Cite as: Bugaj G, Mania A, Lubarski K, Tomaszewski M, Mazur-Melewska K, Małecki P, Figlerowicz M: Human herpesvirus 6 as the underestimated causative agent of seizure disorders in febrile children. Aktualn Neurol 2024; 24 (1): 20–34. DOI: 10.15557/AN.2024.0004

Grażyna Bugaj[1], Anna Mania[1], Karol Lubarski[1], Mateusz Tomaszewski[2], Katarzyna Mazur-Melewska[1], Paweł Małecki[1], Magdalena Figlerowicz[1]

Received: 01.06.2024
Accepted: 03.07.2024
Published: 29.07.2024

Human herpesvirus 6 as the underestimated causative agent of seizure disorders in febrile children

Ludzki herpeswirus typu 6 – niedoceniony czynnik sprawczy stanów napadowych u gorączkujących dzieci

[1] Department of Infectious Diseases and Child Neurology, Institute of Paediatrics, Poznan University of Medical Sciences, Poznań, Poland
[2] Department of Orthodontics and Temporomandibular Disorders, Poznan University of Medical Sciences, Poznań, Poland
Correspondence: Grażyna Bugaj, Department of Infectious Diseases and Child Neurology, Institute of Paediatrics, Poznan University of Medical Sciences, Szpitalna 27/33, 60-572 Poznań, Poland, e-mail: grazyna.bugaj@op.pl

https://doi.org/10.15557/AN.2024.0004

ORCID iDs
1. Grażyna Bugaj https://orcid.org/0000-0003-3054-1580
2. Anna Mania https://orcid.org/0000-0003-0141-2560
3. Karol Lubarski https://orcid.org/0000-0003-2354-4484
4. Mateusz Tomaszewski https://orcid.org/0000-0002-2632-0438
5. Katarzyna Mazur-Melewska https://orcid.org/0000-0003-2695-4649
6. Paweł Małecki https://orcid.org/0000-0002-0651-4454
7. Magdalena Figlerowicz https://orcid.org/0000-0003-4731-0658

Abstract

Introduction and objective: The aim of the study was to analyse the clinical symptoms and laboratory abnormalities of seizure disorders in febrile children infected with pathogens from the *Herpesviridae* family – human herpesvirus 6 (HHV-6), human cytomegalovirus (HCMV), and Epstein–Barr virus (EBV). **Materials and methods:** A total of 75 children were included in the study, including 64 patients after a febrile seizure and 11 patients after an epileptic seizure triggered by infection. The control group consisted of 36 children with developmental delay. Routine inflammatory markers were analysed including C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), and white blood count (WBC). Pathogens were detected using standard diagnostic methods. **Results:** Compared to control group, median CRP and PCT were significantly higher in children with all types of febrile seizures, and ESR was significantly higher in children with simple and complex seizures. Most children with WBC below and above the normal range were children with simple febrile seizures plus and those with complex seizures, respectively. HHV-6 was detected in 33% of children. HCMV was found in 5%, and EBV in 4% of children. There was no significant correlation between children with and without primary HHV-6 infection regarding age, gender, febrile seizures type and first-time seizures, nor significant differences in inflammatory markers except for WBC. The difference between the number of children with three-day fever and those without rash was borderline significant ($p = 0.06$); children with primary HHV-6 infection without rash had more frequent first-time seizures ($p = 0.04$). **Conclusions:** The clinical course of seizure disorders and the intensity of the inflammatory reaction in children were mild. HHV-6 was the most common causative agent of fever and seizure disorders.

Keywords: infection, inflammatory response, primary HHV-6 infection, febrile seizures, generalised epilepsy

Streszczenie

Wprowadzenie i cel: Celem badania była analiza kliniczno-laboratoryjna stanów napadowych u gorączkujących dzieci zakażonych wirusami z rodziny *Herpesviridae* – ludzkim herpeswirusem typu 6 (*human herpesvirus* 6, HHV-6), ludzkim wirusem cytomegalii (*human cytomegalovirus*, HCMV) i wirusem Epsteina–Barr (*Epstein–Barr virus*, EBV). **Materiał i metody:** Do badania włączono 75 dzieci, w tym 64 po napadzie drgawek gorączkowych i 11 po napadzie padaczkowym wywołanym infekcją. Grupę kontrolną stanowiło 36 dzieci z opóźnionym rozwojem. Analizowano rutynowe wskaźniki zapalenia – białko C-reaktywne (*C-reactive protein*, CRP), prokalcytoninę (*procalcitonin*, PCT), wskaźnik sedymentacji erytrocytów (*erythrocyte sedimentation rate*, ESR) i liczbę białych krwinek (*white blood count*, WBC). Patogeny wykrywano przy użyciu standardowych metod diagnostycznych. **Wyniki:** W porównaniu z grupą kontrolną mediany CRP i PCT były istotnie wyższe we wszystkich typach drgawek gorączkowych, mediany ESR były istotnie wyższe u dzieci z prostymi

Proofreading by Agnieszka Kosarzycka.

i złożonymi drgawkami gorączkowymi. Wśród dzieci z WBC poniżej zakresu normy najwięcej było dzieci z drgawkami gorączkowymi prostymi plus, a powyżej zakresu normy – dzieci z drgawkami gorączkowymi złożonymi. Zakażenie HHV-6 stwierdzono u 33% dzieci, a HCMV i EBV odpowiednio u 5% i 4% dzieci. Pomiędzy grupą dzieci z pierwotnym zakażeniem HHV-6 a grupą dzieci bez zakażenia HHV-6 nie wykazano istotnych zależności dla wieku, płci, typu i sekwencji drgawek gorączkowych ani istotnych różnic markerów stanu zapalnego z wyjątkiem WBC. Różnica między liczbą dzieci z gorączką trzydniową a liczbą dzieci z pierwotnym zakażeniem HHV-6 bez wysypki była na granicy istotności – $p = 0,06$; u dzieci z pierwotnym zakażeniem HHV-6 bez wysypki częściej występowały pierwszorazowe napady drgawek gorączkowych – $p = 0,04$. **Wnioski:** Stany napadowe u badanych dzieci miały łagodny przebieg, podobnie nasilenie reakcji zapalnej było niskie. Najczęstszym czynnikiem sprawczym stanów napadowych i gorączki był HHV-6.

Słowa kluczowe: infekcja, odpowiedź zapalna, pierwotne zakażenie HHV-6, drgawki gorączkowe, padaczka uogólniona

INTRODUCTION

Inflammation plays an important role in the pathomechanism of febrile seizures (FS) as well as epileptic seizures (ES). It is one of the mechanisms of non-specific (innate) immunity, responsible for reaction to infection or tissue damage. The course of the inflammatory reaction depends on the immune system (IS) and the central nervous system (CNS), which communicate mutually via the nervous and humoral pathways. The vagus nerve (Kobrzycka et al., 2017; Kuzior and Gorczyca, 2010) and inflammatory mediators – cytokines and prostaglandins (Napora et al., 2020) – play an important role in this process. Inflammatory mediators (endogenous pyrogens) and pathogenic microorganisms (exogenous pyrogens) induce fever, which is the body's defence mechanism and, at the same time, may cause FS. Prostaglandin (PG) E2 also plays an important role (Blomqvist and Engblom, 2018; Napora et al., 2020; Walter et al., 2016; van Zeijl et al., 2002). Inflammation is a complex and multi-stage process, involving an interaction between pathogen-associated molecular patterns (PAMPs) and pathogen recognition receptors (PRRs) found in immunocompetent, dendritic cells, and epithelial cells. The stimulated IS triggers an inflammatory response, which results in the release of pyrogenic and proconvulsant cytokines (cytokine storm). As a result of damage to the blood–brain barrier, inflammatory mediators, including PAMPs (e.g. lipopolysaccharide, element of Gram-negative bacterial cell wall) enter the CNS. In the CNS, microglial cells are activated and locally also release cytokines, including interleukin (IL)-1β and IL-1 receptor antagonist (IL-1Ra). Convulsions occur due to disturbances in the regulation of excitatory and inhibitory neurotransmitters. Additionally, in children with FS this is facilitated by the reduced seizure threshold (Akira and Hemmi, 2003; Czerkies and Kwiatkowska, 2013; Kim et al., 2017; Millichap and Millichap, 2006; Mittal, 2014; Pavlidou et al., 2013; Saito and Gale, 2007; Wendorff, 2000; Wendorff and Zeman, 2011; van Zeijl et al., 2002). Proinflammatory cytokines such as interleukin-6 (IL-6), IL-1β and tumour necrosis factor-α (TNF-α) mediate in the synthesis of acute phase proteins: C-reactive protein (CRP), procalcitonin (PCT). Fig. 1 shows a simplified diagram of the FS and fever development mechanism. According to the American Academy of Pediatrics (AAP), FS are divided into simple febrile seizures (SFS) and complex febrile seizures (CFS). SFS are defined as primary generalised, lasting less than 15 minutes, and not recurring within 24 hours. CFS are focal, last longer than 15 minutes, and recur within 24 hours (American Academy of Pediatrics, Provisional Committee on Quality Improvement, Subcommittee on Febrile Seizures, 1996; American Academy of Pediatrics, Subcommittee on Febrile Seizures, 2011). Hesdorffer et al. (2011) proposed a cut-off point of 10 minutes for distinguishing SFS from CFS. Grill and Ng (2013) proposed the term "simple febrile seizures plus" (SFS+) for patients with the SFS phenotype and more than one seizure within 24 hours. The classification of FS into first-time and recurrent is important for determining the risk of developing epilepsy. Pavlidou and Panteliadis (2013) proposed four or more episodes of recurrent FS as the prognostic factors of epilepsy. The most common cause of FS are viral infections which, according to Millichap and Millichap (2006), were previously diagnosed rarely (in 1924–1964 in only 2.6% of patients), except for infection with human herpesvirus 6 (HHV-6). Epidemiological and virological studies are necessary to investigate the association of a specific virus with FS. Based on studies published between 1994 and 2005, the authors showed that the frequency of HHV-6 infection in children with FS was 24% and the frequency of FS was 16.6%. SFS or exacerbations of pre-existing seizure disorders were diagnosed in 1.3% of patients with bronchiolitis caused by human respiratory syncytial virus (HRSV) infection. In another study, the incidence of HRSV infection in children with FS was 10.7%, HHV-6 infection – 35%, human adenoviruses (HADV) infection – 13.8%, herpes simplex virus 1 (HSV-1) – 9.2%, human cytomegalovirus (HCMV) – 3% and human herpesvirus 7 (HHV-7) – 2.3%. In turn, influenza A virus is a common cause of FS in Japan and China (Millichap and Millichap, 2006). In Hong Kong, in 1997 and 1998, 10.8% and 21.7% of children were hospitalised due to influenza A infections, respectively, and 10% and 6.4% of children with human parainfluenza virus (HPIV), HADV, HRSV and influenza B infection, respectively. The overall incidence of FS associated with influenza A was 19.5%, with HPIV – 12.2%, and with HADV infections – 9% (Chiu et al., 2001).

