

[CASE REPORT]

Asymptomatic Pontine Lesion and Diabetic Amyotrophy after Rapid Improvement of Poor Glycemic Control in a Patient with Type 1 Diabetes

Yuri Shimizu¹, Junji Kozawa¹, Tomoaki Hayakawa¹, Yasuha Sakai¹, Takekazu Kimura¹, Tetsuhiro Kitamura¹, Sho Murase², Hisashi Tanaka³, Norikazu Maeda^{1,4}, Michio Otsuki¹, Takaaki Matsuoka¹, Hideki Mochizuki², Hiromi Iwahashi^{1,5} and Iichiro Shimomura¹

Abstract:

We herein report a 28-year-old woman with type 1 diabetes with an asymptomatic pontine lesion and diabetic amyotrophy. She had suffered from diabetes from 10 years old. Treatment in a hospital reduced the hemoglobin A1c level from 14.2% to 7.2% for approximately 2 months. She suffered from acute-onset pain and weakness of the lower limb muscles without central nervous system manifestations. Magnetic resonance imaging showed high-intensity lesions at the brainstem and lower limb muscles on T2-weighted images. These findings and symptoms gradually resolved. Rapid treatment of poor glycemic control might increase the risk of asymptomatic pontine lesions and diabetic amyotrophy.

Key words: asymptomatic pontine lesion, osmotic demyelination syndrome, magnetic resonance imaging, diabetic amyotrophy, type 1 diabetes, glycemic control

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Introduction

Previous large clinical trials have shown that appropriate glycemic control is needed to prevent the onset of diabetic complications or their worsening (1-4). However, a rapid improvement of poor glycemic control is a well-known cause of early worsening of retinopathy (5) or as a trigger of treatment-induced diabetic neuropathy (6, 7). To date, other negative aspects regarding the rapid improvement of glycemic control have not been clarified.

Pontine lesions are observed in various conditions, including osmotic demyelination syndrome (ODS) and central pontine myelinolysis (CPM), which are demyelinating disorders of the central nervous system (8, 9). ODS/CPM is often reported along with hyponatremia or its rapid correc-

tion (8, 9). In recent reports, diabetic patients have also presented with pontine lesions even in the absence of these obvious electrolyte disturbances with and without symptoms (10-13), although whether or not the etiology and pathogenesis are similar to those in typical ODS/CPM cases is unclear.

Diabetic amyotrophy is also called “diabetic lumbosacral radiculoplexus neuropathy” and occurs in approximately 1% of diabetic patients (14). It is considered to be derived from nervous ischemic injury caused by microscopic vasculitis (15). This injury typically accompanies acute or subacute, progressive, asymmetrical pain and weakness of the proximal lower limb muscles, and weight loss is often seen (15). What triggers this diabetic complication is unclear at present.

We herein report the first case of type 1 diabetes present-

¹Department of Metabolic Medicine, Graduate School of Medicine, Osaka University, Japan, ²Department of Neurology, Graduate School of Medicine, Osaka University, Japan, ³Department of Diagnostic and Interventional Radiology, Graduate School of Medicine, Osaka University, Japan, ⁴Department of Metabolism and Atherosclerosis, Graduate School of Medicine, Osaka University, Japan and ⁵Department of Diabetes Care Medicine, Graduate School of Medicine, Osaka University, Japan

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Correspondence to Dr. Junji Kozawa, kjunji@endmet.med.osaka-u.ac.jp

