Radiologic Diagnosis / *Radyolojik Tanı*

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What is Your Radiologic Diagnosis?

Radyolojik Tanınız Nedir?

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A six-year-old girl presented to the pediatric emergency outpatient clinic of our hospital with headache, fever, and vomiting. It was learned from the patient's history that she had been operated for medulloblastoma three months ago, received one course of cisplatin and etoposide treatment two months ago, and radiotherapy was completed one week ago. The patient's body temperature was 39.4 °C on admission.

During observation in the emergency department, the patient became disoriented, had incoherent speech and seizures. Contrast-enhanced cranial magnetic resonance imaging (MRI) showed diffusion restricted areas in the left amygdala, left temporal lobe and left insula (Figure 1A,B). No pathologic signal change was observed at these levels on fluid attenuated inversion recovery (FLAIR) sequence and contrast-enhanced series (Figure 1C,D).

The patient was admitted to the ward with a pre-diagnosis of encephalitis, and intravenous acyclovir and ceftriaxone were started. Herpes simplex virus (HSV) type 1 polymerase chain reaction (PCR) was positive in the cerebrospinal fluid (CSF) sample and *Haemophilus influenza* and *Streptecoccus pneumoniae* were positive in the respiratory panel. During the ward follow-up, confusion, swallowing dysfunction, gibberish and salivation developed, and brain MRI was performed again one day later. In the interim period, it was observed that diffusion restricted areas in the left temporal lobe and insula were enlarged, and diffusion restrictions developed in a large area extending to the vertex in the left parietal lobe, left thalamus and right insula (Figure 2).

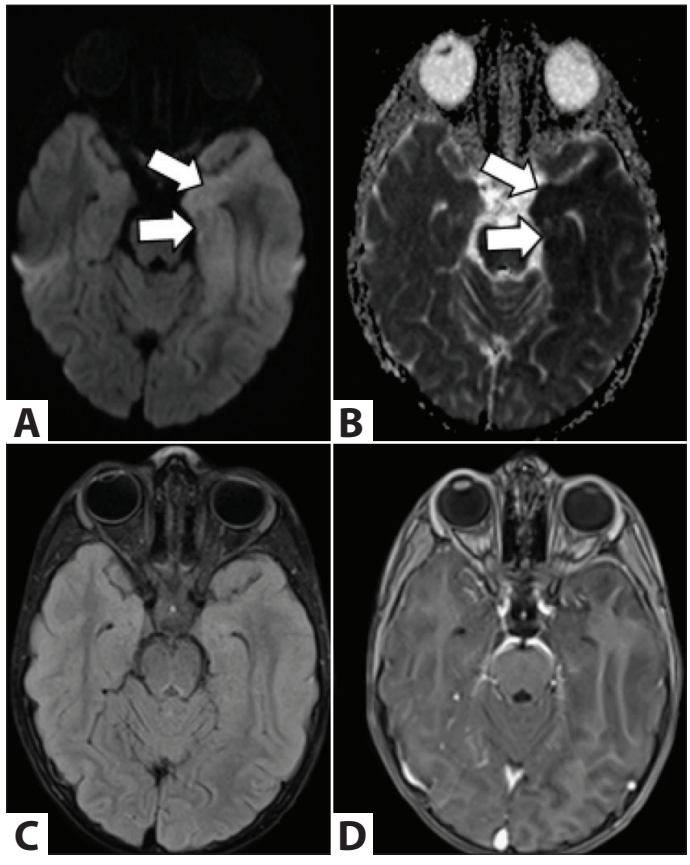

Figure 1. Diffusion-weighted imaging **(A)** shows diffusion restriction in the left amygdala, anterior and mesial temporal lobe (white arrows). On ADC map **(B)**, these areas are hypointense (white arrows). No pathologic signal change is observed on FLAIR sequence **(C)** and post-contrast T1-weighted sequence **(D)**.