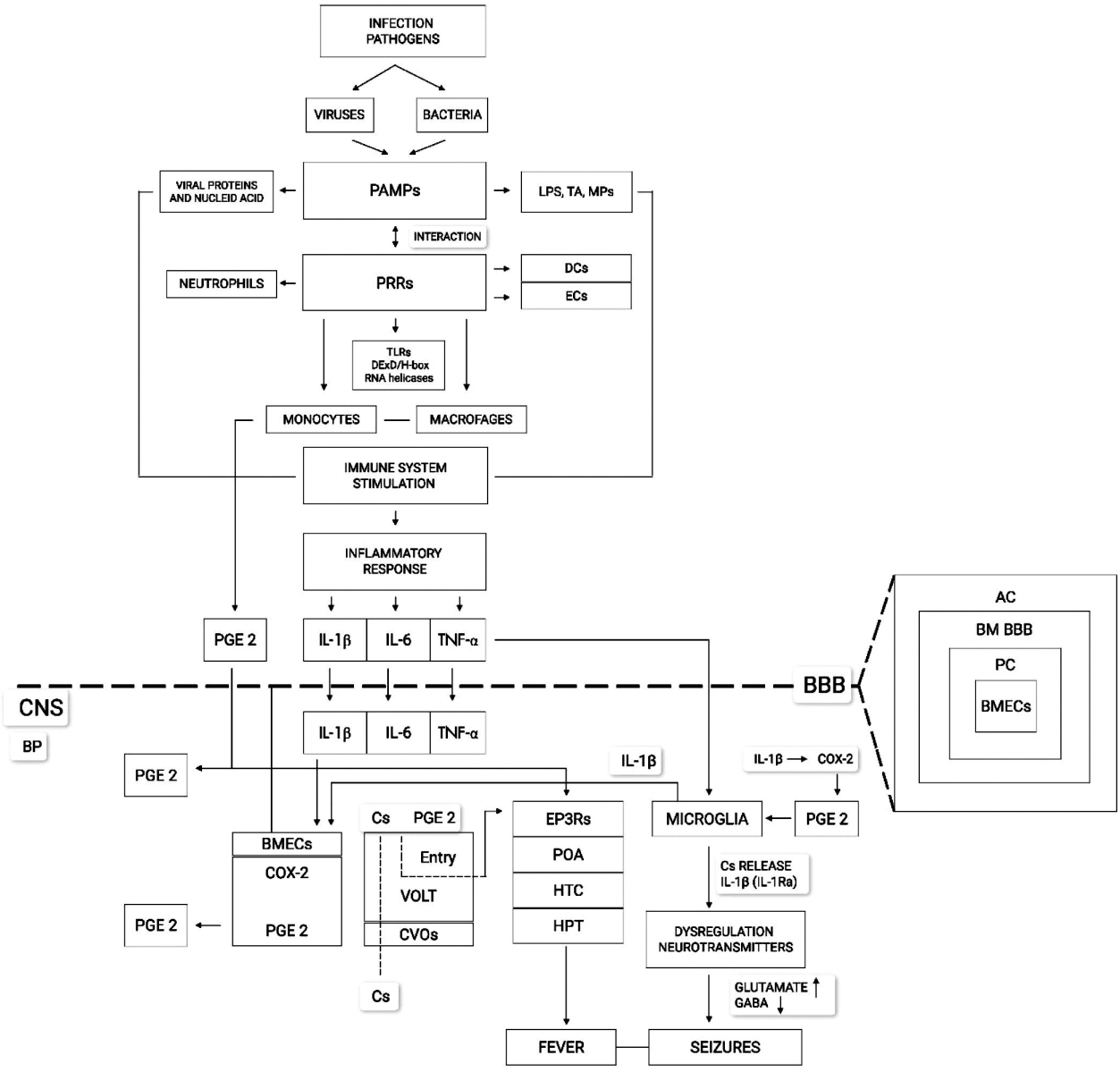
A similar pathogen profile was presented by Chung and Wong (2007), who showed that the five viruses most frequently associated with FS included: influenza virus – 17.6%, HADV – 6.8%, HPIV – 6%, HRSV – 2.7% and rotaviruses – 1.3%. The incidence of FS occurring in the course of infections caused by these viruses was 20.8%, 18.4%, 20.6%, 5.3%, and 4.3%, respectively. Carman et al. (2019) presented the profile of pathogens in respiratory infections in children with FS in Turkey. The most frequently detected viruses were HADV (11.1%), influenza A (8.3%), and influenza B virus (5.5%). At least one virus was detected in 82.7% of children and more than one in 58.3% of children. HADV and influenza B virus caused the most common coexisting infections. Authors indicate the lack of routine recommendations for detecting pathogens associated with FS. In another study, AlFulayyih et al. (2024) assessed the impact of respiratory viruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), on FS in children in Saudi Arabia between 2017 and 2021. The aetiology of the infection was different, and the dominant pathogens included human rhinovirus (HRV)/enterovirus (EV) – 23.9%, influenza A/B virus – 26.8% and SARS-CoV-2 – 14.1%. Coexisting infections were detected in 28.2% of children. No significant relationship between SARS-CoV-2 and the type of FS was demonstrated. Of note, in most of the aforementioned studies, the profile of pathogens associated with FS did not include viruses from the *Herpesviridae* family, especially HHV-6. The HHV-6 deserves special attention for many reasons. The spectrum of clinical symptoms is wide, from asymptomatic infection through typical exanthema subitum (ExS) symptoms (known as roseola infantum, sixth disease or three-day fever) or infection without rash to various neurological symptoms. The virus can enter the CNS through the bloodstream via infected lymphocytes or through the olfactory nerve. Finally, the virus establishes a state of chronic latency in brain tissue, peripheral blood mononuclear cells, tonsils, and salivary glands (Bartolini et al., 2019; Harberts et al., 2011). Historically, HHV-6 was isolated in 1986. In 1992, two variants were distinguished, i.e. HHV-6A and HHV-6B, and in 2012, the International Committee on Taxonomy of Viruses classified HHV-6A and HHV-6B as distinct viruses that differ epidemiologically, biologically and immunologically. Both viruses indicate neurotropism, with HHV-6A being more neurotropic (Ablashi et al., 2014). There are two types of receptors that determine the cell tropism of the virus: CD46 and CD134. The CD46 receptor is commonly found on the surface of all human nucleated cells. The CD134 receptor, a member of the tumour necrosis factor receptors superfamily, is expressed mainly on activated CD4+ T cells. CD46 was considered to be an entry receptor for both HHV-6A and HHV-6B, which was disputed by Tang et al. (2013). According to the researchers, CD134 is a specific entry receptor for HHV-6B. Considering the recognised role of the CD46 receptor for HHV-6A and its controversial role for HHV-6B, Hansen et al. pointed out the role of CD46 isoforms that may influence HHV-6B infection (Hansen et al., 2017; Mori, 2009; Tang et al., 2013). HHV-6 infection may cause a more severe course of FS, i.e. complex, recurrent, prolonged seizures that progress to febrile status epilepticus (FSE). Authors also point to acute damage to the hippocampus in the course of FSE, the development of mesial temporal sclerosis (MTS) over time, which is the cause of mesial temporal lobe epilepsy (MTLE) (Suga et al., 2000; Theodore et al.,2008). The FEBSTAT study was conducted to determine the consequences of prolonged FS. Seinfeld et al. (2014) analysed the management of FSE, which occurs in 10% of children with FS. Epstein et al. (2012) detected HHV-6B infection in 32% of children with FSE, while Shinnar et al. (2012) found acute hippocampal damage in magnetic resonance imaging (MRI) in 11.5% of children with FSE. The rules for performing tests useful in determining the cause of fever in children with FS were defined (Mastrangelo et al., 2014; Pavlidou et al., 2013). In light of published data, the primary aim of this study was to assess the spectrum of clinical and laboratory symptoms in seizure disorders (SeD) in children with fever. The analysis was performed in children with FS and generalised epilepsy (GE). The study was also aimed at the examination of pathogen types, with particular emphasis on the common *Herpesviridae* family members, i.e. HHV-6, HCMV and Epstein–Barr virus (EBV), analysis of primary HHV-6 infection clinical and laboratory characteristics, and assessment of inflammatory response intensity.