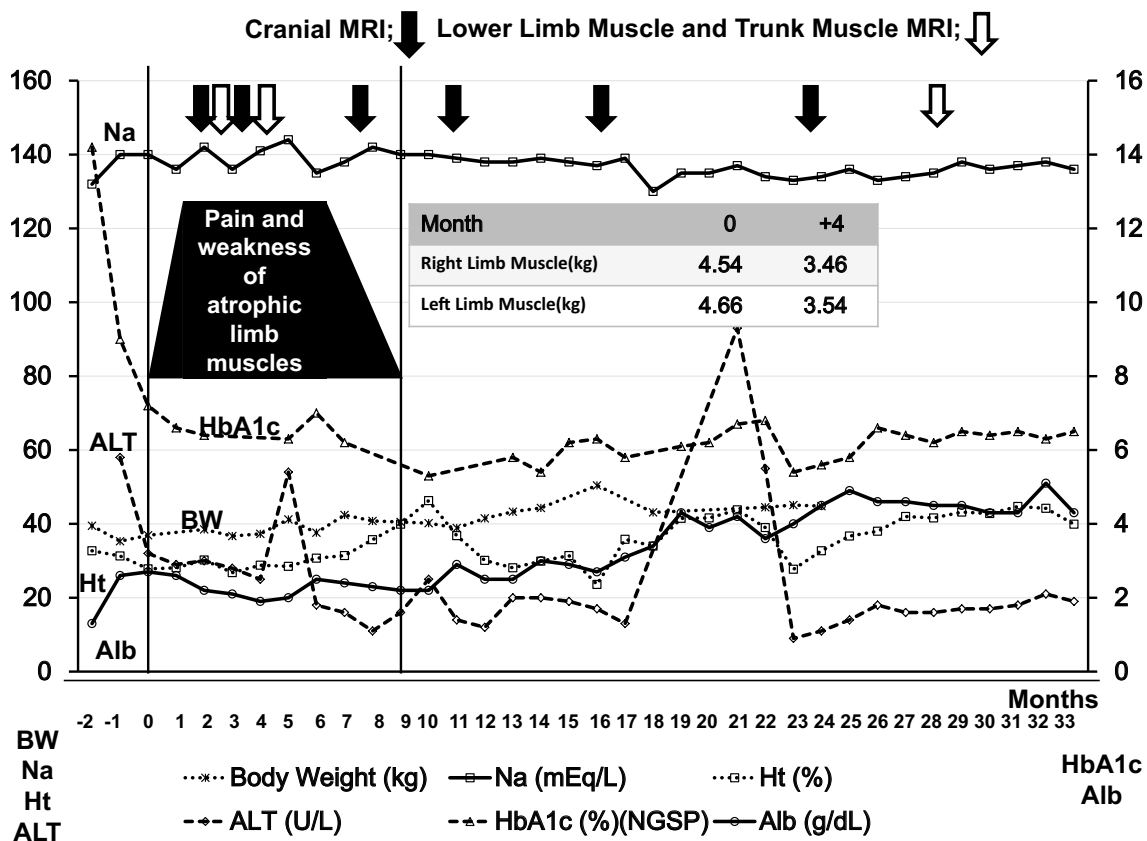


Figure 1. The clinical course. The horizontal axis shows the time course. “Zero month” refers to the onset of acute lower limb symptoms. The vertical axis shows the values of the body weight, serum sodium, hematocrit, alanine aminotransferase (ALT), HbA1c and serum albumin. The HbA1c value decreased from 14.2% to 7.2% for approximately 2 months. After discharge, she began to feel the acute onset of severe bilateral lower limb pain, bilateral lower limb weakness and gait disturbance. The elevated level of ALT nearly normalized and then slightly fluctuated. The values of serum sodium, albumin, hematocrit, and body weight also slightly fluctuated around the onset of the lower limb symptoms, but not markedly. The black and white arrows indicate the timing of cranial MRI and lower limb muscle MRI, respectively.

ing with an asymptomatic pontine lesion and diabetic amyotrophy almost simultaneously after the rapid treatment of poor glycaemic control.

Case Report

A 28-year-old woman with type 1 diabetes was admitted to our hospital for poor glycaemic control and severe hepatic dysfunction. She had been diagnosed with type 1 diabetes at 10 years old. She had diabetic complications, including peripheral neuropathy, proliferative retinopathy and diabetic nephropathy with a nephrotic state. For a few years, she had been consuming an unbalanced diet with restricted carbohydrates along with irregular and low-dose insulin injections and frequent snacks late at night, and her hemoglobin A1c (HbA1c) levels were around 9-14% (NGSP).

On admission, her height was 147.5 cm and body weight was 39.5 kg (body mass index 18.2 kg/m²). She showed severe bilateral lower limb edema. Her fasting plasma glucose and HbA1c levels were 429 mg/dL and 14.2%, respectively.

