Case Report

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A case of reversible splenial lesion syndrome secondary to Fanconi syndrome with white matter swelling as the main manifestation

Jingzhe Han[1,*], Yaye Wang[2,3,*], Yue Wu[2,3], Jinru Zhang[2,3], Xueqin Song[2,3] and Guang Ji[2,3]

Abstract

Reversible splenial lesion syndrome (RESLES) is a rare clinical imaging syndrome that is characterized by magnetic resonance imaging (MRI) findings of reversible abnormal signals in the splenium of the corpus callosum (SCC). There are a variety of pathogenic causes, including infection, metabolic disturbances, and antiepileptic drug use. Moreover, the disease is clinically rare and easily misdiagnosed. Here, we report a unique case of a 32-year-old man with Fanconi syndrome who had an intensified signal in the SCC and diffuse white matter swelling on MRI. We believe this to be the first adult case of RESLES as a manifestation of Fanconi syndrome, which further expands the disease spectrum leading to RESLES. The imaging features of this case included extensive lesions, symmetrical diffuse restricted signals, and reversibility. The identification of these features improves our understanding of the imaging characteristics of RESLES, thus enabling clinicians to better understand this disease, correctly establish its diagnosis, and improve its prognosis in this kind of patient.

[1]Department of Neurology, Harrison International Peace Hospital, Hengshui, Hebei, China
[2]Department of Neurology, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, China
[3]Neurological Laboratory of Hebei Province, Shijiazhuang, Hebei, China

*These authors contributed equally to this work.

Corresponding author:
Xueqin Song, Department of Neurology, The Second Hospital of Hebei Medical University, 215 Heping Road, Shijiazhuang, Hebei 050000, China.
Email: shenjnksxq@163.com

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Introduction

Reversible splenial lesion syndrome (RESLES) is a clinical imaging syndrome that involves the splenium of the corpus callosum (SCC) and has various causes.[1] The typical magnetic resonance imaging (MRI) features are localized oval- or strip-shaped high signal changes of the SCC (generally located in the central area) on T2-weighted images (T2WI), fluid-attenuated inversion recovery (FLAIR) images, and diffusion-weighted images (DWI).[1,2] These MRI features are reversible. The pathogenesis of RESLES remains unclear, although cytotoxic edema of the SCC may be the key pathophysiological change in this disease.[3] The clinical symptoms of RESLES lack specificity. Most patients have a good prognosis, and generally are not left with any neurological dysfunction. It has been reported that Fanconi syndrome in children secondary to drug poisoning can lead to RESLES.[4] This paper reports for the first time a case of adult Fanconi syndrome complicated with RESLES. The main manifestation of this patient was diffuse symmetrical white matter swelling, which differs from the imaging features of other classic types of RESLES. The identification of this case can further enrich our knowledge of the imaging manifestations of RESLES, expand the disease spectrum leading to RESLES, and improve the vigilance of clinicians for adult Fanconi syndrome complicated with RESLES, thus improving the prognosis of such patients.

Case presentation

A 32-year-old man was admitted to hospital for 3 days, mainly because of memory loss and abnormal behavior. He had taken oral medication for diarrhea 3 days previously (details unknown). A physical examination at admission revealed memory impairment (mainly near memory impairment); computational power impairment (93–7 =?); decreased abilities of understanding, judgment, and spatial positioning; horizontal nystagmus in both eyes; and tendon reflex (+++ +) in both upper limbs. His right finger–nose test was not stable, and his heel–knee–tibia test on both lower limbs was not stable. No other nervous system abnormalities were found.

Blood gas analysis showed that pH was 7.23 (normal range 7.35–7.45), K^+ was 2.43 mmol/L (3.5–5.5 mmol/L), and Cl^+ was 114.2 mmol/L (95–107 mmol/L). Blood biochemistry showed that blood phosphorus was low (0.74 mmol/L), carbon dioxide was low (11.7 mmol/L), anion gap was high (17.2 mmol/L), uric acid was low (180.0 μmol/L), and blood ammonia was high (125 μmol/L). The hyperchloremic metabolic acidosis and decreased blood potassium was considered to be renal tubular acidosis. Urine routine showed urine sugar (+ +), proteinuria (1 +), and urine phosphate crystal, with all amino acids in the urine. Twenty-four-hour urine protein showed 24-hour urine volume 2.58 L, and 24-hour urine protein 0.21 g/24 hours. Creatine clearance (CCr) was 200.42 mL/min/1.73 m^2. On day 2

