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Paper Accepted*

ISSN Online 2406-0895

Case Report / Приказ болесника

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Received: May 2, 2020
Revised: November 16, 2020
Accepted: December 27, 2020
Online First: December 31, 2020
DOI: https://doi.org/10.2298/SARH200502117K

*__Accepted papers__ are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.

Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.

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SUMMARY

Introduction Hemorrhagic shock and encephalopathy syndrome (HSES) is a rare disorder with prevalence at the early age. The main features of HSES are: acute diarrhea, shock, disseminated intravascular coagulation, multisystem impairment, and encephalopathy. The prognosis is very poor, with high mortality, especially in the cases with status epilepticus.

Case outline The presented infant had typical features of HSES associated with superrefractory status epilepticus as de novo epileptic event, followed by parmacoresistant epilepsy. Clinical course of disease was very severe and required urgent circulatory and respiratory support, and at the same time, managing of super-refractory status epilepticus by continuous intravenous infusion of midazolam, barbiturate and levetiracetam. The outcome was very poor with serious neurological consequence and resistant epileptic seizures.

Conclusion The treatment of the presented patient with HSES was very challengeable due to life threatening condition associated with superrefractory status epilepticus, and further pharmacoresistant epilepsy. Additionally, the choice of antiepileptic drugs is limited due to multisystem impairment and adverse effects, which might worsen, anyhow, severe course of disease.

Keywords: status epilepticus; hemorrhagic shock encephalopathy syndrome; infant

САЖЕТАК

Увод Синдром хеморагијског шока и енцефалопатије (енг. *hemorrhagic shock and encephalopathy syndrome – HSES*) редак је поремећај који има преваленцију у раном узрасту. Главна обележја овог синдрома су: акутни пролив, дисеминована интраваскуларна коагулација, мултисистемско оштећење и енцефалопатија. Прогноза болести је лоша и удружена је са високим мортетом, нарочито ако је ток компликован епилептичким статусом.

Приказ болесника Приказано је одојче са типичним карактеристикама *HSES* удруженим са суперрефракторним епилептичким статусом као новим епилептичким догађајем, који је праћен фармакорезистентном епилепсијом. Клинички ток болести је био веома тежак, а одојче је захтевало хитну респираторну и циркулаторну потпору, а у исто време збрињавање суперрефрактарног епилептичког статуса применом континуиране инфузије мидазолама, барбитурата и леветирацетама. Исход болести је неповољан, са тешким неуролошким секвелама и фармакорезистентном епилепсијом.

Закључак Лечење приказаног болесника са *HSES* је велики изазов због животно угрожавајућег стања које је удружено са суперрефрактарним епилептичким статусом и резистентном епилепсијом у каснијем току болести. Отежавајућа околност је ограничен избор антиепилептичких лекова због мултисистемсог оштећења и нежељених ефеката, који додатно могу погоршати, ионако тежак ток болести.

Кључне речи: *status epilepticus*; хеморагијски шок енцефалопатија синдром; одојче

INTRODUCTION

Hemorrhagic shock and encephalopathy syndrome (HSES) was described by Levin et al. [1] as new syndrome in 1983. Only a few series or case reports of patients with HSES have been presented over the last thirty years. The authors suggested very severe clinical course of disease, with poor prognosis [2]. Nine criteria for HSES have been defined: shock; coma and/or seizures; diarrhea; disseminated intravascular coagulation; fall of hemoglobin and platelet

count; elevated liver enzymes; renal dysfunction; acidosis; negative blood and cerebrospinal fluid cultures. Diagnosis of HSES is definitive if all nine criteria are satisfied, while, probable HSES is if either eight criteria are satisfied or at least seven, with no information on the remainder. The initial manifestation of disease is acute diarrhea with very rapid development of circulatory shock, encephalopathy associated with epileptic seizures, disseminated intravascular coagulopathy (DIC) with multisystem impairment including liver and kidneys [1, 2, 3]. Status epilepticus in children with HSES frequently emerged in preceding etiologies with augmented neuronal excitability by distinct pathomechanism from the "cytokine storm" mediated acute seizures during childhood [4]. Superrefractory status epilepticus (SRSE) is defined if status epilepticus continued or recurred 24 hours or more after the onset of anesthetic drugs in continuous infusion, and is associated with morbidity and mortality [5]. The main neuroradiological feature during the first phase of disease is cerebral edema, followed by brain atrophy [6]. Treatment of HSES is very urgent and includes intensive care therapy with multidisciplinary approach. Despite prompt and adequate treatment, morbidity and mortality are still very high [2, 3].

The literature data about characteristics of epileptic seizures in infants with HSES are insufficient, and there is no data about association with SRSE.

The aim of our case presentation is to point out the challenge in diagnosis and treatment in the infant with HSES, particularly if it is associated with SRSE and epileptic seizures

CASE REPORT

We present a infant aged three months with severe course of HSES, SRSE and resistant epilepsy. Somnolence with progression to coma started in the morning on the admission day, with signs of cyanosis and periods of apnea, together with jerking of right side of the body for hours, followed by secondary generalization of the seizure. The data about previous history were insufficient, but we found out that the infant was the third child in family from uneventful pregnancy and delivery.