Her serum sodium level was 132 mEq/L, and her serum creatinine level was 0.63 mg/dL. Serum aspartate aminotransferase, alanine aminotransferase and γ -glutamyl transferase levels were 1,129, 928 and 564 U/L, respectively. We ruled out viral or autoimmune hepatitis as well as drug-induced hepatic damage. Her serum albumin level was 1.3 g/dL, and total daily uric protein was 4.7 g. A balanced diet without snacks and regular insulin injections in the hospital led to a decrease in glucose levels more quickly than we had expected, and we had to adjust the insulin dose. A diuretic was used to reduce her limb edema.

After 2 months of treatment in the hospital, the HbA1c level had decreased to 7.2% (Fig. 1), and her liver function was nearly normalized without specific medications. After discharge, she began to feel the acute onset of severe bilateral lower limb pain, which was relieved by the oral administration of acetaminophen. Two months after discharge, she was admitted again due to bilateral lower limb weakness and gait disturbance in addition to increased pain.

At the second admission, her Glasgow Coma Scale was

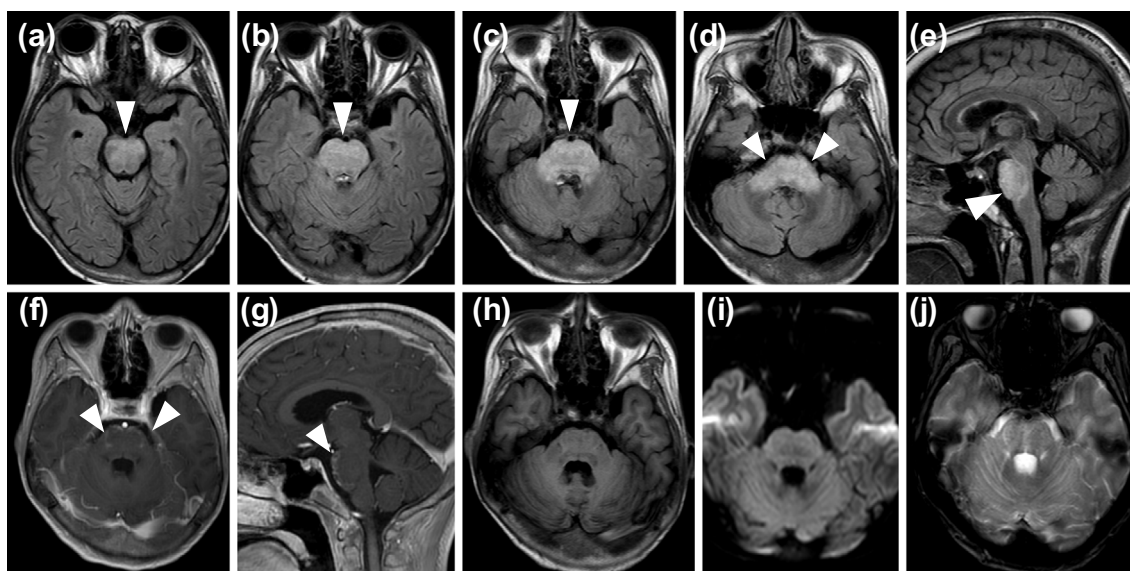


Figure 2. Cranial MRI findings. Two months after the onset of bilateral lower limb weakness and gait disturbance. The white arrow indicates a symmetric diffuse high-intensity lesion in the pons on fluid-attenuated inversion recovery (FLAIR) images (a-e). The lesion was peripherally enhanced in a T1-weighted contrast MRI image (f, g). T1-weighted (h), diffusion-weighted (i) and T2*-weighted images (j) showed no abnormal findings.

E4V5M6, and her body weight was 38.5 kg (body mass index 17.7 kg/m²). Her blood pressure was 121/91 mmHg, pulse rate was 109 beats per minute, and body temperature was 36.4°C. She showed slight anemia and decreased respiratory sounds because of bilateral pleural effusion. She had persistent pitting edema in her bilateral lower limbs with atrophic muscles and reduced muscle strength. Manual muscle testing of the iliopsoas and hamstring showed grade 3, whereas testing of the anterior tibialis and gastrocnemius showed grade 4. Regarding the neurological findings, except for muscle weakness, there were no cranial nerve abnormalities or pathological reflexes, such as jaw jerk reflex or Babinski's reflex.

