



Leigh Syndrome Mimicking Wernicke's Encephalopathy: A Case Report

베르니케 뇌병증으로 오인된 리 증후군: 증례 보고

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Leigh syndrome or subacute necrotizing encephalomyelopathy is a rare, rapidly progressive neurodegenerative disorder. In general, symptoms such as shortness of breath and decreased cardiac function usually occur within 1 year of life. It is a serious disease with a mortality rate of 75% in 2–3 years. The cause of Leigh syndrome is DNA mutation. Approximately 75% of patients have nuclear DNA mutations while 25% have mitochondrial DNA mutations. Clinical symptoms vary depending on the affected brain area. Neuroimaging plays an important role in diagnosing patients with Leigh syndrome. Late-onset Leigh syndrome is rarer and progresses more slowly compared to the classic form. Here, we report a case of late-onset Leigh's syndrome mimicking Wernicke's encephalopathy.

Index terms Leigh Syndrome; Wernicke's Encephalopathy; Mitochondria

INTRODUCTION

Leigh syndrome (LS) or subacute necrotizing encephalomyelopathy (SNE) is a rapidly progressive neurodegenerative disorder of childhood (1). It is an extremely genetically heterogeneous mitochondrial disorder. Newly identified nuclear genetic causes are increasing, largely as a result of the use of next-generation and whole-exome sequencing. Most pathological gene mutations are ultimately involved in the process of energy production in the mitochondria (2). A clinically and etiologically highly variable, progressive LS is seen particularly in pediatric population although a few juvenile and adult cases are known (3). Clinical symptoms also depend on the affected brain area (3). Neuroimaging plays an important role in diagnosis of patients with LS (4). In the present report, we describe imaging findings of LS patients mimicking Wernicke's encephalopathy.

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
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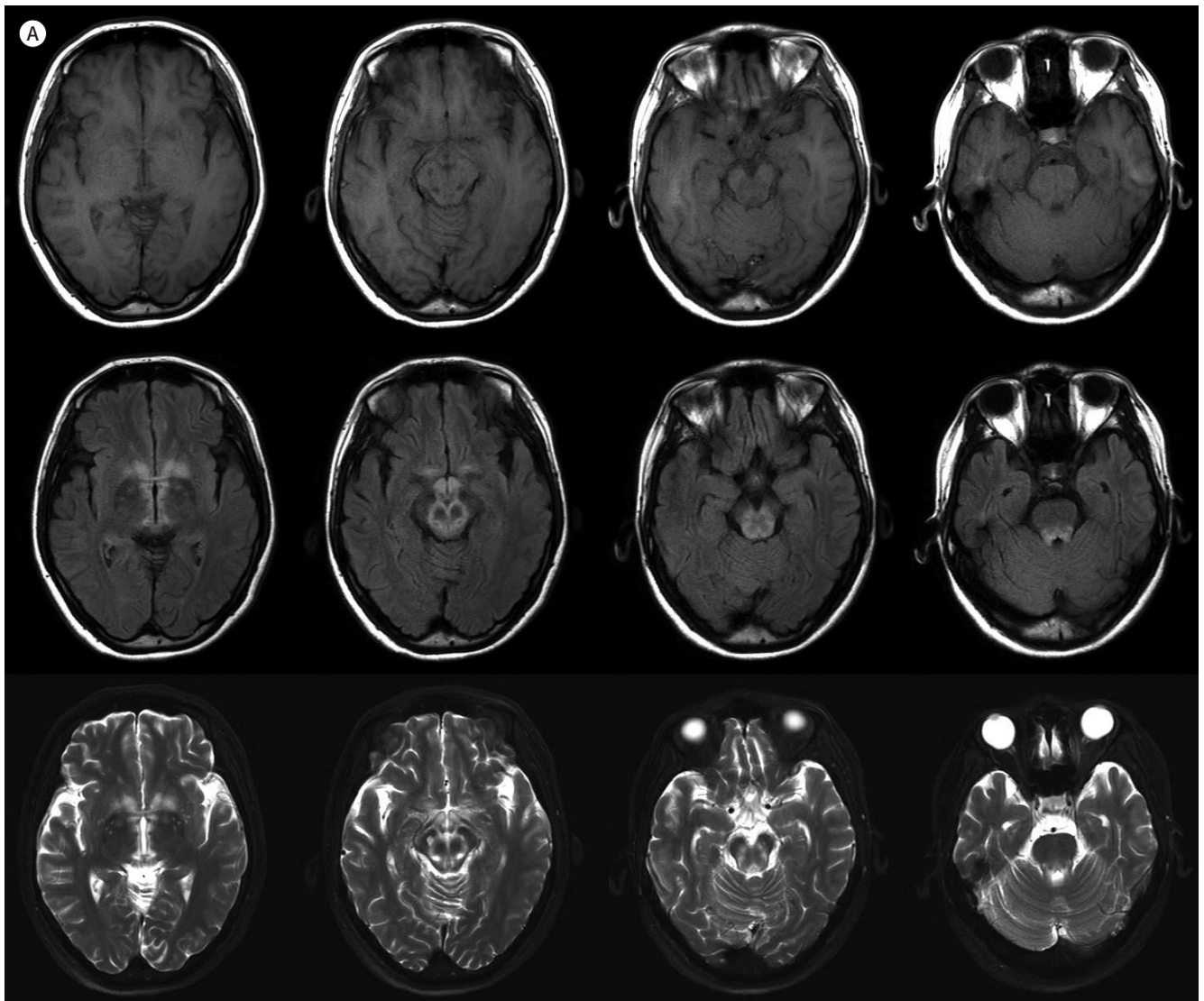
CASE REPORT