The infant was admitted to pediatric intensive care unit (PICU) of Institute due to coma and generalized status epilepticus with irregular respiration. The patient was febrile, paled with perioral cyanosis, extremely dehydrated with signs of circulatory shock associated with numerous watery diarrheas. Hart rate was increased, 180-200 beats/min for the first three days, while blood pressure was decreased. Oliguria to anuria lasted for two days despite hydration, circulatory support and diuretics. During the first five days in hospital, the infant suffered severe watery and bloody diarrhea with more than fifteen stools per day. Results of biochemical and hematology analyses are presented in table 1. Focal onset seizures with secondary generalization repeated frequently for seven days despite anticonvulsive treatment and hemodynamic stabilization. The signs of right hemiparesis were noted after seven days when the child became more active with spontaneous movements. Imaging chest X ray and abdomen ultrasound were normal. Microbiological and serological analyses of the blood, urine, stool and cerebrospinal fluid were negative for bacteria and viruses (herpes simplex virus, enterovirus, adenovirus, and rotavirus). Initial computerized tomography (CT) showed significant brain edema (figure 1), especially above posterior regions, and it was the reason to postpone the lumbar puncture.

Initial treatment included intensive care measures of circulatory and respiratory support, rehydration, correction of acidosis and electrolyte disturbances, diuretic stimulation and antibiotics, Antiedematous therapy (manitol, dexamethasone) started after brain edema CT scan evidence and was given for seven days. During the first few days, the function of circulatory and respiratory systems, kidney and liver was improved. Despite circulatory and respiratory stabilization, the condition of infant was very critical due to coma and frequent and prolonged epileptic seizures, mostly with jerking of right side of the body, with spreading to the left side and generalization. The seizures were resistant to the high dosage of intravenous bolus of benzodiazepines (midazolam 0.2 mg/kg), phenobarbital (20 mg/kg) and levetiracetam (60 mg/kg). Since the failure of the first and second antiseizure drugs, anesthesia with continuous intravenous infusion of midazolam started and the dosage was increasing up to 0.4 mg/kg/h. Every withdrawing of anesthesia was associated with seizure recurring, and continuous infusion of midazolam was lasting for eight days. After cessation of generalized tonic-clonic SRSE, and midazolam withdrawal, the infant continued to suffer frequent focal onset seizures with adverse of the head, and jerking of the right side of the body, with secondary generalization. Valproate was started, as soon as the liver enzymes were normalized. Since the infant suffered the episodes of irritability, agitation and long-lasting monotone crying,

clonazepam was added to valproate. Serial video EEG showed very slow and low amplitude background activity with multifocal epileptic discharges. The focal seizures were resistant to combination of valproate and clonazepam, so carbamazepine was introduced. After seven days when the dosage was increased up to 15 mg/kg, the infant started to have terrible myoclonic jerks. Ictal video EEG showed multiple spikes and poly-spikes and waves synchronized with myoclonic jerks. Since carbamazepine might provoke myoclonic jerks, the drug was stopped and topiramate was introduced. With the increasing dosage of topiramate up to 5mg/kg/day, the frequency of seizures decreased and further good control of seizures was achieved. We noticed improvement in seizure control, but not in neurological status. After seventy days of hospitalization, the infant was discharged and referred to regional hospital with very severe neurological consequences presented as: cortical blindness, right spastic hemiparesis, increased muscle tone of extremities with bilateral positive Babinski sign and feet clonus, the only voice was in the form of monotonic crying, the feeding was through nasogastric tube because of loss of sucking and swelling reflex. CT scan during hospitalization showed progressive brain atrophy (figure 2). During two years follow-up period, the child was seizure free, while neurological consequences were severe including blindness, microcephaly, and right-sided hemiparesis, unable to sit, stand and walk.

DISCUSSION

HSES is a very severe complication of gastroenteritis with high mortality of 60%, and with severe neurological consequences in survived patients [2]. Predictors for poor prognosis are status epilepticus, prolonged coma and biphasic course of disease [2]. Our patient had two of three predictors for poor outcome, status epilepticus and prolonged coma. Neuroradiological finding was typical for HSES in our case, showing severe brain edema at the onset, and later, progressive brain atrophy. Literature data suggested correlation between severity of neuroradiological brain abnormalities and poor outcome like in our case, as well [2, 6, 7]. Pathogeneses of neurological manifestations of HSES is still unknown, so there are several hypotheses. According to some of them, the main roles have ischemia and hypoxia due to circulatory impairment, while hyperthermia is less probable. Direct bacterial or viral neurotoxicity is also possible in pathogenesis of HSES [8, 9]. A very recent study supports “cytokine storm” pathogenesis of HSES, showing significant increases in levels of most

inflammatory cytokines and all chemokines in six patients with HSES but no significant difference in levels of some cytokines (IL-2,IL-4) within 24h of symptom onset [10]. Similarly as other studies have reported, no effect on mortality when immunomodulatory treatments, such as corticosteroids, are used [10, 11].

