The Journal of Emergency Medicine, Vol. 57, No. 5, pp. e153–e156, 2019

0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2019.06.047

Clinical Communications: Adult

REVERSIBLE ACUTE BLINDNESS IN SUSPECTED METFORMIN-ASSOCIATED LACTIC ACIDOSIS

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☐ **Abstract—Background: Metformin is commonly used for the treatment of type 2 diabetes mellitus. Renal insufficiency is one of the contraindications for its use. Inadvertent prescription in patients with renal insufficiency may lead to metformin-associated lactic acidosis (MALA), which is associated with a high risk of mortality. Consequently, the early recognition and management of MALA is essential. Case Report: We present the case of a 68-year-old man who had reversible blindness resulting from severe lactic acidosis. On presentation, he was alert, oriented, and had no complaints except mild abdominal discomfort and blindness. He denied any history of trauma or drug abuse. The results of the laboratory studies showed severe metabolic acidosis with a high anion gap and increased levels of serum creatinine. There were no predisposing ocular or neurologic lesions that could have induced the blindness. Although the blood levels of methanol, ethanol, and metformin were not estimated, correction of acidosis and hemodialysis led to a complete recovery. Why Should an Emergency Physician Be Aware of This?: Rarely, transient blindness may occur in patients with fatal severe metabolic acidosis. Evaluation for the presence of metabolic acidosis and a detailed medical history are essential in the management of acute blindness in such patients.** © 2019 Elsevier Inc. All rights reserved.

☐ **Keywords—metformin; blindness; lactic acidosis**

Ethics statement: Informed consent was obtained from the patient for this case report.

INTRODUCTION

Metformin is commonly prescribed for patients with type 2 diabetes mellitus. However, its use in patients with decreased renal function may lead to metformin-associated lactic acidosis (MALA) (1–3). States of severe metabolic acidosis are usually accompanied by unstable vital signs and high mortality (1–4). Therefore, determination of the cause of acidosis has an impact on patient prognosis. Severe metabolic acidosis may cause transient blindness in a few cases (5–8). Diabetic or alcoholic ketoacidosis and MALA are the most commonly encountered causes of reversible blindness associated with acidosis. The mechanism of acidosis-induced transient blindness has not yet been clearly identified (9–11). In previous reports, unstable vital signs were usually noted along with the blindness (5–8). However, in our case, distinct from other reported cases, the initial vital signs were relatively stable. In routine practice this would usually indicate blindness from ocular or cerebrovascular disease, and consequently, delay the management of metabolic acidosis, with fatal consequences. Here, we present the case of a 68-year-old man with acute-onset blindness due to severe metabolic lactic acidosis.

RECEIVED: 14 January 2019; FINAL SUBMISSION RECEIVED: 5 March 2019;
ACCEPTED: 29 June 2019

CASE REPORT

A 68-year-old man with a history of type 2 diabetes and hypertension was brought to the Emergency Department (ED) with a complaint of complete binocular blindness of acute onset. He noticed his blindness on waking up in the morning, an hour prior to being admitted to the ED. On the evening prior to admission, he ate sushi for dinner, and drank a small amount of alcohol (ethanol) with his family. He started having nausea, vomiting, and dizziness, starting about 3 h after dinner. However, he did not have these symptoms on admission. He and his family denied any history of trauma or drug abuse, including methanol, salicylate, ethylene glycol, or isopropyl alcohol. His medications included telmisartan 80 mg, amlodipine 5 mg, glimepiride 2 mg, aspirin 100 mg, and metformin hydrochloride 1000 mg a day.

On presentation, his blood pressure was 104/57 mm Hg, heart rate 86 beats/min, respiratory rate 18 breaths/min, temperature 34.3°C, and oxygen saturation was 98%, on room air. The patient was alert, oriented, and complained of only mild abdominal discomfort, and blindness. He had no signs of trauma on the head or body. No focal neurological deficits except ocular findings were noted. Vision was impaired, and he could not perceive any light, or hand movements. Both pupils were small and equal in size but didn't show any direct or indirect light reflexes. Fundoscopic examination revealed bilateral diabetic retinopathy, which was not severe enough to cause acute blindness.

The patient's laboratory data are shown in Table 1. A severe high anion gap metabolic lactic acidosis was noted, with associated renal insufficiency. Blood tests for liver function were normal. His baseline serum creatinine level was 0.75 mg/dL 3 years prior. Magnetic resonance imaging and angiography for evaluation of ocular, periocular, and intracranial lesions revealed nothing remarkable except for an old right frontal lacunar infarct. The blood levels of ethanol, methanol, ethylene glycol, isopropyl alcohol, and metformin could not be estimated, owing to lack of these facilities at our hospital.

The initial management included treatment for acidosis with intravenous crystalloids and sodium bicarbonate, with control of blood glucose. Hemodialysis was subsequently performed via the right internal jugular vein. His visual acuity and light reflexes recovered with correction of acidosis (Table 1, Figure 1). He was admitted to the nephrology ward after hemodialysis, for conservative management and for control of blood glucose.