A 21-year-old woman visited the hospital because she suddenly had difficulty walking due to leg weakness. Her mental status was alert and she measured 22 points on the Mini Mental Status Examination test that showed a cognitive impairment. She had mild right facial palsy in cranial nerve examination. Pain, temperature and proprioception sensation were intact. The language function test showed mild dysarthria. The motor of the lower limb was intact, but proprioception was slightly decreased, so it was possible to gait with walker.

She took brain MRI that shows symmetrical, subtle hypointensity (T1) and hyperintensity (T2-flair) lesions in the basal ganglia, periaqueductal area, and median thalami. In the flair im-

Fig. 1. Leigh syndrome in a 21-year-old woman.

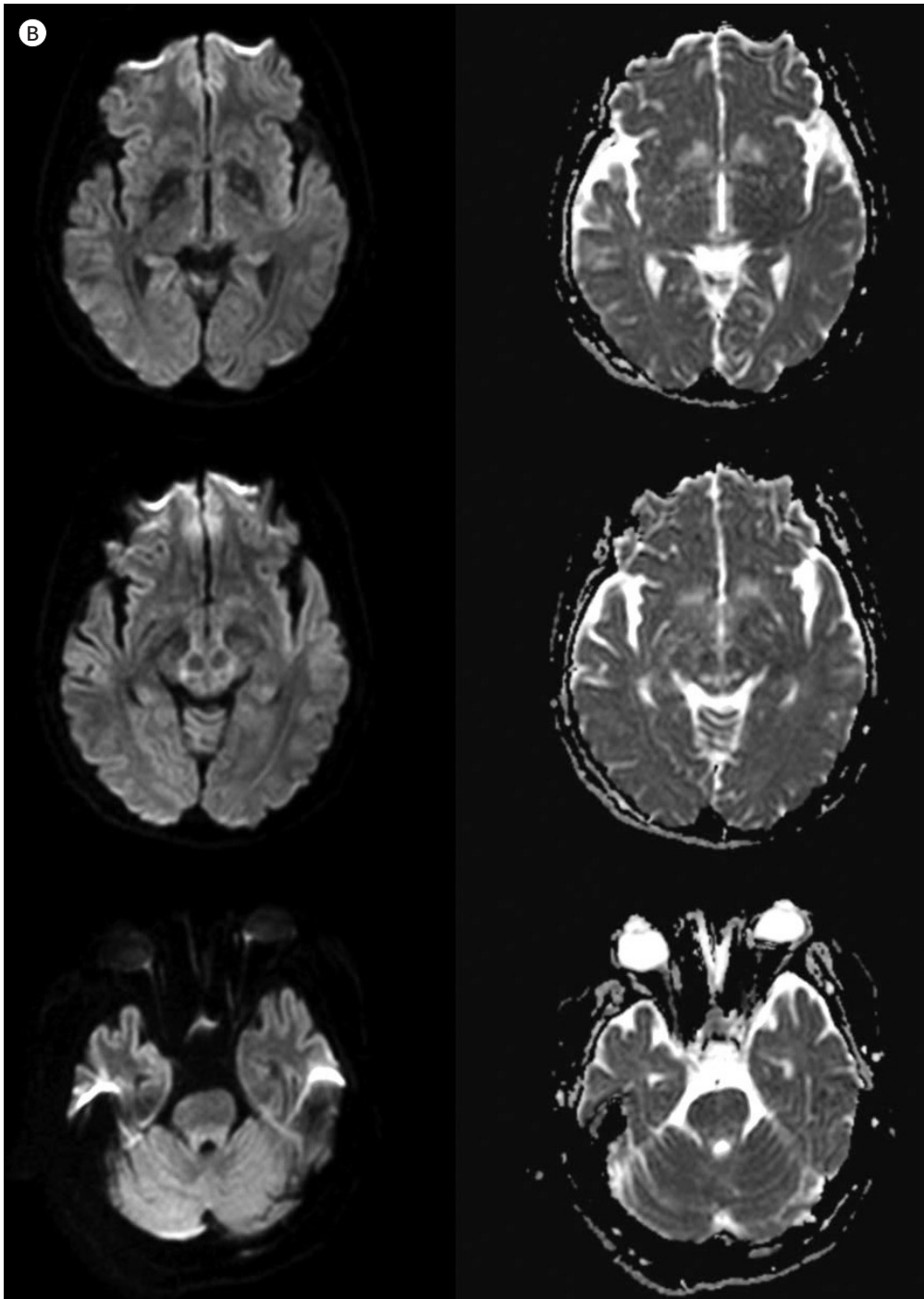
A. T1-weighted (upper), T2-weighted FLAIR (middle), and T2-weighted (lower) images. Symmetrically subtle hypointensity on the T1-weighted image and hyperintensity on the T2-weighted FLAIR image are seen in the basal ganglia, periaqueductal area, and median thalami. On the T2-weighted image (lower), the mammillary body shows no increase in signal intensity. FLAIR = fluid-attenuated inversion recovery



