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Letter to the Editor

Bilateral Basal Ganglia Hyperintensities may not only be Attributable to Metformin-Associated Lactic Acidosis

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Letter to the Editor

We read with interest the article by Fukata *et al*. about a 67-year-old man with diabetes (treated with vildagliptin, luseogliflozin, and metformin) and nephropathy (requiring dialysis for four years) [1]. He suffered from somnolence, dysarthria, and immobility, which were attributed to lactic acidosis after his metformin dose was increased from 500 mg/day to 750 mg/day two months prior to the event [1]. Since cerebral MRI showed bilateral swelling of the basal ganglia, metformin-associated lactic acidosis was diagnosed, and metformin was discontinued [1]. Discontinuation of the medication resulted in clinical and radiological improvement [1]. The study is promising, but several points warrant discussion.

First, other causes of lactic acidosis were not adequately ruled out [1]. Although metformin is a known cause of lactic acidosis, other potential causes must be carefully excluded. In general, lactic acidosis can be caused by hypoxic factors (e.g., shock, hypoxia due to respiratory failure, carbon monoxide poisoning, physical overexertion) or non-hypoxic factors (e.g., medications such as antiretroviral drugs, linezolid, propofol, isoniazid, paracetamol), liver failure, uncontrolled diabetes (ketoacidosis), HIV, lymphoma, alcohol or drug abuse, severe thiamine deficiency, mitochondrial diseases) [2].

Second, the nature of the basal ganglia hyperintensity in the diffusion-weighted MRI (DWI) images was not sufficiently clarified [1]. Were ischemic stroke, cerebral venous sinus thrombosis, cerebral hypoxia, extrapontine myelinolysis, encephalitis, hepatic encephalopathy, posterior reversible cerebral syndrome (PRS), Leigh syndrome, or Creutzfeldt-Jakob disease completely ruled out [3]? The results of ADC maps, susceptibility-weighted imaging (SWI), oxygen extraction fraction (OEF), and perfusion-weighted imaging (PWI) would have been helpful in clarifying the nature of the basal ganglia lesions. The findings of contrast-enhanced magnetic resonance angiography (MRA) should also be reported.

Third, the cerebrospinal fluid (CSF) lactate level was not measured [1]. The lactate concentration in the cerebrospinal fluid (CSF) can be determined either by direct measurement of the CSF lactate or by magnetic resonance spectroscopy (MRS) [4]. To correlate the imaging abnormalities with lactic acidosis, it would have been necessary to also detect lactic acidosis in the brain.

Fourth, the patient did not have an electroencephalogram (EEG) to determine whether he had experienced an unnoticed seizure the night before admission. Were there signs of tongue biting, or did he report urinary incontinence? A seizure could also explain the increase in creatine kinase to 2715 U/L. Were causes other than seizure and hypoglycemia ruled out as the cause of hyper-CKemia?

Fifth, we disagree with the statement that ketoacidosis could not be confirmed due to the patient's anuria [1]. Ketone bodies can also be detected in serum.

Sixth, comorbidities and concomitant medications were not documented in detail. Did the patient have any other comorbidities besides diabetes or diabetic nephropathy?

Seventh, it was not explained why the lactic acidosis only occurred two months after the metformin dose was increased from 500 mg to 750 mg/day and not earlier. Did renal function deteriorate during these two months? Why did the symptoms not appear earlier?

Eighth, it was not explained what is meant by “swollen basal ganglia” [1]. Do the authors mean cytotoxic or vasogenic edema? Was the volume of the basal ganglia actually increased?

Finally, no reference values were given in Table 1 [1]. This makes it difficult to assess which of the presented values were elevated and which were normal. The HbA1c value is also missing.

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