Case Report

DOI: 10.5152/NSN.2019.9772

Lentiform fork sign in a diabetic uremic patient: pathophysiology is still not clear

Bilge Piri Çınar[1], Tülin Akagün[2], Alper Aydın[3], Selim Turfan[4]

[1]Clinic of Neurology, Samsun Training and Research Hospital, Samsun, Turkey
[2]Clinic of Nephrology, Giresun University Prof. Dr. İlhan Özdemir Giresun Training and Research Hospital, Giresun, Turkey
[3]Clinic of Radiology, Giresun University Prof. Dr. İlhan Özdemir Giresun Training and Research Hospital, Giresun, Turkey
[4]Clinic of Emergency Medicine, Giresun University Prof. Dr. İlhan Özdemir Giresun Training and Research Hospital, Giresun, Turkey

Abstract

Neurological disorders observed in end stage renal disease (ESRD) other than clouding of consciousness, involuntary movements and uremic encephalopathy capable of causing seizures include wakefulness defect caused by effects on basal ganglia associated with metabolic acidosis, movement disorder and, independent of these, progressive cognitive impairment of insidious onset. A 57-year-old male patient was started on hemodialysis (HD) with a diagnosis of ESRD secondary to diabetic nephropathy 5 months ago while under monitoring for diabetes mellitus and hypertension known for the previous 10 years. The patient presented to our hospital emergency service due to clouding of consciousness, wakefulness defect and lack of appetite that had begun 2 days ago. Computed tomography (CT) and diffusion magnetic resonance imaging (MRI) of the brain were performed during assessment in the emergency department. CT of the brain revealed symmetrical hypodensity in bilateral basal ganglia. Diffusion MRI of the brain revealed diffusion restriction not accompanied by hypointensity on apparent diffusion coefficient images in bilateral lentiform nucleus. Mannitol therapy was tapered and discontinued on day 3. The patient was enrolled on a 3-times-weekly HD program. Although the pathophysiology of lentiform fork sign (LFS) is still not fully clear, in our case, LFS may have developed due to insufficient dialysis and consequent metabolic acidosis and uremia. We report this case due to the rarity of LFS.

Keywords: Acidosis, diabetic kidney disease, end stage renal disease, hemodialysis, magnetic resonance imaging

INTRODUCTION

End-stage renal disease (ESRD) is defined as a glomerular filtration rate of less than 15 mL/min/1.73 m^2 when renal replacement therapy in the form of dialysis or transplantation has to be considered to sustain life (1). Uremic encephalopathy is a syndrome of delirium seen in untreated or inadequately treated ESRD (2). Neurological disorders observed in ESRD other than clouding of consciousness, involuntary movements and uremic encephalopathy capable of causing seizures include wakefulness defect caused by effects on basal ganglia associated with metabolic acidosis, movement disorder and, independent of these, progressive cognitive impairment of insidious onset. More than one cause of neurological findings can be seen in many cases, and the pathophysiology is highly complex. While the cortex is frequently involved in uremic encephalopathy, it is uncertain whether the basal ganglia are also affected. Lentiform fork sign (LFS) is a rare, typical magnetic resonance imaging (MRI) finding that can be seen in ESRD that is derived from an accumulation of toxic metabolic products in the lentiform nucleus as a result of metabolic acidosis, uremia or both pathological processes (3, 4).

CASE PRESENTATION

A 57-year-old male patient was started on hemodialysis (HD) with a diagnosis of ESRD secondary to diabetic nephropathy 5 months ago while under monitoring for diabetes mellitus (DM) and hypertension known for the previous 10 years. We learned that the patient received metformin 2x1 g for DM. He initially underwent HD twice a week, but 3 times a week was then recommended as this was insufficient. The patient refused HD therapy 3 times a week, but