age, hypersignal intensities were suspected along the margin of the mammillary body, but in the T2 weighted image, the mammillary body itself did not increase the signal (Fig. 1A). These images required differentiation from Wernicke's encephalopathy and Wilson's disease, and we checked serum thiamine and copper level. In laboratory tests, thiamine and copper

Fig. 1. Leigh syndrome in a 21-year-old woman.

B. Diffusion-weighted (left) and apparent diffusion coefficient (right) images. Lesions observed on T1-weighted and T2-weighted fluid-attenuated inversion recovery images show no diffusion restriction.



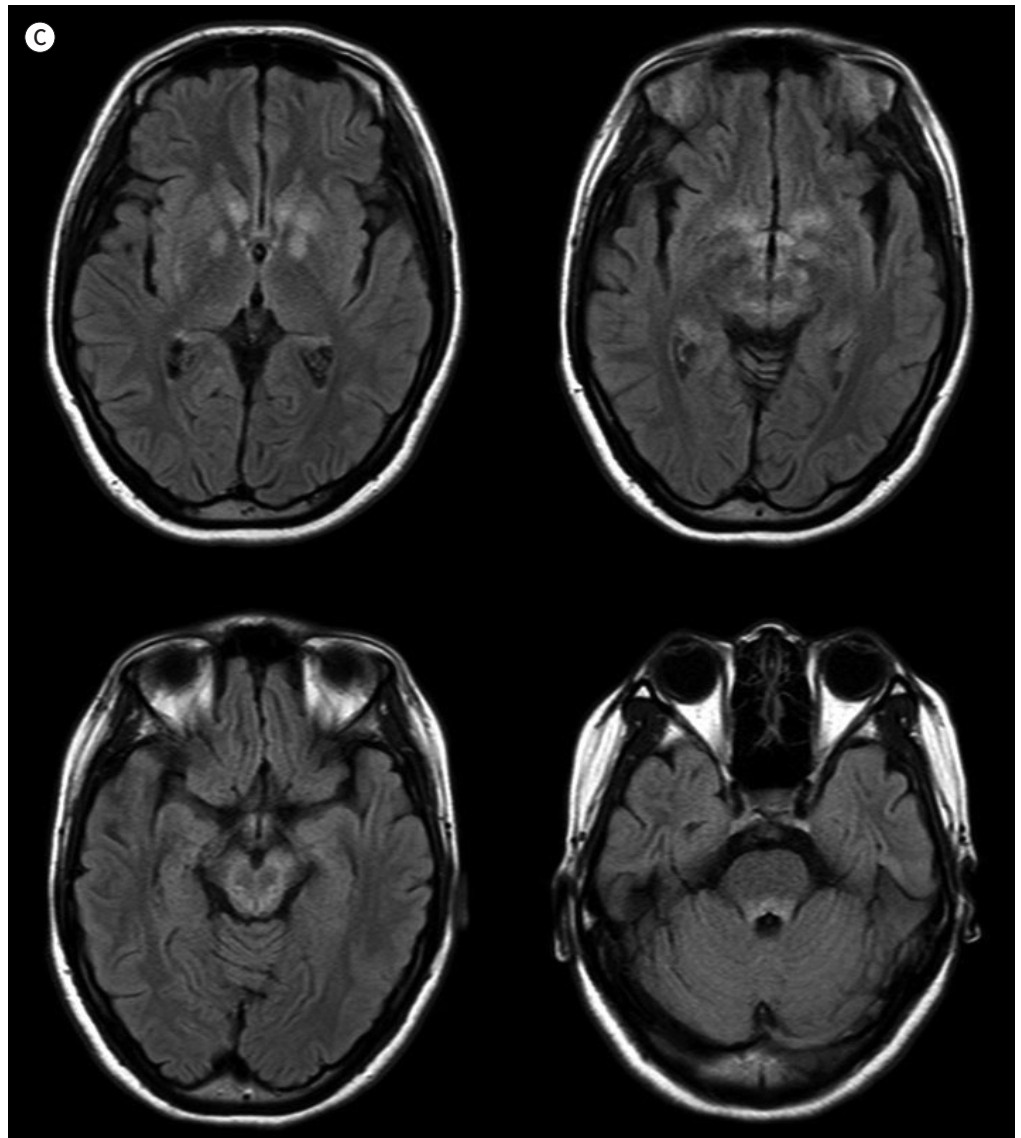
levels showed a normal range. We also tried to differentiate poisoning, such as CO intoxication, which could invade deep gray matter nuclei. But there was no history of poisoning. No diffusion restriction was observed in the diffusion weighted image and apparent diffusion coefficient (ADC) images (Fig. 1B). MR angiography was performed to confirm vascular abnormality, but nonspecific findings were observed.