MATERIALS AND METHODS

Patients

A prospective study was conducted in children with seizure disorders at the Department of Infectious Diseases and Child Neurology in Poznań from 19 January 2017 to 5 December 2020. The study group (SG) included children hospitalised due to FS or ES during acute infection. Data were obtained from medical history taken from parents/legal guardians, neurological examination, and the results of additional tests. The control group (CG) consisted of children with developmental delay, admitted for planned diagnostics. On admission, symptoms of acute infection were ruled out in this group, taking into account the clinical condition and inflammatory markers testing. There were no FS or epilepsy in the patients' medical history in CG. Immunodeficiency was the exclusion criterion in both groups. FS was diagnosed based on the AAP criteria (American Academy of Pediatrics, Subcommittee on Febrile Seizures, 2011). There were the following inclusion criteria: seizures associated with fever ≥38°C, age between 6 and 60 months, no evidence of CNS infection or inflammation, and no other specific causes of seizures. Children with previous afebrile seizures were excluded from the study. Taking into account the criteria proposed by Grill and Ng (2013) and Hesdorffer et al. (2011), children with FS were divided into three subgroups:

DOI: 10.15557/AN.2024.0004



AC – astrocytes; **BBB** – blood–brain barrier; **BM** – basement membrane; **BMECs** – brain microvascular endothelial cells; **BP** – brain parenchyma; **CNS** – central nervous system; **COX-2** – cyclooxygenase 2; **Cs** – cytokines; **CVOs** – circumventricular organs; **DCs** – dendritic cells; **DExD/H-box** – motif of DExD/H-box RNA helicases; **ECs** – epithelial cells; **EP3Rs** – prostaglandin E receptors 3; **GABA** – gamma aminobutyric acid; **HPT** – hypothalamus; **HTC** – hypothalamic thermoregulatory centre; **IL-1β** – interleukin 1β; **IL-1Ra** – interleukin 1 receptor antagonist; **IL-6** – interleukin 6; **LPS** – lipopolysaccharide; **MPs** – muramyl peptides; **PAMPs** – pathogen associated molecular patterns; **PC** – pericytes; **PGE 2** – prostaglandin E2; **POA** – preoptic region; **PRRs** – pathogen recognition receptors; **TA** – teichoic acid; **TLRs** – Toll-like receptors; **TNF-α** – tumour necrosis factor α; **VOLT** – vascular organ of the lamina terminalis.

Fig. 1. Simplified mechanism of fever and febrile seizures during infection

- SFS – children with simple febrile seizures: generalised seizures, duration <10 minutes, one seizure during a febrile episode within 24 hours;
- SFS+ – children with simple febrile seizures plus: SFS phenotype, more than one seizure within 24 hours, normal neurological status between seizures; children after SFS+ were included to study whether this new type of FS differs significantly from SFS;
- CFS – children with complex febrile seizures: focal seizures, duration ≥10 minutes, more than one seizure during a febrile episode within 24 hours.

Based on the medical history, children were assigned to the group with first FS (FFS) and subsequent FS (SSFS) episodes. The classification made it possible to examine the structure of the FS group and the relationship between the FS type/primary HHV-6 infection and FFS/SSFS.

 DOI: 10.15557/AN.2024.0004

Parameter		SG *n* = 75	CG *n* = 36	*p*-value
Sex (*n*, %)	F	39 (52)	13 (36.1)	0.1163[(1)]
	M	36 (48)	23 (63.9)	
Fever ≥38°C (*n*, %)	Yes	68 (90.7)	0 (0.0)	<0.0001[(1)]
	No	7 (9.3)	36 (100.0)	
VI (*n*, %)	Yes	38 (50.7)	0 (0.0)	<0.0001[(1)]
	No	37 (49.3)	36 (100.0)	
BI (*n*, %)	Yes	6 (8.0)	0 (0.0)	0.1948[(3)]
	No	69 (92.0)	36 (100.0)	
UI (*n*, %)	Yes	32 (42.7)	0 (0.0)	<0.0001[(1)]
	No	43 (57.3)	36 (100.0)	
Age [years]	*M* (*SD*)	3.23 (3.30)	3.11 (1.99)	0.2647[(2)]
	Me (IQR)	2.00 (2.33)	3.00 (2.50)	
WBC[(A)] [G/L]	*M* (*SD*)	11.14 (6.51	9.30 (3.51)	0.5063[(2)]
	Me (IQR)	9.38 (9.80)	8.29 (4.48)	
ESR [mm/h]	*M* (*SD*)	17.37 (14.82)	7.40 (3.89)	<0.0001[(2)]
	Me (IQR)	12.00 (14.00)	6.00 (5.00)	
CRP [mg/dL]	*M* (*SD*)	2.19 (3.04)	0.20 (0.10)	<0.0001[(2)]
	Me (IQR)	0.88 (2.69)	0.20 (0.00)	
PCT [ng/mL]	*M* (*SD*)	0.96 (2.37)	0.04 (0.03)	<0.0001[(2)]
	Me (IQR)	0.20 (0.45)	0.04 (0.03)	
CSF [cell/µL]	*M* (*SD*)	1.90 (1.17)	-	-
	Me (IQR)	1.50 (1.50)	-	
CSF protein [mg/dL]	*M* (*SD*)	21.05 (13.33)	-	-
	Me (IQR)	18.00 (12.50)	-	
CSF glucose [mg/dL]	*M* (*SD*)	62.68 (15.35)	-	-
	Me (IQR)	63.00 (19.00)	-	
WBC[(B)] [G/L] (*n*, %)	Below normal range	7 (9.3)	1 (2.8)	<0.0001[(4)]
	Within normal range	44 (58.7)	34 (94.4)	
	Above normal range	24 (32.0)	1 (2.8)	
HHV-6 (*n*, %)	Positive	25 (33.3)	0 (0.0)	<0.0001[(1)]
	Negative	49 (65.3)	36 (100.0)	
	No data	1 (1.3)	0 (0.0)	
HCMV (*n*, %)	Reactive	4 (5.3)	0 (0.0)	0.3980[(3)]
	Non-reactive	70 (93.3)	36 (100.0)	
	No data	1 (1.3)	0 (0.0)	
EBV (*n*, %)	Reactive	3 (4)	0 (0.0)	0.0853[(4)]
	Inr	3 (4)	0 (0.0)	
	Non-reactive	68 (90.7)	36 (100.0)	
	No data	1 (1.3)	0 (0.0)	

BI – bacterial infection; **CG** – control group; **CRP** – C-reactive protein; **CSF** – cerebrospinal fluid; **EBV** – Epstein–Barr virus; **ESR** – erythrocyte sedimentation rate; **F** – female; **HCMV** – human cytomegalovirus; **HHV-6** – human herpesvirus 6; **Inr** – inconsistent result; **M** – male; ***M* (*SD*)** – mean (standard deviation); ***Me* (IQR)** – median (interquartile range); ***n*** – sample number; **PCT** – procalcitonin; **SG** – study group; **UI** – unspecified infection; **VI** – viral infection; **WBC** – white blood count; **WBC[(A)]** – WBC as quantitative variable; **WBC[(B)]** – WBC as qualitative variable.
[(1)] – Pearson's chi-square test of independence.
[(2)] – Mann–Whitney *U* test.
[(3)] – Yates's correction chi-square test.
[(4)] – maximum likelihood chi-square test.
p-value <0.05.

