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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Infantile hemiconvulsion–hemiplegia epilepsy syndrome associated with *GRIN2A* gene mutation

Ružica Kravljanac[1,2], Slobodan Gazikalović[1], Biljana Vučetić-Tadić[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 Infantile hemiconvulsion–hemiplegia and epilepsy (IHHE) syndrome is defined as a specific syndrome in patients < 2 years of age, presenting as a new onset refractory status epilepticus with unilateral motor seizures and acute imaging abnormalities, fever, hemiparesis > 24 hours, and excluding infectious encephalitis.
Case outline We present the results of a follow-up in a 11-year-old girl with IHHE, associated with *GRIN2A* mutation. The girl had normal development until the first febrile hemiconvulsive status epilepticus at the age of seven months. Neuroimaging initially showed right hemisphere edema, followed by progressive right side hemiatrophy. The patient has resistant epilepsy, left side hemiparesis, and good language and cognitive development.
Conclusion Despite IHHE described many years ago, some syndrome's features, including etiology, have remained unexplained. The association between IHHE and *GRIN2A* mutation stated in the current manuscript is described in scientific literature for the first time.
Keywords: infantile hemiconvulsion; hemiplegia epilepsy; *GRIN2A*; status epilepticus

INTRODUCTION

Infantile hemiconvulsion–hemiplegia and epilepsy (IHHE) syndrome is defined as a specific syndrome in a patient younger than two years of age, presenting as a new onset refractory status epilepticus (NORSE). IHHE characteristics are: unilateral motor seizures, high grade fever at the time of onset of refractory status epilepticus (SE), and unilaterally abnormal acute imaging, followed by hemiparesis lasting at least 24 hours, and excluding infectious encephalitis [1]. In a variable period, from a few months to years later, intractable epilepsy emerges in two-thirds to three-fourths of children with IHHE. The mechanisms underlying the IHHE syndrome remain unclear. A neuronal injury induced by venous thrombosis and/or hypoxia, and previous abnormalities of the brain were suggested as an underlying mechanism [2]. Gene mutations associated with IHHE syndrome have been described in the literature, such as *CACNA1A*, *SCN1A, HNRNPU, ATP1A3* genes [3, 4, 5]. Initial acute cytotoxic edema of the affected hemisphere at the time of SE is followed by chronic atrophic changes of the same hemisphere [6]. Clinical presentation is characterized by prolonged hemiconvulsions followed by hemiplegia and medication-resistant epilepsy [6–9]. The motor deficit has a variable course, from definitive hemiplegia to complete resolution [6]. The long-term cognitive outcome following IHHE syndrome has been poorly studied [9].

CASE REPORT

We present an 11-year-old girl with resistant focal epilepsy and left side hemiparesis. The girl was the second child from an uneventful pregnancy and perinatal history. She had normal global development until the first epileptic attack at the age of seven months. The child was febrile (39°C) for three days before the first seizure and had facial exanthema. NORSE started with the head and eyes deviation toward the left side, clonic jerks of the left limbs and impaired consciousness lasting for hours, and repeating in clusters within three days. All hematological, coagulation factors, biochemical and metabolic blood analyses were normal. Cytological, biochemical and microbiological analyses of the cerebrospinal fluid were normal. Fundoscopy was normal. Electroencephalographic (EEG) record showed continuous slow epileptic discharges above the right hemisphere (Figure 1). Urgent brain computed tomography showed edema of the right hemisphere (Figure 2). The girl was treated according to the protocol for SE: benzodiazepine as the first line (intravenously midazolam in a dosage of 0.2 mg/kg), Phenobarbital as a second line (20 mg/kg), and since it was ineffective, midazolam was given in continuous intravenous infusion (0.2 mg/kg/h). Anti-edematous therapy was given (mannitol, dexamethasone). From the fourth day of hospitalization, the infant was seizure-free. Phenobarbital was continued in the maintaining dosage of 5 mg/kg. After two months, focal seizures started in afebrile,

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Correspondence to:
Ružica KRAVLJANAC
Faculty of Medicine
University of Belgrade
Institute for Mother and Child Healthcare of Serbia
Radoje Dakić 6–8
11070 Belgrade, Serbia
ruzica.kravljanac@gmail.com