We did not make an accurate diagnosis when considering history, imaging, and laboratory tests. Although thiamine levels were normal, she was treated with thiamine under the suspected of Wernicke's encephalopathy in imaging.

She took a follow up brain MRI two weeks later. Hypersignal intensity lesions mildly decreased in the flair image, which were symmetrically distributed in both basal ganglia, peri-

Fig. 1. Leigh syndrome in a 21-year-old woman.

C. On follow up brain MRI after two weeks, hyperintensity has mildly decreased on the fluid-attenuated inversion recovery image, which was symmetrically distributed in bilateral basal ganglia, periaqueductal area, and median thalami.



aqueductal area, and median thalami (Fig. 1C). Her symptoms were improved and she was discharged.

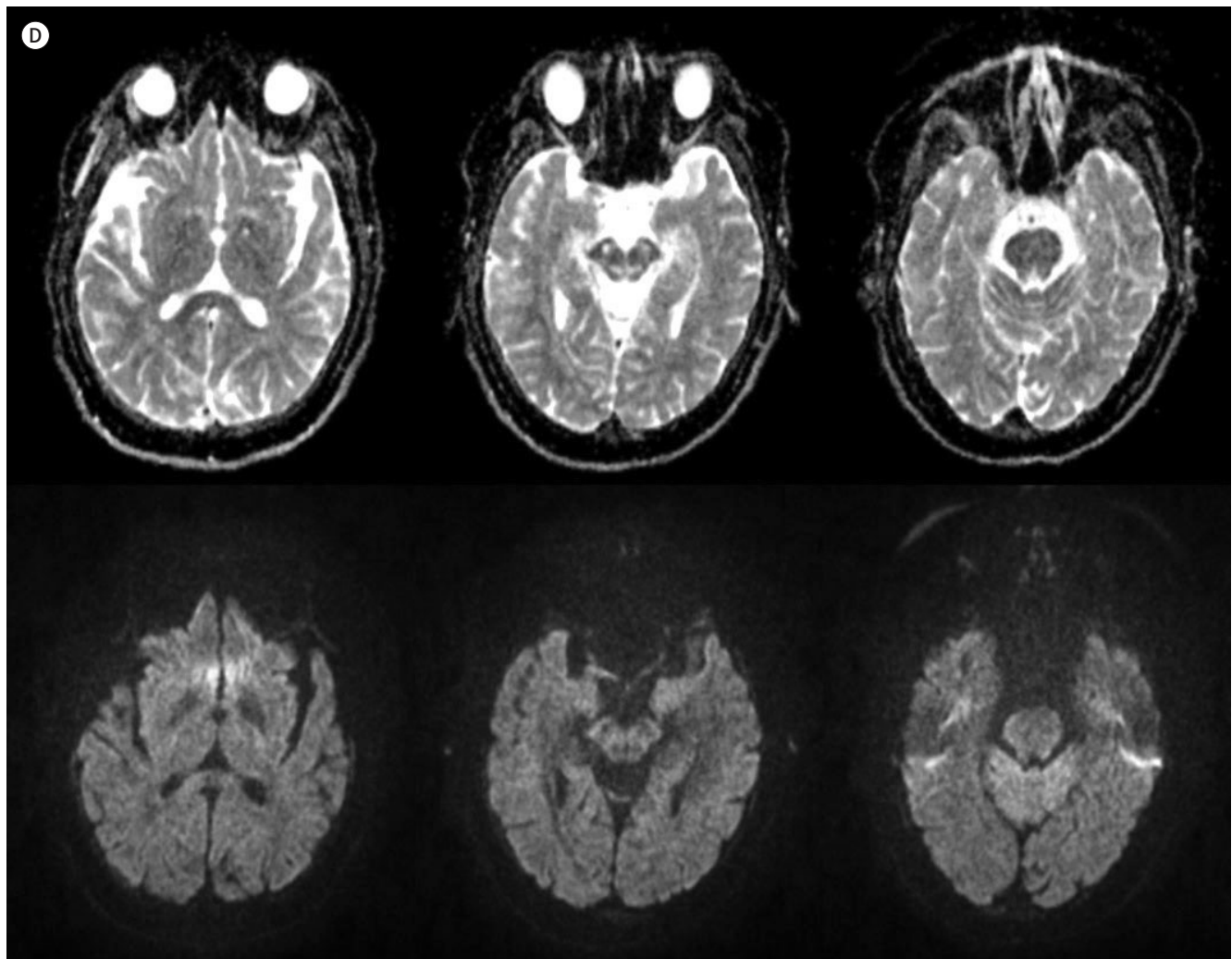
The second episode occurred one year later. She had diplopia and headache and took brain CT and brain MRI diffusion. Her brain had relatively cortical atrophy, especially both cortical sulci and cistern of frontal lobe were prominent. There was no definite diffusion restriction. Symmetrical increased diffusivity was still observed in periaqueductal gray matter of cerebral peduncle and midbrain in the ADC images. However, due to the limitation of image resolution, accurate comparison with previous images was difficult (Fig. 1D).

She has been taking thiamine and the thiamine level was in the normal range. We considered the possibility of other diseases and further investigated her family history. We found out her sister died of unknown cause at the age of ten, and suspected genetic disorder such as LS, which involve the similar lesions. She took a target exome sequencing and was diag-

Fig. 1. Leigh syndrome in a 21-year-old woman.

