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Assessment of basic immunological parameters in children with seizure disorders during acute infection

Ocena podstawowych parametrów immunologicznych u dzieci ze stanami napadowymi w przebiegu ostrej infekcji

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Abstract

Introduction and objective: The objective of the study was to assess basic immunological parameters in children presenting with seizure disorders during acute infection. **Materials and methods:** The study was conducted from 19 January 2017 to 5 December 2020 at the Department of Infectious Diseases and Child Neurology in Poznań, and involved 121 patients aged 5–188 months: 64 with febrile seizures and 11 with generalised epilepsy. The control group comprised 46 patients with delayed psychomotor and intellectual development, pervasive developmental disorders, and neurodeficits. A complete blood count with differential white cell count, inflammatory markers, immunoglobulin classes (IgG, IgA, IgM), and the aetiology of infection were analysed using standard laboratory methods in all the cases. **Results:** Lower IgG was found in the febrile seizures group, and lower IgA was observed in the simple febrile seizure group compared to the patients after epileptic seizures. Patients with first-time simple febrile seizures showed lower IgG levels than the control group. Patients with generalised epilepsy and human herpesvirus 6 (HHV-6) showed lower IgG than the non-infected subjects. Patients with first-time complex febrile seizures had the lowest lymphocyte count compared to the control group. The lowest neutrophil count and total leukocyte count were found in HHV-6-infected patients with simple febrile seizures compared to the non-infected patients. **Conclusions:** Monitoring basic haematological parameters and immunoglobulin levels is an effective strategy in the diagnosis of seizure disorders in children. Screening tests provide an initial quantitative assessment of humoral and cellular responses, as well as impaired phagocytosis.

Keywords: infection, febrile seizures, immunological parameters, HHV-6, generalised epilepsy

Streszczenie

Wprowadzenie i cel: Celem pracy była ocena podstawowych parametrów immunologicznych u dzieci ze stanami napadowymi w przebiegu ostrej infekcji. **Materiał i metody:** Badanie przeprowadzono w okresie od 19 stycznia 2017 do 5 grudnia 2020 roku w Klinice Chorób Zakaźnych i Neurologii Dziecięcej w Poznaniu. Badaniem objęto 121 pacjentów w wieku 5–188 miesięcy: 64 z drgawkami gorączkowymi i 11 z padaczką uogólnioną. Grupę kontrolną stanowiło 46 pacjentów z opóźnionym rozwojem psychomotorycznym, intelektualnym, całościowymi zaburzeniami rozwoju i deficytami neurologicznymi. Analizowano morfologię krwi obwodowej z rozmazem krwinek białych, wskaźniki reakcji zapalnej, stężenia immunoglobulin – IgG, IgA, IgM i etiologię infekcji. Parametry zbadano przy użyciu standardowych metod laboratoryjnych. **Wyniki:** W grupie drgawek gorączkowych wykazano niższe stężenie IgG, a w grupie drgawek gorączkowych prostych niższe stężenie IgA w porównaniu z pacjentami po napadzie padaczkowym. U pacjentów z pierwszorazowymi napadami drgawek gorączkowych prostych wykazano niższe stężenie IgG w porównaniu z grupą kontrolną. U pacjentów z padaczką uogólnioną i zakażeniem ludzkim wirusem *herpes* typu 6 (HHV-6) odnotowano niższe stężenie IgG w porównaniu z pacjentami niezakażonymi. U pacjentów z pierwszorazowymi napadami drgawek gorączkowych złożonych stwierdzono najniższą liczbę limfocytów w odniesieniu do grupy kontrolnej. Najniższą liczbę neutrofili i leukocytów wykazano u pacjentów zakażonych HHV-6 z drgawkami gorączkowymi prostymi w odniesieniu do pacjentów niezakażonych. **Wnioski:** Monitorowanie podstawowych parametrów hematologicznych i stężeń immunoglobulin jest przydatne w diagnostyce stanów napadowych u dzieci. Testy przesiewowe umożliwiają wstępną ocenę ilościową odpowiedzi humoralnej, komórkowej i upośledzenia fagocytozy.

Słowa kluczowe: infekcja, drgawki gorączkowe, parametry immunologiczne, HHV-6, padaczka uogólniona

INTRODUCTION

Seizures in children are characterised by a variety of clinical manifestations, depending on whether the seizures are epileptic or non-epileptic. Epilepsy is more common in children than in adults. In Europe, the incidence rate of epilepsy in infants under 1 year of age is 146/100,000, while in children under 10 years of age – 63/100,000 per year[1]. According to Korff and Dale, the average prevalence of recurrent non-febrile seizures in developed countries ranges from 3.5 to 5/1,000 children, and the cumulative incidence rate of epilepsy up to 15 years of age is approximately 0.8%[2]. Febrile seizures (FS) are the most common seizure disorder in children between 6 months and 5 years of age, occurring in 2–5% of children. Nevertheless, the incidence of FS varies worldwide. In North America and Western Europe, it amounts to 2–5%, in South India – 10.3%, in China – 0.5–1.5%, and in Japan – 8.8%[3–7]. In Poland, FS occur in 2.9% of children[8]. Classic FS with a single episode affect 70% of children, whereas multiple episodes are observed in 30% of cases[9]. The child's age and immaturity of the central nervous system (CNS) are vital for the development of both conditions. The semiology of epileptic seizures (ES) in children changes over time – the younger the child, the more frequent are the different types of ES[1,10]. Similarly, the classification of FS into simple (SFS), complex (CFS), and a separate subcategory of simple febrile seizures plus (SFS+), depends on the type of seizures, their duration and frequency within a 24-hour period[5,6,11]. The type of FS determines further diagnostic and therapeutic management. Various authors have reported different incidences of SFS and CFS, with SFS accounting for approximately 2/3 of all FS cases[3,5,6].