Spinal magnetic resonance imaging (MRI) revealed no space-occupying lesions. However, cranial MRI findings were remarkable. Fluid-attenuated inversion recovery imaging revealed swelling and symmetric diffuse high signal intensity in the pons, which extended to the bilateral middle cerebellar peduncles (Fig. 2a-e). The lesion was peripherally enhanced on T1-weighted contrast images (Fig. 2f and g). T1-weighted (Fig. 2h), diffusion-weighted (Fig. 2i) and T2*-weighted (Fig. 2j) images showed no abnormal findings. Blood examinations showed no inflammation, no elevated muscle enzymes and no antibodies correlated with collagen diseases (Table). Regarding the neurological examination, a cerebrospinal fluid (CSF) test was negative for herpes simplex virus (HSV)-, Epstein-Barr virus (EBV)-, cytomegalovirus (CMV)- and varicella-zoster virus (VZV)-related DNA, aspergillus antigen, cryptococcus antigen, mycobacterium tuberculosis DNA, adenosine deaminase (ADA), soluble interleukin-2 receptor (sIL-2R), tumor cells and oligoclonal bands. There was no albuminocytologic dissociation. The

IgG index was 0.55 (<0.6). The CSF test showed that the concentration of cells was 1/μL, the amount of protein was 52 mg/dL, and the glucose level was 100 mg/dL when the plasma glucose was 194 mg/dL. Needle electromyography (iliopsoas muscle, tibial muscle) showed no myogenic changes. A nerve conduction study (median, ulnar, peroneal, tibial nerve) revealed polyneuropathy consistent with diabetic polyneuropathy, and the lower limb sensory nerve was dominantly disrupted. T2-weighted images of pelvis-to-thigh MRI showed a high signal intensity in the erector spinae muscles (Fig. 3a, b), pelvic floor muscles (Fig. 3c) and adductor and quadriceps muscles (Fig. 3d, e). Given these findings, she was diagnosed with an asymptomatic pontine lesion and diabetic amyotrophy, which occurred in almost the same period.

The pain was relieved by the oral administration of mexiletine hydrochloride. She started rehabilitation, and the lower limb pain, weakness and gait disturbance gradually improved. The abnormalities on cranial MRI did not change after 11 days (Fig. 4b) but decreased 1 month later (Fig. 4c). Slight abnormal signal intensity remained even after six and nine months (Fig. 4d and e). The abnormalities in the lower limb and pelvic floor muscle MRI had disappeared completely by 27 months from the onset (Fig. 5).

Discussion

Our patient presented with an asymptomatic pontine lesion and diabetic amyotrophy almost simultaneously after the rapid treatment of poor glycemic control. Some asymptomatic cases with pontine lesions have been reported as ODS/CPM (16-18), but the histological confirmation of de-

Table. Results of Laboratory Tests.

Complete Blood Count		Blood Chemistry			
WBC	4,080 / μ L	TP	5.6 g/dL	CRP	<0.04 mg/dL
RBC	297 \times 10 ⁴ / μ L	Alb	2.0 g/dL	Vit B1	3.0 μ g/L
Hb	8.9 g/dL	Na	139 mEq/L	Vit B12	3,515 pg/mL
Ht	28.5 %	K	5.0 mEq/L	Ferritin	61 ng/mL
MCV	96.0 fL	CL	106 mEq/L	Fe	22 μ g/L
MCHC	31.2 %	Ca	8.0 mg/dL	UIBC	213 μ g/L
Plt	28.2 \times 10 ⁴ / μ L	P	5.5 mg/dL		
Coagulation		Mg	2.4 mg/dL		
PT	98 %	BUN	28 mg/dL	Urinalysis	
APTT	32 second	Cr	0.71 mg/dL	pH	6.0
FDP	1.62 μ g/L	UA	3.7 mg/dL	specific gravity	1.014
Antibody		T.Bil	0.2 mg/dL	urobilinogen	normal
anti-nuclear antibody	(-)	AST	22 U/L	bilirubin	(-)
anti-SS-A, SS-B antibody	(-)	ALT	23 U/L	protein	(3+)
p-ANCA, c-ANCA	(-)	γ GTP	18 U/L	occult blood	(+)
anti-cardiolipin antibody	(-)	ALP	477 U/L	ketone body	(-)
anti-Tg antibody	(-)	CK	240 U/L	glucose	(+)
anti-TPO antibody	(-)	Myoglobin	52.7 ng/mL	WBC	(-)
anti-GM1 IgG antibody	(-)	Glucose	91 mg/dL	RBC	(-)
anti-GQ1b IgG antibody	(-)	HbA1c	6.4 %	granular casts	(2+)
		C-peptide	<0.1 ng/mL	epithelial casts	(+)
		TSH	7.25 μ U/L	protein	6.67 g/day
Immunoelectrophoresis		FT4	0.9 ng/dL	β 2MG	3,847 mg/mL
normal		FT3	2.3 pg/mL	NAG	60.9 U/gCr

