Uremic encephalopathy: A definite diagnosis by magnetic resonance imaging?

Farzad Sina (1,2), Darya Najafi (3), Alireza Aziz-Ahari (4), Elham Shahraki (5), Tahere Zarouk Ahimahalle (6), Zeinab Namjoo (7), Sajad Hassanzadeh (1)

(1) Skull Base Research Center, The Five Senses Institute, School of Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran (2) Department of Neurology, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran; (3) School of Medicine, Iran University of Medical Sciences, Tehran, Iran; (4) Department of Radiology, School of Medicine Hazrat Rasool General Hospital, Iran University of Medical Sciences, Tehran, Iran; (5) Department of Internal Medicine, Ali Ibne Abitaleb Hospital, Zahedan University of Medical Sciences, Zahedan, Iran; (6) Department of Internal Medicine, School of Medicine, Hazrat Rasool General Hospital, Iran University of Medical Sciences, Tehran, Iran. (7) Department of Anatomical Sciences, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran

Abstract

The aim of this study was to investigate the magnetic resonance imaging (MRI) findings for the diagnose uremic encephalopathy and describe the usefulness of MRI findings in the ultimate diagnosis of uremic encephalopathy (UE). A total of 20 patients with uremic encephalopathy admitted to the hospital were evaluated in this prospective study. The clinical manifestations, laboratory and MRI imaging findings, demographic information, and clinical outcome were analyzed for each patient. We observed that the 20 prospectively reviewed patients with UE had no involvement of the basal ganglia or the lentiform fork sign (LFS). However, two-thirds of the patients had white matter involvement, and 80% of the subjects had cerebral or cortical atrophy. The arterial blood gas (ABG) analysis revealed that 50% of the patients suffered from metabolic acidosis (n=10). The results of the present study demonstrated that although the observation of Lentiform Fork Sign and Basal Ganglia involvement in MRI of UE patients is a specific finding the absence of which does not rule out UE. Thus, simultaneous examination of clinical manifestation and laboratory test analyses, along with imaging findings, should also be taken into account.

Key Words: Uremic encephalopathy; magnetic resonance imaging; lentiform fork sign; basal ganglia.

Eur J Transl Myol 32 (3): 10613, 2022 doi: 10.4081/ejtm.2022.10613

Uremic encephalopathy is a metabolic disorder, a syndrome with a wide range of reversible neurologic symptoms triggered by untreated or inadequately treated severe renal failure.[1,2] The syndrome produces a spectrum of brain anomalies ranging from mild to severe. Previous studies demonstrated that the paradigm of MRI findings in patients with UE falls into three major types including a) basal ganglia, b) cortical or subcortical areas, and c) many areas of white matter.[1-8] A large number of studies have confirmed that some abnormalities such as increased blood urea nitrogen (BUN), creatinine, and acidosis metabolic observed in laboratory tests in patients with renal failure are also directly related to uremic encephalopathy.[2,8] In patients suffering from uremic encephalopathy, there exist a wide range of specific imaging features and variable alterations including cortical and subcortical involvement being manifested as posterior reversible encephalopathy syndrome (PRES). The FLAIR images of these patients show the hyperintensity in the parieto-occipital and posterior frontal cortical and subcortical white matter.[9-11] Moreover, the presence of lentiform fork sign (LFS) has recently been used as an important neurological sign for the diagnosis of uremic encephalopathy, though it has been more limited to case studies.[12-15] All of these criteria can help the physician diagnose UE in the shortest time possible; but can imaging findings alone help diagnose uremic encephalopathy at early stage? Or which of these diagnostic methods (lab blood results, imaging, and

clinical examination) is preferred to another? These questions are still debated by researchers in the clinical setting and will be discussed in the present study.

Materials and Methods

Design and Participants

This was a prospective multicenter (N=3) study conducted on 20 patients (9 males and 11 females; mean age: 54.3 ± 22.2 years; age range: 17–85 years). The patients were diagnosed with UE using clinical and MRI imaging methods, admitted to hospitals of Iran University of Medical Sciences (IUMS) Tehran-Iran, for two years between September 2018 and October 2020. The definitive diagnosis of uremic encephalopathy in the patients was made according to their clinical evidence recorded in the file as well as their neurological complaints and laboratory findings indicating renal dysfunction. All patients gave their informed consent prior to their inclusion in the study, and all stages of the project were supervised by the Ethics Committee of the Iran University of Medical Sciences, according to the ethical code IR.IUMS.REC.1398.1182. All steps were explained separately to each patient before starting the project, and a written informed consent was taken from all the participants.