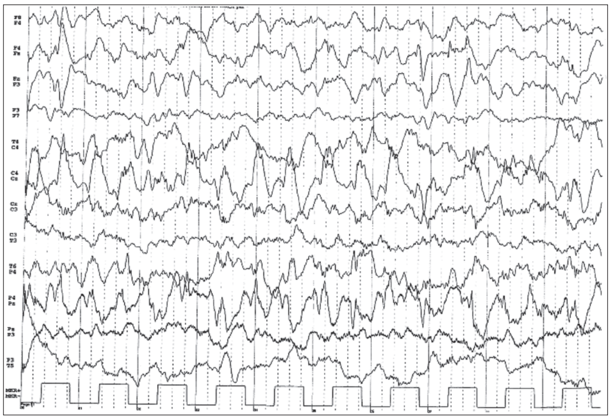

Figure 1. Interictal electroencephalogram during the first day of seizure onset, showing high-amplitude, slow, 2 Hz spikes and waves, above the right centro-parietal region with spreading to the entire right region

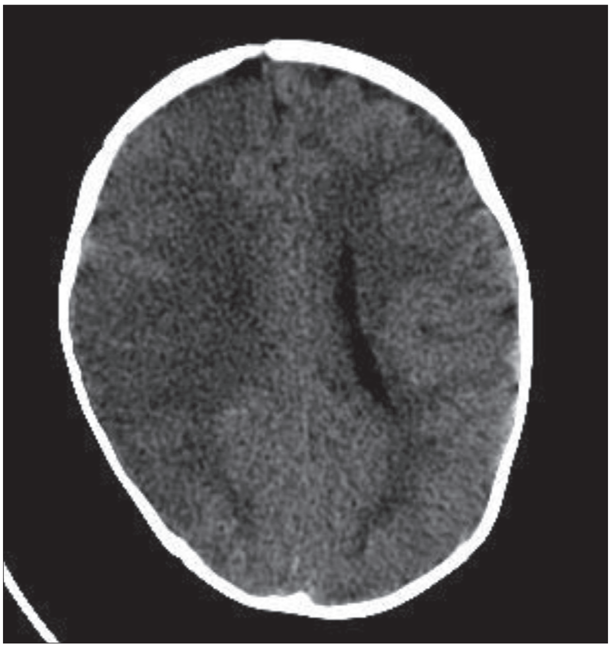

Figure 2. Brain computed tomography scan during hemiconvulsive status epilepticus, showing right cerebral edema

awake state: the infant interrupted activities, had staring, cyanosis, deviation of the head lasting up to two minutes. Left side hemiparesis persisted from NORSE. At the age of 10 months, the child was referred to our clinic. EEG showed asymmetric background activity, slower above the right hemisphere with almost continuous discharges above parietotemporal right region. Brain magnetic resonance imaging (MRI) showed right cerebral white mater hypotrophy. Diagnosis of IHHE was based on the data of febrile refractory hemiconvulsive SE at the early age followed by recurrent focal-onset seizures, persistent hemiparesis, and MR evidence of brain hemiatrophy. Antiepileptic therapy was corrected, phenobarbital was withdrawn, and carbamazepine was introduced leading to seizure control for one year (25 mg/kg). At the age of 18 months, hemiconvulsive seizures reappeared, and clobazam (1.2 mg/kg) was added. At the age of 28 months, brain MRI showed progressive right side hemiatrophy (Figure 3). Despite this progression

