Unusual Case of Initially Misdiagnosed Acute Disseminated Encephalomyelitis Following Herpes Simplex Virus Type 1 Infection

Tip 1 Herpes Simpleks Virüsü Enfeksiyonunu Takiben Başlangıçta Yanlış Tanı Konmuş, Sıradışı Bir Akut Yayılmış Ensefalomiyelit Vakası

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ABSTRACT Acute disseminated encephalomyelitis (ADEM) is a monophasic, immune-mediated demyelinating disease that can arise spontaneously, however it most frequently follows an infectious illness (acute central nervous system infection), or immunization. As there are important variations with regard to treatment and prognosis, it is important to differentiate between ADEM and acute infections of the central nervous system, however it may not be easy in all cases. We report a 9-year-old case of atypical ADEM involving the brainstem following the Herpes Simplex Encephalitis Type 1; who has been initially misdiagnosed, and had high fever till the initiation of corticosteroid treatment.

Key Words: DNA polymerase, simplex virus; adult children

ÖZET Akut yaygın ensefalomiyelit (ADEM) kendiliğinden ortaya çıkabilen, tek fazlı, bağışıklık sistemi-aracılı miyelinizasyonu bozucu bir hastalıktır; bununla birlikte, en sık olarak enfeksiyöz bir hastalığı (akut santral sinir sistemi enfeksiyonu) veya aşılamayı takip etmektedir. Tedaviye ve prognoza göre önemli değişkenlikler bulunduğundan, ADEM ve santral sinir sisteminin akut enfeksiyonları arasında ayırım yapmak önemlidir; bununla birlikte bu ayırım tüm vakalarda kolay olmayabilir. Biz, Tip 1 Herpes Simpleks Ensefaliti'ni takiben beyin sapını da tutan, başlangıçta yanlış tanı konan ve kortikosteroid tedavisinin başlangıcına kadar yüksek ateşi süren, 9 yaşında bir atipik ADEM vakasını bildiriyoruz.

Anahtar Kelimeler: Herpes simpleks tip 1; genç adolesan

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Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disorder of the central nervous system (CNS) that is usually monophasic, but a relapsing variant, is also well-described.[1,2] However, the children with this disease sometimes pose a difficult diagnostic dilemma for the treating physician, as it may be difficult to clinically distinguish ADEM from CNS infections, with a consequence of delayed treatment and possible neurologic sequelae.[3,4] The pathogenesis is unknown; but there is evidence of autoimmune-mechanisms initiated by autoreactive CNS-specific T-cells causing demyelization following an antecedent infection, vaccination, or even with no recognized preceding illness.[5]

In this paper, an initially misdiagnosed, unusual case of ADEM following *Herpes simplex virus* type 1 infection, involving the optic tracts, mesencep-

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halon, and the brainstem is presented with serial magnetic resonance imaging (MRI) and positron emission tomography (PET) follow-up findings.