Inclusion and exclusion criteria

UE diagnoses in patients were made on the basis of clinical manifestation, corroborated by laboratory findings suggesting deterioration of renal function, and typical neurologic complications. All of these patients underwent MRI imaging following the confirmation of uremic encephalopathy disease. The results were then reviewed and analyzed by two experienced radiologists. Patients who had known cases of cerebral stroke, drug-induced movement disorder, diabetes, neurodegenerative disease, intracerebral infections, or other metabolic disturbances, were excluded from the study. Patients who had a reduced level of consciousness (GCS scale) for whatever reason other than uremic encephalopathy were also excluded from the study.

Data Collection

After a definitive diagnosis of uremic encephalopathy, the medical records of the 20 patients were divided into five main categories: 1) Demographic information such as age, sex, and any evidence of chronic kidney diseases (CKD); 2) Laboratory findings on arterial blood gas, serum urea, blood sugar, nitrogen, sodium, calcium, potassium, creatinine levels, and metabolic acidosis. The criteria for definitive diagnosis of metabolic acidosis in patients include low pH value (<7.35) and decreased bicarbonate level (<24 mmol/L; normal range: 19–24 mmol/L). 3) Investigation of the frequency of clinical and neurological manifestation in patients with astrexia, seizure, and decreased level of consciousness (GCS scale); 4) Analysis of the CT scan of the patients for pleural and pericardial effusion; and 5) All the 20 patients underwent MRI imaging immediately after the onset of symptoms. The MRI imaging was performed using a 1.5T scanner (Siemens 1.5T Symphony, Siemens, Germany). Two experienced radiologists evaluated all MRI imaging data for the basal ganglia involvement, white matter damages, the lentiform fork sign (LFS), PRES-like manifestation, and cortical or subcortical atrophy. We also scrutinized the MRI for any lesions in various parts of the white matter in the brain. For this, we utilized the Fazekas scale to determine the amount of white matter T2 hyperintense lesions and classified them into three levels of severity — mild, moderate, and severe.[16] To assess cerebral atrophy in the patients we applied the global cortical atrophy (GCA) scale first developed by Pasquier et al. in 1996.[17] The score for each region can range from 0 to 3 according to the following four criteria: normal volume/no ventricular enlargement = 0, opening of sulci/mild ventricular enlargement = 1, volume loss of gyri/moderate ventricular enlargement = 2, and 'knife blade' atrophy/severe ventricular enlargement = 3. According to previous studies, LFS is considered a meaningful sign in the diagnosis of uremic encephalopathy on MRI images. Thus, these images were scrutinized in terms of the existence of constitutive components of the lentiform fork: 1) The stem is located in the infero-posterior end of the putamen and lateral to the thalamus and created by a fusion of edematous external and internal capsules. 2) The lateral arm, created by edematous external capsule lateral to the putamen extending from the anterior end thereof to the stem in the vicinity of the lateral ventricle. 3) The medial arm is located medial to the putamen and lateral to the thalamus, extending from the stem anteriorly and split into two slightly less T2/FLAIR hyperintense branches engulfing the globus pallidus.[14,15] The protocol was implemented on seven MRI sequences: T1-weighted FSE Axial plane TR/TE 780/10, T2-weighted FSE Axial plane TR/TE 5280/100), T2-weighted FSE coronal plane (TR/TE 5660/123, T2-weighted FSE Sagittal plane TR/TE 4640/97, DWI b-vales 0/1000), FLAIR Axial plane (TR/TE 8000/120, and T2 Axial plane TR/TE 675/14.

Statistical Analysis

The data relevant to demographic and other clinical and laboratory variables were entered into a data matrix in Microsoft Excel and then analyzed using SPSS version 26. The normality and skewness of the data were assessed with the Shapiro Wilk test and QQ plot. A p-value of less than 0.05 was defined as statistically significant for all the analyses in the study.

Results

A review of the demographic data demonstrated that the prevalence of both sexes was roughly equal (9 men and 11 women; mean age: 57.4 ± 21.08 years; age range: 17–88 years). Half of the patients (n=10) who came to our hospitals suffered from chronic kidney disease or had a history of CKD. Processing the data from the analyses

Table 1. *Information of main parameters of blood and arterial blood gas samples in our patients*

variable	mean	Standard deviation	minimum	maximum
Cr (mg/dl) *	6.71	6.12	2	29.5
BUN (mg/dl) *	92.95	70.17	24	271
BS (mg/dl) *	172.25	78.89	77	353
AST (mg/dl) *	101.70	204.74	13	875
ALT (mg/dl) *	57.85	103.76	11	425
Alkaline Phosphatase (mg/dl)	327.65	190.56	95	773
PH	7.32	0.12	7.13	7.50
PCO_2	29.77	9.11	12.10	47
HCO_3	16.51	6.93	3.90	27
Albumin (mg/dl)	3.35	0.51	2.40	4.30
Calcium (mg/dl)	8.28	1.11	5.90	11.20
Sodium (meq/l)	137.30	6.77	127	154
Potassium (meq/l)	5.05	1.12	3.40	7.80

