CASE REPORT

KETOACIDOSIS ACCOMPANIED BY EPILEPTIC SEIZURES IN A PATIENT WITH DIABETES MELLITUS AND MITOCHONDRIAL MYOPATHY, ENCEPHALOPATHY, LACTIC ACIDOSIS AND STROKE-LIKE EPISODES (MELAS)

S. NAKAMURA (1), M. YOSHINARI (1), M. WAKISAKA (1), H. KODERA (2), Y. DOI (1), H. YOSHIZUMI (1), T. ASANO (1), M. IWASE (1), F. MIHARA (3), M. FUJISHIMA (1)

SUMMARY

- We herein report a rare case of MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) and diabetes mellitus with ketoacidosis. An 18-year-old female patient was diagnosed to have diabetes mellitus and insulin therapy was thereafter initiated. At 26 years of age, she was hospitalized for diabetic ketoacidosis, soon followed by a loss of consciousness, left-sided dysmetria, and ataxic speech. MELAS was diagnosed because of the presence of ragged red fibers in a muscle biopsy. At 33 years of age, she was admitted to our hospital because of ketoacidosis and partial status epilepticus. A blood gas examination revealed as follows; arterial pH, 6.88; bicarbonate, 2.1 mmol/l; base excess – 29.8 mmol/l. The serum level of glucose had also increased to 30 mmol/l. The serum levels of lactate and β-hydroxybutyrate were elevated to 11.4 mmol/l and 1,990 µmol/l, respectively. Ketoacidosis improved by fluid replacement and continuous intravenous insulin infusion. A brain MRI demonstrated hyperintensity areas on FLAIR images in the bilateral temporal lobes and the cerebellum. A proton MRS demonstrated the abnormal lactate accumulation in the bilateral temporal and occipital lobes. Since epileptic seizures are rare in patients with diabetic ketoacidosis, such seizures may indicate the existence of MELAS syndrome.

Key-words: ketoacidosis, stroke-like episodes, seizure, MELAS, diabetes mellitus.

RéSUMÉ - Acidocétose avec crises comitiales chez un patient diabétique avec myopathie mitochondriale, encéphalopathie, acidose lactique évocant un AVC.

Nous rapportons ici l’observation rare d’un MELAS (myopathie mitochondriale, encéphalopathie, acidose lactique et équivalent d’AVC) associé à un diabète sucré avec cétoacidose. Une femme a révélé un diabète sucré à l’âge de 18 ans et une insulinothérapie alors instaurée. À l’âge de 26 ans, elle est hospitalisée pour cétoacidose diabétique, bientôt suivie d’une perte de connaissance, d’une dysmétrie gauche, et d’une altération ataxique. Un MELAS est diagnostiqué en raison de la présence de fibres rouges déchiquetées sur la biopsie musculaire. À l’âge de 33 ans, elle est admise dans notre hôpital pour cétoacidose et épilepsie partielle. Les gaz du sang montrent : pH artériel, 6,88 ; bicarbonate, 2,1 mmol/l ; trou anionique – 29,8 mmol/l. La glycémie est augmentée à 30 mmol/l. Les taux sériques de lactate et de β-hydroxybutyrate sont élevés respectivement à 11,4 mmol/l et 1,990 µmol/l. La cétoacidose est corrigée par réhydratation et insulinothérapie continue intraveineuse. Une IRM cérébrale démontre des zones d’hiperintensité sur les images FLAIR dans les deux lobes temporaux et le cervelet. Une spectroscopie RMN à protons révèle une accumulation anormale de lactate dans les deux lobes temporaux et occipitaux. Dans la mesure où les convulsions épileptiques sont rares lors de la cétoacidose diabétique, leur survenue peut signifier l’existence d’un syndrome MELAS.

Mots-clés : cétoacidose, équivalents d’AVC, convolution, MELAS, diabète sucré.

ELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) is one of the subgroups of mitochondrial encephalopathy, characterized by the presence of stroke-like episodes, in addition to the presence of ragged red fibers on muscle biopsy specimens, a short stature, cardiomyopathy, hearing loss and diabetes mellitus [1]. This syndrome is associated with the substitution of guanine for adenine at position 3243 of the leucine tRNA gene of mitochondrial DNA, which was described in approximately 80% of cases [2]. This mitochondrial DNA mutation has also been associated with diabetes mellitus and hearing loss [3]. Diabetic ketoacidosis is the metabolic disturbance that results from either an absolute or relative insulin deficiency. Although diabetic patients associated with this mitochondrial DNA mutation have an impaired insulin secretory capacity [3], there are few reports of diabetic ketoacidosis in patients with MELAS [4, 5]. We herein present a rare manifestation of ketoacidosis and partial status epilepticus in a patient with MELAS and diabetes mellitus.

**CASE PRESENTATION**

Diabetes mellitus was diagnosed in an 18-year-old female patient when she visited a clinic due to symptoms of thirst, polyuria, polydipsia and general fatigue. Insulin therapy was thus initiated because of severe hyperglycemia at that time. At the age of 26, she developed nausea, vomiting and dysesthesia in the legs. Four months later, she was admitted to a hospital because of diabetic ketoacidosis and thereafter developed a consciousness loss, left-sided dysmetria, and ataxic speech. She was suspected to have MELAS since a muscle biopsy was performed and revealed the presence of ragged red fibers. At the age of 29, she was first admitted to our hospital because of further examination of her disease. A T2-weighted MR image demonstrated hyperintensity areas in the bilateral cerebral hemisphere and an atrophy of the cerebellum and brain stem. Since an analysis of her mitochondrial DNA prepared from peripheral leukocytes revealed the presence of a mutation in the mitochondrial tRNA<sup>LEU(UUR)</sup> gene at bp 3243, she was diagnosed to have MELAS. The serum level of C-peptide was 1.1 ng/ml at 6 minutes after a glucagon injection, which thus suggested an impairment of insulin secretion. Her glycemic control was improved by intensive insulin therapy consisting of 4 daily injections. She failed to comply with her insulin injection regimen at 33 years of age due to symptoms of nausea and vomiting. Three months later, she experienced the sudden onset of partial status epilepticus and was therefore admitted secondarily to our hospital. The epilepsy was characterized by focal jerking of the right hand always leading to secondary generalization. Both her mother and brother also suffered from diabetes mellitus and hearing loss. Her mother died of diabetic ketoacidosis at the age of 51. Her sister had had growth retardation with gait disturbance and died after an episode of high fever and convulsion at the age of 9.

On admission, a physical examination showed the following: height, 153.9 cm; body weight, 37.1 kg; blood pressure, 88/48 mmHg; and pulse rate, 106 beats/min. The optic fundi showed pre-proliferative diabetic retinopathy. The thyroid gland was diffusely enlarged. The lungs, heart, and abdomen were normal. The deep tendon reflexes were diminished. A blood gas examination showed severe metabolic acidosis; arterial pH, 6.88; bicarbonate, 2.1 mmol/l; and base excess -29.8 mmol/l. The serum glucose level had increased to 30 mmol/l. A urinalysis disclosed overt ketonuria and glycosuria. The seizures subsided after the intravenous administration of anticonvulsant drugs. Regular insulin was thereafter administered as a continuous intravenous infusion at a starting dose of 8U/h. Fluid substitution was begun with 500 ml/h saline. The serum levels of lactate and β-hydroxybutyrate were elevated to 11.4 mmol/l (normal range, 0.3 to 1.6 mmol/l) and 1,990 µmol/l (< 85 µmol/l), respectively, at 1 hour following treatment initiation. The arterial pH rose to 7.29, the plasma bicarbonate level increased to 10.3 mmol/l, while the plasma glucose decreased to 15.7 mmol/l 4 hours later. The elevated serum β-hydroxybutyrate was reduced in parallel to the increase of arterial pH. Twenty-four hours after admission, the arterial pH normalized to 7.37 and the serum level of β-hydroxybutyrate reduced to 190 µmol/l. However, the serum level of lactate was still elevated at 6.6 mmol/l. When she was able to take meals 2 days following admission, subcutaneous insulin injection and oral administration of phenytoin was started. An electroencephalogram (EEG) 3 days after admission showed α waves and occasional δ waves predominantly in the occipital areas. The FLAIR MR images (FLAIR sequence can null the signals from the cerebrospinal fluid and yield heavily T2-weighted images) obtained 4 days after stroke-like episode demonstrated new hyperintensity areas in the bilateral temporal lobe in addition to the previous MR findings obtained 5 years before. The lesion in the left temporal lobe was larger than that in the right temporal lobe (Fig. 1). The FLAIR MR images revealed the disappearance of the hyperintensity areas in the bilateral temporal lobe 35