after admission, blood gas analysis again showed hyperchloremic metabolic acidosis (pH 7.245, HCO_3^- 11.7 mmol/L, K^+ 2.43 mmol/L, Na^+ 140.1 mmol/L, and Cl^+ 123 mmol/L) combined with renal glucosuria, renal aminoaciduria, and phosphaturia, which is consistent with the diagnosis of Fanconi syndrome. Considering that the patient had a history of diarrhea and oral medication before admission, although the specific description was unclear, we did not exclude the possibility that the patient's Fanconi syndrome might have been caused by drug poisoning. No known gene mutations were found in the gene package and exon sequencing for hereditary Fanconi syndrome, which ruled out the possibility of hereditary Fanconi syndrome.

Cranial MRI and DWI with enhancement showed diffuse high signal on T2WI and FLAIR sequences in the SCC and bilateral frontal, parietal, and occipital lobes (mainly in the parietal and occipital lobes). DWI showed limited diffusion (Figure 1) and the enhanced scan did not show obvious enhancement. The patient's cerebrospinal fluid (CSF) pressure was 145 mmH_2O, CSF total protein was 0.41 g/L, and glucose (5.15 mmol/L) was increased. The patient's CSF routine,

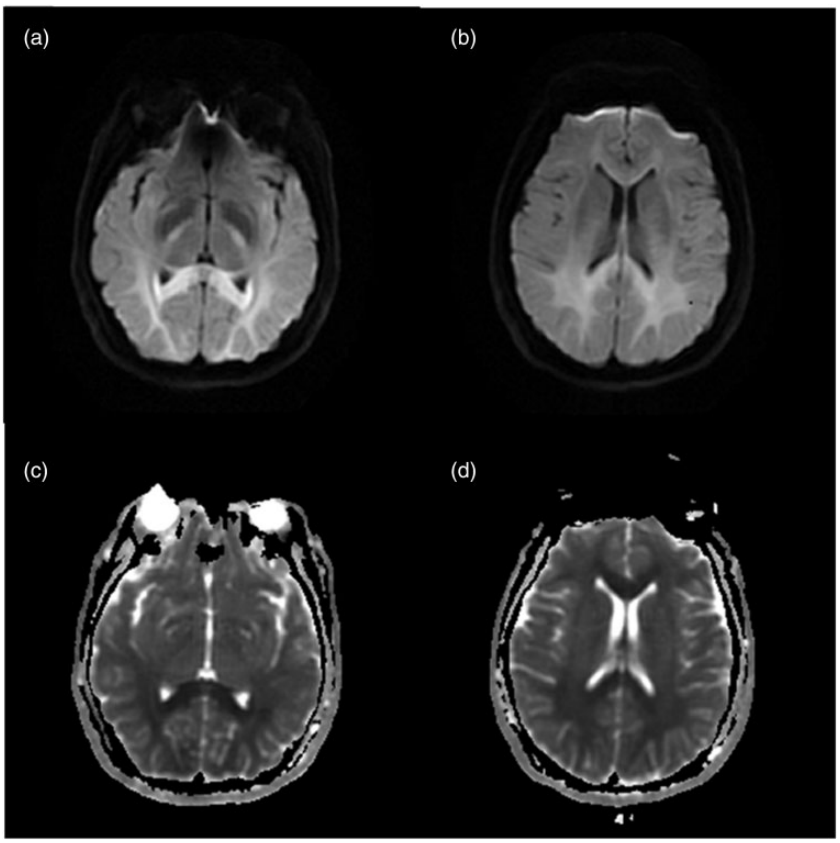

Figure 1. Magnetic resonance imaging of the patient. (a,b) The entire splenium of the corpus callosum, the genu of the corpus callosum, and the bilateral frontal, parietal, and occipital lobes showed high signal on cross-section diffusion-weighted imaging. (c,d) The corresponding lesions decreased on cross-section apparent diffusion coefficient imaging.