CASE REPORT

A 9-year-old boy with no antecedent illness presented with uncontrolled fever. He had developed headache and nausea two days prior to his presentation. Prediagnosed with meningitis, he was put on an initial antibiotic and non-steroidal anti-inflammatory drug regimen. A brain computed tomography (CT) on day four of his admission was normal. As the patient did not show any improvement, with persistent seizures during his hospitalization, he was transferred to a pediatric neurology unit for further evaluation. His blood count, blood biochemistry, C-reactive protein, throat, urine and blood cultures were within normal limits. Cerebrospinal fluid (CSF) examination revealed 12 leukocytes (80% lymphocytes), 28 mg/dl protein, 49 mg/dl glucose (serum glucose 94 mg/dl), and 125 mEq/l chloride. CSF was negative for oligoclonal bands. Cranial MRI showed patchy areas of hyperintensity at the right thalamus, periventricular white matter, and optic tracts (Figure 1). Serum and CSF antibodies for neurotropic viruses were negative, except for *Herpes simplex virus* (HSV)-1 [serum HSV-type 1 IgM: 1.7 RU/ml, HSV-type1 IgG: 28.3 RU/ml; CSF HSV-type 1 IgM: (±) (no titrates), HSV-type 1 IgG: 182.7 RU/ml]. Convalescent titers of HSV-type 1 IgG antibodies showed significant HSV-1 IgG titer seroconversion, which was greater than four-fold. Acyclovir was initiated for the treatment of HSV-1 encephalitis. At the second week of acyclovir treatment, the patient did not show any clinical improvement, with persistent fever. Repeated blood and CSF cultures failed to produce a causative agent. Considering familial history and a positive purified protein derivative (PPD) test, antituberculosis agents were added to his treatment. On further laboratory investigation, urine and plasma amino acids, urine organic acids, arterial blood gas, and ammonium levels were found to be normal. There was no ewidence for mitochondrial diseases in muscle biopsy. CSF lactate (20.6 mg/dl; range: 4.5-19.5), pyruvate (0.52 mg/dl; range: 0.36-0.59), and plasma lactate: (34.2 mg/dl; range: 4.5-19.5) levels were within normal limits. Serological vasculitis screening tests (i.e. complement factors, anti-cardiolipin antibodies, anti-SSA, anti-SSB, rheumatoid factor and anti-double stranded-DNA antibody) were negative. Immunoglobulin levels were found high (IgA: 330 mg/dl, IgM: 343 mg/dl, IgG: 3410 mg/dl). Peripheral screening for other primary site of malignancy, including bone marrow sampling, abdominal sonography and thoracic CT failed to reveal any pathology. The patient's fever still persisted, with additional onset of visual disturbances, deteriorating of consciousness, and quadriparesis. A repeated MRI on day 45 revealed multiple new hyperintense foci, some of which showing intense contrast enhancement at the pons, left cerebral peduncle, thalamus, and optic chiasm (Figure 2). PET scan revealed reduced levels of brain metabolism on the left thalamus, compared to the right (Figure 3). In light of these findings, the patient was diagnosed with ADEM secondary to a HSV infection, and put on a high-dose intravenous steroid regimen. On day three of the steroid therapy, the patient was unfebrile with fast clinical improvement. Two control MRI, performed one month apart, showed resolution of the lesions (Figure 4). Four years after admission, the patient was doing well, with no residual neurologic sequelae except for impairment in discriminating red and green colors.

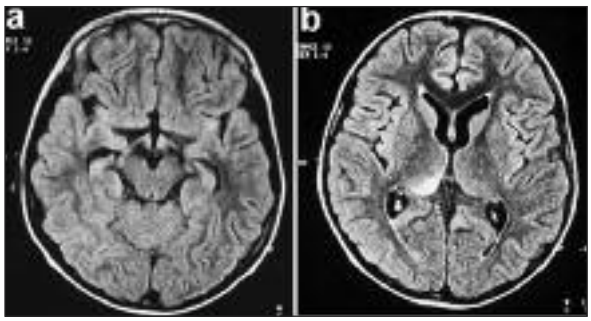

FIGURE 1: Axial FLAIR images obtained at the level of mesencephalon **(a)** and basal ganglia **(b)**. Note diffuse increased signal intensity at the right thalamus.

DISCUSSION

It is important to recognize the spectrum of both clinical and MRI findings in ADEM not only in order to limit the inflammatory process involving the