**ABBREVIATIONS**

MELAS: mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes
MRI: magnetic resonance imaging
FLAIR: fast fluid-attenuated inversion recovery
MRS: magnetic resonance spectroscopy
days after stroke-like episode (Fig. 2). The proton MR spectroscopy demonstrated an accumulation of lactate in the bilateral temporal and occipital lobes 35 days after stroke-like episode (Fig. 3). An audiogram revealed bilateral sensorineural hearing loss. Both an electrocardiogram and echocardiogram showed no cardiac abnormality. After discharge, she was treated with phenytoin for two years without any epileptic seizures.

## DISCUSSION

There have been few reports published so far on MELAS patients who developed diabetic ketoacidosis [4, 5]. Epileptic seizures were also present in these cases. The cause of the seizures, however, was not described in these case reports. Epileptic seizures are rare in patients with diabetic ketoacidosis while, in contrast, they show a higher frequency in patients with diabetic non-ketotic hyperglycemia [6]. It has been suggested that ketosis and acidosis associated with starvation have an anticonvulsant effect and therefore a ketogenic diet is thought to be beneficial for epileptic children, although the exact mechanism for this is still not clearly understood. As a result, the presence of seizures in patients with ketoacidosis may indicate the existence of organic neurological disease.

Epileptic seizures are the most common manifestations of MELAS and are considered to be one type of a stroke-like episode, which may also show either alternating hemiparesis, hemianopsia, or cortical blindness [1]. Although the transient MRI hyperintensity of temporal region in our patient at second episode of diabetic ketoacidosis might suggest edema after status epilepticus, we considered these abnormalities likely to be stroke-like lesions because the proton MRS showed an extremely high accumulation of lactate in the left temporal lobe [7, 8]. Proton MRS can show stroke-like regions to be the accumulation of lactate even though the MRI findings are normal or nonspecific [8]. Although our patient did not show epileptic seizure at first episode of diabetic ketoacidosis, we supposed that cerebellar ataxia at first diabetic ketoacidosis might be also stroke-like episodes since MRI obtained at the age of 29 demonstrated hyperintensity areas in the bilateral cerebellar hemisphere.

The pathophysiology of stroke-like episodes in MELAS is still not well understood. Several hypotheses have been raised to explain such episodes, including an energy failure caused by an impaired oxidative metabolism secondary to defects in the electron transport chain and brain ischemia related to vascular abnormalities. An analysis of the cerebral blood vessels in a few autopsied patients with MELAS demonstrates a striking increase in the number of mitochondria in the smooth muscle and endothelial cells, which are the most prominent in the pial arterioles and small arteries [9]. Since these small arterial vessels play an important role in the autoregulation of the cerebral blood flow, a failure in their function could lead to ischemic changes in the brain, resulting in stroke-like episodes.
flow, Ohama et al. [9] postulated that there might be an impairment in the autoregulation secondary to mitochondrial angiopathy. Although limited information is available on the microvascular hemodynamics of the cerebral blood flow during diabetic ketoacidosis, a transcranial doppler study has suggested the presence of vasoparalysis in cerebral circulation [10]. The ketoacidosis and hypotension observed in our patient may promote an impairment of the cerebral autoregulatory circulation, thus resulting in stroke-like episodes associated with mitochondrial angiopathy.

In summary, we herein reported a rare case of MELAS who developed diabetic ketoacidosis and seizures. Diabetic ketoacidosis may precipitate stroke-like episodes in MELAS patient. Since seizures are rare in diabetic ketoacidosis, such seizures may indicate the existence of MELAS syndrome.

REFERENCES


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FIG. 3. A proton MR spectroscopy spectrum in the left temporal lobe obtained 35 days after stroke-like episodes shows a peak at 1.3 ppm [4], thus indicating an accumulation of lactate. 1 indicates choline; 2, creatine; 3, N-acetyl aspartate; 4, lactate.