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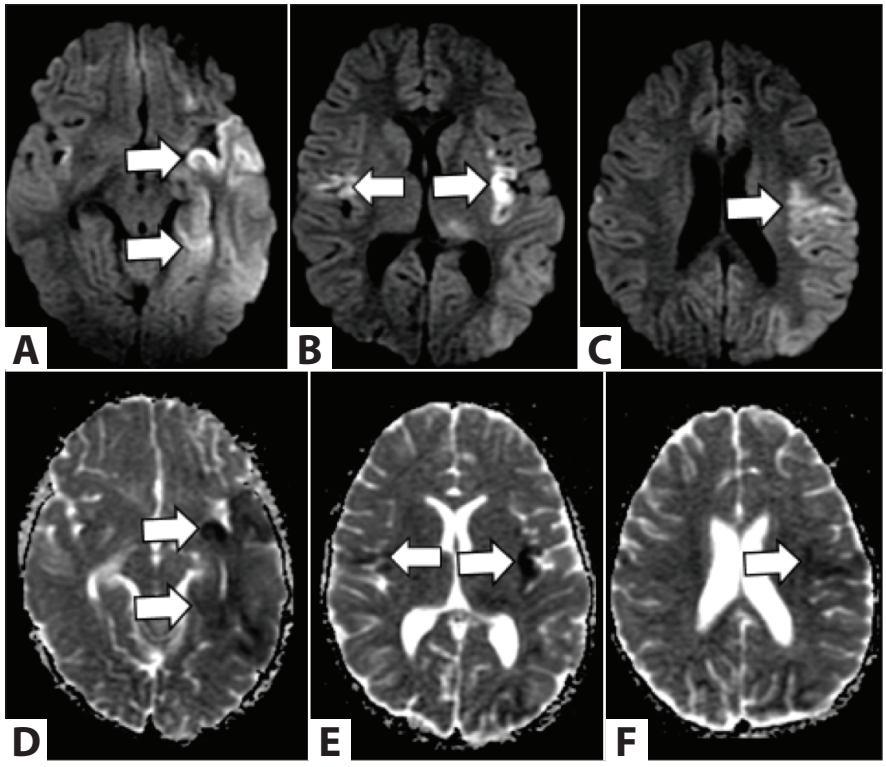

Figure 2. Diffusion-weighted images in the top row **(A-C)** and ADC maps from sections passing through the same level in the bottom row **(D-F)**. Cortical diffusion restrictions are observed in the left temporal lobe (**A** and **D**), bilateral insular cortex (**B** and **E**), left frontal and parietal lobes (**C** and **F**) (white arrows).

On the fourth day of hospitalization, the clinical picture of the patient with hypotensive values requiring inotropes was evaluated as septic shock, and ceftriaxone was discontinued and vancomycin, meropenem and amikacin treatment was started. Considering that the hypotensive values of the patient might be secondary to central adrenal insufficiency due to high dose steroid treatment used during radiotherapy, methylprednisolone treatment was initiated. Although the patient's positive HSV type 1 CSF PCR result and imaging findings were incompatible, intravenous immunoglobulin (IVIG) treatment was given in the early period considering possible causes such as limbic encephalitis.

On the fifteenth day of hospitalization, the general condition of the patient deteriorated and repeated brain MRI was performed to check brain findings. On post-contrast T1-weighted sequence, cortico-juxtacortical linear contrast enhancement was observed in the left temporal lobe and fronto-insular region (Figure 3A). Axial magnetic susceptibility-weighted imaging revealed diffuse hemorrhagic changes, more prominent in the left anterior and mesial temporal regions (Figure 3B). On axial FLAIR sequence, there were expansile signal increases in the entire left temporal lobe, at the base of the left frontal lobe, bilateral insular and frontoparietal operculum, more prominent on the left, and associated compression of the left lateral ventricle and obliteration of the sulci (Figure 3C). MR angiography revealed patent vascular structures (Figure 3D).

Intravenous acyclovir and meropenem treatments were completed for 28 days, and general condition improved. HSV type 1 PCR was negative in the CSF sample sent before discharge.

Contrast-enhanced cranial MRI performed as follow-up at four months after discharge revealed the development of larger sequel cystic encephalomalasic areas in bilateral insula, left fronto-insular cortex and left temporal lobe, and disappearance of contrast enhancements observed in the previous examination (Figure 4).

What is your diagnosis based on these findings in the patient whose MRI sections are given?

Diagnosis: Herpes Simplex Virus (HSV) Encephalitis

Short Discussion

Herpes simplex virus is the most common agent of acute fatal sporadic encephalitis. The causative agent is HSV type 1 in more than 90% of patients and the mortality rate is over 70% in patients who do not receive treatment for the causative agent at the appropriate time (1). The causative agent of