He was discharged with his usual vision and condition, 6 days after admission, and has been under the management of the endocrinology and ophthalmology outpatient clinics at our institute.

DISCUSSION

Although the occurrence of MALA is very rare, it is extremely likely to have fatal outcomes (1–3). The present guideline for metformin prescription warns against its use in males and females with serum creatinine levels of 1.5 mg/dL or higher and 1.4 mg/dL or higher, respectively. However, improper administration is not uncommon (12–14).

The biguanide class of drugs, including metformin, increase the lactate levels of plasma, mainly by inhibiting mitochondrial respiration in the liver (15). Particularly in cases where renal impairment is accompanied by cirrhosis, sepsis, or shock, the metabolism of lactate is dysfunctional, and the likelihood of development of MALA is higher (15). It is, therefore, essential to be cautious about the development of MALA in patients taking metformin.

The diagnostic criterion of MALA is "hyperlactatemia, caused solely by metformin," and is defined by a serum lactate level of 5 mmol/L or higher, a blood pH below 7.35, and metformin assay showing drug levels higher than 5 mg/L (16). The diagnostic criteria of MALA include the measurement of plasma concentrations of metformin, but there are few hospitals that have adequate infrastructure, and this test is also time consuming (17). It is, therefore, impossible to measure blood concentrations of metformin in routine clinical practice. Consequently, MALA should be suspected in patients with a history of metformin intake, irrespective of whether plasma levels of metformin are known (17–20). In our case, although the plasma concentration of metformin was not estimated, treatment for MALA was instituted immediately, based on the history of metformin intake, the presence of metabolic acidosis, and renal insufficiency, with successful results.

According to previous research and some case reports, blindness in MALA might be caused by severe acidosis (5–8). However, the definite mechanism of transient blindness caused by acidosis is not yet known. According to some animal studies, the retinal horizontal cells are very sensitive to changes in pH, with uncoupling in the event of acidosis. Photoreceptor-transmission to the visual neurons may be interrupted, resulting in blindness (9–11).

Unlike in the other reports, this patient had stable vital signs, and the only symptoms were blindness and mild gastrointestinal discomfort. It may prove difficult to come to the correct diagnosis in the absence of indicative clinical features, which may delay management of acidosis. In this case, the presence of acidosis and the patient's history of metformin were confirmed on presentation to the ED, which facilitated timely management.

Table 1. Laboratory Data and Ocular Findings

	Time from Emergency Department Arrival				
	0 h (VBGA)	2 h	4 h	7 h (After HD)	9 h (Ward)
Arterial blood gas					
pH	6.78	6.93	7.11	7.39	7.49
PCO_2 (mm Hg)	26	16	18	27	30
PO_2 (mm Hg)	38	120	77	56	111
Base excess (mmol/L)	< −30.0	−27.5	−21.8	−7	0.4
Bicarbonate (mEq/L)	4	3.4	5.7	16.3	22.9
Serum					
Lactate (mmol/L)	> 11				1.7
BUN (mg/dL)	36.9			26.7	29.1
Creatinine (mg/dL)	2.31			1.56	1.48
Sodium (mEq/L)	141.1	139.0		137.1	138.3
Potassium (mEq/L)	5.8	5.8		4.3	4.8
Glucose (mg/dL)	64	325	371	309	321
Calculated data					
Anion gap (mmol/L)	37.9	35.6		18.4	10.9
eGFR (CKD-EPI Cr, mL/min/1.73 m^2)	28.0			45.0	47.9
Ocular finding					
Visual acuity (Rt/Lt; near vision test)	Blind	Light perception	$\frac{20}{400}/\frac{20}{400}$	$\frac{20}{70}/\frac{20}{70}$	
Pupil size (Rt/Lt, mm)	2/2	3/3	4/4	4/4	
Light reflex	No	Sluggish	Normal	Normal	

VBGA = venous blood gas analysis; HD = hemodialysis; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; CKD-EPI Cr = chronic kidney disease-epidemiology collaboration creatinine equation.

Ophthalmic evaluation and brain imaging were also performed simultaneously, to exclude other causes. As per our knowledge, this is the first case report in Korea, on transient blindness in a patient with metformin-associated lactic acidosis.

In conclusion, metabolic disease can bring about acute blindness. In patients with sudden blindness, with the presence of conditions predisposing to acidosis, it would be prudent to manage the acidosis urgently, without waiting for results of other examinations. Moreover, metabolic acidosis in a patient with a history of metformin intake should suggest the possibility of MALA, necessitating immediate management. And further study about reversible blindness-associated severe metabolic acidosis will be needed.

