J Nephropharmacol. 2024; 13(2): e11681.

https://jnephropharmacology.com DOI: 10.34172/npj.2024.11681

Journal of Nephropharmacology

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

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ARTICLE INFO

Article Type:
Case Series

Article History:
Received: 3 Mar. 2024
Accepted: 8 Jun. 2024
ePublished: 29 Jun. 2024

Keywords:
Metformin-induced encephalopathy, Chronic kidney disease, Hemodialysis, Lentiform fork sign

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

Case Series

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 risk of lactic acidosis, symptomatic improvement was noted following hemodialysis, highlighting the importance of recognizing and managing this rare neurological complication.

Please cite this paper as: Claudine Ancilla L, Sundaram B, Pathak N, Raj A. Twin neurological enigmas radiological and medical insight into a dual encounter with metformin induced encephalopathy. J Nephropharmacol. 2024;13(2):e11681. DOI: 10.34172/npj.2024.11681.

Introduction

Oral hypoglycemic agent metformin associated lactic acidosis is most commonly encountered toxicity even when used in therapeutic doses (1). It is not recommended for people who have liver disease or renal failure because it raises the risk of lactic acidosis. Abnormal basal ganglia due to cytotoxic edema in an encephalopathy has been reported in hemodialysis individuals (2). Ingestion of toxins present mushroom, star fruit, and drugs (e.g., anti-herpes virus drugs) patients can present with encephalopathy (3). Indeed, in diabetic patients undergoing dialysis, certain neuroimaging findings can be indicative of specific conditions. One such finding is bilateral symmetrical low densities in the basal ganglia observed on brain CT. Additionally, on T2-weighted MRI, a bilateral symmetrical hyperintensity in the same area along with a lentiform fork sign may be present. In addition to diabetic uremic syndrome (DUS), the lentiform fork sign can be observed in severe metabolic acidosis, dialysis disequilibrium syndrome and metformin-associated encephalopathy (4,5). Metformin encephalopathy in end-stage renal disease is rare and has only been reported in a few case reports (6). We describe two such instance involving a patient receiving maintenance hemodialysis who had end-stage kidney failure.

Objectives

To present a case series describing the occurrence, clinical manifestations, imaging findings, management strategies and outcomes of metformin associated encephalopathy

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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

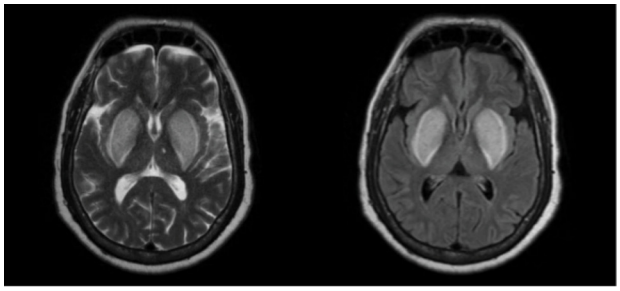

Figure 1. T2 and T2 fat suppression sequence axial section well-defined T2/FLAIR hyperintense area with surrounding T2/FLAIR hyperintense rim is noted involving bilateral lentiform nucleus and head of caudate nucleus.

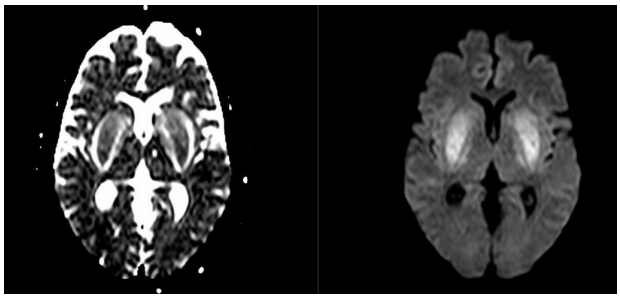

Figure 2. Apparent diffusion coefficient (ADC) and diffusion-weighted imaging (DWI) maps axial sections. There is evidence of restricted diffusion notes in the above-mentioned area.

MRI findings

MRI brain after one month period

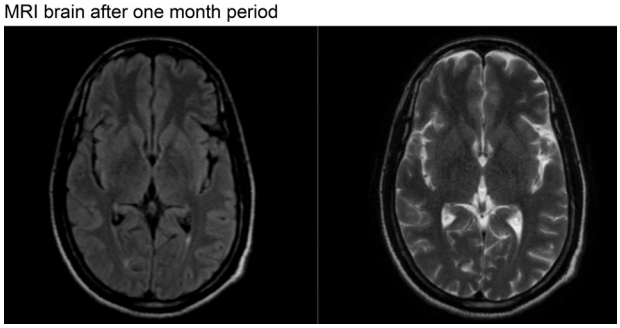

Figure 3. T2 and FLAIR sequence axial section shows complete resolution of the lentiform fork sign.

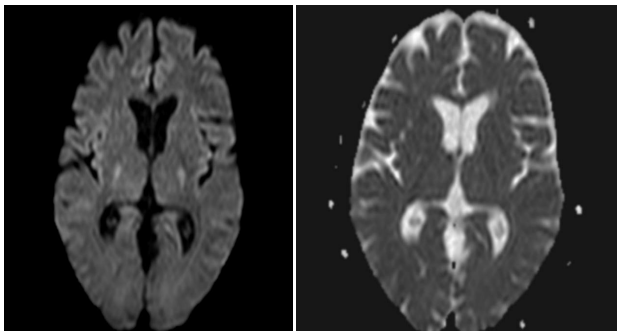

Figure 4. Apparent diffusion coefficient (ADC) and diffusion-weighted imaging (DWI) maps axial section. There is no evidence of restricted diffusion noted.

session. 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/mm^3. Furthermore, the results indicated a plasma hemoglobin level of 10.7 g/dL, a platelet count of 292 000/mm^3, 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). This discovery is found in the basal ganglia, which are susceptible to metabolic products and addictive toxins. In our case the patient exhibited lentiform fork sign but it can be nonspecific and needs to be differentiated between metformin encephalopathy and DUS as described in Table 1.