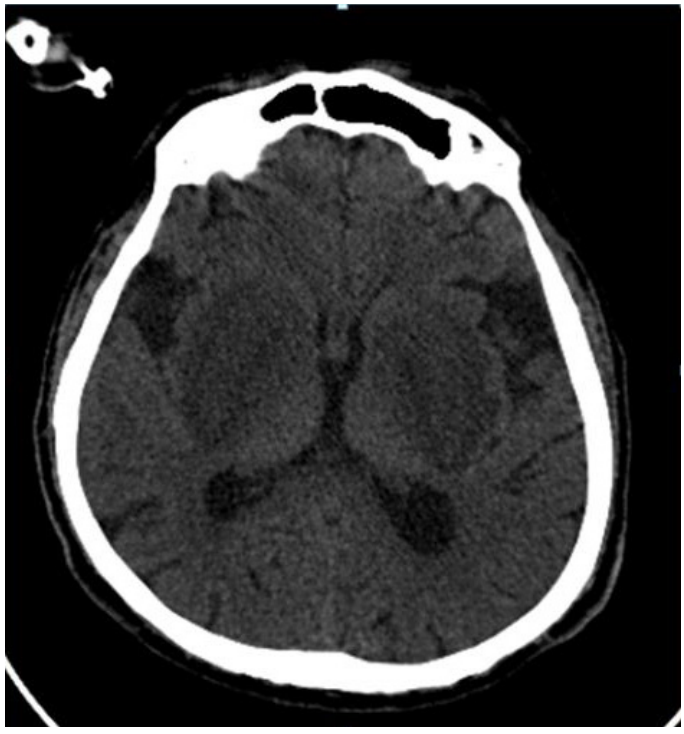
This study was presented at the 50th National Neurology Congress, 21-27 November 2014, Antalya, Turkey.

You may cite this article as: Piri Çınar B, Akagün T, Aydın A, Turfan S. Lentiform fork sign in a diabetic uremic patient: pathophysiology is not clear still. Neurol Sci Neurophysiol 2019; 36(3): 167-70.

Corresponding Author: Bilge Piri Çınar **E-mail:** bilge.cinarpiri@gmail.com **Submitted:** 24 September 2016 **Accepted:** 30 May 2019

presented to our hospital emergency service due to clouding of consciousness, wakefulness defect and lack of appetite that had begun 2 days ago. Mixed metabolic acidosis (pH: 7.41, HCO_3: 14.7 and pCO_2: 23 mmHg) was determined at tests during admission. Anion gap metabolic acidosis was determined (anion gap=28.3). Findings at the time of presentation were lactate: 1.4, blood glucose level: 75 mg/dL, urea: 91 mg/dL, creatinine (Cr): 8.18 mg/dL, sodium: 130 mmol/L, potassium: 4.73 mmol/L and chloride: 87 mmol/L. Computerized tomography (CT) (16 slice somatom sensation Siemens, Forcheim, Germany) and diffusion (Dif) MRI (1,5 Tesla, MR Magnetom Avanto, Siemens, Erlangen, Germany) of the brain were performed during assessment in the emergency department. Computerized tomography of the brain revealed symmetrical hypodensity in the bilateral basal ganglia (Figure 1). Dif MRI of the brain revealed diffusion restriction not accompanied by hypointensity on apparent diffusion coefficient (ADC) images in the bilateral lentiform nucleus, and this was interpreted as compatible with vasogenic edema (Figure 2). At neurological examination, the patient was somnolent, non-cooperative and disoriented. Speech was dysarthric, and muscle strength on the left was 3/5. The patient was started on mannitol and acetylsalicylic acid. On the 2nd day, the patient was assessed as lucid, and speech and muscle strength were normal, although occasional restricted cooperation and orientation defect persisted. Mannitol therapy was tapered and discontinued on day 3. Electroencephalography (EEG) (Nihon Kohden Neurofax EEG-1200, Tokyo, Japan) was performed, but no abnormality was determined apart from base rhythm consisting of 6-7 Hz theta waves. The patient was enrolled on a 3-times-weekly HD program. MRI and CT images were interpreted as LFS, which is rarely seen in ESRD, and the patient was monitored with regular HD. The patient's HD catheter was not functioning effectively, and replacement was planned, but the patient refused. Cerebral MRI was repeated, but no change was determined. Repeat EEG was performed 3 days later and resulted normal. Since the patient was referred to another center, no clinical and radiological follow-up was possible. Written and verbal informed consent could not obtained from the patient or patients' parent who participated in this study.

