



Case report

Clinical outcomes in children with herpes simplex encephalitis receiving steroid therapy



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ABSTRACT

Background: Herpes simplex virus encephalitis (HSE) is a significant cause of morbidity and mortality. Neurologic sequelae are common even after early initiation of acyclovir treatment. The host immune response during HSE can also lead to brain damage. There are an increasing number of reports favoring steroid use in HSE.

Objectives: We aimed to compare the prognosis of children with HSE with and without steroid therapy. **Study design:** We retrospectively screened our hospital archive from 2009 to 2014 for patients diagnosed with HSE with a positive result for herpes simplex virus polymerase chain reaction in cerebrospinal fluid. Patients ≥ 1 month and ≤ 18 years at diagnosis were included in the study. Clinical outcomes in terms of cognitive function, motor function, electroencephalographic findings, seizure frequency, and radiologic findings were compared in patients who received adjuvant steroid therapy with those who did not.

Results: Six patients (1 boy, 5 girls; aged 4 months to 10 years) were included. Overall symptom duration before hospital admission was ≤ 5 days. Patients received acyclovir treatment for 21–28 days. Three received steroid therapy early during the disease and three patients did not. No adverse effects related to steroids were observed. Follow-up duration was 6 months to 5 years. All patients had radiologic sequelae of encephalitis. Cognition, motor function, and seizure control were better in patients who received steroid therapy.

Conclusions: Adjuvant steroid therapy seems to be effective in decreasing morbidity in children with HSE but the radiologic sequelae were the same in both groups.

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1. Background

Herpes simplex virus encephalitis (HSE), the most common sporadic encephalitis, is associated with significant morbidity and mortality. Acyclovir treatment, inhibits viral replication in infected cells and decreases mortality from 70% to 8%–18% [1–4]. Despite early acyclovir treatment, most survivors have significant neuropsychiatric sequelae; fewer than half of adult patients with HSE return to normal health [4].

The host immune response to bacterial, viral, or mycoplasma infections may cause further morbidity and mortality. Steroids

are recommended in tuberculous meningitis in conjunction with appropriate antibiotic treatment [5]. Adjunctive steroids given before or concurrently with the first dose of antibiotics are recommended for *Haemophilus influenzae* type b and pneumococcal meningitis in high-income countries. But it is a topic of debate for other pathogens [5–7]. Cytokines and chemokines produced by glial cells in response to herpes virus infection initiate a cascade of neuroimmune responses with neurotoxic effects that can lead to brain damage [8]. Although steroids are not used routinely for HSE, there are animal studies and single case reports favoring their use. In 2008, a multicenter, multinational, randomized, double-blind, placebo-controlled clinical trial (GACHE trial) of treatment with acyclovir and adjuvant dexamethasone compared with acyclovir and placebo in adults with HSE was designed; the study includes 372 patients but abandoned due to insufficient enrolment [9].

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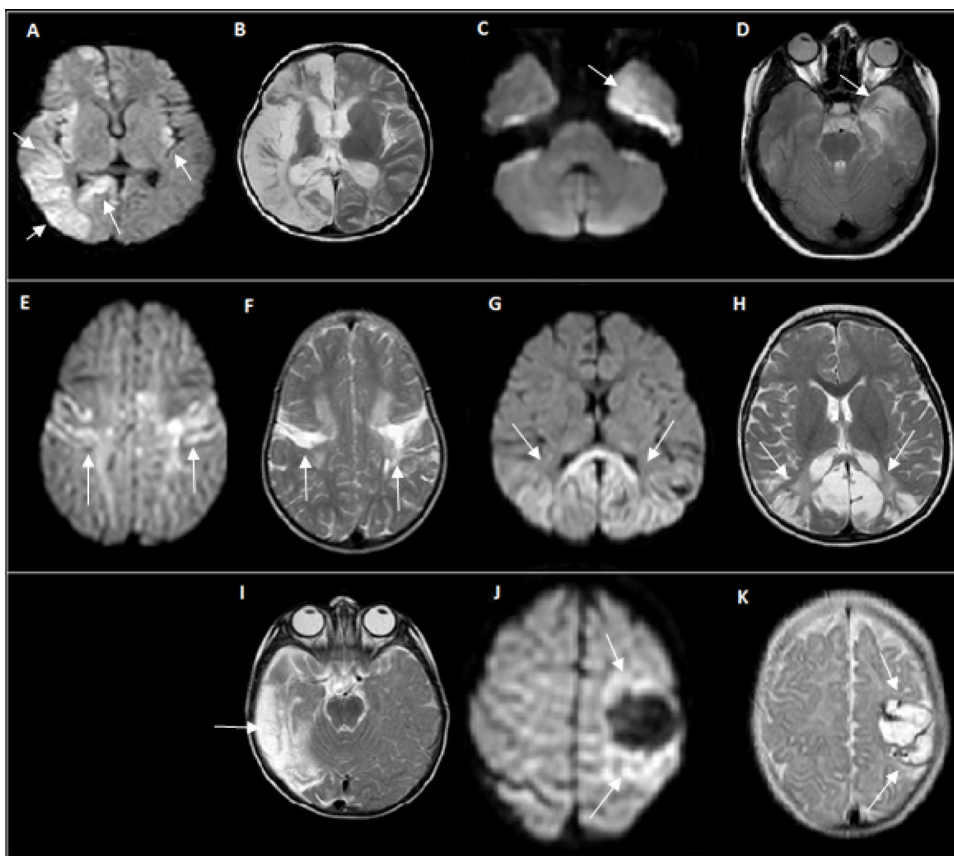


