Twin neurological enigmas radiological and medical insight into a dual encounter with metformin induced encephalopathy

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ABSTRACT

Metformin induced encephalopathy is an infrequent but critical neurological complication associated with metformin therapy. Lentiform fork sign, an infrequent radiological imaging (MRI), presents a distinctive image in basal ganglia pathology. It manifests as a V-shaped or fork-like hyperintensity in the globus pallidus and putamen regions. While it has been associated with various conditions like diabetic uremic encephalopathy, toxins like methanol and ethylene glycol, Neurodegenerative etiologies. Its occurrence following metformin administration remains rare because of contraindication of prescribing metformin in a hemodialysis patient due to its well-known side of lactic acidosis. This abstract aims to report and discuss two cases presenting the lentiform forks sign following metformin administration in patients undergoing hemodialysis due to end-stage renal disease. Symptomatic involvement of basal ganglia as metformin induced encephalopathy and resolution with clinical recovery following hemodialysis are rarely reported. We hereby report two such cases which shows symptomatic improvement clinically as well as radiologically following hemodialysis.

Implication for health policy/practice/research/medical education:
In this study we discuss two rare cases of metformin-induced encephalopathy in patients undergoing hemodialysis for end-stage renal disease. The lentiform fork sign, a distinctive MRI finding associated with basal ganglia pathology, was observed. Despite metformin’s contraindication in hemodialysis patients due to its risk of lactic acidosis, symptomatic improvement was noted following hemodialysis, highlighting the importance of recognizing and managing this rare neurological complication.

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in individuals with end-stage kidney failure undergoing maintenance hemodialysis. This case series contribute to the existing literature on the rare but clinically significant complication of metformin associated encephalopathy in the unique population of end stage renal disease patients.

**Case Presentation**

**Case 1**

A 55-year-old male patient with a history of chronic kidney disease on hemodialysis and diabetes mellitus for 7 years presented to the emergency department with chief complaints of slurred speech and mental confusion for the past 7 days.

The patient has a history of intake of metformin 1000 mg one time a day × 1 month which was prescribed to him elsewhere. Despite undergoing dialysis sessions, there has been no noticeable symptomatic improvement. There is no history of fever, headache, or focal neurological deficits. The last hemodialysis session was conducted two days prior to admission, and the patient's vital signs were within normal range. HbA1c level of 6.8%, lactate concentration of 73.5 mg/dL, urea level of 117 mg/dL, creatinine level of 1.9 mg/dL, potassium concentration of 6.4 mg/dL, sodium level of 120 mEq/L, urea concentration of 22 mg/dL, bicarbonate level of 19 mmol/L, calcium concentration of 10 mg/dL, phosphorus level of 8.4 mg/dL, chloride concentration of 89 mEq/L, and serum osmolality of 265 mOsm/kg.

Patient underwent magnetic resonance imaging of brain to rule out central cause of encephalopathy. As shown in Figures 1 and 2, differential diagnosis of uremic encephalopathy and due to presence of history of metformin intake metformin induced encephalopathy was given. Following which metformin was abruptly stopped, and intensive hemodialysis was started right away, lasting six hours a day for five days after hospitalisation. This treatment was conducted to eliminate uremic toxin and metformin, as well as to treat lactic acidosis. He had a 74 mmol/L drop in lactic acid during the first dialysis session and gradually on 6th day the level dropped to normal value. His symptoms subsided following six hemodialysis sessions in a row. After that, he underwent hemodialysis three times a week.

As shown in Figure 3 and 4 MRI which were conducted after one-month, the T2-weighted brain MRI revealed complete resolution of the lentiform fork sign. Patient neurological symptoms and discharged.

**Case 2**

A 58-year-old male who had been undergoing hemodialysis three times per week over the course of two years was admitted to our hospital with complaints of a gradual decrease in the sensorium, unsteadiness of gait, dysarthria, and intermittent nonprojectile vomiting for the past 6 months. He was compliant with the hemodialysis

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**Figure 1.** T2 and T2 fat suppression sequence axial section well-defined T2/FLAIR hyperintense area with surrounding T2/FLAIR hyperintense rim is noted involving bilateral lentiform nucleus and head of caudate nucleus.

**Figure 2.** Apparent diffusion coefficient (ADC) and diffusion-weighted imaging (DWI) maps axial sections. There is evidence of restricted diffusion notes in the above-mentioned area.

**Figure 3.** T2 and FLAIR sequence axial section shows complete resolution of the lentiform fork sign.

**Figure 4.** Apparent diffusion coefficient (ADC) and diffusion-weighted imaging (DWI) maps axial section. There is no evidence of restricted diffusion noted.
Metformin induced encephalopathy

He had no habit of consuming alcohol and smoking.