Cr: Creatinine, BUN: Blood Urea Nitrogen, BS: Blood Sugar, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase

of the laboratory information and blood chemistry indicated that all the patients had uremia and considerably increased level of blood urea nitrogen (mean: 92.95 ± 70.17 mg/dL) and Cr (mean: 6.71 ± 6.12 mg/dL). Other serum electrolytes and blood sugar levels were not significantly abnormal, excluding other causes of encephalopathy (Table. 1). The data of arterial blood gas were also analyzed for all the 20 patients. Thirteen patients had metabolic acidosis (mean pH: 7.32 ± 0.12; mean bicarbonate: 16.51 ± 6.93), and the rest (n=7) had a normal pH level. The serum potassium levels were also measured in all patients; 12 had a normal potassium level, 8 suffered from hyperkalemia, and none of the patients had hypokalemia. Of the 20 patients who had the neurological clinical manifestation, 16 (80%) suffered from consciousness dysfunction associated with a decrease in the Glasgow Coma Scale (GCS< 12), and 7 (35%) exhibited the sign of asterexia. Four patients had seizure attacks at the time of admission to the hospital. A significant relationship was found between PRES symptoms in MRI and the presence of seizures in the patients (p = 0.016). A close examination of the 20 CT scans of the patients revealed that only 4 (20%) had pleural effusion. Moreover, an analysis of magnetic resonance imaging of all patients disclosed that none of them had involvement of basal ganglia and lentiform fork sign. One of the patients had PRES-like symptoms in FLAIR axial view involving bilateral cerebrum and

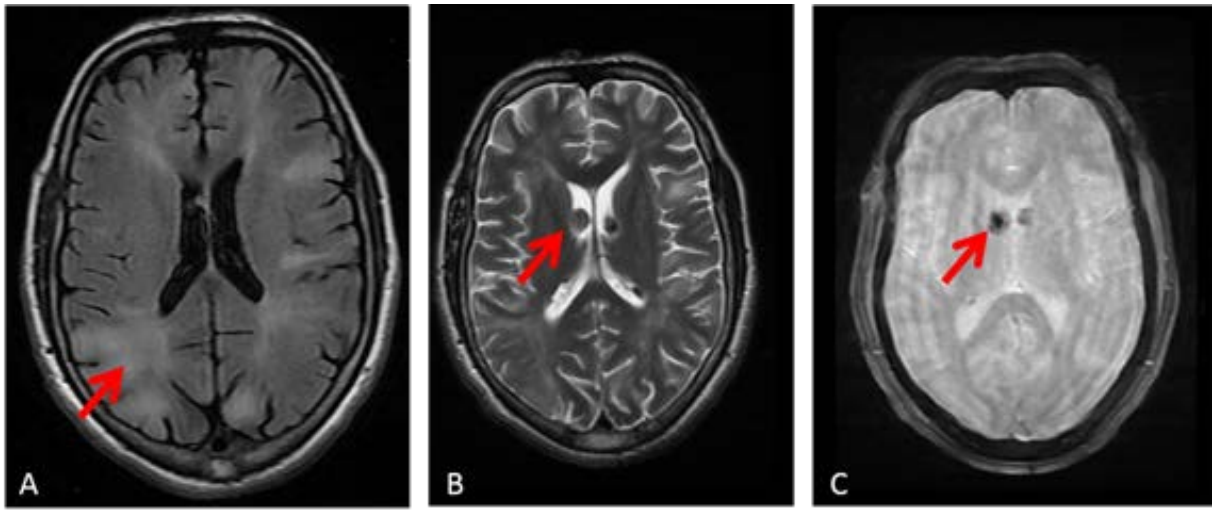

Fig 1. *(A) The axial FLAIR section illustrates diffuse PRES-like syndrome involved Bilateral cerebrum and subcritical white matter (red arrow). (B) Axial T2 section shows bleeding or calcification areas (red arrow) around Monro foramen. (C) The exact section in the T2 star sequence (red arrow).*

subcortical white matter (Figure 1). Bleeding or calcification areas around Monro foramen and mild diffuse cortical atrophy were observed in that patient — more than expected for age. We also examined the MRI for any lesions in different parts of the white matter in the brain. For this purpose, the Fazekas scale was applied to estimate the amount of T2 hyperintense lesions in white matter and the results were categorized into three levels of mild, moderate, and severe.[18-20] Of 14 (70%) patients with white matter lesions, 8 (40 %) were mild in regions such as Putamen, cingulate gyrus, and splenium of corpus callosum areas, and 6 (30 %) were moderate to severe with microvascular changes. In addition, 16 (80%) patients had cortical or cerebral atrophy, of whom 10 (50%) had severe atrophy (more than age-appropriate) and 6 (30%) had mild atrophy (age-appropriate).