Fig. 1. Cranial MRI of patients, diffusion weighted axial image at the acute stage (A, C, E, G, J), and T2-weighted axial image (B, D, F, H, I, K) at the chronic stage. Diffusion restriction in the acute phase resulted in encephalomalacic changes at the chronic stage in all patients (arrows). Patient-1 at 20 months old (A), and 34 months old (B), has diffuse right hemisphere involvement, mild involvement in left frontal, temporal and occipital lobes. Patient-2 at 22 months old (E), and 29 months old (F), has perirolandic involvement bilaterally more prominent in the left hemisphere. Initial MRI of patient-3 taken at 11 months old is not available, at 17 months old there is right temporo-occipital encephalomalacia. Patient-4 at 10 years old (C) and 11 years old (D), has left temporal lobe involvement. Patient-5 at 18 months old (G) and 23 months old (H), has corpus callosum splenium and bilateral occipital lobe involvement. Patient-6 at 4 months old (J) and 5 months old (K), has left perirolandic involvement, with some hemorrhagic component, extending to left temporo-occipital lobes.

2. Objectives

Here, we report the clinical, neuroradiologic, and electroencephalographic findings in six children with HSE and aim to compare the clinical outcomes with or without steroid therapy.

3. Study design

Laboratory based screening was performed retrospectively in Kocaeli University Medical Faculty, Department of Pediatrics, from 2009 to 2015 for patients with cerebrospinal fluid (CSF) positive for herpes simplex virus (HSV) polymerase chain reaction (PCR). Patients ≥ 1 month and ≤ 18 years of age at diagnosis were included in the study. One patient who was lost to follow-up was excluded from the study. Clinical outcomes were noted and compared in patients who received adjuvant steroid therapy versus those who did not. Acyclovir was given intravenously at a dose of 15 mg/kg every 8 h. Steroid was given together with acyclovir treatment at a dose of 2 mg/kg/day prednisone (maximum 60 mg) or equivalent methyl prednisolone orally for 2 weeks, weaned off over a month. Two patients (patient 4 and patient 5) also received intravenous pulse steroid (30 mg/kg methyl prednisolone, maximum 1 g) for 1–3 days before oral steroid therapy. Antacid treatment, either a proton pump inhibitor or an H2 receptor blocker, was given during steroid therapy. Psychometric evaluation was performed by the same psychologist using the Wechsler Intelligence Scale for

Children Revised (WISC-R) in patients aged 6–16 years and the Denver-II test in patients ≤ 6 years old.

4. Results

Six patients (1 boy, 5 girls; aged 4 months to 10 years) were included in the study (Table 1). Patients are listed in Table 1 according to chronological order in terms of first admission to our clinic. All patients were previously healthy. Fever, focal seizures, and encephalopathy were the initial symptoms and CSF was positive for HSV type 1 in all patients. Overall symptom duration before hospital admission was ≤ 5 days. All patients received acyclovir treatment for at least 21 days until control CSF HSV PCR was negative. Three patients (aged 10 years, 18 months, and 4 months) received steroid therapy early in the disease; three patients did not receive steroid therapy.

The duration of follow-up was 6 months to 5 years. No side effects associated with steroids were seen in terms of hyperglycemia, hypertension, gastrointestinal bleeding, or secondary infections requiring medication. All patients had radiologic sequelae of encephalitis (Fig. 1). Cognitive function, motor function, and seizure frequency were better in patients who received steroid therapy (Table 1).

In the steroid-negative group, patient 1 and patient 2 have severe global developmental delay. Patient 3 has mild hemiparesis; he is attending the first class in a primary school and has some learning problems. All three patients have drug-resistant epilepsy.

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