DOI: https://doi.org/10.2298/SARH200502117K
UDC: 616.853-06-085-053.3

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Super-refractory status epilepticus and pharmacoresistant epilepsy in an infant with hemorrhagic shock and encephalopathy syndrome

Ružica Kravljanac[1,2], Marija Đaković[1], Biljana Vučetić-Tadić[1,2], Đorđe Kravljanac[1,2]

[1]Dr Vukan Čupić Institute for Mother and Child Health Care of Serbia, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SUMMARY

Introduction Hemorrhagic shock and encephalopathy syndrome (HSES) is a rare disorder with prevalence at an 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 cases with status epilepticus.

Case outline The presented infant had typical features of HSES associated with super-refractory status epilepticus as *de novo* epileptic event, followed by pharmacoresistant epilepsy. Clinical course of the disease was very severe and required urgent circulatory and respiratory support, and simultaneous management 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 challenging due to a life-threatening condition associated with super-refractory status epilepticus, and further pharmacoresistant epilepsy. Additionally, the choice of antiepileptic drugs is limited due to multisystem impairment and adverse effects which might worsen the already severe course of the disease.

Keywords: status epilepticus; hemorrhagic shock and encephalopathy syndrome; pharmacoresistant epilepsy

INTRODUCTION

Hemorrhagic shock and encephalopathy syndrome (HSES) was described by Levin et al. [1] as a new syndrome in 1983. Few series or case reports of patients with HSES have been presented over the last 30 years. The authors described a very severe clinical course of the 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 the disease is acute diarrhea with very rapid development of circulatory shock, encephalopathy associated with epileptic seizures, disseminated intravascular coagulopathy with multisystem impairment including liver and kidneys [1, 2, 3]. Status epilepticus (SE) 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]. Super-refractory status epilepticus (SRSE) is defined if SE 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 the 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 the association with SRSE.

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

CASE REPORT

We present an infant aged three months with a severe course of HSES, SRSE, and resistant epilepsy. Somnolence with progression to coma started in the morning of the admission day, with signs of cyanosis and periods of apnea, together with jerking of the 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

Received • Примљено: May 2, 2020
Revised • Ревизија: November 16, 2020
Accepted • Прихваћено: December 27, 2020
Online first: December 31, 2020

Correspondence to:
Ruzica KRAVLJANAC
Dr Vukan Čupić Institute for Mother and Child Health Care of Serbia
University of Belgrade
Faculty of Medicine
6 Radoja Dakića
Belgrade 11070, Serbia
ruzica.kravljanac@gmail.com

Table 1. Initial laboratory findings

Analyses	Results	Comment according to referent value
White blood cell count Hemoglobin (g/L) Platelets	10.4 117 86	Normal Decreased 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
Uric acid (µmol/L)	1156	Increased
Albumin (g/l)	29	Decreased
Liver enzymes AST (IU/l) ALT (IU/l)	 603 343	 Increased 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

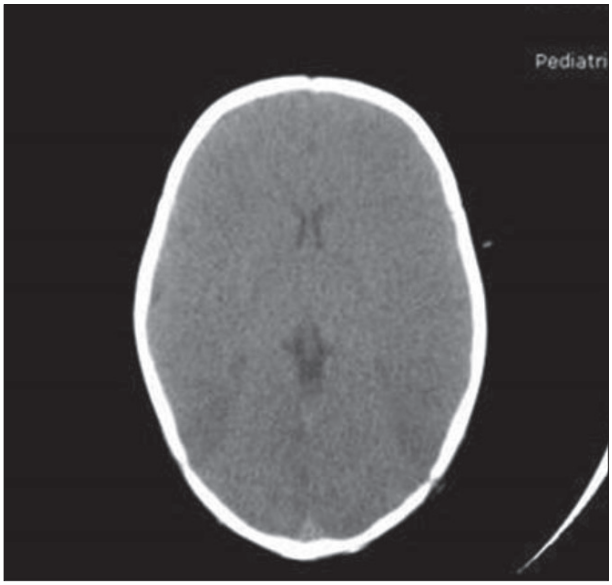

Figure 1. Brain computerized tomography scan at the level of the lateral ventricles showing a severe cerebral edema with obliteration of the lateral ventricles, loss of differentiation of the gray/white matter, and cortical sulci and gyri

that the infant was the third child in the family, from an uneventful pregnancy and delivery.