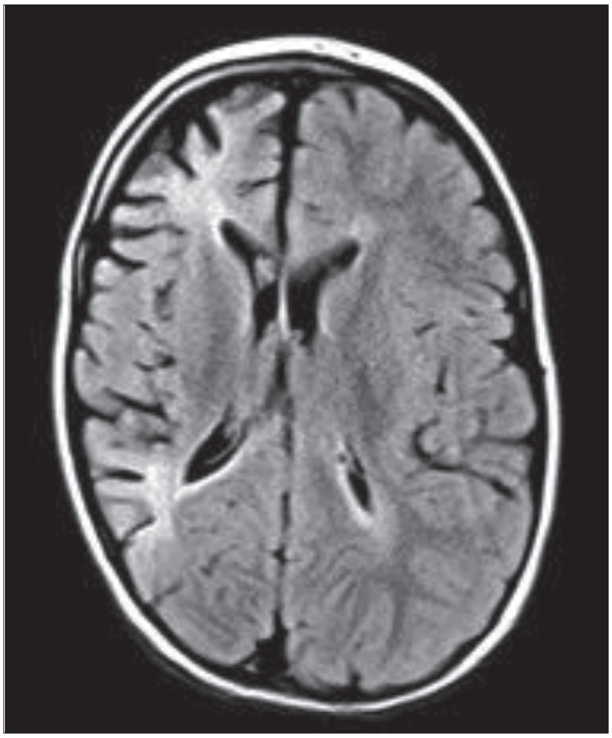

Figure 3. Brain magnetic resonance scan at the age of 28 months, showing progressive right hemisphere atrophy

in brain atrophy, the girl had improvement in global development. Psychological testing showed mild language delay, and developmental quotient of 80–90. Levetiracetam was introduced due to the worsening of seizure control. The girl was continuing to have sporadic focal seizures in frequency up to five seizures per month. At the age of six, the girl started to complain of feeling of fast heart beating, chest pain, and tremor of the hands. If it happened during sleep, the girl awoke and complained of fast heart beating. These episodes were short, repeating up to 10 per day and night. Cardiologist found normal clinical and heart ultrasound findings, while second degree A-V block was registered on 24-hour ECG Holter. Since carbamazepine might contribute to ECG changes, the dosage was reduced and substituted by oxcarbazepine. Two repeated 24-hour ECG Holter recordings over a period of two months showed normal heart rhythm. Since the symptoms were continuing at the age of eight, long-term video EEG was performed. No clinical seizures were observed during the recording, while EEG showed clear asymmetric background activity, slower above the right hemisphere with frequent epileptic discharges. Sulthiame was added, but since the girl became drowsy, the drug was excluded. At the age of nine, topiramate was introduced with good effect to both seizure control and episodes of paroxysmal tachycardia. With current medications (levetiracetam 40 mg/kg/day, clobazam 0.9 mg/kg/day, topiramate 5 mg/kg/day) seizure control was achieved. At the end of the follow-up period, the speech and intelligence are normal, as well as physical findings, and only discrete spastic left side hemiparesis was observed. She goes to a regular school and she is successful in obtaining academic education.

Whole gene sequencing showed that the patient has an extremely rare heterozygous nonsense likely pathogenic variant in the mutation of the *GRIN2A* gene (NM 001134407:c.2776C>T).

All procedures performed were in accordance with the ethical standards of the institutional and 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

IHHE was described more than half a century ago, but still many features of the syndrome have remained unexplained [6]. There is a diagnostic challenge since clinical presentation of IHHE has similarities with other neurological disorders, such as Rasmussen's encephalitis, cerebrovascular insult, and mitochondrial disorders, which have to be considered in differential diagnosis. Infective, genetic, and structural underlying causes are proposed in IHHE etiology [10]. There are case reports of acute infantile hemiplegia associated with exanthema subitum caused by *Human betaherpesvirus* 7 (HHV-7) [11]. In our case, at the time of NORSE, exanthema was observed for two days, but PCR for HHV-6 and HHV-7 was not done in the regional hospital. Various gene mutations are associated with IHHE, and this is the first case with IHHE associated with the mutation of the *GRIN1A* gene [3, 4, 5, 12]. *GRIN1A* mutation is associated with different epileptic disorders, such as Rolandic epilepsy, Landau–Kleffner syndrome, and continuous spike waves during slow-wave sleep [13, 14]. A great number of variants in the GRIN genes that encode N-methyl-D-aspartate (NMDA) glutamatergic receptor subunits have been found in patients with neuropsychiatric disorders, including epilepsy. There is evidence that NMDA receptor activation might play an important role in epilepsy, and NMDA receptor antagonists have been considered in treating epilepsy, including SE ($MgSO_4$, felbamate, ketamine). The results of preclinical studies showed that excessive activation of NMDA receptors has been implicated in the pathogenesis of neuronal injury in acute neurologic disorders, and that magnesium reduced NMDA-mediated brain injury [15, 16]. Magnesium normally does not readily penetrate the fully developed blood–brain barrier (BBB), but BBB permeability is greater in infants especially during seizures; thus, systemically administered magnesium may provide effective therapy in these conditions [15]. NMDA receptors play an important role in the induction of programmed cell death during SE [17, 18]. If further genetic investigation shows more frequent association of IHHE with mutation of the genes responsible for NMDA receptors, the strategy for the treatment of hemiconvulsive SE in IHHE syndrome should include NMDA antagonists, such as $MgSO_4$ in high dosage or ketamine [19, 20].