Discussion

Twenty UE patients were enrolled in this study, that was the highest in terms of statistical population. The maximum rate of UE patient contribution that has been reported so far was 10 patients in a study conducted by Kim et al., in 2016.[2] However, according to the present study (mean age: 57.4 years) and the Kim's study (mean age: 58 years), it can be concluded that the elderly people are more susceptible to UE. Thus, age seems to be an influential factor in the incidence of UE. UE is a metabolic and neurologic disorder with direct relation to acute or chronic renal failure. Renal dysfunction causes the accumulation of uremic toxins such as creatinine and guanine in the body, which in turn enhances the neurotoxic effects of excitatory N-Methyl-D-aspartate receptors and the inhibition of inhibitory aminobutyric acid receptors simultaneously. This alteration in the excitatory-inhibitory amino acid balance may lead to UE in patients.[2,18] UE causes a spectrum of clinical manifestations and neurologic symptoms in patients, including movement disorders (tremor, asterixis, myoclonus, and hyperreflexia), cognitive impairment (memory dysfunction, dementia, and impaired level of consciousness), and psychological disturbance (depression, lack of concentration, and sleep disorders).[5,19-21] The majority of patients suffering from UE presents three paradigms of imaging findings in their MRI or CT scan: basal ganglia involvement,[1, 3, 4] cortical or subcortical involvement,[5,6] and white matter involvement.[7, 8] Basal ganglia involvement is rare in UE patients; however, previous cases have reported that it occurs more commonly in Asian patients with diabetes mellitus (DM). [22,23] The rationale behind it is that diabetes disrupts the function of endothelial cells in the cerebral vessels, which in turn makes the basal ganglia more vulnerable to uremic toxin conditions. Furthermore, uremic toxins impair mitochondrial function in the brain stem, thereby destroying pallidum and Putamen.[24] However, in a case study in 2018 Liu reported a non-diabetic UE with typical bilateral basal ganglia lesions.[25] In our study, none of the 20 patients showed symptoms of basal ganglia involvement on their MRI images. Since the presence of DM was considered as an exclusion criterion in our study, the DM can be suggested as an exacerbating, not a definite, factor for basal ganglia involvement. Cortical involvement of UE is a category of posterior reversible encephalopathy syndrome (PRES). It is a reversible clinical-radiologic syndrome characterized by various presenting symptoms from headache, confusion, seizures, and visual disturbance to loss of consciousness. In our study, a significant relationship was found between PRES symptoms in MRI and the presence of seizures in the patients ($p = 0.016$). The result of the study is in consistence with those of many other studies and explains a direct relationship between cortical damage in UE and neurological symptoms.[26,27] PRES occurs more commonly in the cortical or subcortical white matter regions and less commonly in the brain stem or basal ganglia.[6, 28, 29] The pathophysiology is not fully understood but is assumed to be related to a hyper-perfusion condition, with blood-brain-barrier disruption, leakage of fluid, potentially containing blood or macromolecules, into the surrounding tissues, leading to cortical or subcortical edema.[30-32] Some patients with PRES show vasogenic edema in the subcortical white matter and cortex, but cytotoxic edema has also been reported in a smaller percentage of such patients.[33] Clinical MRI examination of patients with PRES shows a hyperintensity on FLAIR images in some areas, particularly parieto-occipital and posterior frontal white matter, and rarely cerebellum and basal ganglia.[9, 10, 34-36] In our study, one of the patients had PRES-like symptoms in T1-T2 star and FLAIR involving bilateral cerebrum and subcortical white matter (Figure 1). We also observed bleeding or calcification areas around Monro foramen and mild diffuse cortical atrophy, greater than expected for the patient's age. Taking into account that the PRES patient presented seizure activity, the relation between PRES and seizures activity in UE patients is recommended to be considered in future research. The vulnerability of white matter in UE patients is rare but possible and may occur in the supratentorial white matter areas. The relation between LFS and metabolic acidosis in UE patients is unclear. Many studies have shown that UE is associated with metabolic acidosis.[5,37,38] According to the literature, metabolic acidosis can be an essential key factor in the pathogenesis of LFS. As shown in a table by Kumar et al. (l), of 22 patients 14 had metabolic acidosis, one had normal pH, and in 7 patients the pH/acidosis-related data was unavailable.[14] The mechanism behind might be that metabolic acidosis can cause blood-brain barrier disruption, finally leading to the development of LFS.[15] In contrast, in the Kim's study, only 1 of 10 patients had both LFS and metabolic acidosis simultaneously, which means that the LFS can be observed in UE regardless of the presence of metabolic acidosis.[2] However, in our study, 13 patients had metabolic acidosis (mean pH: 7.32 ± 0.12; mean bicarbonate: 16.51 ± 6.93), and 7 patients had normal pH