Tab. 1. Baseline characteristics of the study and control groups

The GE group consisted of patients diagnosed with GE. The inclusion criterion for patients with epilepsy was the generalised type of ES that occurred during an acute infection. According to Eriksson and Koivikko (1997), GE occurs more often in children in the age range of 0–5 years. The following blood tests were performed: white blood count (WBC; G/L), C-reactive protein (CRP; mg/dL), procalcitonin (PCT; ng/mL), and erythrocyte sedimentation rate

(ESR; mm/h), which is a non-specific inflammation marker. Blood samples were collected on the first day of clinical symptoms and within an hour after hospital admission. Follow-up tests were performed in the case of abnormal results. The aetiology of infection was determined in all children depending on the clinical symptoms presented. Particular attention was paid to *Herpesviridae* family viruses: HCMV, EBV and HHV-6. In children with suspected CNS infection and in infants <12 months of age after a FS (n = 20), a lumbar puncture (LP) was performed. Biochemical, microbiological, and molecular tests of cerebrospinal fluid (CSF) were performed. Cranial ultrasound, computed tomography (CT), MRI of the head, and electroencephalography (EEG) were performed according to indications. The characteristics of the study group are presented in Tab. 1.

Testing methods

Laboratory tests were performed in the Central Laboratory of the Karol Jonscher Hospital in Poznań. Inflammatory markers (WBC, CRP, PCT and ESR) were assessed in peripheral blood using standard laboratory methods. WBC was determined in whole venous blood collected with an anticoagulant (edetate disodium) based on the flow cytometry method in the Sysmex XN-1000 haematology analyser. CRP was determined in blood serum using the immunoturbidimetric method in the Alinity c analyser. PCT was determined in blood serum using the immunochemical method with microparticles and a chemiluminescent marker (Chemiluminescent Microparticle Immunoassay, CMIA) in the Alinity i analyser. ESR was determined using the manual Westergren method in whole venous blood collected with an anticoagulant (sodium citrate). Antibodies against HCMV were determined by immunochemistry using CMIA in blood serum. IgM antibodies were determined qualitatively, and IgG antibodies were determined both qualitatively and semi-quantitatively. The tests were performed in the Alinity i analyser. Antibodies against EBV viral capsid antigen (VCA) (IgM/IgG) and against EBV nuclear antigen-1 (EBNA-1) (IgG) were determined in blood serum by a qualitative immunochemical method using CMIA in the Alinity i analyser.

HHV-6 was detected in whole venous blood (anticoagulant) based on the qualitative real-time polymerase chain reaction (RT-PCR) method. Respiratory tract infections were confirmed by microbiological examination, i.e. culture and molecular examination, using the qualitative RT-PCR method. The sampled material included nasopharyngeal swab/aspirate and tracheal aspirate. Gastrointestinal infections were detected by stool sample testing using immunochromatography, culture or culture and latex test. Urinary tract infection was detected by microbiological examination using urine culture. The CSF examination included cytosis, biochemical parameters (glucose, protein) and pathogens/pathogens' genetic material. Leukocytes in the CSF were determined by flow cytometry or in a Fuchs-Rosenthal counting chamber, protein by turbidimetry, and glucose by the enzymatic-amperometric method. Pathogens were detected by qualitative RT-PCR and CSF culture. The reference values of the tested parameters are presented in Tab. 2.

Statistical analysis

Statistical analysis was performed using appropriate statistical tests. Due to non-normal age, WBC, ESR, CRP and PCT distribution, non-parametric tests were used (the number indicates the statistical test used in the study):

- Mann–Whitney U test[2] [the number indicates the statistical test used in the study] to determine the significance of the difference between the two groups.
- ANOVA Kruskal–Wallis test[5] to determine the significance of the difference in at least three groups. The Dunn–Bonferroni post-hoc test was used to precisely determine for which pairs of groups the difference is significant[5a]. Quantitative variables were presented using the arithmetic mean (M) and standard deviation (SD) and as the median (Me) and interquartile range (IQR).

Pearson's chi-square test of independence[1] was used to examine the relationship between qualitative variables and in the case of too small, expected sample sizes in a 2 × 2 contingency table, the chi-square test with Yates' correction[3] was used. In a contingency table larger than 2 × 2, the maximum likelihood (M-L) chi-square test was used[4]. Fisher's exact test[6] was used for tables of size 2 × 2 and sample size less than 40. Pearson's chi-square goodness-of-fit test[1a] was used to compare children's equipotency. A value of $p < 0.05$ was considered statistically significant. Statistical calculations were performed using the STATISTICA 10 PL package.

Ethical considerations

The study was approved by the Bioethics Committee of the Poznan University of Medical Sciences (No. 1281/18). The patients' legal guardians gave written consent to participation in the study.

RESULTS

Patients

In total, the study included 111 children. In SG (n = 75), there were n = 64 children with FS and n = 11 with GE. CG included of 36 children correctly matched in terms of age and gender. The structure of SG is presented in Tab. 1. A significant correlation was found between FS subgroups, GE group and CG and participant gender. CFS and GE were observed more frequently in females, while SFS+ in males. The children's age also differed significantly. Children with GE were considerably older than children with FS. Children with SFS+ were the youngest (M 1.82 ± 0.94 years; Me 1.42 years). The age difference between children with SFS and SFS+ without primary HHV-6 infection was of borderline significance (p = 0.0775), with SFS+ children being younger.

Parameter		SFS	SFS+	CFS	GE	CG	*p*-value	Value range
		***n* = 43**	***n* = 10**	***n* = 11**	***n* = 11**	***n* = 36**		
Sex	Female	20	2	9	8	13	0.0086[4]	-
	Male	23	8	2	3	23		
Fever ≥38°C	Yes	43	10	11	4	0	<0.0001[4]	-
	No	0	0	0	7	36		
Age [years]	*M* (*SD*)	2.28 (1.45)	1.82 (0.94)	2.34 (1.46)	9.11 (4.92)	3.11 (1.99)	0.0005[5]	-
							0.0006[5a] (SFS vs. GE)	
	Me (IQR)	1.83 (1.92)	1.42 (1.67)	1.83 (2.42)	10.33 (7.00)	3.00 (2.50)	0.0023[5a] (SFS+ vs. GE)	
							0.0236[5a] (CFS vs. GE)	
WBC	Below	4	2	1	0	1	0.0015[4]	7 days – 12 months 4.0–20.0 [G/L] 2–6 y/a 4.5–13.0 [G/L] 7–12 y/a 4.0–12.0 [G/L] Adults 4.0–10.0 [G/L]
	Normal	26	6	4	8	34		
	Above	13	2	6	3	1		
ESR	Normal	16	6	3	6	32	<0.0001[4]	1–6 months 11–22 [mm/h] >6 months F 3–15/M 1–10 [mm/h]
	Above	23	3	8	3	4		
	ND	4	1	0	2	0		
CRP	Normal	13	3	5	7	36	<0.0001[4]	≤0.5 [mg/dL]
	Above	30	7	6	4	0		
PCT	Normal	29	6	9	9	36	0.0001[4]	<0.5 [ng/mL]
	Above	14	4	1	1	0		
	ND	0	0	1	1	0		
HCMV	Non-reactive	40	10	10	10	36	0.2997[4]	IgM <0.85 non-reactive [S/CO] IgM ≥1.00 reactive [S/CO] IgG <6.00 non-reactive [AU/mL] IgG ≥6.00 reactive [AU/mL]
	Reactive	2	0	1	1	0		
	ND	1	0	0	0	0		
EBV	Non-reactive	39	10	10	9	36	0.2981[4]	EBV-VCA IgM [S/CO] <0.50 non-reactive; 0.50 to <1.00 grey zone; ≥1.00 reactive; EBV-VCA IgG [S/CO] <0.75 non-reactive; 0.75 to <1.00 grey zone; ≥1.00 reactive EBV-EBNA IgG [S/CO] <0.50 non-reactive; 0.50 to <1.00 grey zone; ≥1.00 reactive
	Inconsistent result	1	0	1	1	0		
	Reactive	2	0	0	1	0		
	ND	1	0	0	0	0		
HHV-6	Negative	27	5	8	9	36	<0.0001[4]	No HHV-6 DNA
	Positive	15	5	3	2	0		
	ND	1	0	0	0	0		
VI	Yes	24	6	4	4	0	<0.0001[4]	-
	No	19	4	7	7	36		
BI	Yes	4	0	0	2	0	0.0470[4]	-
	No	39	10	11	9	36		
UI	Yes	16	4	7	5	0	<0.0001[4]	-
	No	27	6	4	6	36		

BI – bacterial infection; **CFS** – complex febrile seizures, **CG** – control group; **CRP** – C-reactive protein; **EBNA** – Epstein–Barr nuclear antigen; **EBV** – Epstein–Barr virus; **ESR** – erythrocyte sedimentation rate; **GE** – generalised epilepsy; **HCMV** – human cytomegalovirus; **HHV-6** – human herpesvirus 6; **IgG** – immunoglobulin G; **IgM** – immunoglobulin M; ***M* (*SD*)** – mean (standard deviation); ***Me* (IQR)** – median (interquartile range); ***n*** – sample number; **ND** – no data; **PCT** – procalcitonin; **SFS** – simple febrile seizures; **SFS+** – simple febrile seizures plus; **UI** – unspecified infection; **VCA** – viral capsid antigen; **VI** – viral infection; **WBC** –white blood count; **y/a** – years of age.
[4] – maximum likelihood chi-square test.
[5] – Kruskal–Wallis test.
[5a] – Dunn–Bonferroni post-hoc test.
p-value <0.05.