cytology, CSF next-generation sequencing, and autoimmune encephalitis antibodies (N-methyl-D-aspartate receptor [NMDAR], leucine-rich glioma-inactivated 1 [LGI1], contactin-associated protein 2 [CASPR2], gamma-aminobutyric acid B receptor [GABABR], α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor 1 [AMPAR1], and AMPAR2) were normal. The autoantibodies, aquaporin 4 (AQP4), oligoclonal bands, and paraneoplastic syndrome antibodies (Hu, Yo, Ri, CV2, Ma1, Ma2, amphiphysin, and SOX1) were negative. Parathyroid hormone and thyroid function were normal. Based on the comprehensive analysis and related differential diagnosis, we consider the possibility of RESLES. The patient was given symptomatic support and correction of acidosis, and his cognitive behavior gradually improved. The patient was hospitalized for 10 days and then discharged. Two weeks after discharge, the patient's cognitive symptoms had improved completely, and brain MRI showed that the lesions had subsided (Figure 2). After 3 months of follow-up, the patient returned to normal work. The prognosis and imaging changes of the patient further confirmed our diagnosis.

Discussion

RESLES is a relatively new clinical radiological syndrome, and its clinical symptoms are mostly encephalitis.[1,5] The pathophysiological mechanisms of RESLES remain unclear. The main pathological changes in RESLES are the accumulation of intracellular fluid and sodium, which result in the swelling of neurons and astrocytes.[3] In the present report, we describe for the first time the typical clinical manifestations and rare imaging features of an adult man with Fanconi syndrome complicated with RESLES. Fanconi syndrome is a rare cause of imaging manifestations of RESLES.

Although the adult patient was admitted to hospital with cognitive impairment and

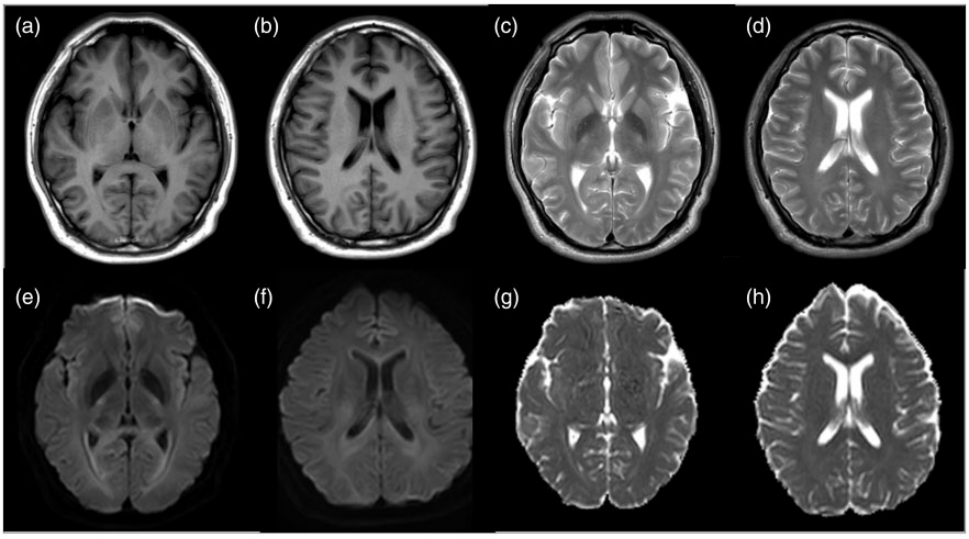

Figure 2. Magnetic resonance imaging of the patient (after 2 weeks of follow-up). Re-examination of brain magnetic resonance imaging showed that most of the lesions were reduced. (a,b) T1-weighted images. (c,d) T2-weighted images. (e,f) Regression of the lesion was visible on cross-section diffusion-weighted imaging. (g,h) Regression of the lesion was visible on cross-section apparent diffusion coefficient imaging.