The infant was admitted to the pediatric intensive care unit of our institute due to coma and generalized SE with irregular respiration. The patient was febrile, pale with perioral cyanosis, extremely dehydrated, with signs of circulatory shock associated with numerous watery diarrheas. Hart rate was increased, 180–200 beats/minute for the first three days, while blood pressure was decreased. Oliguria to anuria lasted two days despite hydration, circulatory support, and diuretics. During the first five days in the hospital, the infant suffered severe watery and bloody diarrhea, with more than 15 stools per day. The 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 a significant brain edema (Figure 1), especially above the posterior regions, which was the cause of postponing 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 (mannitol, dexamethasone) started after brain edema CT scan evidence and was administered for seven days. During the first few days, the function of circulatory and respiratory systems, the kidney, and the liver was improved. Despite circulatory and respiratory stabilization, the condition of the infant was very critical due to coma and frequent and prolonged epileptic seizures, mostly with jerking of the 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 was started and the dosage was increased up to 0.4 mg/kg/h. Every withdrawal of anesthesia was associated with recurring seizures, and continuous infusion of midazolam lasted eight days. After the cessation of generalized tonic–clonic SRSE, and midazolam withdrawal, the infant continued to suffer frequent focal onset seizures with aversive head-turning, 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 episodes of irritability, agitation, and long-lasting monotone crying, clonazepam was added to valproate. Serial video electroencephalography (EEG) showed very slow and low amplitude background activity with multifocal epileptic discharges. The focal seizures were resistant to the 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 having 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 increasing the dosage of topiramate up to 5 mg/kg/day, the frequency

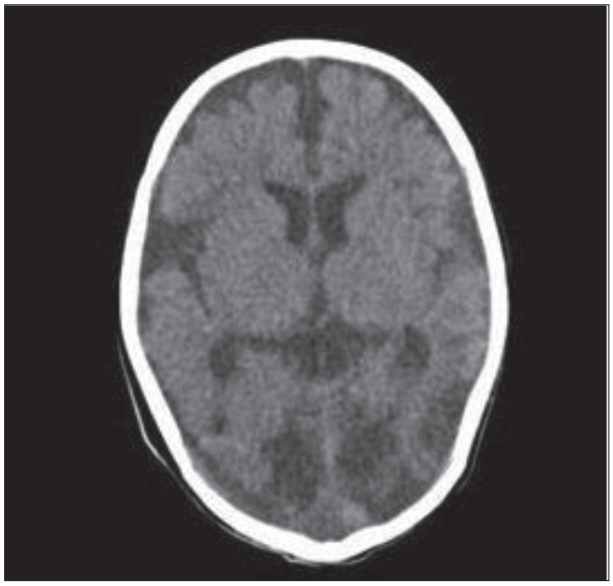

Figure 2. Brain computerized tomography scan at the level of the lateral ventricles showing structural changes: encephalomalacia, brain atrophy, hydrocephalus ex vacuo with sparing of the basal ganglia, cerebellum, and brain stem

of seizures decreased and further good control of seizures was achieved. We noticed improvement in seizure control, but not in neurological status. After 70 days of hospitalization, the infant was discharged and referred to a 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.

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.

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 SE, prolonged coma, and biphasic course of the disease [2]. Our patient had two of the three predictors for poor outcome – SE 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 also suggest a correlation between the severity of neuroradiological brain abnormalities and poor outcome, as was in our case [2, 6, 7]. Pathogeneses of the neurological manifestations of HSES is still unknown, so there are several hypotheses. According to some of them, ischemia and hypoxia have the main roles 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 24 hours of symptom onset [10]. Similar to other reported studies, there is no effect on mortality when immunomodulatory treatments, such as corticosteroids, are used [10, 11].

The treatment of seizures including SE is 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 a new-onset seizure presenting as *de novo* refractory SE, it is very important to explore the underlying etiology, especially the central nervous system 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 the 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 have been caused by midazolam withdrawal and/or were the manifestation of the disease. Nevertheless, the treatment by clonazepam was effective in those episodes. There is no data on patients with HSES having 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 children with HSES is poor and associated with high mortality and morbidity rate, although a recent publication on HSES in several adult patients suggested a 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 features of the disease. Some antiepileptic drugs are limited due to multisystem impairment and adverse effects which might worsen already severe course of the disease. SE in HSES has a 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.

Conflict of interest: None declared.

