례 보고가 늘어나고 있다. 국내에서 갑상선 기능 항진증과 모야모야병과의 관련성에 대해서 일부 증례가 보고되고 있으나 갑상선 질환의 동반 없이 항체 양성 제2형 당뇨병과 모야모야병과의 동시 발생에 대해서는 보고된 바가 없다.

이에 저자는 의식저하를 주소로 본 병원을 방문한 환자에서 모야모야병과 당뇨병을 동시에 진단한 환자가 있어서 증례로 보고하는 바이다. 신체 진찰, 혈청 검사에서 자가면역성 제2형 당뇨병이 진단되었고 자가면역성 갑상선 질환의 소견은 보이지 않았다. 뇌자기공명영상에서 좌측 대뇌 반구에서 허혈성 뇌졸중 소견을 보였으며 뇌자기공명 혈관조영술에서 양측 모야모야병에 합당한 뇌혈관 병변을 보였다. 이에 신경학적 증상으로 응급실을 방문한 환자에서 당뇨병성 케톤산증과 급성 허혈성 뇌졸중이 발생한 증례를 보고하는 바이다.

References

- 1) Chen JB, Liu Y, Zhou LX, Sun H, He M, You C. Prevalence of autoimmune disease in moyamoya disease patients in Western

- Chinese population. J Neurol Sci 2015;351(1-2):184-6.
- 2) Bower RS, Mallory GW, Nwojo M, Kudva YC, Flemming KD, Meyer FB. Moyamoya disease in a primarily white, midwestern US population: increased prevalence of autoimmune disease. Stroke 2013;44:1997-9.
- 3) Lee R, Sung K, Park YM, Yu JJ, Koh YC, Chung S. A case of moyamoya disease in a girl with thyrotoxicosis. Yonsei Med J 2009;50:594-8.
- 4) Kamasaki H, Takeuchi T, Mikami T, Komeichi K, Tsutsumi H. A case of graves' disease diagnosed in the course of bilateral carotid artery stenoses (moyamoya disease); a case report and review of the literature. Clin Pediatr Endocrinol 2013;22:39-44.
- 5) Watanabe C, Oishi T, Yamamoto T, Sasaki K, Tosaka M, Sato T, et al. Chorea and broca aphasia induced by diabetic ketoacidosis in a type 1 diabetic patient diagnosed as moyamoya disease. Diabetes Res Clin Pract 2005;67:180-5.
- 6) Suzuki S, Mitsuyama T, Horiba A, Fukushima S, Hashimoto N, Kawamata T. Moyamoya disease complicated by graves' disease and type 2 diabetes mellitus: report of two cases. Clin Neurol Neurosurg 2011; 113:325-9.
- 7) Noh BH, Cho SW, Ahn SY. Simultaneous occurrence of diabetic ketoacidosis, thyroid storm, and multiple cerebral infarctions due to moyamoya disease. J Pediatr Endocrinol Metab 2016;29:221-5.
- 8) Krebs A, Schmidt-Trucksäss A, Wagner J, Krebs K, Doerfer J, Schwab KO. Adult-like but regressive increase of intima-media thickness and roughness in a child with type 1 diabetes. Pediatr Diabetes 2005;6: 161-4.
- 9) American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes care 2007;30(1):S42-7.
- 10) Liu LL, Yi JP, Beyer J, Mayer-Davis EJ, Dolan LM, Dabelea DM, et al. Type 1 and type 2 diabetes in Asian and Pacific Islander U.S. youth: the SEARCH for Diabetes in Youth Study. Diabetes Care 2009;32 Suppl 2:S133-40.
- 11) Kobayashi T, Itoh T, Kosaka K, Sato K, Tsuji K. Time course of islet cell antibodies and beta-cell function in non-insulin-dependent stage of type I diabetes. Diabetes 1987;36:510-7.
- 12) Writing Group for the SEARCH for Diabetes in Youth Study Group, Dabelea D, Bell RA, D'Agostino RB Jr, Imperatore G, Johansen JM, Linder B, et al. Incidence of diabetes in youth in the United States. JAMA 2007;297:2716-24.
- 13) Klingensmith GJ, Pyle L, Arslanian S, Copeland KC, Cuttler L, Kaufman F, et al. The presence of GAD and IA-2 antibodies in youth with a type 2 diabetes phenotype: results from the TODAY study. Diabetes Care 2010;33:1970-5.