Figure 1. Symmetrical hypodensity in bilateral basal ganglia



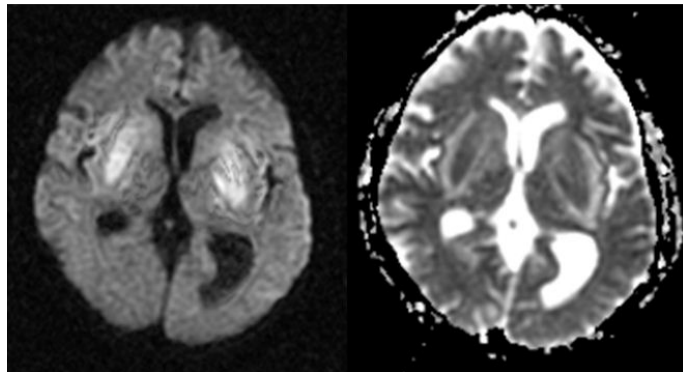
DISCUSSION

Frequently seen neurological complications in ESRD include uremic encephalopathy, uremic neuropathy, cognitive impairment, cerebral atrophy and movement disorders. Neurological disorder that develops frequently has an insidious onset. Early diagnosis is of assistance to the physician in managing treatment, and this makes multidisciplinary monitoring of patients with ESRD essential. The basal ganglia deep gray matter structures consisting of the caudate nucleus, putamen and globus pallidus are the most frequently affected part of the brain in ESRD and are more sensitive than other brain tissues to both toxic metabolic products and vasogenic edema. Since the basal ganglia have a high adenosine triphosphate (ATP) requirement, increased regional blood flow and a high neurotransmitter content, important elements in cerebral activity, they are sensitive to all types of metabolic change increase in intracellular calcium. While the cerebral cortex is frequently affected in uremic encephalopathy, the area affected in the uremic basal ganglion involvement leading to LFS, with its different etiopathogenesis, is the basal ganglia (5).

The most important characteristic feature of neurological impairment in uremic encephalopathy is that findings fluctuate, and visual hallucinations, impaired consciousness, tremor, asterixis, multifocal clonus and seizures are frequently seen in association with cerebral cortex involvement (6). However, onset in LFS may be clinically acute or subacute, and it may exhibit a wide spectrum including extrapyramidal findings, psychomotor retardation, confusion, abulia and cognition impairment, and treatment consists particularly of effective dialysis, and antiedema and support therapy.

Figure 2. Diffusion-weighted and ADC images of brain MRI

ADC: apparent diffusion coefficient; MRI: magnetic resonance imaging

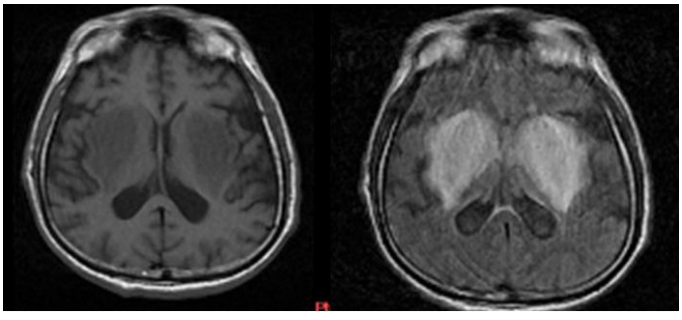


Although the pathophysiology of LFS is still not fully clear, a combination of uremia, metabolic acidosis and imbalance in glucose levels is regarded as being involved in the etiopathogenesis. In uremia, a secondary increase in parathormone restricts ATP production by increasing brain calcium levels. In addition, increased calcium in the presynaptic terminals of the nerve cell reduces the activity of Na-K ATPase and Ca-ATPase, which play an important role in cell metabolism and function in an ATP-dependent manner, and this further increases calcium levels in the nerve terminals. Neuron loss is seen secondary to energy deficiency in the basal ganglia and increasing intracellular calcium (7). In the light of this information, a continuous state of acidosis in the basal ganglia, which have a high energy need and meet that need through mitochondrial oxidative phosphorylation, a decrease in ATP and an increase in intracellular calcium can lead to severe damage. In hyperglycemia, which is thought to play a role in the etiopathogenesis, more H^+ ions accumulate since increased glucose cannot be effectively removed, and this contributes to cell damage. In normal individuals, the kidneys expel H+ ions through urine in order to balance an increase in acid load for any reason. However, as in our patient, as a result of a compensation mechanism that is compromised by kidney failure, cell damage occurs in the basal ganglia in the brain, together with a combination of acidosis, hyperglycemia and uremia. What makes the early detection of LFS important is that effective dialysis and short-term antiedema therapy is an option for regulating intracellular acidosis and reducing moderate cytotoxic edema and more significant vasogenic edema developing secondary to acute cellular injury.