Auvin et al. [2] suggested that anti-edema therapy should be discussed to prevent cell injury, since pathological studies showed that cytotoxic edema in HHE is responsible for neuronal damage playing a role in the development of a later epilepsy. Very aggressive anti-edema treatment by mannitol and corticosteroids, and antiseizure therapy in the acute phase in our patient, did not prevent further damage and epilepsy.

In patients with IHHE, MRI of the brain reveals evidence of abnormal diffusion within the white matter in the acute phase, and hippocampal sclerosis and/or hemiatrophy later in life [2, 21]. In our case, three months after initial brain edema, increased T2 hyperintensity, severe gliosis and unilateral brain atrophy were evident by MRI of the brain. Similar MRI unilateral changes have been described in the literature, only one month after initial hemiconvulsive febrile SE [21]. Recently, some unusual IHHE presentations and etiology were published, such as IHHE in adult cases, or association with cortical dysplasia type III, or cobalamin C deficiency [22, 23, 24].

The long-term cognitive outcome following HHE syndrome has been poorly studied, although mental retardation has been reported in cases with IHHE. A recent study reported that mental retardation is not a uniform feature of the IHHE syndrome and demonstrated that a reorganization of language to the right cerebral hemisphere or its bilateral representation is common in patients with IHHE syndrome affecting the left cerebral hemisphere [9]. In our patient, the right cerebral hemisphere was affected, and language delay was present initially, but during the follow-up, the girl developed normal speech, and had normal intellectual and school performance. A study which included 10 patients with IHHE showed that peri-insular hemispherotomy provides excellent long-term seizure control in patients with drug-resistant hemispheric epilepsy [25]. Recent reports pointed out the rule of inflammation in epilepsy associated with *GRIN2A* mutation and good response to intravenous immunoglobulin, and this therapy might have been considered in our patient as well if other treatment had failed [26].

In conclusion, we suggest further exploration of genetics underlying all cases with IHHE. Our case with IHHE and *GRIN1A* mutation has favorable neurological and cognitive development despite resistant epilepsy from an early age. Since the disorder is very rare, multicenter investigation is recommended, with particular attention to genetics underlying IHHE. It seems that genetic factors contribute to IHHE pathogenesis in addition to all other proposed factors, such as excessive neuronal excitation, hyperthermia, inflammation, and BBB damage [27, 28]. Further investigations are necessary in order to find the answers to present questions about pathogenesis, treatment, and prognosis of IHHE.

Conflict of interest: None declared.

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Синдром инфантилне хемиконвулзије–хемиплегије и епилепсије удружен са мутацијом гена *GRIN2A*

Ружица Крављанац[1,2], Слободан Газикаловић[1], Биљана Вучетић-Тадић[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 инфантилне хемиконвулзије–хемиплегије и епилепсије (ИХХЕ) специфичан је ентитет код болесника млађих од две године. Представља новонастали рефрактарни *status epilepticus* кога карактеришу: унилатерални моторички напади и акутне неурорадиолошке промене на мозгу, фебрилност, хемипареза у трајању већем од 24 сата, у одсуству инфективног енцефалитиса.

Приказ болесника Приказујемо резултате праћења једанаестогодишње девојчице са ИХХЕ удруженим са мутацијом гена *GRIN2A*. Девојчица је имала нормалан развој до првог фебрилног хемиконвулзивног епилептичког статуса у седмом месецу живота. Неурорадиолошки налаз је иницијално показао едем десне хемисфере мозга, а касније прогресивну деснострану хемиатрофију мозга. Болесница је имала резистентну епилепсију, левострану хемипарезу и задовољавајући когнитивни развој и говор.

Закључак Иако је ИХХЕ давно описан, бројне карактеристике синдрома, укључујући етиологију, још су увек необјашњене. Удруженост ИХХЕ и мутације гена *GRIN2A* сада је први пут описана у стручној литератури.

Кључне речи: инфантилне хемиконвулзије; хемиплегија; епилепсија; *GRIN2A*; *status epilepticus*