REFERENCES

1. Levin M, Hjelm M, Kay JD, Pincott JR, Gould JD, Dinwiddie R, et al. Haemorrhagic shock and encephalopathy: a new syndrome with a high mortality in young children. Lancet. 1983;2(8341):64–7.
2. Thébaud B, Husson B, Navelet Y, Huault G, Landrieu P, Devictor D, et al. Haemorrhagic shock and encephalopathy syndrome: neurological course and predictors of outcome. Intensive Care Med. 1999;25(3):293–9.
3. Ince E, Kuloglu Z, Akinci Z. Hemorrhagic shock and encephalopathy syndrome: neurologic features. Pediatr Emerg Care. 2000;16(4):260–4.
4. Hirayama Y, Saito Y, Maegaki Y. "Symptomatic" infection-associated acute encephalopathy in children with underlying neurological disorders. Brain Dev. 2017;39(3):243–7.
5. Ferlisi M, Hocker S, Trinka E, Shorvon S; on behalf of the International Steering Committee of the StEp Audit. Etiologies and characteristics of refractory status epilepticus cases in different areas of the world: Results from a global audit. Epilepsia. 2018;59(Suppl 2):100–7.
6. Kuki I, Shiomi M, Okazaki S, Kawawaki H, Tomiwa K, Amo K, et al. Characteristic neuroradiologic features in hemorrhagic shock and encephalopathy syndrome. J Child Neurol. 2015;30(4):468–75.
7. Weinstein M. Seizures and encephalopathy as the presenting sign of viral gastroenteritis. Pediatr Emerg Care. 2006;22(8):579–81.
8. Arii J, Tanabe Y, Miyake M, Mukai T, Matsuzaki M, Niinomi N, et al. Clinical and pathologic characteristics of nontyphoidal salmonella encephalopathy. Neurology. 2002;58(11):1641–5.
9. Straussberg R, Harel L, Levy Y, Amir J. A syndrome of transient encephalopathy associated with adenovirus infection. Pediatrics. 2001;107(5):E69.
10. Yamaguchi H, Nishiyama M, Tokumoto S, Ishida Y, Tomioka K, Aoki K, et al. Elevated cytokine, chemokine, and growth and differentiation factor-15 levels in hemorrhagic shock and encephalopathy syndrome: A retrospective observational study. Cytokine. 2021;137:155324.
11. Ranieri VM, Thompson BT, Barie PS, Dhainaut JF, Douglas IS, Finfer S, et al. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med. 2012;366(22):2055–64.
12. Kravljanac R, Djuric M, Jankovic B, Pekmezovic T. Etiology, clinical course and response to the treatment of status epilepticus in children: A 16-year single-center experience based on 602 episodes of status epilepticus. Eur J Paediatr Neurol. 2015;19(5):584–90.
13. Kravljanac R, Jovic N, Tadic BV, Kravljanac D, Pekmezovic T. New-onset seizure presenting as status epilepticus: Etiology and clinical characteristics in a cohort of 236 children. Seizure. 2018;63:79–84.
14. Fukuda M, Yoshida T, Moroki M, Hirayu N, Nabeta M, Nakamura A, et al. Influenza A with hemorrhagic shock and encephalopathy syndrome in an adult: A case report. Medicine (Baltimore). 2019;98(14):e15012.
15. Komori Y, Uchida N, Soejima N, Fujita Y, Matsumoto H. Successful Outcome in an Adult Patient with Influenza-associated Hemorrhagic Shock and Encephalopathy Syndrome. Intern Med. 2020;59(18):2321–6.

Суперрефрактарни епилептички статус и фармакорезистентна епилепсија код одојчета са синдромом хеморагијског шока и енцефалопатије

Ружица Крављанац[1,2], Марија Ђаковић[1], Биљана Вучетић-Тадић[1,2], Ђорђе Крављанац[1,2]

[1]Институт за здравствену заштиту мајке и детета Србије „Др Вукан Чупић", Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија

САЖЕТАК

Увод Синдром хеморагијског шока и енцефалопатије 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 морталитетом, нарочито ако је ток компликован епилептичким статусом.

Приказ болесника Приказано је одојче са типичним карактеристикама синдрома хеморагијског шока и енцефалопатије 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 синдромом хеморагијског шока и енцефалопатије 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 мултисистемског оштећења и нежељених ефеката, који додатно могу погоршати ионако тежак ток болести.

Кључне речи: *status epilepticus*; синдром хеморагијског шока и енцефалопатије; фармакорезистентна епилепсија