D. Follow up brain MRI on recurrent episode one year later, ADC (upper) and diffusion-weighted (lower) images. Brain diffusion-weighted MRI after the 2nd episode shows no definite diffusion restriction. Symmetrically increased diffusivity persists in the periaqueductal gray matter of the cerebral peduncle and midbrain on ADC images.

ADC = apparent diffusion coefficient



nosed as later-onset LS with m.9176T>C mutations.

DISCUSSION

LS or SNE is a progressive neurodegenerative disorder of childhood with an estimated incidence of 1:40000 births in the United States (1). The onset of symptoms usually begins before age 2 in the infantile form. But, it is also present in children and rarely in adulthood (4). Our patient had m.9176T>C mutations. The m.9176T>C mutation is pathogenic because it leads to the replacement of a highly conserved leucine with proline at amino acid position 217 in the alpha subunit. Few case reports of late- or adult-onset LS with the m.9176T>C mutation, however, have been reported. Particularly the m.9176T>C mutation, may cause a variety of phenotypes including late-onset LS (5).

Clinically, LS is characterized by psychomotor delay or regression, muscular hypotonia, brainstem signs, ataxia, pyramidal signs, respiratory insufficiency, lactate acidemia and acute deterioration following common infections (1). Laboratory test shows metabolic acidosis with elevated blood, cerebrospinal fluid (CSF) lactate, and pyruvate concentrations (6). Most patients with LS have a mutation in nuclear DNA, and about 25% have a mutation in mitochondrial DNA (2). Recently, introduction and utility of massively parallel sequencing technology has facilitated the identification of patients with mutations. This neurodegenerative disorder is genetically heterogeneous, and to date pathogenic mutations in > 75 genes have been identified, encoded by 2 genomes (mitochondrial and nuclear), involving all five respiratory chain complexes (7).