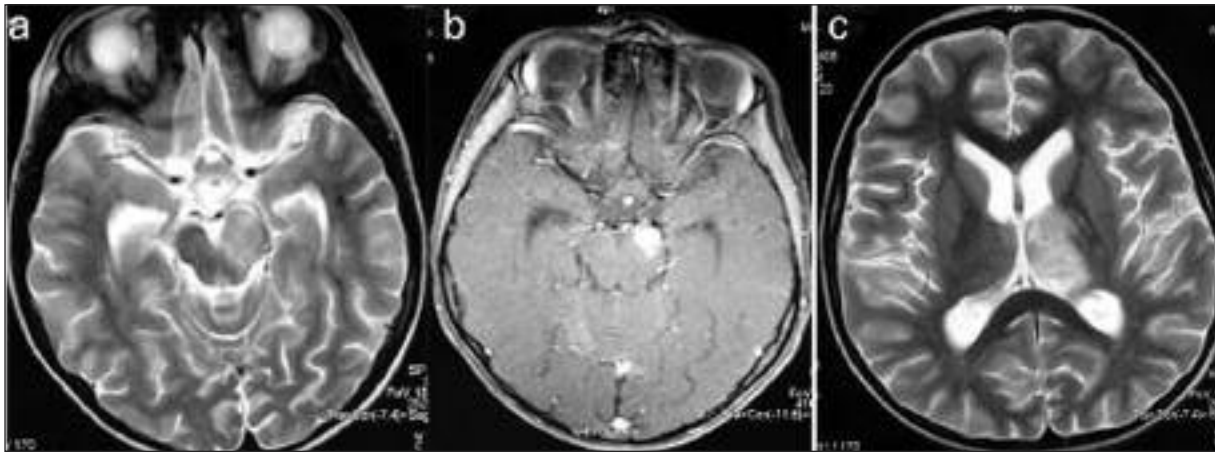

FIGURE 2: Repeated MR images at day 45. Axial T2 weighted **(a)**, postcontrast T1 weighted **(b)** images obtained at the same level and axial T2 weighted image from the basal ganglia **(c)** shows newly developed increased signal intensity at the optic chiasm, left thalamus and left cerebral peduncle. The left cerebral peduncle is enlarged and shows nodular enhancement. Please note that the right thalamus is normal at this stage.

CNS, but also to prevent sequelae or even mortality.[3] The characteristic clinical features of ADEM include fever, headache, meningismus, seizures, optic neuritis, lethargy and diffuse encephalopathy.[4-6] In the case presented, the patient was initially misdiagnosed with bacterial meningitis, and then as HSV type 1 encephalitis, and treated accordingly in a state hospital. Although it is well known that HSV type 1 is an established cause of encephalitis, it must be emphasized that there is a form of encephalitis not due to direct viral infection of the brain parenchyma, but an alteration of normal immune function following a viral infection; it is commonly known as ADEM.[7] Kaji et al. reported a case series in which approximately 10% of the patients with HSV infection subsequently developed ADEM.[8] In this setting, MRI plays an important role in differentiating ADEM from herpes encephalitis, since both have distinct established imaging findings.[7,8] On MRI, ADEM characteristically involves areas including the corona radiata, periventricular white matter, optic nerve, cerebellar peduncles, and brainstem in an asymmetrical fashion. Deep gray matter involvement may also be seen. On the contrary, HSV encephalitis is generally symmetrically confined to the fronto-temporal area and the deep gray matter is generally spared.[7] PET may also be used as an adjunct to MRI in differentiating tumors and encephalitis from ADEM, when the lesion is not entirely characteristically located, such as in the brainstem or pons. On PET scans, the demyelinating process is identified by decreased levels of metabolism, like in the presented case, as opposed to encephalitis.[9]

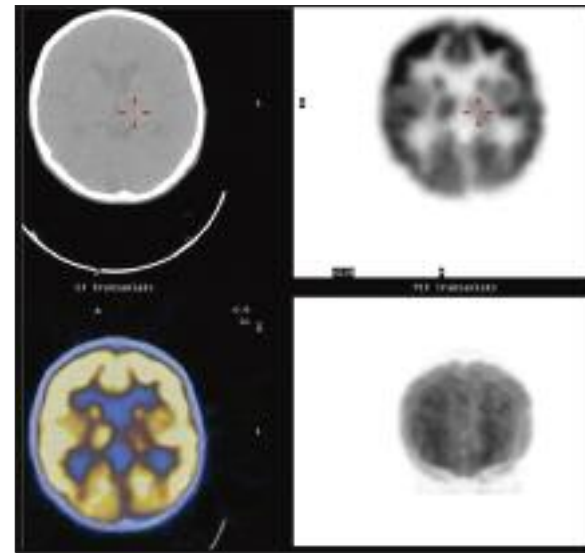

FIGURE 3: Cerebral FDG-PET study depicts decreased levels of metabolism at the left thalamus supportive of a demyelinating process.