Tab. 2. Analysis of demographic and clinical data and laboratory test results in children with various types of seizures

There was no significant correlation between these groups in terms of gender. In SG, 68/75 (91%) children had fever and 7/75 (9%) had no fever (children after ES). In FS group, there was a significant difference between the number of children with FFS and SSFS (48/64 and 16/64, respectively; $p < 0.0001$) (Tab. 3). However, no significant relationship was found between FS subgroups according to FFS occurrence (Tab. 4). In FS group, there were more children with simple FS (53/64; 83%) than CFS (11/64; 17%). In GE group, there were nine children with epilepsy of unknown

DOI: 10.15557/AN.2024.0004 AKTUALN NEUROL 2024, 24 (1), p. 20–34

and two with genetic aetiology (Dravet syndrome, *SCN1A* mutation). The data are presented in Tabs. 1–5.

Laboratory tests

Inflammatory markers (ESR, CRP, PCT) were significantly higher in SG compared to CG, except WBC. The normal range for WBC depended on the child's age. The analysis of WBC as a categorical variable showed a significant relationship between SG and CG ($p < 0.0001$). WBC below or exceeding reference values were found in 7/75 (9%) and 24/75 (32%) children, respectively, and within the normal range in 44/75 (59%) children. Levels below refence values were observed more frequently in SFS+, while values higher than upper limit of normal were observed in CFS children. Normal WBC counts were observed in CG and GE children. ESR above normal range was most often found in children with CFS, and within normal range in children from CG, SFS+ and GE groups. CRP level above normal range was most common in children with SFS and SFS+, and within normal range in children from CG and, GE. PCT above normal range was noted more often in children with SFS+. PCT within normal range was detected in children from CG, GE, and CFS groups. The analysis of inflammation parameters as quantitative variables showed significantly higher CRP and PCT levels in children with SFS, SFS+ and CFS, and ESR in children with SFS and CFS compared to CG. Moreover, PCT level was significantly higher in children with SFS than in children with GE. The highest ESR was observed in children with CFS (*M* 19.27 ± 11.13; *Me* 17.00 mm/h). The highest CRP level was found in children with SFS (*M* 2.68 ± 3.59; *Me* 1.07 mg/dL) and PCT in children with CFS (*M* 1.93 ± 5.61; *Me* 0.17 ng/mL). There was no significant correlation in terms of inflammatory markers between children with SFS and SFS+ without primary HHV-6 infection. The data are presented in Tabs. 1, 2, 5, 6.

Parameter	SG $n = 64$	*p*-value
FFS	48	<0.0001[1a]
SSFS	16	

FFS – first febrile seizures; **SG** – study group; **SSFS** – subsequent febrile seizures.
[1a] – Pearson's chi-square goodness-of-fit test.
p-value <0.05.

Tab. 3. Children with first and subsequent febrile seizures

Clinical manifestations and pathogens

The most common infections in the study population included upper respiratory tract infections (URTI) and/or lower respiratory tract infections (LRTI). Seven children with FS presented symptoms of ExS, while 16 children had HHV-6 infection without rash. Primary HHV-6 infection also resulted in acute otitis and sinusitis. One child with FS had chickenpox, four children had acute gastroenteritis, and two children presented symptoms of urinary tract infection with URTI or LRTI (children with FS and ES). Children with GE had fever less often (4 vs. 7), one child had typical symptoms of ExS, another child had HHV-6 infection without rash and fever, and URTI. Eight children with GE had single ES, five of them without fever. One child experienced cluster seizures (CS) without fever, and two children experienced status epilepticus (SE), including one child with preceding CS without fever. The other child with SE had a fever. HCMV and EBV infection was milder in the GE group than in the FS group and without fever. Children with FS and GE presented symptoms of respiratory infections, without typical symptoms of infectious mononucleosis. Significant correlations were found between SG and CG and the type of infection. The most common were viral infections (VI), 51% (Tab. 1). Among children with VI, the most common were children with SFS+, in children with GE bacterial infection (BI), and in children with CFS unspecified infections (UI) (Tab. 2). The following viral pathogens were detected in SG: HHV-6, influenza virus, HCMV, EBV, HRSV, rotaviruses, varicella-zoster virus (VZV) and human coronavirus HKU1 (HCoV-HKU1). Five children with SFS had concurrent infections: HHV-6 (without rash) and influenza virus; HHV-6 (no rash), HCMV and rotavirus; HHV-6 (with rash) and HRSV; HRSV and EBV; Escherichia coli (E. coli) and HCMV. Bacterial pathogens in SG included *Streptococcus pyogenes* (*S. pyogenes*), *Staphylococcus aureus* (*S. aureus*), *E. coli* and *Campylobacter jejuni* (*C. jejuni*). The occurrence of pathogens in respective groups is presented in Tab. 7.

Parameter		SFS		SFS+		CFS		*p*-value
		$n = 43$	%	$n = 10$	%	$n = 11$	%	
FS	First	29	67.44	9	90.00	10	90.90	0.1049[4]
	Subsequent	14	32.56	1	10.00	1	9.10	
HHV-6	Unknown	1	2.32	0	0.00	0	0.00	0.5514[4]
	Negative	27	62.79	5	50.00	8	72.72	
	Positive	15	34.89	5	50.00	3	27.28	

CFS – complex febrile seizures; **FS** – febrile seizures; **HHV-6** – human herpesvirus 6; ***n*** – sample number; **SFS** – simple febrile seizures; **SFS+** – simple febrile seizures plus.
[4] – maximum likelihood chi-square test.
p-value <0.05.

Tab. 4. Comparison of correlation between the types of febrile seizures, the sequence of seizures and HHV-6 infection

Parameter		(+) HHV-6					(–) HHV-6				
		SFS		SFS+		*p*-value (+)	SFS		SFS+		*p*-value (–)
		***n* = 15**	**%**	***n* = 5**	**%**		***n* = 27**	**%**	***n* = 5**	**%**	
Age [years]	*M*	1.78	100.00	2.18	100.00	0.3359[(2)]	2.53	100.00	1.45	100.00	0.0775[(2)]
	SD	0.98		0.82			1.63		0.99		
	Me	1.42		2.42			1.92		1.00		
	IQR	1.33		1.25			2.17		0.50		
Sex	Female	8	53.33	1	20.00	0.2214[(6)]	11	40.75	1	20.00	0.3657[(6)]
	Male	7	46.67	4	80.00		16	59.25	4	80.00	
WBC	Below	3	20.00	1	20.00	0.9369[(4)]	1	3.70	1	20.00	0.3944[(4)]
	Normal	10	66.67	3	60.00		15	55.55	3	60.00	
	Above	2	13.33	1	20.00		11	40.75	1	20.00	
ESR	Normal	7	53.85	4	80.00	0.6314[(6)]	8	32.00	2	50.00	0.4288[(6)]
	Above	6	46.15	1	20.00		17	68.00	2	50.00	
CRP	Normal	5	33.33	3	60.00	0.2962[(6)]	8	29.62	0	0.00	0.2111[(6)]
	Above	10	66.67	2	40.00		19	70.38	5	100.00	
PCT	Normal	12	80.00	4	80.00	0.7183[(6)]	17	62.96	2	40.00	0.3167[(6)]
	Above	3	20.00	1	20.00		10	37.03	3	60.00	
ExS	Yes	5	33.33	2	40.00	0.5942[(6)]	-	-	-	-	-
	No	10	66.67	3	60.00		-	-	-	-	

(+) – for children with primary human herpesvirus 6 infection; **(–)** – for children without primary human herpesvirus 6 infection; **CRP** – C-reactive protein; **ESR** – erythrocyte sedimentation rate; **ExS** – exanthema subitum; **(+) HHV-6** – primary human herpesvirus 6 infection; **(–) HHV-6** – no primary human herpesvirus 6 infection; **IQR** – interquartile range; ***M*** – mean; ***Me*** – median; ***n*** – sample number; **PCT** – procalcitonin; ***SD*** – standard deviation; **SFS** – simple febrile seizures; **SFS+** – simple febrile seizures plus; **WBC** – white blood count.
[(2)] – Mann–Whitney *U* test.
[(4)] – maximum likelihood chi-square test.
[(6)] – Fisher's exact test.
p-value <0.05.