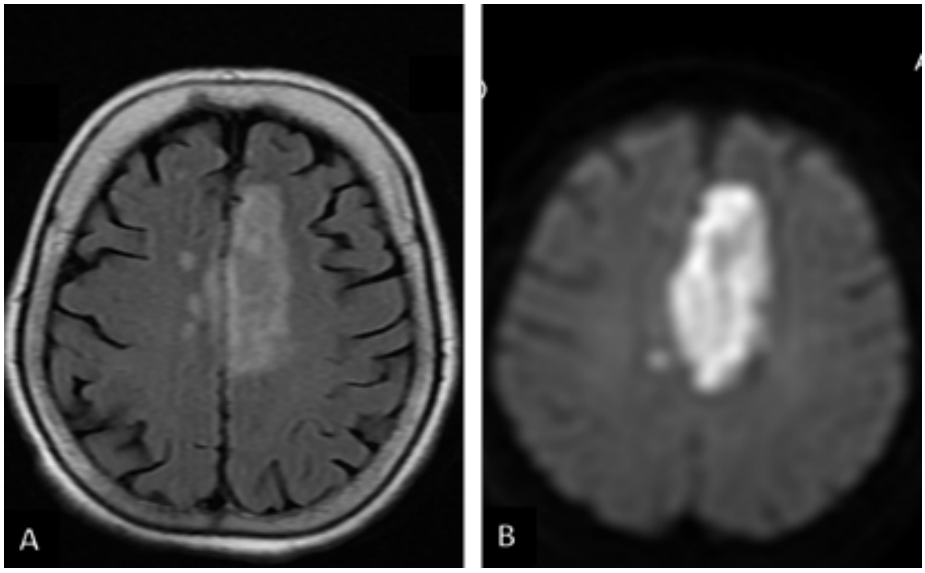

Fig 2. *(A) The axial FLAIR section illustrates an abnormal signal in the left medial of the frontal lobe. The cingulate gyrus and splenium of the corpus callosum are also involved (not shown). (B) The axial DWI section shows restricted diffusion in the involved regions. Infarction due to embolism in ACA territory is possible.*

levels on arterial blood gas. Interestingly, none of the 13 patients showed LFS in their MRI images. These results are different from the findings of a literature review which suggested that metabolic acidosis is the basis of the LFS, the lack of which might be reflective of a normal pH level,[14] although one reason for this result might be an absence of severe metabolic acidosis in our patients. Whether the occurrence of LFS in patients with uremic encephalopathy is directly related to the duration or degree of metabolic acidosis or depends on the underlying etiology needs further investigation. In our study, we also analyzed the T2WI/FLAIR images for any lesions in different areas of the brain's white matter using the Fazekas scale to quantify the amount of white matter lesions subcategorized into the three levels: mild, moderate, and severe.[16] Most of the patients (n=14) in our study suffered from lesions in their brain areas, particularly frontal lobe, cingulate gyrus, and splenium of corpus callosum and putamen with microvascular changes in these regions (Figure 2). Many studies have shown that the basal ganglia components such as corpus callosum and putamen are more susceptible to cytotoxic damage, which correspond well with our findings. All of these parts require high energy consumption to have proper functioning. Thus, the lack of imperative energy leads to mitochondrial and nuclear dysfunction in these tissues, particularly in some conditions like toxic/metabolic injuries.[24, 39, 40] To overcome the limitations of the previous designs, we increased the sample size (n = 20) in this study so as to make the results obtained more reliable. The advantages of this study include high statistical population, liver function test, and ABG of all patients, which make the results more reliable. Nevertheless, some limitations remain also in this study. Hemodialysis and peritoneal dialysis are one of the treatments for patients suffering from UE that help them have a better recovery by removing toxic compounds. In this study, due to its multicenter design, we could not follow up patients for dialysis and MRI after recovery.

In conclusion, the results obtained in the present study show that the observation and specificity of lentiform fork sign and basal ganglia involvement in MRI of uremic encephalopathic patients are a specific finding, the absence of which, however, does not rule out uremic encephalopathy. Thus, it is recommended to utilize a combination of clinical manifestations, laboratory test results, and imaging findings to make a definitive diagnosis.