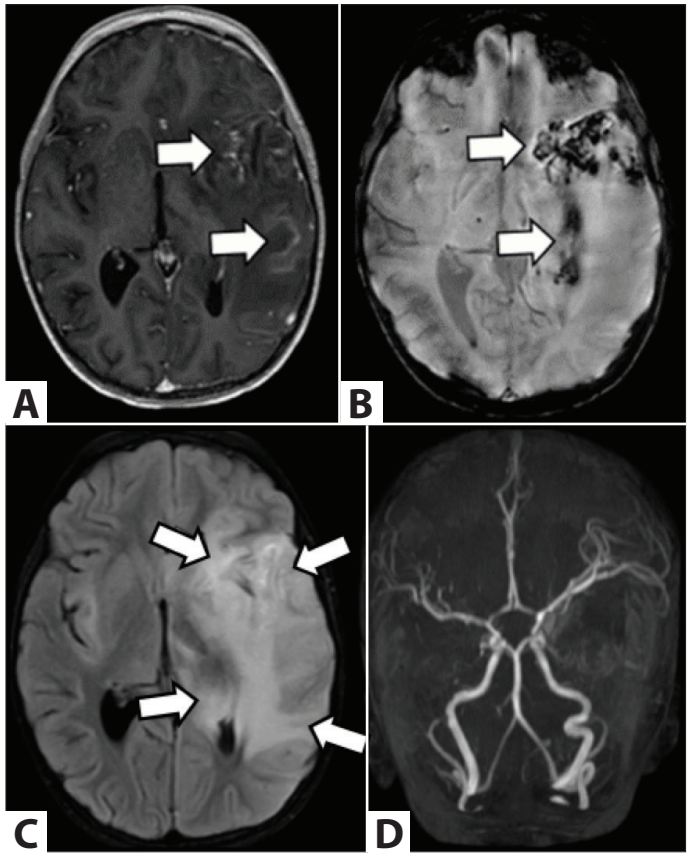

Figure 3. Post-contrast T1-weighted images **(A)** show superficial cortico-juxtacortical linear contrast enhancements in the affected areas (white arrows). Magnetic susceptibility-weighted imaging **(B)** shows left fronto-insular and temporal hemorrhagic changes, more prominent in the left temporal pole (white arrows). Axial FLAIR **(C)** sequence shows diffuse T2 hyperintense parenchymal signal changes in the left fronto-insular and left temporal lobe, which significantly narrow the left hemispheric sulci (white arrows). Multiplanar reconstruction MR angiography **(D)** shows patent major intracranial vascular structures.

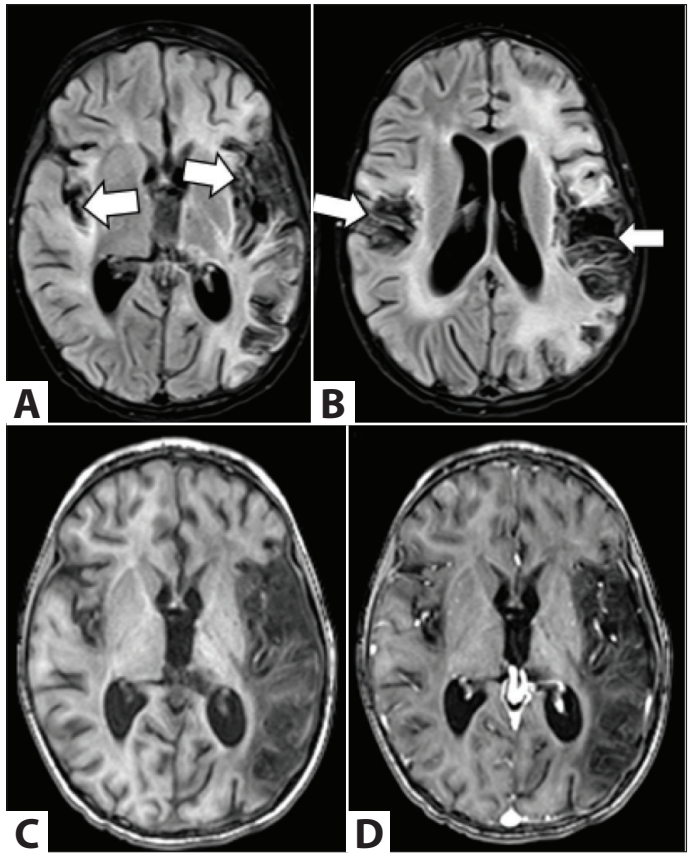

Figure 4. Axial FLAIR sequence (**A** and **B**) shows sequel cystic encephalomalasic areas in the parenchyma of bilateral insular cortex (**A**, white arrows) and frontoparietal region (**B**, white arrows), more prominent on the left. Pre-contrast T1-weighted **(C)** and post-contrast T1-weighted **(D)** sequences show no pathologic contrast enhancement in the sequel encephalomalasic brain parenchyma.

HSV encephalitis in adults and older children is HSV type 1 and typically causes bilateral asymmetric involvement of the temporal and frontal lobes. In neonates, encephalitis caused by HSV type 2, usually acquired during vaginal delivery, causes diffuse brain involvement.