Tab. 5. Comparison of age, sex, and inflammatory markers in children with/without primary HHV-6 infection with simple and simple plus febrile seizures

In SG, HCMV infection was present in 4/75 (5%) of children. There was no significant correlation between SG and CG and the HCMV result ($p = 0.3980$). Similarly in the analysis of five groups ($p = 0.2997$). EBV infection was found in 3/75 (4%) children. There was a correlation close to significance ($p = 0.0853$) between SG and CG regarding EBV result, which was not confirmed in the whole group analysis. There was a significant correlation between SG and CG and the HHV-6 result, which was positive in 25/75 (33%) children and occurred most often in children with SFS+ (Tabs. 1, 2).

Clinical and laboratory features of primary HHV-6 infection

There was no significant difference in age and gender between children with FS and with/without primary HHV-6 infection. No significant correlations and differences were found for inflammatory markers between children with or without primary HHV-6 infection, except for WBC. In HHV-6-positive children, WBC was lower than in HHV-6-uninfected children (*M* 8.21±4.57 vs. 13.19±7.13 G/L; *Me* 7.27 vs. 12.53 G/L, respectively). There was no relationship between the sequence of seizures (FFS/SSFS) and the HHV-6 results. The above data are presented in Tab. 8. There was no significant correlation between the types of FS and the HHV-6 result (data presented in Tab. 4). No significant relationship was found between SFS and SFS+ children infected with HHV-6 regarding gender, inflammatory markers, course of primary HHV-6 infection and age difference (Tab. 5).

In children with FS and primary HHV-6 infection, there was no significant difference between the number of children with ExS and the number of children with HHV-6 infection without rash, however, $p = 0.0606$ is close to borderline significance. There was no significant correlation between the types of FS and the type of ES and the nature of primary HHV-6 infection symptoms ($p = 0.4326$). There was no significant correlation between primary HHV-6 infection symptoms and FFS and SSFS ($p = 0.5084$). Primary HHV-6 infection without rash occurred more often in children with FFS than in children with SSFS ($p = 0.0455$). In children with ExS, there was no significant difference between the number of children with FFS and SSFS ($p = 0.0588$). The above data is presented in Tab. 9.

The seizures were self-limited (or stopped after diazepam was administered) except for two cases of epilepsy that required treatment in the intensive care unit (ICU) according to generally accepted principles. In one patient, the infection was treated according to an antibiogram, and in the other empirically (ICU). Viral infections associated with FS

DOI: 10.15557/AN.2024.0004 AKTUALN NEUROL 2024, 24 (1), p. 20–34

Parameter	Group	*n*	*M* (*SD*)	*Me* (IQR)	*p*-value	*p*-value Dunn–Bonferroni test
WBC [G/L]	SFS	43	11.32 (6.65)	9.38 (10.30)	0.5334[5]	-
	SFS+	10	9.70 (7.60)	7.34 (7.42)		
	CFS	11	12.92 (6.14)	13.90 (11.45)		
	GE	11	9.95 (5.52)	8.68 (4.81)		
	CG	36	9.30 (3.51)	8.29 (4.48)		
ESR [mm/h]	SFS	39	18.59 (13.94)	13.00 (16.00)	<0.0001[5]	SFS vs. CG <0.0001[5a] CFS vs. CG 0.0010[5a]
	SFS+	9	17.33 (25.22)	11.00 (5.00)		
	CFS	11	19.27 (11.13)	17.00 (13.00)		
	GE	9	9.78 (6.92)	8.00 (8.00)		
	CG	35	7.40 (3.89)	6.00 (5.00)		
CRP [mg/dL]	SFS	43	2.68 (3.59)	1.07 (4.38)	<0.0001[5]	SFS vs. CG <0.0001[5a] SFS+ vs. CG 0.0017[5a] CFS vs. CG 0.0357[5a]
	SFS+	10	2.17 (2.42)	1.01 (3.24)		
	CFS	11	1.65 (2.14)	0.53 (2.72)		
	GE	11	0.78 (0.89)	0.20 (1.15)		
	CG	36	0.20 (0.10)	0.20 (0.00)		
PCT [ng/mL]	SFS	43	0.82 (1.23)	0.32 (0.54)	<0.0001[5]	SFS vs. GE 0.0058[5a] SFS vs. CG <0.0001[5a] SFS+ vs. CG 0.0005[5a] CFS vs. CG 0.0179[5a]
	SFS+	10	1.39 (2.09)	0.27 (1.73)		
	CFS	10	1.93 (5.61)	0.17 (0.17)		
	GE	10	0.17 (0.29)	0.04 (0.08)		
	CG	33	0.04 (0.03)	0.04 (0.03)		

CFS – complex febrile seizures; **CG** – control group; **CRP** – C-reactive protein; **ESR** – erythrocyte sedimentation rate; **GE** – generalised epilepsy; ***M* (*SD*)** – mean (standard deviation); ***Me* (IQR)** – median (interquartile range); ***n*** – sample number; **PCT** – procalcitonin; **SFS** – simple febrile seizures; **SFS+** – simple febrile seizures plus; **WBC** – white blood count.
[5] – Kruskal–Wallis test.
[5a] – Dunn–Bonferroni post-hoc test.
p-value <0.05.

Tab. 6. Comparison of inflammatory markers in children with febrile seizures and generalised epilepsy

and ES were also mild and required only symptomatic treatment, except for children with influenza who were treated with oseltamivir. A few bacterial infections were treated based on the antibiogram.

DISCUSSION

In the presented study, we analysed the spectrum of clinical and laboratory symptoms of seizures in febrile children. The inflammatory response was studied in all types of seizures, and inflammatory response was compared between children with primary HHV-6 infection and children without primary HHV-6 infection. The intensity of the inflammatory response was determined using routine inflammatory markers. FS and epilepsy are among the most common neurological conditions during childhood. FS occurs in 3–5% of paediatric population (American Academy of Pediatrics, Subcommittee on Febrile Seizures, 2011) and the incidence of epilepsy ranges from 41 to 187/100,000 (Camfield and Camfield, 2015). The present study included children with a new type of SFS+ proposed by Grill and Ng (2013) and children with infection after a generalised epileptic seizure. Children with FS and GE are characterised by similar seizure morphology and age range in which both seizure states occur (Eriksson and Koivikko, 1997). The current study showed only two children under five years of age in the GE group. Generalised seizures occur in 80–85% of children with FS, and focal seizures constitute approximately 15–20% (Mittal, 2014; Pavlidou et al., 2013). According to different authors, viral infections are the predominant cause of FS, with pathogen profiles differing across studies (AlFulayyih et al., 2024; Carman et al., 2019; Chiu et al., 2001; Chung and Wong, 2007). In the study by Bertolani et al. (1996) viral infections in children with FS accounted for 67.7%. Francis et al. (2016) in the FEVER study detected at least one virus in over 2/3 of the tested cases, with frequent viral co-infections. According to Millichap and Millichap (2006), bacterial infections are rare (1.3%) causes of FS, and one aetiology is *S. pneumoniae*. The presented study showed that FSs are associated with various types of infections. Bacterial infections occurred most often in children with GE with *S. pyogenes* as dominant bacterial pathogen. In turn, viral infections (in our study group 51%) occurred most often in children with SFS+, and unspecified

Pathogens	SFS *n* = 43	SFS+ *n* = 10	CFS *n* = 11	GE *n* = 11	CG *n* = 36	*p*-value
	n	*n*	*n*	*n*	*n*	
HHV-6	15	5	3	2	0	**<0.0001**[(4)]
Influenza	3	1	0	0	0	0.1836[(4)]
HCMV	2	0	1	1	0	0.2997[(4)]
EBV	2	0	0	1	0	0.2981[(4)]
Bacteria	4	0	0	2	0	**0.0470**[(4)]
HRSV	3	0	0	0	0	-
Rotaviruses	2	0	0	0	0	-
HCoV-HKU1	1	0	0	0	0	-
VZV	1	0	0	0	0	-

CFS – complex febrile seizures; **CG** – control group; **EBV** – Epstein–Barr virus; **GE** – generalised epilepsy; **HCMV** – human cytomegalovirus; **HCoV-HKU1** – human coronavirus HKU1; **HHV-6** – human herpesvirus 6; **HRSV** – human respiratory syncytial virus; **SFS** – simple febrile seizures; **SFS+** – simple febrile seizures plus; **VZV** – varicella-zoster virus.
(4) – maximum likelihood chi-square test.
p-value <0.05.