List of acronyms

ABG - Arterial Blood Gas
ALT - Alanine Aminotransferase
AST - Aspartate Aminotransferase
BS - Blood Sugar
BUN - Blood Urea Nitrogen
CKD -Chronic Kidney Diseases
Cr – Creatinine
DM - Diabetes Mellitus
GCA -Global Cortical Atrophy
GCS - Glasgow Coma Scale
LFS - Lentiform Fork Sign
MRI - Magnetic Resonance Imaging
PRES - Posterior Reversible Encephalopathy Syndrome
UE - Uremic Encephalopathy

Contributions of Authors

Study conception and design: Sajad Hassanzadeh, Farzad Sina and Elham Shahreki. Data collection: Darya Najafi and Tahere Zarouk Ahimahalle. Data analysis and interpretation: Sajad Hassanzadeh and Alireza Aziz-Ahari. Drafting of the article: Sajad Hasanzad, Zeinab Namjoo and Farzad Sina. All authors participated in Critical revision of the Manuscript. All authors read and approved the final edited typescript.

Acknowledgments

We would like to express our thanks to the patients who participated in this study.

Funding

This study was funded by Iran University of Medical Sciences. (no. 98-3-15-15951).

Conflict of Interest

The authors declare no conflict of interests.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Corresponding Author

Sajad Hassanzadeh, Skull Base Research Center, Hazrat Rasoul Hospital, The five Senses Institute, Iran University of Medical Sciences, Tehran, Iran.
Phone: +989126956905
ORCID ID: 0000-0002-5310-0334
E-mail: hassanzadeh.sa@iums.ac.ir

E-mails and ORCID iD of co-authors

Farzad Sina: sina.f@iums.ac.ir
ORCID ID: 0000-0002-6934-2442
Darya Najafi: Daryanajafi8574@gmail.com
ORCID ID: 0000-0002-6364-8256
Alireza Aziz-Ahari: azizahari.ar@iums.ac.ir
ORCID ID: 0000-0003-4543-4307
Elham Shahraki: shahrekie@gmail.com
ORCID ID: 0000-0001-6396-4120
Tahere Zarouk Ahimahalle: zarouk.t@iums.ac.ir
ORCID ID: 0000-0003-4973-1982
Zeinab Namjoo: z.namjoo@arums.ac.ir
ORCID ID: 0000-0001-8541-1359

References

1. Wang HC, Cheng SJ. The syndrome of acute bilateral basal ganglia lesions in diabetic uremic patients. J Neurol. 2003 Aug;250(8):948-55. doi: 10.1007/s00415-003-1122-0.
2. Kim DM, Lee IH, Song CJ. Uremic Encephalopathy: MR Imaging Findings and Clinical Correlation. AJNR Am J Neuroradiol. 2016 Sep;37(9):1604-9. doi: 10.3174/ajnr.A4776. Epub 2016 Apr 28.
3. Lee EJ, Park JH, Ihn Yk, Kim YJ, Lee SK, Park CS. Acute bilateral basal ganglia lesions in diabetic uraemia: diffusion-weighted MRI. Neuroradiology. 2007 Dec;49(12):1009-13. doi: 10.1007/s00234-007-0299-9. Epub 2007 Oct 6.
4. Yoon CH, Seok JI, Lee DK, An GS. Bilateral basal ganglia and unilateral cortical involvement in a diabetic uremic patient. Clin Neurol Neurosurg. 2009 Jun;111(5):477-9. doi: 10.1016/j.clineuro.2009.01.007. Epub 2009 Feb 12.
5. Schmidt M, Sitter T, Lederer SR, Held E, Schiffl H. Reversible MRI changes in a patient with uremic encephalopathy. J Nephrol. 2001 Sep-Oct;14(5):424-7.
6. Tatsumoto N, Fujisaki K, Nagae H, Ono-Fujisaki A, Kura-Nakamura N, Taniguchi M, Masutani K, Tsuruya K, Iida M. Reversible posterior leukoencephalopathy syndrome in a patient with severe uremic encephalopathy. Clin Nephrol. 2010 Aug;74(2):154-8. doi: 10.5414/cnp74154.
7. Prüss H, Siebert E, Masuhr F. Reversible cytotoxic brain edema and facial weakness in uremic encephalopathy. J Neurol. 2009 Aug;256(8):1372-3. doi: 10.1007/s00415-009-5125-3. Epub 2009 Apr 12.
8. Kang E, Jeon SJ, Choi SS. Uremic encephalopathy with atypical magnetic resonance features on diffusion-weighted images. Korean J Radiol. 2012 Nov-Dec;13(6):808-11. doi: 10.3348/kjr.2012.13.6.808. Epub 2012 Oct 12.
9. Casey SO, Sampaio RC, Michel E, Truwit CL. Posterior reversible encephalopathy syndrome: utility of fluid-attenuated inversion recovery MR imaging in the detection of cortical and subcortical lesions. AJNR Am J Neuroradiol. 2000 Aug;21(7):1199-206.
10. Jarosz JM, Howlett DC, Cox TC, Bingham JB. Cyclosporine-related reversible posterior leukoencephalopathy: MRI. Neuroradiology. 1997 Oct;39(10):711-5. doi: 10.1007/s002340050492.
11. McKinney AM, Short J, Truwit CL, McKinney ZJ, Kozak OS, SantaCruz KS, Teksam M. Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. AJR Am J Roentgenol. 2007 Oct;189(4):904-12. doi: 10.2214/AJR.07.2024.
12. Mansoor, S, De Klerk L, Lineen J,Fahad M, Ali I, Murphy K Lentiform fork sign in a uremic patient with a high anion gap metabolic acidosis with seizures: a case report from North West of Ireland. The Egyptian Journal of Neurology, Psychiatry and Neurosurgery, 2020. 56(1): 101. doi.org/10.1186/s41983-020-00234-8
13. Jaryal A, Thakur S, Pathania JS, Vikrant S, Kumar D, Verma L. Lentiform fork sign: Uremia alone or multifactorial causation? Hemodial Int. 2020 Jan;24(1):E10-E12. doi: 10.1111/hdi.12810. Epub 2019 Dec 16.