The treatment of seizures including status epilepticus was a very challenging part of therapeutic approach in HSES. Literature data presented that SRSE was associated with resistance on antiseizure medication and high case-fatality rate (21.3%) [12, 13]. In new-onset seizure presenting as *de novo* refractory status epilepticus, it is very important to explore the underlying etiology, especially CNS inflammation, as well as to start appropriate etiological treatment early [13]. We showed that continuous infusion of midazolam in high dosage with careful monitoring of vital signs, could be a good choice for treatment of SRSE in patients with the HSES, The subsequent episodes of excitability and crying in our case might be caused by midazolam withdrawal and/or were the manifestation of disease. Anyhow, the treatment by clonazepam was effective in those episodes. There is no data if the patients with HSES could have myoclonic jerks spontaneously, but we observed myoclonus in our patient provoked by carbamazepine. Topiramate in combination with clonazepam was very successful in our patient for the long-term seizure control and irritability. Prognosis in most of the children with HSES is poor and associated with high mortality and morbidity rate, although, a recent publication about HSES in a few adult patients suggested favorable outcome [14, 15].

In conclusion, encephalopathy and epileptic disorders might exist during and, after the recovery of multisystem impairment in patients with HSES. In our patient, SRSE and epileptic seizures were dominant and long-lasting feature of disease. Some antiepileptic drugs are limited due to multisystem impairment and adverse effects which might worsen, anyhow, severe course of disease. Status epilepticus in HSES has predictive value, and despite adequate treatment, SRSE contributed to poor prognosis in our case. Multicenter studies are recommended to achieve better understanding of pathogenesis including epileptogenesis, and treatment of this rare disorder.

Ethical standards: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research

committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Written consent to publish all shown material was obtained from the patient's caregiver.

Conflict of interest: None declared.

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Table 1. Initial laboratory findings

Analyses	Results	Comment according to referent value
White blood cell count	10.4	Normal
Hemoglobin (g/L)	117	Decreased
Platelets	86	Decreased
C-reactive protein (mg/l)	0.9	Normal
Blood pH	7.27	Decreased
Base excess	-10.7	Increased
Bicarbonate (mmol/l)	13	Decreased
Glycaemia (mmol/l)	1.6	Decreased
Urea (mmol/l)	13.7	Increased
Sodium (mmol/l)	133	Decreased
Potassium (mmol/l)	1.6	Decreased
Calcium total (mmol/l)	1.83	Decreased
Lactate dehydrogenase (U/l)	4622	Increased
Creatine phosphokinase (µg/l)	5705	Increased
Bilirubin total (mg/dl)	12.2	Decreased
Ammonium (µmol/L)	44	Normal
Acidum uricum (µmol/L)	1156	Increased
Albumin (g/l)	29	Decreased
Liver enzymes		
AST (IJ/l)	603	Increased
ALT (IJ/l)	343	Increased
Prothrombin time (s) (%)	47.4 (13)	Prolonged
Partial prothrombin time (s)	53.8	Prolonged
D-dimmers	5100	Increased

AST – aspartate aminotransferase, ALT – alanine transaminase

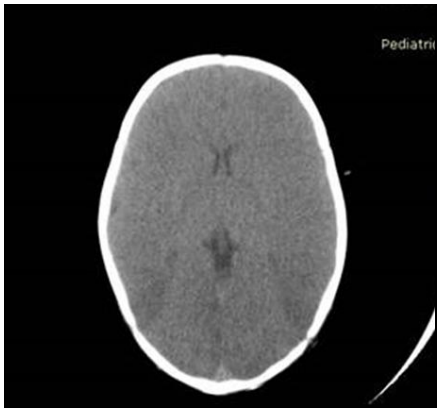

Figure 1. Brain computerized tomography scan at the level of the lateral ventricles showed severe cerebral edema with obliteration of the lateral ventricles, loss of differentiation of gray/white matter, and cortical sulci and gyri

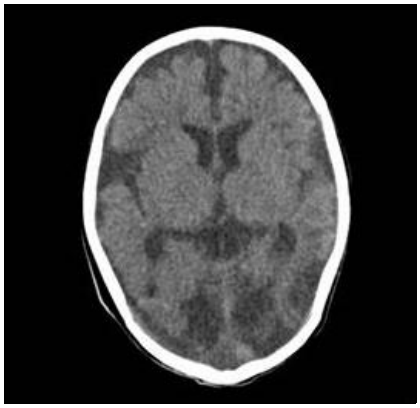

Figure 2. Brain computerized tomography scan at the level of the lateral ventricles showed structural changes: encephalomalatia, brain atrophy, ex vacuo hydrocephalus with sparing the basal ganglia, cerebellum and brain stem