Tab. 7. Pathogens in children with various types of febrile seizures and generalised epilepsy

infections in children with CFS. Chen et al. (2023) investigated the incidence of CNS infections in patients hospitalised for FS. EV, EBV, HHV-6, *Haemophilus influenzae*, *S. pneumoniae*, *Mycobacterium tuberculosis*, and *Shewanella putrefaciens* were identified in the CSF. Determination of pathogens in the CSF is important for timely therapeutic decisions. Differentiating FS from other CNS disorders based on clinical examination and laboratory tests is not always possible. In Abdelrahim et al. (2022) study, HHV-6 positive results were found in 33% of children with meningitis. All patients with a positive HHV-6 result presented with fever and vomiting, and 86% experienced convulsions. In the present study, no pathogens were detected in the CSF in any patients undergoing LP. Primary HHV6 infection is common among children. Up to 90% of children become infected during the first two years of life (Bartolini et al., 2019).

Parameter		(–) HHV-6			(+) HHV-6			*p*-value (1)	*p*-value (2)
		n	%	*M* (*SD*) *Me* (IQR)	*n*	%	*M* (SD) *Me* (IQR)		
Age		40	100.00	2.38 (1.54) 1.83 (2.08) [years]	23	100.00	1.91 (1.03) 1.50 (1.42) [years]	-	0.3994[(2)]
Sex	Female	18	45.00	2.30 (1.36) 1.83 (1.75) [years]	12	52.20	1.80 (1.14) 1.38 (1.12) [years]	0.5831[(1)]	0.2992[(2)]
	Male	22	55.00	2.44 (1.70) 1.79 (2.25) [years]	11	47.80	2.03 (0.93) 2.17 (1.42) [years]		0.9087[(2)]
FS	First	29	72.50	-	18	78.30	-	0.6130[(1)]	-
	Subsequent	11	27.50		5	21.70			
WBC	Below	3	7.50	13.19 (7.13) 12.53 (11.24) [G/L]	4	17.40	8.21 (4.57) 7.27 (8.42) [G/L]	0.0873[(4)]	0.0050[(2)]
	Normal	20	50.00		15	65.20			
	Above	17	42.50		4	17.40			
ESR	Normal	12	32.40	20.35 (17.01) 17.00 (13.00) [mm/h]	12	57.10	15.57 (12.21) 12.00 (14.00) [mm/h]	0.0663[(1)]	0.1840[(2)]
	Above	25	67.60		9	42.90			
CRP	Normal	12	30.00	3.11 (3.71) 1.70 (5.10) [mg/dL]	9	39.10	1.32 (1.68) 0.76 (1.21) [mg/dL]	0.4592[(1)]	0.0858[(2)]
	Above	28	70.00		14	60.90			
PCT	Normal	27	67.50	1.02 (1.57) 0.27 (0.64) [ng/mL]	17	77.30	1.16 (3.77) 0.14 (0.32) [ng/mL]	0.4173[(1)]	0.0669[(2)]
	Above	13	32.50		5	22.70			

(1) – for qualitative variables; **(2)** – for quantitative variables; **CRP** – C-reactive protein; **ESR** – erythrocyte sedimentation rate; **FS** – febrile seizures; **(–) HHV-6** – no primary human herpesvirus 6 infection; **(+) HHV-6** – primary human herpesvirus 6 infection; ***M* (*SD*)** – mean (standard deviation); ***Me* (IQR)** – median (interquartile range); ***n*** – sample number; **PCT** – procalcitonin; **WBC** – white blood count.
(1) – Pearson's chi-square test of independence.
(2) – Mann–Whitney *U* test.
(4) – maximum likelihood chi-square test.
p-value <0.05.

Tab. 8. Comparison of demographics and clinical data and inflammatory markers in children after febrile seizure with/without primary HHV-6 infection

DOI: 10.15557/AN.2024.0004 AKTUALN NEUROL 2024, 24 (1), p. 20–34

Parameter			(+) HHV-6									
			SFS *n* = 15	SFS+ *n* = 5	CSF *n* = 3	GE *n* = 2	FS total *n* = 23	*p*-value (1)	FS total *n* = 23	*p*-value (2)	FS total *n* = 23	*p*-value (3)
ExS	Yes	FFS	4	2	0	-	6	(A) 0.0588[1a]	6	0.5084[6]	7	0.0606[1a]
		SSFS	1	0	0	-	1		1			
	No	FFS	7	2	3	-	12	(B) 0.0455[1a]	12		16	
		SSFS	3	1	0	-	4		4			
ExS	Yes		5	2	0	1	8	(C) 0.4326[4]	-			
	No		10	3	3	1	17					

(1A) – in children with ExS, between FFS and SSFS; **(1B)** – in children with primary HHV-6 infection and without rash, between FFS and SSFS; **(1C)** – between seizure types and primary HHV-6 infection; **(2)** – between children with primary HHV-6 infection and FFS and SSFS; **(3)** – between children with ExS and children without rash;
CFS – complex febrile seizures; **ExS** – exanthema subitum; **FFS** – first febrile seizures; **FS** – febrile seizures; **GE** – generalised epilepsy; **HHV-6** – human herpesvirus 6; ***n*** – sample number; **SFS** – simple febrile seizures; **SFS+** – simple febrile seizures plus; **SSFS** – subsequent febrile seizures.
(1a) – Pearson's chi-square goodness-of-fit test.
(4) – maximum likelihood chi-square test.
(6) – Fisher's exact test.
p-value <0.05.

Tab. 9. Characteristics of selected clinical symptoms of primary HHV-6 infection in children with febrile seizures and generalised epilepsy

FS are the most common complication of primary HHV-6 infection due to viral neurotropism. In Asano et al. (1994) study, FS occurred in 8% of children infected with HHV-6, in Hall et al. (1994) study in 13%, in Laina et al. (2010) study in 18%, and in Hattori et al. (2019) study in 37.3%. In turn, according to Bertolani et al. (1996) the percentage of HHV-6 infections was 35.4% in children with first SFS (17% of children presented with ExS), while in other studies 9.7–19% in children with SFS and CFS (Barone et al., 1995; Francis et al., 2016; Hall et al., 1994; Hattori et al., 2019; Laina et al., 2010). In Miyake et al. (2020) study, 48% of children were infected with HHV-6 only in the first CFS. In the studies by Laina et al. (2010), and Hattori et al. (2019), ExS were found in 60% and 79.6%, respectively. In the present study, primary HHV-6 infection occurred in 33% of children with FS (first-time and subsequent) and GE. This percentage was similar to the results reported by Bertolani et al. (1996), however in that study children with first-time SFS were analysed. The differences between studies resulted from the structure of studied groups. In the present study, SFS+ were most common among children infected with HHV-6 (50%). In children with FS and GE, the percentage of typical ExS was 11%. Unlike the study by Francis et al. (2016), HHV-6 occurred in children as a single infection. The authors reported predominant simultaneous viral infections (82%).The difference may result from not all children being tested using the RT-PCR due to the costs of molecular testing. Molecular diagnostics in children with respiratory infections was performed when clinically indicated. The pathogens from *Herpesviridae* family were tested in all but one child. Some authors suggest a more frequent occurrence of CFS and a correlation between CFS and primary infection with HHV-6 and other pathogens. The study by Laina et al. (2010) showed that CFS occurred more often in children with primary HHV-6 infection than in children not infected with HHV-6, but the difference was not statistically significant. Hattori et al. (2019) confirmed a higher incidence of CFS in children with primary HHV-6 infection compared to uninfected children (95.5% vs. 67.1%, respectively). In Francis et al. (2016) study, children with CFS were hospitalised more often than children with SFS (74% vs. 33%). Moreover, the percentage of CFS was the highest in cohorts with influenza and HHV-6 infections (42% vs. 41%, respectively). In another study, human bocavirus was more common in children with CFS, while HRSV was more common in children with SFS. Influenza B virus was most often identified in children with first-time FS (Carman et al., 2019). Miyake et al. (2020) analysed 906 febrile children under five years of age, with 62 children with first-time CFS, and found a high incidence of primary HHV-6B infection (48%). In his study, children with primary HHV-6 infection were significantly younger than children uninfected with HHV-6 (median 13 vs.19 months, respectively), the interval between the onset of fever and seizure was longer than 24 hours, and male gender predominated in the group of children uninfected with HHV-6B. In the presented study, simple FS (SFS and SFS+ together) were more common than CFS – 53/64 (83%) vs. 11/64 (17%), respectively. Primary HHV-6 infection occurred more often in this group than in children with CFS – 20/53 (38%) vs. 3/11 (27%), respectively. We found no significant correlation for gender, FS type (simple, simple+ and complex) or age difference between children with primary HHV-6 infection and children without primary HHV-6 infection. Similarly, we did not demonstrate a correlation between the sequence (first or subsequent) of FS and the primary HHV-6 infection symptoms, except for children with primary HHV-6 infection without rash, where first-time FS were more common. Inflammation markers in children with FS were analysed by Barone et al. (1995) and Bertolani et al. (1996). Similarly to Barone et al. (1995), in the present study we observed a lower median WBC in children infected with HHV-6, while HHV-6 infection had no effect on the

