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Herpes simplex and Ebstein Barr virus encephalitis complicated with Klüver-Bucy syndrome

Case Report

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Abstract: A case of sixteen-year-old boy with initial herpes simplex virus (HSV) and Epstein–Barr virus (EBV) encephalitis is reported. Herpesviruses are often found in cerebrospinal fluid (CSF) along with EBV. After eradication of HSV in CSF in this case, a positive polymerase chain reaction (PCR) to EBV in CSF remained along with a severe clinical picture (segmental myoclonus and Klüver-Bucy syndrome) and worsening of brain magnetic resonance imaging (MRI) findings. Neurological and psychological improvement occurred after treatment with intravenous immunoglobulin.

Keywords: *Herpes simplex • Ebstein Barr virus • Rncephalitis • Klüver-Bucy syndrome*

1. Introduction

Herpes simplex virus encephalitis (HSVE) in children older than 3 months, adolescents and adults occurs as a complication of primary HSV infection in one-third of cases. The rest of the cases are a result of HSV reactivation. After primary infection, the virus persists in latent form in the trigeminal sensory ganglion. In some cases, the virus reactivates, and after retrograding along branches of trigeminal nerve, it causes brain infection, especially of the frontal and temporal lobes. The cornerstone of diagnostics is detection of HSV DNA [1] by polymerase chain reaction (PCR) testing.

Epstein–Barr virus (EBV) is a lymphotropic virus that causes infective mononucleosis. Primary EBV infection leads to complications in approximately 20% of cases, and central nervous system (CNS) involvement (encephalitis, meningoencephalitis, optical neuritis) occurs in 5% of cases. Different pathogens, including herpesviruses, are often found in CSF along with EBV. Immunological mechanisms are probably responsible for more CNS involvement in EBV infections than direct viral invasion. EBV is the most frequent agent to mimic HSVE. Although infection resolves in most cases without neurological sequelae, persistent deficits occur in 10% of cases, but few lethal outcomes have been registered [2].

Kluver-Bucy syndrome (KBS) is a rare behavioral impairment associated with damage to both the anterior temporal lobes of the brain. It causes individuals to put objects in their mouths and engage in inappropriate sexual behavior. Other symptoms may include visual agnosia, loss of normal fear and anger responses, memory loss, distractibility, and dementia. The syndrome occurs with head trauma, Alzheimer's disease, Pick's disease, ischemia, anoxia, progressive subcortical gliosis, Rett syndrome, porphyria, carbon monoxide poisoning and after herpes encephalitis. KBS may be transient after head trauma, but it can be a persistent feature of the postencephalitic syndrome [3].

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We report a case of a 16-year-old boy with initial HSV and EBV encephalitis. After eradication of HSV in CSF with acyclovir treatment, a positive polymerase chain reaction (PCR) result to EBV in CSF remained, along with a severe clinical picture that included segmental myoclonus and Klüver-Bucy syndrome and worsening of brain findings on MRI. After treatment with intravenous immunoglobulin (IVIG), the neuroimaging findings improved, as did the patient's neurological and psychological status.

2. Case study

A 16-year-old previously healthy boy became ill 7 days prior to admission with a fever to 39 degrees Celsius and headaches. He was treated with amoxicillin and antipyretics. On the day of admission, he was sub-febrile. Generalized tonic seizures followed a postictal state with severe psychological and motor agitation, periodical aggressiveness, visual hallucinations and only short periods of lucidity. At a regional hospital, he was sedated and endotracheally intubated because of respiratory depression. A computed tomographic (CT) scan of the brain was performed, with normal findings. The patient was transferred to our institution.

On admission he was sedated and afebrile. Other clinical findings were normal.

Laboratory findings showed a negative C-reactive protein. A complete blood count and other biochemical findings, including function of kidneys and liver, were normal.

A lumbar puncture was performed three times during the hospitalization. The findings are shown in the Table 1. Oligoclonal bands in CSF were negative. CSF cultures were repeatedly negative.

Table 1. CSF findings.

Lumbar puncture	Cells/mm^3	CSF protein	CSF glucose	PCR DNA HSV type 1	PCR DNA EBV
1st day	436 lymphocytes	0.56 g/L (↑)	Normal	Positive	Positive
7th day	18 lymphoc ytes	Normal	Normal	-	-
14th day	0	Normal	Normal	Negative	Positive

IgM enzyme linked immunosorbent assay (ELISA) for *Chlamydia pneumoniae*, adenoviruses, EBV was positive and negative for HSV type 1 and 2.

Serum immunoglobulin (IgM, IgG, IgA), C3, C4 complement components were within the referral ranges. Testing for lupus anticoagulant, antinuclear antibody, and anti-neutrophil cytoplasmic antibodies was negative.