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

MALA can occur as a complication of metformin, commonly used in the treatment of type 2 diabetes mellitus. MALA has been reported in several cases with a high mortality and can cause reversible acute blindness. However, very few patients are referred for blindness as

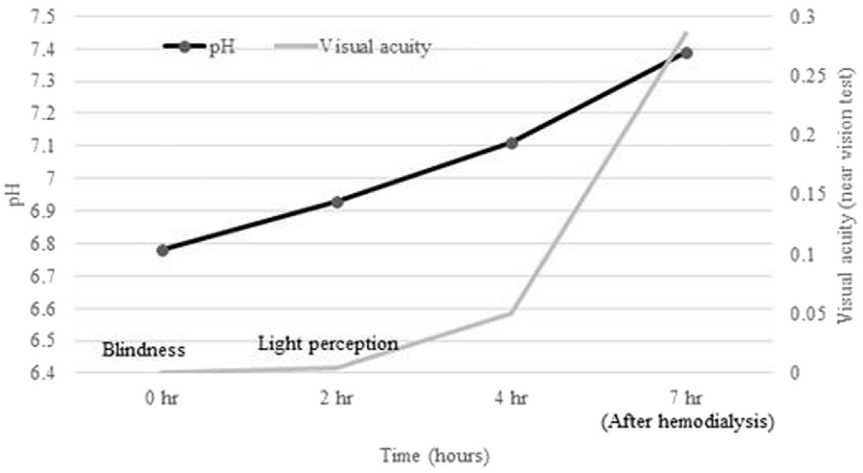

Figure 1. Visual acuity and pH changes according to the metabolic acidosis management. Visual acuity was improved with acidosis correction.

the chief complaint. There is also a risk of delayed treatment due to ophthalmic examinations in patients with relatively stable vital signs, despite presenting severe metabolic acidosis. Emergency physicians should be aware that MALA may cause acute blindness, vision can be recovered by treatment of acidosis, and stable vital signs may also occur in severe metabolic acidosis.

REFERENCES

1. Cryer DR, Nicholas SP, Henry DH, Mills DJ, Stadel BV. Comparative outcomes study of metformin intervention versus conventional approach the COSMIC Approach Study. Diabetes Care 2005;28:539–43.
2. Stang M, Wysowski DK, Butler-Jones D. Incidence of lactic acidosis in metformin users. Diabetes Care 1999;22:925–7.
3. Chang C, Sakaguchi M, Dolin P. Epidemiology of lactic acidosis in type 2 diabetes patients with metformin in Japan. Pharmacoepidemiol Drug Saf 2016;25:1196–203.
4. Gunnerson KJ, Saul M, He S, Kellum J. Lactate versus nonlactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. Crit Care Med 2006;10:R22.
5. Feeney C, Muller M, Bryzman S, Nakada T. Reversible blindness associated with alcoholic ketoacidosis: pseudomethanol intoxication. J Emerg Med 1998;16:597–9.
6. Pareek J, Trivedi J. Reversible blindness associated with severe diabetic ketoacidosis. Glob J Obes Diabetes Metab Syndr 2017;4:66–7.
7. Cigarrán S, Rodriguez ML, Pousa M, Menéndez H, Mendez MJ. Transient vision loss in a patient with severe metformin–associated lactic acidosis. QJM Int J Med 2012;105:781–3.
8. Kreshak AA, Clark RF. Transient vision loss in a patient with metformin-associated lactic acidosis. Am J Emerg Med 2010;28:1059.e5–7.
9. Barnes S, Merchant V, Mahmud F. Modulation of transmission gain by protons at the photoreceptor output synapse. Proc Natl Acad Sci U S A 1993;90:10081–5.
10. Hampson EC, Weiler R, Vaney DI. pH-gated dopaminergic modulation of horizontal cell gap junctions in mammalian retina. Proc Biol Sci 1994;255:67–72.
11. Harsanyi K, Mangel SC. Modulation of cone to horizontal cell transmission by calcium and pH in the fish retina. Vis Neurosci 1993;10:81–91.
12. Emslie-Smith AM, Boyle DI, Evans JM, Sullivan F, Morris AD, DARTS/MEMO Collaboration. Contraindications to metformin therapy in patients with Type 2 diabetes–a population-based study of adherence to prescribing guidelines. Diabet Med 2001;18:483–8.
13. Sulkin TV, Bosman D, Krentz AJ. Contraindications to metformin therapy in patients with NIDDM. Diabetes Care 1997;20:925–8.
14. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care 2011;34:1431–7.
15. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: current perspectives on causes and risk. Metabolism 2016;65:20–9.
16. Lalau J-D, Kajbaf F, Protti A, Christensen MM, Broe MED, Wiernsperger N. Metformin-associated lactic acidosis (MALA): moving towards a new paradigm. Diabetes Obes Metab 2017;19:1502–12.
17. Nguyen H-L, Concepcion L. Metformin intoxication requiring dialysis. Hemodial Int 2011;15:S68–71.
18. Krowl L, Al-Khalisy H, Kaul P. Metformin-induced lactic acidosis (MILA): review of current diagnostic paradigm. Am J Emerg Med 2018;36:908.e3–5.
19. Kalantar-Zadeh K, Uppot RN, Lewandrowski KB. Case 23-2013. A 54-year-old woman with abdominal pain, vomiting, and confusion. N Engl J Med 2013;369:374–82.
20. Friesecke S, Abel P, Roser M, Felix SB, Runge S. Outcome of severe lactic acidosis associated with metformin accumulation. Crit Care 2010;14:R226.