WBC: white blood cells, RBC: red blood cells, Hb: hemoglobin, Ht: hematocrit, MCV: mean corpuscular volume, MCHC: mean corpuscular hemoglobin concentration, Plt: platelets, PT: prothrombin time, APTT: activated partial thromboplastin time, FDP: fibrinogen degradation products, anti-SS-A, SS-B antibody: anti-Sjögren's syndrome-A, B antibody, p-ANCA, c-ANCA: p-,c-anti-neutrophil cytoplasmic antibody, anti-Tg antibody: anti-thyroglobulin antibody, anti-TPO antibody: anti-thyroid peroxidase antibody, anti-GM1 IgG antibody and anti-GQ1b IgG antibody: Anti-ganglioside antibodies associated with Guillain-Barré syndrome and/or Fisher syndrome, TP: total protein, Alb: albumin, Na: sodium, K: potassium, Cl: chlorine, Ca: calcium, P: phosphorus, Mg: magnesium, BUN: blood urea nitrogen, Cr: creatinine, UA: uric acid, T.Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ GTP: γ -glutamyltransferase, ALP: alkaline phosphatase, CK: creatine kinase, HbA1c: hemoglobin A1c, TSH: thyroid stimulating hormone, FT4: free thyroxine, FT3: free triiodothyronine, CRP: C-reactive protein, Vit B1: vitamin B1, Vit B12: vitamin B12, Fe: iron, UIBC: unsaturated iron binding capacity, pH: potential of hydrogen, β 2MG: β 2-microglobulin, NAG: N-acetyl- β -D-glucosaminidase

myelination was not performed in those cases. Therefore, we simply described the cranial MRI abnormality in this case as a "asymptomatic pontine lesion". There have been no case reports showing pontine lesions or diabetic amyotrophy in association with the rate of glycemic control change. The findings in this case might clinically suggest that both the brainstem and lumbosacral plexus were vulnerable to rapid changes in glycemic control. The rapid improvement of glycemic control might increase the risk of pontine lesions and diabetic amyotrophy.

This case showed no obvious severe electrolyte abnormalities, but there were advanced diabetic complications, including nephropathy and neuropathy as well as pre-existing liver damage. This outcome was partly consistent with the findings of a previous report in which diabetic patients presented with ODS without obvious electrolyte disturbances, although they had complications such as hypertension and hepatorenal problems (10). It was speculated that diabetes mellitus itself or the pre-existing complications, including

malnutrition, observed in this case might have exaggerated the development of the pontine lesion (10) independently from the rapid improvement of the glycemic control, although the mechanism or underlying pathophysiology is unclear. While the present and previous cases (16-18) showed no central nervous system manifestations, others with diabetes have shown serious central nervous system manifestations (11, 13). We should not overlook asymptomatic pontine lesions that can occur in diabetes patients, especially in those with the complications described above, and try to identify the possible pathophysiology between patients with and without manifestations.