mental and behavioral changes as the initial symptoms, his blood gas analysis showed hypokalemia and renal tubular acidosis. In addition, multiple blood gas analyses showed hyperchloremic metabolic acidosis. The laboratory indicators showed urine glucose (+ +), proteinuria (1 +), urinary phosphate crystal, and all amino acids in the urine, with decreased blood phosphorus, blood potassium, and serum uric acid. The patient's comprehensive manifestations were renal glucosuria, renal aminoaciduria, and phosphaturia, accompanied by clinical thirst and polyuria, which is consistent with the diagnosis of Fanconi syndrome. Fanconi syndrome is caused by extensive hereditary or acquired renal tubular dysfunction.[6] It has many causes and can be divided into primary and secondary categories. Primary Fanconi syndrome is divided into infantile, adult, and brush margin loss. Secondary Fanconi syndrome also includes secondary genetic diseases and secondary acquired diseases. Fanconi syndrome in children is mostly related to genetics, while in adults it is mainly secondary to immune diseases, metal poisoning, kidney diseases (e.g., nephrotic syndrome), renal damage caused by drugs (e.g., aminosaccharide antibiotics or 6-mercaptopurine), or tumor-related nephropathy.[6,7] In the present case, our patient had transient tubular dysfunction. Because he was an adult and male, there was a high risk of renal damage caused by genetics, immune metabolism, and/or drug intoxication. During hospitalization, his laboratory findings did not detect any toxic, metabolic, autoimmune, or infectious processes, and there was no evidence of a related genetic history. The patient did have a history of diarrhea medication; however, drug-related Fanconi syndrome was unable to be excluded because the patient refused a renal biopsy.

It has been reported that the classic imaging features of the acute stage of RESLES are transient and localized oval- or strip-shaped lesions of the SCC (generally located in the central area).[5,8] Based on the extent of the lesions, they can be divided into two types: type I lesions are limited to the SCC on MRI, while type II lesions spread to the entire corpus callosum, adjacent white matter, or both.[9] The MRI and DWI of this patient showed that the lesions were located in the whole SCC, with a clear boundary and strip-shaped changes, showing the "boomerang sign". In addition, symmetrical diffuse limited signals were also observed in the genu of the corpus callosum, and in the bilateral frontal, parietal, and occipital lobes (especially the parietal and occipital lobes), which highly suggested cytotoxic edema. This imaging appearance led us to strongly suspect RESLES (type II). The differential diagnosis mainly includes posterior reversible encephalopathy syndrome, acute disseminated encephalomyelitis, and infarction of the corpus callosum, but these were all unlikely in our patient. After symptomatic treatment, his cognitive, behavioral, and mental disorders gradually recovered. An MRI examination revealed that most of his lesions were reduced, which further confirmed the diagnosis of RESLES. Recent studies have proposed that a pathogenic mechanism for the reversible lesion in the SCC might be related to AQP4 receptors. This is because various conditions that have been reported to trigger reversible lesions in the SCC can also affect AQP4 protein expression, leading to increased expression levels through a complex cell–cytokine mechanism or an intracranial microenvironment osmotic mechanism.[10,11] The mechanism of RESLES occurrence in the present patient may have been his transient Fanconi syndrome, which can significantly increase the levels of pro-inflammatory mediators such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), as reported in a previous study of rats with transient Fanconi syndrome.[12] We hypothesize that these

cytokines are released, thus triggering the excitotoxic action of receptors (such as AQP4 receptor activation) through a complex cell–cytokine mechanism. This results in an influx of water into both astrocytes and neurons, which leads to cytotoxic edema, reversible lesions of the corpus callosum, and extensive white matter swelling. Unfortunately, the patient in the current report chose to leave the hospital without the further examination of cytokines such as IL-6, so this hypothesis needs to be confirmed by future studies.

In the present case, the prominent imaging features were the involvement of the entire SCC, presenting a "boomerang sign", with involvement of the genu of the corpus callosum as well as diffuse and symmetrical white matter lesions. This imaging manifestation is very rare in previous RESLES case reports. In clinical practice, it is important to strengthen clinicians' vigilance for the rare manifestations of Fanconi syndrome combined with RESLES. By establishing the correct diagnosis at disease onset and adopting reasonable treatment methods, clinicians can greatly improve the prognosis of such patients and reduce the occurrence of sequelae.

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Ethics statement

This study was approved by the Institutional Review Board of The Second Hospital of Hebei Medical University. Informed consent was obtained from the patient and his family.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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ORCID iDs

Jingzhe Han https://orcid.org/0000-0002-6086-7533

Xueqin Song https://orcid.org/0000-0003-0463-8450

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