14. Kumar G, Goyal MK. Lentiform Fork sign: a unique MRI picture. Is metabolic acidosis responsible? Clin Neurol Neurosurg. 2010 Nov;112(9):805-12. doi: 10.1016/j.clineuro.2010.06.006. Epub 2010 Jul 7.
15. Grasso D, Borreggine C, Perfetto F, Bertozzi V, Trivisano M, Specchio LM, Grilli G, Macarini L. Lentiform fork sign: a magnetic resonance finding in a case of acute metabolic acidosis. Neuroradiol J. 2014 Jun;27(3):288-92. doi: 10.15274/NRJ-2014-10041. Epub 2014 Jun 17.
16. Fazekas F, Kleinert R, Offenbacher H, Payer F, Schmidt R, Kleinert G, Radner H, Lechner H. The morphologic correlate of incidental punctate white matter hyperintensities on MR images. AJNR Am J Neuroradiol. 1991 Sep-Oct;12(5):915-21.
17. Pasquier F, Leys D, Weerts JG, Mounier-Vehier F, Barkhof F, Scheltens P. Inter- and intraobserver reproducibility of cerebral atrophy assessment on MRI scans with hemispheric infarcts. Eur Neurol. 1996;36(5):268-72. doi: 10.1159/000117270.
18. Vanholder R, De Smet R, Glorieux G, Argilés A, Baurmeister U, Brunet P, Clark W, Cohen G, De Deyn PP, Deppisch R, Descamps-Latscha B, Henle T, Jörres A, Lemke HD, Massy ZA, Passlick-Deetjen J, Rodriguez M, Stegmayr B, Stenvinkel P, Tetta C, Wanner C, Zidek W; European Uremic Toxin Work Group (EUTox). Review on uremic toxins: classification, concentration, and interindividual variability. Kidney Int. 2003 May;63(5):1934-43. doi: 10.1046/j.1523-1755.2003.00924.x. Erratum in: Kidney Int. 2020 Nov;98(5):1354.
19. Thimmaiah R, Murthy KK, Pinto D. Cognitive dysfunction in patients with renal failure requiring hemodialysis. Indian J Psychol Med. 2012;34(3):237-241. doi:10.4103/0253-7176.106019
20. Biasioli S, D'Andrea G, Feriani M, Chiaramonte S, Fabris A, Ronco C, La Greca G. Uremic encephalopathy: an updating. Clin Nephrol. 1986 Feb;25(2):57-63.
21. Etgen T. Kidney disease as a determinant of cognitive decline and dementia. Alzheimers Res Ther. 2015;7(1):29. Published 2015 Mar 17. doi:10.1186/s13195-015-0115-4.
22. Wang HC, Brown P, Lees AJ. Acute movement disorders with bilateral basal ganglia lesions in uremia. Mov Disord. 1998 Nov;13(6):952-7. doi: 10.1002/mds.870130615.
23. Wali GM, Khanpet MS, Mali RV. Acute movement disorder with bilateral basal ganglia lesions in diabetic uremia. Ann Indian Acad Neurol. 2011 Jul;14(3):211-3. doi: 10.4103/0972-2327.85899.
24. Albin RL. Basal ganglia neurotoxins. Neurol Clin. 2000 Aug;18(3):665-80. doi: 10.1016/s0733-8619(05)70217-6.
25. Gong WY, Li SS, Yu ZC, Wu HW, Yin LH, Mei LF, Liu FN. Syndrome of uremic encephalopathy and bilateral basal ganglia lesions in non-diabetic hemodialysis patient: a case report. BMC Nephrol. 2018 Dec 19;19(1):370. doi: 10.1186/s12882-018-1174-0.
26. Heo K, Cho KH, Lee MK, Chung SJ, Cho YJ, Lee BI. Development of epilepsy after posterior reversible encephalopathy syndrome. Seizure. 2016 Jan;34:90-4. doi: 10.1016/j.seizure.2015.12.005. Epub 2015 Dec 18.
27. Hobson EV, Craven I, Blank SC. Posterior reversible encephalopathy syndrome: a truly treatable neurologic illness. Perit Dial Int. 2012 Nov-Dec;32(6):590-4. doi: 10.3747/pdi.2012.00152.
28. Bartynski WS, Boardman JF. Distinct imaging patterns and lesion distribution in posterior reversible encephalopathy syndrome. AJNR Am J Neuroradiol. 2007 Aug;28(7):1320-7. doi: 10.3174/ajnr.A0549.
29. Kastrup O, Schlamann M, Moenninghoff C, Forsting M, Goericke S. Posterior Reversible Encephalopathy Syndrome: The Spectrum of MR Imaging Patterns. Clin Neuroradiol. 2015 Jun;25(2):161-71. doi: 10.1007/s00062-014-0293-7. Epub 2014 Feb 20.
30. Johansson BB. The blood-brain barrier and cerebral blood flow in acute hypertension. Acta Med Scand Suppl. 1983;678:107-12. doi: 10.1111/j.0954-6820.1984.tb08668.x.
31. Tamaki K, Sadoshima S, Baumbach GL, Iadecola C, Reis DJ, Heistad DD. Evidence that disruption of the blood-brain barrier precedes reduction in cerebral blood flow in hypertensive encephalopathy. Hypertension. 1984 Mar-Apr;6(2 Pt 2):I75-81. doi: 10.1161/01.hyp.6.2_pt_2.i75.
32. MacKenzie ET, Strandgaard S, Graham DI, Jones JV, Harper AM, Farrar JK. Effects of acutely induced hypertension in cats on pial arteriolar caliber, local cerebral blood flow, and the blood-brain barrier. Circ Res. 1976 Jul;39(1):33-41. doi: 10.1161/01.res.39.1.33.
33. Gao B, Yu BX, Li RS, Zhang G, Xie HZ, Liu FL, Lv C. Cytotoxic Edema in Posterior Reversible Encephalopathy Syndrome: Correlation of MRI Features with Serum Albumin Levels. AJNR Am J Neuroradiol. 2015 Oct;36(10):1884-9. doi: 10.3174/ajnr.A4379. Epub 2015 Jul 2.
34. Casey SO, Truwit CL. Pontine reversible edema: a newly recognized imaging variant of hypertensive encephalopathy? AJNR Am J Neuroradiol. 2000 Feb;21(2):243-5.
35. De Seze J, Mastain B, Stojkovic T, Ferriby D, Pruvo JP, Destée A, Vermersch P. Unusual MR findings of the brain stem in arterial hypertension. AJNR Am J Neuroradiol. 2000 Feb;21(2):391-4.