Cranial MRI in this case showed diffuse high-intensity lesions in the pons on T2-weighted images that were peripherally enhanced. These findings were different from those observed in typical cases of ODS involving the central pons, which manifest as a "trident" or "bat-wing"-shaped abnormality on MRI (13). Some previous cases with diabetes also showed massive pontine lesions (10). This outcome suggests

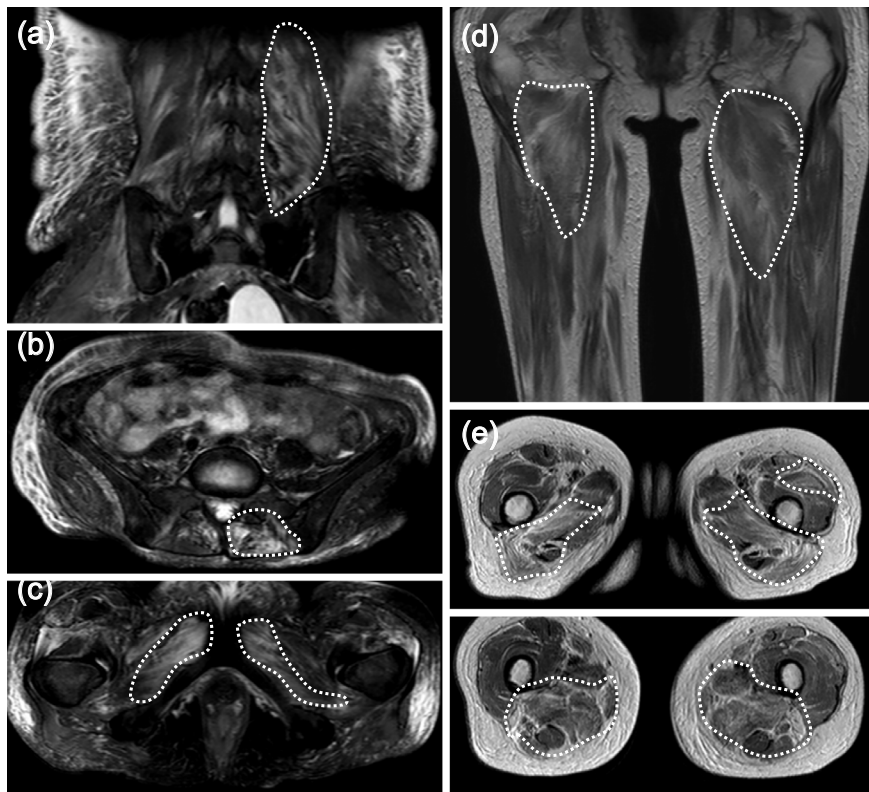


Figure 3. Lower limb muscle MRI findings at 6 months after the onset. T2-weighted fat-suppressed coronal (a) and transverse (b) images of the erector spinae muscles are shown. A T2-weighted fat-suppressed transverse image of the pelvic floor muscles (c) is shown. T2-weighted coronal (d) and transverse (e) images of the adductor muscles and quadriceps muscles are also shown. The high-signal-intensity lesions in these muscles are surrounded by dashed lines.