median ESR, CRP and PCT. We performed a broader analysis of inflammation markers in all FS and GE groups, and found that WBC was most often reduced in children with SFS+ and increased in children with CFS. Moreover, the medians ESR, CRP and PCT were significantly higher in children with FS compared to CG. The inflammatory response in children with GE was significantly weaker. The extraction of a new SFS+ subtype from CFS by Grill and Ng (2013) allowed clinicians and primary care physicians not only to recognise FS types correctly but also to avoid unnecessary neuroimaging and EEG tests, and to better predict FS recurrences and the risk of developing epilepsy. Although there are no absolute indications for performing laboratory tests in children with the first episode of simple FS, routine tests help determine the source of infection in simple and complex FS (American Academy of Pediatrics, Subcommittee on Febrile Seizures, 2011; Mastrangelo et al., 2014). This study analysed inflammatory parameters in children with SFS+ and compared them with inflammatory parameters in children with SFS. The impact of primary HHV-6 infection on inflammatory markers in this patient group was also assessed. Considering the aim of the study and the conclusions drawn by Grill and Ng (2013), the analysis of inflammatory markers in children with SFS+ and SFS in the presented study did not show any significant correlations in the group of children with primary HHV-6 infection and children not infected with HHV-6. Children infected with HHV-6 did not differ in age. SFS+ children not infected with HHV-6 were younger than SFS children not infected with HHV-6 (*p*-value of borderline significance). The age of children with SFS+ may have influenced seizure recurrence within 24 hours. The publications emphasise the role of CNS immaturity and a reduced seizure threshold for body temperature in young children with FS and epilepsy (Mittal, 2014; Służewski and Służewska-Niedźwiedź, 2010; Wendorff et al., 2009). The study provides various age ranges for children with FS, both below and above the typical age for FS (Kiliç, 2019; MacDonald et al.,1999; Mastrangelo et al., 2014). In the present study, in the SFS subgroup, there were three children aged 5.6, 5.8 and 5.9 years with SSFS, without afebrile seizures during hospital stay. The medical history revealed that neither FS nor afebrile seizures occurred after discharge from the hospital. During the COVID-19 pandemic, nonpharmaceutical interventions (NPIs) aimed at limitation of the spread of SARS-CoV-2 infections reduced the incidence of many infectious diseases in children. A change in the pattern of pathogens responsible for seasonal respiratory diseases, e.g. influenza, was also found in adult patients (Rodgers et al., 2021). According to Kozawa et al. (2023), NPIs could have influenced the epidemiology of infections with pathogens from the β and γ *Herpesviridae* subfamily in children. The authors showed what changes occurred in infections with herpes viruses β and γ and CFS of viral aetiology during the pandemic (from April 2020 to March 2021) compared to the previous period (from April 2017 to March 2020) in febrile children ≤5 years. The authors showed a reduction in the average number of febrile children from 384 (pre-pandemic period) to 281 (during the pandemic); the number of cases with primary EBV, HCMV or HHV-7 infections was 1–6 per year during the whole observation period (differences in the percentage of patients before and during the pandemic were not significant). The average number of patients with primary HHV-6B infection increased slightly from 35 (9.3%) before the pandemic to 43 (15.5%) during the pandemic (p = 0.005). The authors showed that the total number of patients with CFS decreased during the pandemic (from 25 to 10). The annual number of patients with primary EBV, HCMV, HHV-7 infection and CFS was 0–2 before the pandemic, and none during the pandemic (no significant differences were found in the number of patients with CFS associated with these viruses between the period before and during the pandemic). The number of CFS cases caused by primary HHV-6B infection remained unchanged (8–11 cases per year). The proportion of patients with CFS caused by HHV-6B infection increased significantly from 42% (before the pandemic) to 90% (during the pandemic) due to the relative increase in the number of HHV-6B infections with CFS after the COVID-19 pandemic. We analysed the impact of HCMV and EBV infections on the occurrence of FS. We did not anticipate the outbreak of the COVID-19 pandemic during our study. Finally, the pandemic period overlapped the short period of our study (about nine months). Tracking changes in these infection trends before and during the COVID-19 pandemic is difficult. Moreover, the number of children with HCMV and EBV infections was low. There was a significant correlation between SG and CG only for the EBV infections (*p*-value of borderline significance), while no such relationship was found for the HCMV infections. EBV positive cases and HCMV positive cases accounted for 4% and 5% of children in SG, respectively. As in the study by Kozawa et al. (2023), the frequency of primary EBV and HCMV infections was low compared to primary HHV-6 infection. The presented study also showed no significant correlation between five groups (SFS, SFS+, CFS, GE and CG) and the EBV and HCMV infections. Although this study did not analyse changes in trends of infections complicated with FS, it is possible that NPIs may have an impact on the small number of patients with primary EBV and HCMV infection. We did not detect FSE, which may frequently occur in HHV-6 infection, in any of the hospitalised children. In our study, FS were mild in nature, with a predominance of simple ones. Seizures in children with GE were also mild, except for two children who developed SE. One child had a fever due to *S. aureus* infection, the other had no fever, and a CT scan revealed acute sinusitis. The inflammatory response measured by inflammation markers was more intense in the FS group than in the GE group. Based on the aforementioned studies and the presented study, it can be concluded that HHV-6 is a strong pathogen associated with convulsive activity in children,

DOI: 10.15557/AN.2024.0004

and should always be considered in the aetiology of infections manifested with seizures. Only 10–30% of HHV-6 infections present with typical ExS symptoms (Rodgers et al., 2021). It should be highlighted that the absence of rash does not rule out HHV-6 infection. In the light of published data, HHV-6 infections may have various phenotypes, including neurological complications. Despite its common occurrence, HHV-6 is still an underestimated pathogen that also has a prognostic potential for both FS recurrence and epilepsy development in children or later in life. Seizures, including FS, are a traumatic experience for children's parents and constitute a life-threatening disturbance. In this study, the first-time simple FS caused by HHV-6 infection were mild, which should help reassure caregivers about the prognosis when this event occurs. Patients do not require highly specialised treatment or diagnostics. In the case of epilepsy resulting from FS, the medical history should always include previous FS episodes, the occurrence of seizures in first-degree relatives, and infection aetiology, e.g. HHV-6. The present study has some limitations. The small sample size of FS subgroups and GE group was significant. Therefore, the conclusions should be drawn with caution. We did not estimate the sample size. The selection of patients in the study was not random. Another limitation was that we did not perform respiratory viral tests using the RT-PCR method in all children due to clinical and economic reasons. This made it impossible to detect the most common respiratory pathogens and co-infections. In diagnosing seizures in febrile children, it would be helpful to determine pathogen profiles typical for given countries or regions, which should be examined routinely. In the present study, we did not analyse treatment effectiveness. We did not hospitalise children with COVID-19 in this study. According to the study by Cadet et al. (2022), FS is not a commonly diagnosed symptom of COVID-19 (0.5%). Taking the above into account, it is necessary to continue the study on a larger population. Numerous studies on primary HHV-6 infection and the presented study prove that primary HHV-6 infections may have different courses and HHV-6 is still an underestimated pathogen.

CONCLUSIONS

Febrile seizures and epileptic seizures during infection were mild except for two children with status epilepticus not caused by HHV-6 infection. The inflammatory response during seizures measured by inflammatory markers was mild. The most common causative agent of seizures in febrile children was HHV-6. Primary HCMV and EBV infections were rare in this study. There was no significance relationship between study group and control group and HCMV results and was close to significance borderline for EBV results. The profile of primary HHV-6 infection differed from those reported in the literature. In children with febrile seizures, primary HHV-6 infection should be considered regardless of the sequence of seizures, even in the absence of rash. There were no correlations or differences between children with simple and simple febrile seizures plus regarding demographic data and inflammation markers.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study: GB, AM. Collection, recording and/or compilation of data: GB, KL, MT. Analysis and interpretation of data: GB, AM, MT. Writing of manuscript: GB. Critical review of manuscript: AM, KMM, PM, MF. Final approval of manuscript: GB, AM, MF.

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DOI: 10.15557/AN.2024.0004 AKTUALN NEUROL 2024, 24 (1), p. 20–34