Due to the delay in diagnosis and initiation of proper treatment, the presented patient exhibited a progressive form, with appearance of new lesions involving the thalamus, mesencephalon and pons during the 45 days of hospitalization, which in fact reflected a radiological relapse typical of ADEM. Involvement of the mesencephalon and pons, as in

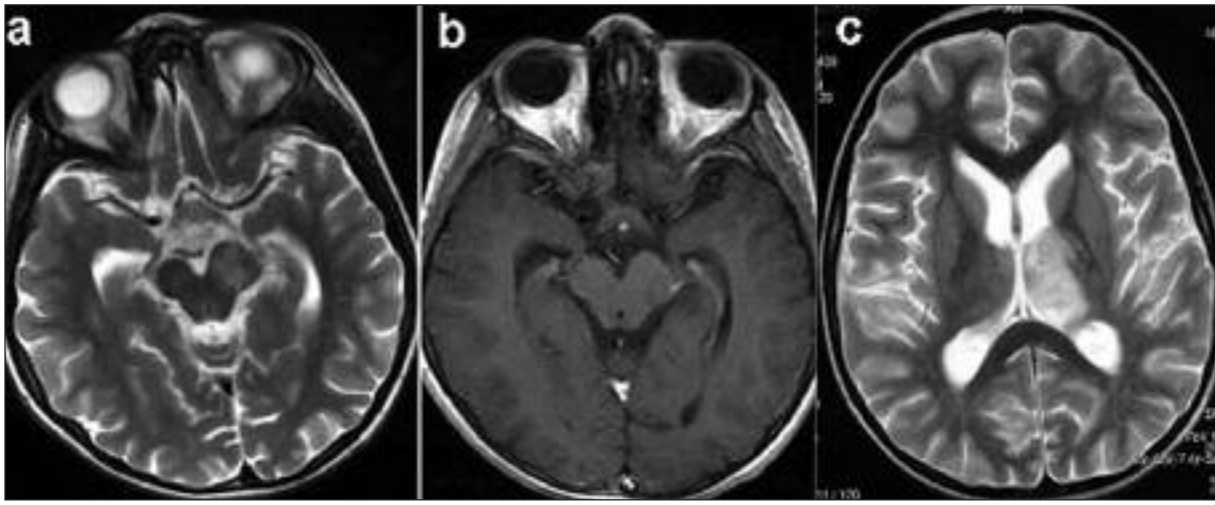

FIGURE 4: Control MRI performed three months after the first presentation. Axial T2 weighted **(a),** postcontrast T1 weighted **(b)** images obtained at the same level and axial T2 weighted image from the basal ganglia **(c)** shows a significant resolution of the increased intensities at the left cerebral peduncle, thalamus and optic chiasm. No enhancement was observed at the left cerebral peduncle at this stage.

this case, is unusual and seldomly reported.[9,10] Contrast enhancement in ADEM is not an attributable feature and, when reported, it is in ring, diffuse or nodular pattern.[10] In the presented case, only the pons lesion showed nodular contrast enhancement simulating a tumefactive process. This selective enhancement may be due to different degrees of damage in blood-brain barrier in different lesions. Considering the multiphasic nature of the disease, it might also be considered that this selective enhancement may be partly dependent on the age of each lesion.[9]

Although the pathogenesis of ADEM is considered to be autoimmune, a number of authors still sustain the hypothesis of an infectious etiology.[11] The lack of response to anti-infectious therapy and even the worsening of the clinical status in this case supports the autoimmune theory in ADEM. Additionally, the fact that CSF HSV-1 IgG levels were much higher than those of plasma IgG is also supportive of the intrathecal antibody production. This demonstrates that an infected host could mount an immune reaction, resulting in the production of antiviral antibodies, which can, in turn, cross-react with myelin autoantigens, such as myelin basic protein, proteolipid protein, and myelin oligodendrocyte protein. This process finally leads to the pathological picture of ADEM.[12]

CONCLUSION

Acknowledgement of the clinical and radiological characteristics is essential for the early diagnosis and accurate treatment of the post-infectious demyelinating process. Neuroimaging, especially MRI or, in less characteristic cases, PET, plays an important role in the correct diagnosis and distinction of ADEM from other CNS pathologies, including MS and encephalitis.

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