On neurological examination his mental status as drowsy and dysarthria with moderate gait disturbance present. His peripheral white blood count was 7000/mm³. Furthermore, the results indicated a plasma hemoglobin level of 10.7 g/dL, a platelet count of 292,000/mm³, a lactate level of 116 mg/dL, a blood urea level of 183 mg/dL, a serum creatinine level of 7.0 mg/dL, a sodium bicarbonate level of 125 mEq/L, and a serum vitamin B12 concentration of 1430 pg/mL. No abnormalities in the liver function test. Blood gas analysis shows a pH of 7.35.

He was unintentionally prescribed metformin 500 mg + glimepiride 1 mg twice daily six months ago.

We considered the possibility of metformin-induced encephalopathy due to lactic acidosis and MRI brain was proceeded.

As shown in Figures 5 and 6, MRI brain revealed the presence of metformin induced encephalopathy metformin was withdrawn, and hemodialysis was immediately initiated for metformin removal from the serum and tissue. His neurological abnormalities had completely resolved after 7 sessions of hemodialysis over 10 days of hospital stay. After his neurological status improved and serum lactate was 10.3 mg/dL, follow-up MRI brain imaging as shown in Figures 7 and 8 shows resolution after 10 days.

Discussion

This case series describes the diabetic end stage renal disease patient who experienced a disruption in consciousness and displayed the lentiform fork sign on a T2-weighted brain MRI. The exact pathogenesis of this lesion is still not clear. This kind of white matter pattern common mechanism is secondary to the combination of vasogenic and cytotoxic edema and consequently it explains the radiological regression of this lesion following the treatment and as well clinical improvement (7,8).

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MRI findings

Figure 5. T2 and T2 fat suppression sequence axial section well defined T2/FLAIR hyperintense area is noted involving bilateral lentiform nucleus.

Figure 6. Apparent diffusion coefficient (ADC) and diffusion-weighted imaging (DWI) maps axial section there is evidence of restricted diffusion noted in the above-mentioned area.

Figure 7. Apparent diffusion coefficient (ADC) and diffusion-weighted imaging (DWI) maps axial section there is no evidence of restricted diffusion noted.

Figure 8. Apparent diffusion coefficient (ADC) and diffusion-weighted imaging (DWI) maps axial section there is no evidence of restricted diffusion noted in the above-mentioned area.
muscle more prone to rupture or leakage. This may lead to injury to the basal ganglia, including vasogenic edema, which has a good prognosis and is reversible.

In our cases the presence of restricted diffusion on DWI/ADC indicates cytotoxic edema, lactic acidosis and controlled HbA1c levels confirms the diagnosis of metformin induced encephalopathy.

**Conclusion**

This article highlights a rare presentation of metformin induced encephalopathy in end stage renal disease patient despite the contraindication of metformin. This presentation underscores the importance of recognizing metformin induced encephalopathy as a potential complication in hemodialysis patient. Both cases demonstrated symptomatic improvement clinically and radiologically following hemodialysis. Therefore, this highlights the therapeutic utility of hemodialysis in managing metformin toxicity in hemodialysis Further studies are warranted to elucidate the precise mechanisms underlying the resolution of metformin induced encephalopathy with hemodialysis.

**Limitations of the study**

The sample size may be limited due to rarity of encephalopathy due to metformin end stage renal disease. Despite the limitation this retrospective case series aims to provide insights into the clinical characteristics, image findings and outcomes of metformin associated encephalopathy in the unique population of end stage renal disease patient.

**Authors’ contribution**

**Conceptualization:** Leyole Claudine Ancilla, Bala Sundaram, Nabadjwip Pathak.

**Data curation:** Leyole Claudine Ancilla, Nabadjwip Pathak.

**Formal analysis:** Bala Sundaram.

**Investigation:** Leyole Claudine Ancilla, Arawinth Raj.

**Resources:** Leyole Claudine Ancilla, Nabadjwip Pathak.

**Software:** Leyole Claudine Ancilla, Nabadjwip Pathak.

**Supervision:** Nabadjwip Pathak.

**Validation:** Leyole Claudine Ancilla, Nabadjwip Pathak.

**Visualization:** Leyole Claudine Ancilla, Nabadjwip Pathak.

**Writing—original draft:** Leyole Claudine Ancilla, Nabadjwip Pathak.

**Writing—review & editing:** Bala Sundaram.

**Conflicts of interest**

The authors declare that they have no competing interests.

**Ethical issues**

This case report was conducted in accord with the World Medical Association Declaration of Helsinki. Patients have given us a written informed consent for publication as the case report. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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