On admission to the Intensive Care Unit, artificial ventilatory support was started along with continuous sedation (midazolam), acyclovir, antibiotics (ceftazidime, macrolide) and antiedematous therapy. Recurrent, generalized myoclonic seizures primarily precipitated with somatosensory stimulation were treated with diazepam. An electroencephalogram (EEG) showed low-voltage rapid activity at 15 to 20 cps. A continuous midazolam infusion was discontinued after 48 hours; the patient was extubated on day 3. An MRI scan of the endocranium, performed on day 4 of treatment, revealed the presence of several subtle foci of increased signal on fluid-attenuated inversion recovery (FLAIR) sequences, associated with a restricted diffusion signal on diffusion-weighted imaging (DWI) sequences, involving only the cortex in several locations in both cerebral hemispheres (both frontal and parietal lobes and right occipital and left temporal lobes) (Figure 1 A-C).

During the next days, the patient was somnolent with sporadic segmental myoclonus of muscles in the right upper portion of the face (without neurophysiological correlate); therefore, sodium-valproate was started. As a decreased level of consciousness persisted, an MRI scan of endocranium was repeated on the 12th day of hospitalization and revealed a massive, multifocal, diffuse pathological process localized solely in the cerebral cortex of both hemispheres, most prominently in the insula and left parietal lobe. The patient became conscious with reduced myoclonus, but with severely changed cognitive functions. He was disoriented, and verbal contact could be established but not kept in the desired direction. Sexual automatisms, such as exhibitionism and flirting with nurses, were observed. He put his hands and other objects in his mouth, and he experienced amnesia and episodes of fear and anxiety because of visual and acoustic hallucinations. He also had aggressive episodes and was especially aggressive towards his father, while he was gentle and calm with his mother. He was unable to name common objects. After some periods where he was talkative and active, he would be apathetic. After introduction of clonazepam along with sodium-valproate, the myoclonus diminished. As acute psycho-organic syndrome persisted, an MRI scan of the endocranium repeated on the 18th day revealed further deterioration, with enlargement of the inflammatory process in the right temporoinsular region with a concomitant reduction of the previously noticed changes in the insula and left parietal lobe (Figure 1 D-F). Because of worsened neuroimaging findings, electro-cortical activity 7 to 8 csp and altered behavior, intravenous immunoglobulin, 400 mg/kg/day for 5 days, was started on the 18th day of hospitalization. The patient became fully alert on the 26th day, with normal sleeping patterns and recall of some past events. He was tested for intellectual functions after 2 weeks, and the results were in average range, with significantly diminished function of