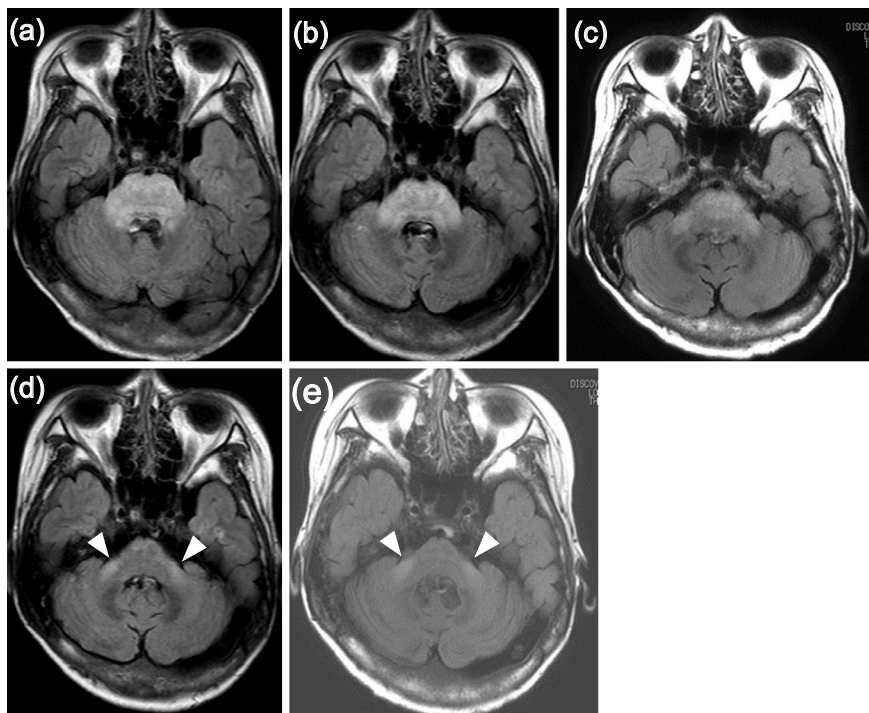


Figure 4. Cranial MRI findings. FLAIR transverse images on admission (a) and after 11 days (b), 1 month (c), 6 months (d) and 9 months (e) are shown. The high-signal-intensity lesion gradually diminished in parallel with her symptoms after 1 month (c) but still slightly persisted at 6 and 9 months (d, e). The white arrowheads indicate the remaining high-signal-intensity lesions.

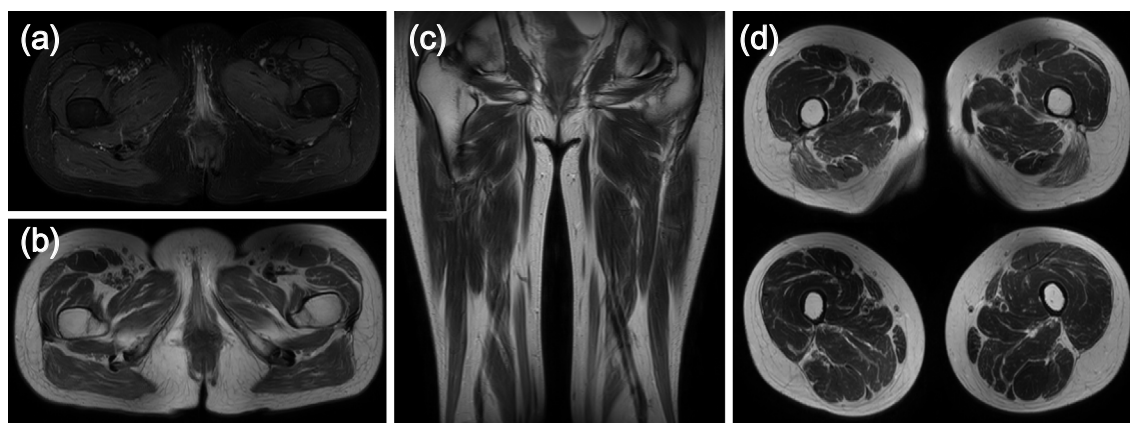


Figure 5. Lower limb muscle MRI findings 27 months after onset. T2-weighted fat-suppressed (a) and T2-weighted (b) images of pelvic floor muscles, T2-weighted coronal (c) and transverse (d) images of the adductor and quadriceps muscles are shown. The high-intensity lesions disappeared.

that diabetes mellitus itself might affect the extent of the pontine lesion, although the exact mechanism involved is unclear. Given the high-intensity signals observed on T2-weighted images, one possible mechanism is edema caused by some inflammation or osmotic changes induced by rapid changes in glycemic control.

This patient showed somewhat atypical clinical manifestations for diabetic amyotrophy. She showed symmetrical symptoms, and apparent weight loss was not seen on admission. Pitting edema and pleural effusion derived from nephrotic syndrome might have obscured the weight loss in this case. Indeed, her body weight decreased to 36.2 kg when her edema and pleural effusion had almost disappeared. High-intensity signals were observed on T2-weighted images of lower limb muscles, suggesting muscle edema caused by acute denervation, and similar results were recently reported in a case of diabetic amyotrophy (19) that were consistent with the findings of this case. MRI in cases with suspected but atypical manifestation of diabetic amyotrophy might be a useful tool for making a diagnosis.

In conclusion, we report a patient with type 1 diabetes who presented with an asymptomatic pontine lesion and diabetic amyotrophy after the rapid treatment of poor glycemic control. The gradual improvement of glycemic control might be a safe approach to avoid these complications.

The authors state that they have no Conflict of Interest (COI).

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