A diagnosis of ESRD and DM and insufficiency of HD were present in our patient, who exhibited subacute onset clouding of consciousness, speech impairment and left side weakness. Blood glucose level at presentation was normal, while we thought that blood glucose might not be stable due to significant impairment of oral intake before presentation. In addition, MRI of the brain in our patient, who also had metabolic acidosis, revealed hyperintensity in the bilateral basal ganglia on T2 weighted images and hypointensity on T1 weighted images, and bilateral diffusion restriction in basal ganglia on diffusion weighted images (Figure 3). These findings were interpreted as compatible with LFS. At normal MRI examination, the basal ganglia are isointense on T1 weighted images, isointense with the cerebral cortex on T2 weighted images and moderately more hyperintense compared to white matter. Marked hypointensity is seen in LFS in the bilateral basal ganglia on symmetrical T1 and hyperintensity on T2, while hypodensity is detected at CT.

Figure 3. T1 (hypointensity) and T2-flair (hyperintensity) weighted images of brain MRI

MRI: magnetic resonance imaging



Vasogenic edema cannot be differentiated from cytotoxic edema at CT of the brain, and conventional MRI has low sensitivity. Massive ion and water ingress into the cell occurs following acute cellular injury, extracellular volume decreases as intracellular volume increases, and water movement is restricted. This is known as cytotoxic edema and diffusion weighted images are obtained by recording signal loss resulting from interactions between the diffuse movements of proteins in water molecules in the early period. Areas of cytotoxic edema appear as low intensity at ADC and as 'bright' hyperintensity on diffusion weighted images. In vasogenic edema, however, no high signal is expected, because there is no restriction of water molecules' diffusion motility. In conclusion high signal observed on diffusion weighted images can be distinguished as deriving from true restricted diffusion (cytotoxic edema) or from an increased T2 signal effect (vasogenic edema). In our case, vasogenic edema and partial cytotoxic edema were determined in the basal ganglia at MRI. Muscle strength returning to normal and partial resolution of confusion with antiedema therapy suggest that vasogenic edema is more prominent in LFS. No change was observed at Dif MRI and conventional MRI examination in the early period.

In LFS, patients may present with Parkinsonism associated with basal ganglia involvement or, similar to our case, with subacute onset clouded consciousness, lateralized muscle weakness and dysarthria (8). Clinically, the degree of involvement of the basal ganglia may be associated with the degree of effect of vasogenic edema. In our case, LFS may have developed due to insufficient dialysis and consequent metabolic acidosis and uremia. We report this case due to the rarity of LFS.

Informed Consent: Informed consent could not obtained from the patient or patients' parent who participated in this study. Because the patient was referred to another hospital upon request of his relatives.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – B.P.Ç., T.A.; Design – B.P.Ç., A.A.; Supervision – T.A., S.T.; Resources – A.A.; Materials – A.A., S.T.; Data Collection and/or Processing – B.P.Ç., T.A.; Analysis and/or Interpretation – A.A., B.P.Ç., S.T.; Literature Search – B.P.Ç., A.A.; Writing Manuscript – B.P.Ç., T.A.; Critical Review – S.T., A.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Floege J, Johnson JR, Feehally J. Comprehensive Clinical Nephrology. Fourth Edition. Neurologic Complications of Chronic Kidney Disease 2010; 985-986. [CrossRef]
2. Brenner & Rector's. The Kidney. Ninth Edition. Neurologic Aspects of Kidney Disease 2012; 2146-2149.
3. Kumar G, Goyal MK. Lentiform Fork sign: a unique MRI picture. Is metabolic acidosis responsible? Clin Neurol Neurosurg 2010; 112: 805-12. [CrossRef]
4. Fabiani G, Teive HAG, Munhoz RP. Lentiform fork sign and fluctuating, reversible parkinsonism in a patient with uremic encephalopathy. Mov Disord 2013; 28: 1053. [CrossRef]
5. Gong WY, Li SS, Yu ZC, et al. Syndrome of uremic encephalopathy and bilateral basal ganglia lesions in non-diabetic hemodialysis patient: a case report. BMC Nephrol 2018; 19: 370. [CrossRef]
6. Jabbari B, Vaziri ND. The nature, consequences, and management of neurological disorders in chronic kidney disease. Hemodial Int 2018; 22: 150-160. [CrossRef]
7. Hanna JD, Scheinman JI, Chan JC. The kidney in acid-base balance. Pediatr Clin North Am 1995; 42: 1365-1395. [CrossRef]
8. Altunore O, Kaya B, Sayarlıoglu H, Gökçe M, Dogan E, Diabetic uremic basal ganglia ınvolvement in a patient who treated with regular dialysis. TNDT 2010; 19: 221-223. [CrossRef]