The diagnostic criteria are: 1) progressive neurological disease with motor and intellectual developmental delay; 2) signs and symptoms of brainstem and/or basal ganglia disease; 3) raised lactate levels in blood and/or CSF; 4) characteristic symmetric necrotic lesions in the basal ganglia and/or brainstem (8).

The most characteristic imaging findings are bilateral, symmetric focal hyperintensities in the basal ganglia, thalamus, substantia nigra, and brainstem nuclei on T2-weighted MRI (4). Similar lesions are also seen in Wernicke's encephalopathy, Wilson's disease, amino acid urea, mitochondrial encephalomyelopathies, and various forms of intoxication. LS does not typically involve the mammillary bodies (9). Occasionally, patients may have atypical neuroimaging features such as diffuse supratentorial leukodystrophy, unifocal or multifocal infarctions, diffuse or focal cortical atrophy, or predominant cerebellar atrophy (1). Our patients also had prominent brain atrophy in both frontal lobes. There is no curative treatment at present, and the aim is to improve the symptoms (3).

In the first episode, history, laboratory test, and imaging were considered, and the possibility of other diseases except Wernicke's encephalopathy was excluded. However, thiamine levels were normal. Nevertheless, Wernicke's encephalopathy was suspected in imaging and she was treated with thiamine and her symptoms improved.

We thought of two possibilities. First, it is the possibility of LS accompanied by Wernicke's encephalopathy. In the first episode, since the thiamine levels were normal, we only suspected Wernicke's encephalopathy, but did not make a diagnosis. According to the literature, a normal thiamine level does not exclude a diagnosis of Wernicke's encephalopathy. Serum

thiamine levels are a poor measure of thiamine status and thiamine assays are well recognized (10). Since we did not perform the thiamine assay, it is possible that Wernicke's encephalopathy was accompanied. However, Wernicke's encephalopathy generally involve mammillary bodies, as opposed to LS (9). Her mammillary body had no signal change and is thought to be closer imaging findings to LS.

Second, she had LS in response to thiamine treatment. In patients with LS with pyruvate dehydrogenase deficiency (PDHA1) or TPK deficiency (TPK1), thiamine treatment may help improve symptoms (7). But, we couldn't find the evidence of thiamine benefits for the m.9176T>C mutation in LS.

LS in adults is particularly rare and it is difficult to consider as a first impression. If the patient has bilateral symmetric T2 hypersignal intensities in multiple brainstem structures, basal ganglia with neurological problems and the symptoms do not improve even with treatment, the possibility of LS should be considered, as well as involve similar lesions with Wernicke's encephalopathy, Wilson's disease, toxic poisoning, degenerative condition, vascular abnormalities.

Author Contributions

Conceptualization, Y.E.; data curation, Y.E.; investigation, O.J.; project administration, Y.E.; resources, O.J.; supervision, Y.E.; validation, C.J., K.S.; visualization, O.J.; writing—original draft, O.J.; and writing—review & editing, C.J., K.S.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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베르니케 뇌병증으로 오인된 리 증후군: 증례 보고

오지수 · 최진옥 · 김수정 · 유은애*

리 증후군 또는 아급성 괴사성 뇌병증은 드물며, 빠르게 진행되는 신경 퇴행성 장애이다. 일반적으로 생후 1년 이내 호흡곤란, 심장기능 저하 등과 같은 증상이 발생하여, 2~3년 동안 환자의 75%가 사망에 이르는 심각한 질환이다. 리 증후군의 원인은 DNA mutation으로, 약 75%의 환자에서 핵 데옥시리보핵산의 돌연변이가 나타나고, 25%의 환자에서 미토콘드리아 데옥시리보핵산의 돌연변이가 발견된다. 임상 증상은 영향을 받은 뇌 영역에 따라 달라지며, 신경영상은 리 증후군 환자의 진단에 있어 중요한 역할을 한다. 성인에서 발생한 리 증후군은 더욱 드물고 어린 나이에 발생한 경우보다 더 느리게 진행된다. 우리는 성인에서 발생한 베르니케 뇌병증으로 오인된 리 증후군 환자의 증례를 보고하고자 한다.

전주예수병원 영상의학과