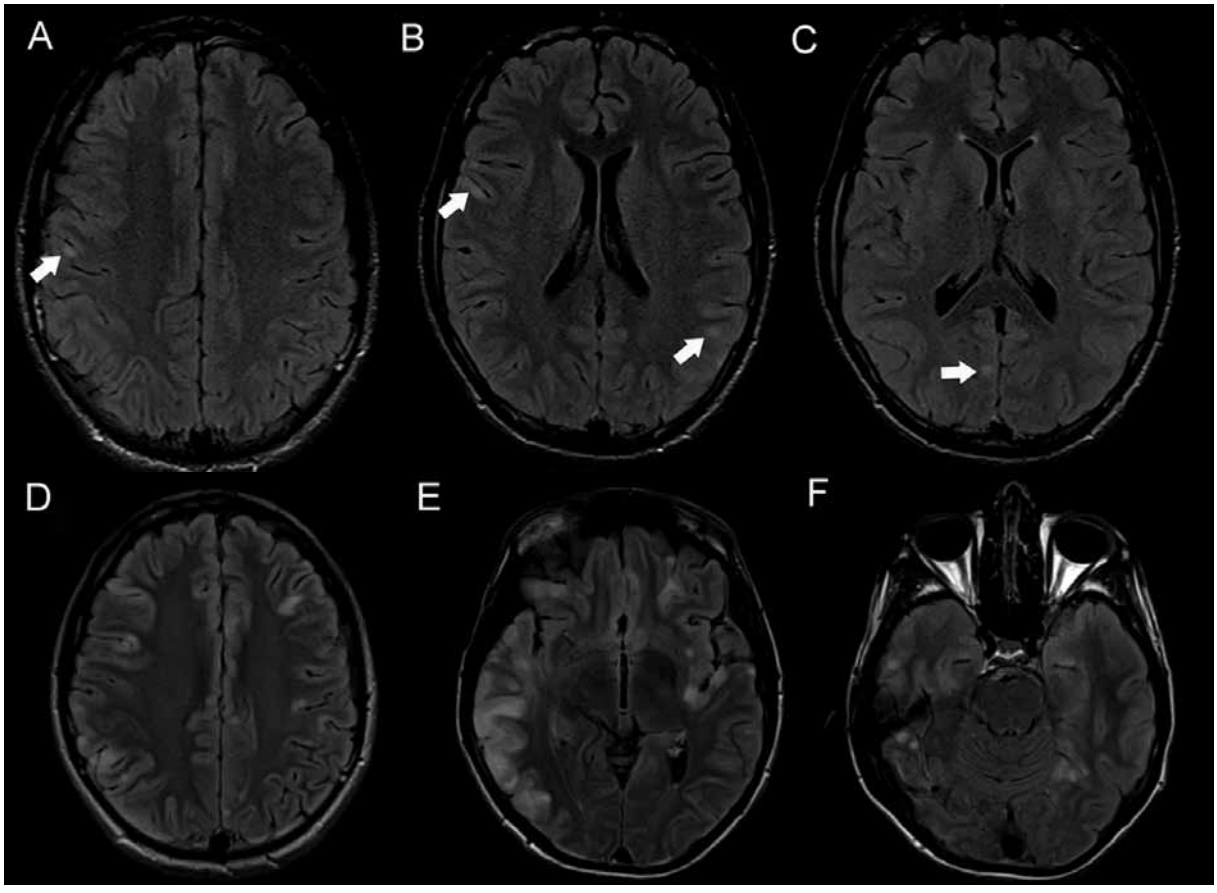

Figure 1. A-C - presence of several subtle foci of increased signal on fluid-attenuated inversion recovery (FLAIR) sequence, associated with restricted diffusion signal on diffusion weighted imaging (DWI) sequence, involving only the cortex on several locations in both cerebral hemispheres. D-F - enlargement of inflammatory process.

short memory. MRI scanning performed 1 month after the initial examination showed regression of numerous lesions, but residual marked signal alteration in the right temporo-occipital cortex.

Five months after discharge, the patient achieved an average result on a mental function test. Neuropsychological examination indicated a significant decrease in the function of immediate memory. Decreased attention tenacity and moderate affective instability were obvious.

3. Discussion

Rarely, in the early reconvalescent stage after HSVE, neuropsychiatric Klüver-Bucy syndrome can develop. This is a rare behavioral disturbance that occurs as a result of impairment of anterior temporal lobes of the brain. Criteria for diagnosing this syndrome are: sexual disinhibition, visual agnosia, hyperorality, withdrawal/apathy, “rage” behavior, hypermetamorphosis, and binge eating. Although the presence of three of these symptoms is sufficient for diagnosis, our patient had all, except the binge eating. Treatment is not precisely defined and includes use of carbamazepine and antipsychotics. Improvement in the Klüver-Bucy syndrome in our patient was achieved with intravenous immunoglobulin (IVIG). Animal studies on monkeys have shown that anatomical pathological mechanisms have a key role in the development of this syndrome [3,4]. It remains unclear whether immune mechanisms are essential in the pathogenesis of Klüver-Bucy syndrome in humans. Further studies are needed in order to answer this question. In HSVE, the mesial temporal lobe is primarily affected, unilaterally or bilaterally, with bilateral spreading of the virus along limbic structures to posterior orbitofrontal gyres and insular cortex. Extratemporal regions are affected in 10% to 30% of cases. MRI scans of our patient showed diffuse cortical lesions. Encephalitis with multifocal cortical lesions that does not affect other regions of the brain is extremely rare. Such a finding has been described in autoimmune processes, i.e., Rasmussen encephalitis and Behcet disease [5].

Interestingly, most patients with EBV encephalitis do not present with infective mononucleosis, and this

was also true in our patient. As for the detection of EBV in CSF in children with encephalitis, other causative agents, mainly HSV and Mycoplasma pneumoniae, can be isolated along with EBV in 25% of cases. Therefore, it is unclear whether the presence of EBV in CSF is a result of the reactivation of latent EBV infection or is due to the presence of latent infected B lymphocytes in CSF. There is also a possibility of true simultaneous infection in which every detected agent has a role in the pathogenesis. EBV encephalitis is treated with acyclovir and corticosteroids, but studies that confirm the value of such a treatment are still lacking [2,5].

In our patient, acyclovir therapy led to the negativization of DNA HSV type 1 and the reduction of lymphocytic pleocytosis in CSF, but a positive PCR to DNA EBV remained. The value of PCR findings in CSF for EBV infection of CNS remains unclear. The presence of EBV DNA due to latent EBV DNA in CSF lymphocytes as part of an inflammatory response to other agents should be considered.

Was the reactivation of HSV type 1 in CNS the cause of an immune-mediated CNS reaction, i.e., parainfective encephalitis, or did persistence of active EBV during first 2 weeks despite acyclovir treatment lead to worsening of the neuroradiological findings in our patient? Besides a characteristic clinical picture of HSVE, the initial EEG and MRI findings were not typical [6], and after the disappearance of HSV in CSF, the symptoms did not resolve. This could imply an important role of EBV in the course of the illness. Rapid clinical and neuroradiological improvement was achieved only after treatment with intravenous immunoglobulins.

Numerous publications regarding MR characteristics of the different types of viral encephalitis exist [6]. However, to the best of our knowledge, there are no reports describing any early MRI signs present before the development of typical imaging features.

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