HSV type 1 reaches the brain via trigeminal nerve branches after primary oropharyngeal infection and remains latent in the trigeminal ganglion until reactivated in conditions such as trauma, stress, and immunosuppression (2). While two thirds of the cases occur with reactivation of latent type 1, the remaining cases occur as a result of primary infection (1).

HSV encephalitis presents with nonspecific symptoms and signs including headache, fever, nuchal rigidity, changes in personality and mental status, focal or generalized seizures and focal neurological deficits. HSV encephalitis characteristically affects the anterior and medial part of the temporal lobes, insula and orbital part of the inferior frontal lobe (3). Although the disease is bilateral, one side is usually more severely affected. During the course of the disease, the infectious process may also affect the frontal and parietal cortex, posterior occipital cortex, limbic system, cingulate gyrus and thalamus.

The gold standard in the diagnosis of HSV encephalitis is demonstration of the viral genome in PCR study performed in CSF samples (2). Detection of HSV-DNA in CSF has 98% sensitivity and 94% specificity in the diagnosis of HSV encephalitis (3).

In the acute period, HSV encephalitis causes acute inflammation, congestion, and petechial hemorrhages especially in the temporal lobes and adjacent meninges. This is followed by hemorrhagic necrosis and liquefaction in the second week of the disease.

Brain MRI examinations including diffusion-weighted imaging (DWI) are more sensitive in the diagnosis of HSV encephalitis than computed tomography (CT) in detecting early findings (3). In up to 25% of patients, CT findings

are normal in the early period and become positive only after the second week. On CT, parenchymal low-density areas compatible with edema forming a mass effect in the temporal lobes and narrowing the sulci and hemorrhagic high-density foci accompanying in the late period are observed. In the chronic period, sequel hypodense areas belonging to parenchymal sequel volume loss representing encephalomalasic areas are observed (4).

T2-weighted (T2W) and FLAIR sequences of brain MRI characteristically show signal increases consistent with parenchymal edema and inflammation affecting especially the inferior and medial temporal lobe and extending to the insula.

Diffusion weighted imaging is superior to T2W and FLAIR imaging in the diagnosis of necrotizing encephalitis. Two different diffusion changes occur in the early phase of the disease. In diffusion restriction due to cytotoxic edema, hyperintensity on DWI and hypointensity on ADC map are observed and these findings usually indicate irreversible neuronal damage. In vasogenic edema, diffusion of water molecules increases and is hyperintense in both DWI and ADC maps. This finding reflects changes that may be reversible with appropriate treatment and has a better prognosis than cytotoxic edema. These two diffusion changes are usually seen together.

A few days after the onset of symptoms, parenchymal or meningeal contrast enhancement in patchy, gyriform or diffuse patterns may be observed in the affected areas (2). However, since these contrast patterns may not be seen in the early period, absence of contrast does not exclude the diagnosis of HSV encephalitis. Diffuse contrast enhancement seen in the early period can be used to differentiate from acute infarction, which causes similar signal changes on diffusion-weighted imaging. Contrast enhancement in the infarct becomes prominent in the subacute period after the second week and is usually in a gyriform pattern. In addition, the fact that the basal ganglia, especially the lentiform nucleus, are not affected may help to differentiate HSV encephalitis from middle cerebral artery infarcts (3).

Gradient echo, T2* sequences such as magnetic susceptibility weighted imaging are superior to spin echo sequences such as conventional T1W and T2W in demonstrating hemorrhagic changes and their addition to routine imaging may help in differential diagnosis and prediction of prognosis. In the chronic period, atrophy and cystic encephalomalasic changes are seen in the affected areas.

Autoimmune limbic encephalitis is included in the differential diagnosis of HSV encephalitis. HSV encephalitis has a more acute onset and psychiatric symptoms are observed more rarely compared to autoimmune limbic encephalitis (5). Involvement of the insular cortex, the fact that the basal ganglia are not affected by the disease and the observation of hemorrhagic changes on magnetic susceptibility weighted imaging are findings supporting HSV encephalitis (6). In limbic encephalitis, predominantly the mesial part of the temporal lobes is affected, and bilateral involvement is observed more frequently compared to herpes encephalitis. Demonstration of HSV PCR positivity in CSF samples has high sensitivity and specificity for the differentiation of these two pathologies, which can be fatal in patients who do not receive appropriate treatment in the early period.

Acyclovir is used as the primary treatment for HSV encephalitis. The mortality rate, which has exceeded 70% in untreated cases, has decreased to 19% in six months and 28% in 18 months with acyclovir treatment (1). Despite early treatment, the highly prominent parenchymal sequelae that developed in our patient may be related to complications developing due to immunosuppression due to the oncologic treatments the patient received.

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