Metformin use in dialyzed patients may result in drug build-up in the brain, which could worsen sensory disturbance, cause neurological abnormalities, make it harder to walk and speak, and make fatigue, drowsiness, and weakness worse. The damage to basal ganglia in MRI imaging shows the restricted diffusion on DWI/ADC sequences due to cytotoxic edema secondary to lactic acidosis caused by metformin.

In DUS alter the brain homeostasis and metabolism by breaching the blood brain barrier by uremic toxins and /or metabolic acidosis. Hyperglycemia compromises the integrity of the microvasculature, making vascular smooth

MRI findings

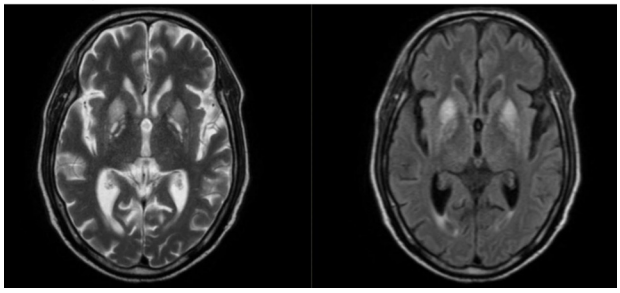

Figure 5. T2 and T2 fat suppression sequence axial section well defined T2/FLAIR hyperintense area is noted involving bilateral lentiform nucleus.

MRI brain imaging done on the 10th day

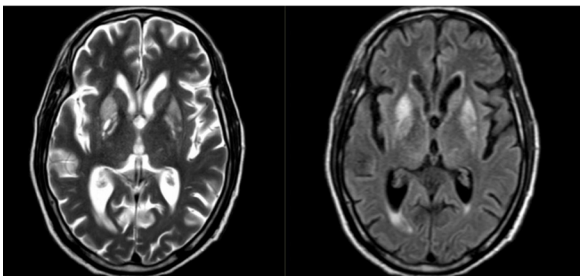

Figure 7. Apparent diffusion coefficient (ADC) and diffusion-weighted imaging (DWI) maps axial section there is no evidence of restricted diffusion noted.

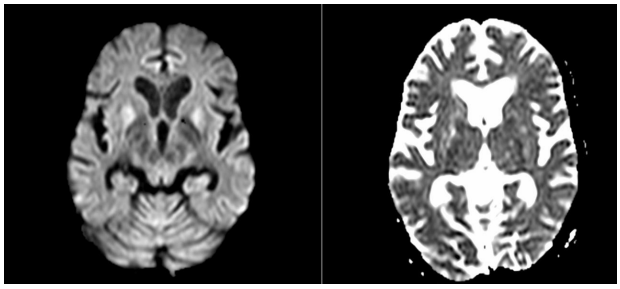

Figure 6. Apparent diffusion coefficient (ADC) and diffusion-weighted imaging (DWI) maps axial section there is evidence of restricted diffusion noted in the above-mentioned area.

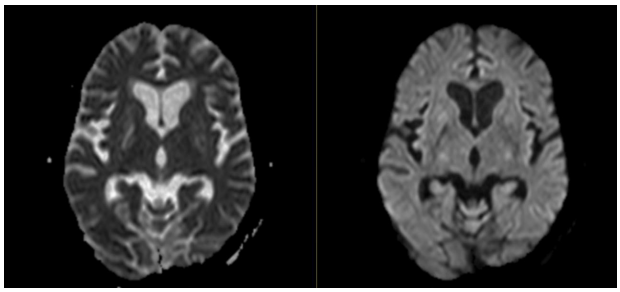

Figure 8. Apparent diffusion coefficient (ADC) and diffusion-weighted imaging (DWI) maps axial section there is no evidence of restricted diffusion noted in the above-mentioned area.

Table 1. Comparison with metformin encephalopathy and diabetic uremic syndrome

	Diabetic uremic syndrome	Metformin induced encephalopathy	Case 1	Case 2
Clinical features	Dysarthria, abnormal gait and altered consciousness	Sensorium, exhaustion, dysarthria, abnormal gait and disturbance of consciousness	Dysarthria, disturbance of the senses and disturbance of consciousness	Dysarthria, disturbance of the senses, gait disturbances and disturbance of consciousness
Acidosis	Metabolic acidosis	Lactic acidosis	Lactic acidosis	Lactic acidosis
Onset	Acute and subacute	Gradual and subacute	Gradual and subacute	Gradual and subacute
Uremia	Positive	Negative	Negative	Negative
Hyperglycemia at time of admission	Present	Absent	Absent	Absent
Type of edema	Vasogenic	Cytotoxic	Cytotoxic	Cytotoxic

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, Nabadwip Pathak.
Data curation: Leyole Claudine Ancilla, Nabadwip Pathak.
Formal analysis: Bala Sundaram.
Investigation: Leyole Claudine Ancilla, Arawinth Raj.
Resources: Leyole Claudine Ancilla, Nabadwip Pathak.
Software: Leyole Claudine Ancilla, Nabadwip Pathak.
Supervision: Nabadwip Pathak.
Validation: Leyole Claudine Ancilla, Nabadwip Pathak.
Visualization: Leyole Claudine Ancilla, Nabadwip Pathak.
Writing–original draft: Leyole Claudine Ancilla, Nabadwip 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.

Funding /Support

None.

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