36. Chang GY, Keane JR. Hypertensive brainstem encephalopathy: three cases presenting with severe brainstem edema. Neurology. 1999 Aug 11;53(3):652-4. doi: 10.1212/wnl.53.3.652.
37. Geboers K, Vanden Bossche S, Dekeyzer S. Lentiform fork sign in a girl with uremic encephalopathy. Acta Neurol Belg. 2022 Apr;122(2):535-536. doi: 10.1007/s13760-021-01764-5. Epub 2021 Aug 3.
38. Soung-Rok SIM, Sang-Hun LEE, Jae-Hoon JAHNG, Jae-Yun LIM, You-Kyoung CHOI, Ki-Sun BAE, Woo-Il PARK, Ki-Joong KIM, Kyung-Yul LEE, Hyeong-Cheon PARK, Sung-Kyu HA. Uremic encephalopathy associated with bilateral basal ganglia and cerebellar lesion in a non-diabetic hemodialysis patient. Korean Journal of Nephrology, 2006. 25(6): 1061-1066. https://pesquisa.bvsalud.org/portal/resource/pt/wpr-226531
39. Sharrief AZ, Raffel J, Zee DS. Vitamin B(12) deficiency with bilateral globus pallidus abnormalities. Arch Neurol. 2012 Jun;69(6):769-772. doi: 10.1001/archneurol.2011.1084.
40. Hassanzadeh S, Jalessi M, Jameie SB, Khanmohammadi M, Bagher Z,Namjoo, Z, Davachi SM. More attention on glial cells to have better recovery after spinal cord injury. Biochemistry and Biophysics Reports, 2021. 25:100905. https://eprints.iums.ac.ir/32885/.

Disclaimer

Submission: May 09, 2022
Revision received: June 17, 2022
Accepted for publication: June 18, 2022