The aetiopathogenesis of both epilepsy and seizures is complex. The 2017 International League Against Epilepsy (ILAE) classification of epilepsy describes the following aetiological agents: structural, genetic, infectious, metabolic, immune, and unknown factors[12]. Viral infections represent the most frequent aetiological factor of FS. Both diseases are associated with an inflammatory response. As a result of immune system (IS) stimulation, pro-inflammatory cytokines (PICs) mediating pyrogenic and pro-convulsive effects are produced. A special role in the inflammatory response and seizure activity is attributed to glial cells, specifically microglial cells, which are involved in the local production of PICs. Cytokine expression in the brain is low and increases during ES. Another ES mechanism is T and B lymphocyte activation and autoantibody production. Antineuronal autoantibodies play a role in the pathogenesis of drug-resistant epilepsy resulting from autoimmune encephalitis, e.g. Rasmussen encephalitis with antibodies against glutamatergic receptors – GluR3, encephalitis with antibodies against *N*-methyl-D-aspartate receptor – NMDAR, limbic encephalitis associated with voltage-gated potassium channel antibodies – VGKC (anti-leucine-rich glioma-inactivated protein 1, LGI1; anti-contactin-associated protein-like 2, CASPR2)[13–15]. Apart from infections, genetic and environmental factors are also involved in FS development. FS were shown to depend on the season, month, and time of day. Schuchmann et al. demonstrated the role of respiratory alkalosis in neuronal excitability. According to the sources, immunoglobulin (Ig) deficiencies – IgG, IgA, IgM, and IgG2, IgG4 subclasses – contribute to the pathogenesis of FS. Abnormal Ig levels may increase susceptibility to infection or, in some cases, may be involved in FS pathogenesis[10,16–21]. Zubiel et al. pointed to the impaired specific humoral immunity in FS patients, particularly those exhibiting single episodes. The researchers hypothesise that autoimmune disorders may underlie this most common FS type[9]. In our study, basic haematological parameters and IgG, IgA, IgM levels were assessed to demonstrate the relevance of screening tests in the diagnosis of seizure disorders in children in terms of evaluating immune system dysfunctions. Additionally, the impact of human herpesvirus 6 (HHV-6) on the analysed components of the immune system was investigated.

MATERIALS AND METHODS

The reported study was conducted from 19 January 2017 to 5 December 2020 at the Department of Infectious Diseases and Child Neurology at the Karol Jonscher Hospital, Poznan University of Medical Sciences, and followed a clinical analysis approach. The study group consisted of a total of 121 patients aged between 5 and 188 months. The exclusion criterion for all the participants was diagnosed immunodeficiency. The study group included 64 patients after FS, and 11 after ES in the course of acute infection. Nine patients were diagnosed with generalised epilepsy (GE), and 2 suffered from combined generalised and focal epilepsy (Dravet syndrome; *SCN1A* mutation). The control group (CG) consisted of 46 patients with delayed psychomotor and intellectual development, pervasive developmental disorders and neurodeficits, who were admitted for clinical evaluation. The exclusion criteria in CG comprised a history of FS and epilepsy, as well as symptoms of infection. The inclusion criteria for FS were: seizures associated with a fever ≥38°C, age 6–60 months, no evidence of CNS infection, or inflammation. The exclusion criteria in the FS group involved: CNS infection, acute metabolic disorder causing seizures, and history of non-febrile seizures[22]. Depending on the FS type (generalised or focal), seizure frequency within 24 hours and their duration (cut-off point of 10 minutes between SFS and CFS, according to Hesdorffer et al.[23]), the patients were classified either into the SFS or CFS group[22]. Another group included patients with the new type of SFS+, as suggested by Grill and Ng in 2013 – SFS phenotype and >1 seizure episode within 24 hours[6]. Patients who experienced FS or ES in the course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were excluded from the study, since they were hospitalised in the

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isolation ward of the same hospital. During the study period, none of the hospitalised patients was diagnosed with febrile status epilepticus (FSE).

Immune system function was evaluated based on the screening tests. The assayed immunological parameters included the serum levels of Ig – IgG, IgA, IgM (mg/dL). A complete blood count with differential white cell count (CBC+DIFF) was performed – a white blood count (WBC – G/L), neutrophil count (Neu – G/L) and lymphocyte count (Lymph – G/L) were analysed. Inflammatory markers were also investigated, including the erythrocyte sedimentation rate (ESR – mm/h), C-reactive protein (CRP – mg/dL), and procalcitonin (PCT – ng/mL). The aetiology of infection included viruses of the *Herpesviridae* family: cytomegalovirus (CMV), Epstein–Barr virus (EBV), and HHV-6. The aetiological agents of respiratory tract, urinary tract and gastrointestinal tract infections were identified depending on the clinical indications. If a CNS infection was suspected, cerebrospinal fluid (CSF) was assessed. Neuroimaging and electroencephalographic examinations were performed before the lumbar puncture and during diagnosis.

The study parameters, including WBC, Neu, Lymph, ESR, CRP, and PCT, were determined by standard laboratory methods. A quantitative immunoturbidimetric procedure using the Alinity c analyser was applied to determine the IgG, IgA, IgM levels. HHV-6, influenza virus, and respiratory syncytial virus (RSV) infections were confirmed by qualitative real-time polymerase chain reaction (RT-PCR) testing in blood/nasopharyngeal swab. Respiratory tract secretions were tested in 1 case by a qualitative RT-PCR test. CMV and EBV infections were confirmed in blood samples using a qualitative immunochemical test on the Alinity i analyser. Viral infections of the gastrointestinal tract (rotaviruses, adenoviruses) were confirmed with a rapid qualitative cassette test by immunochromatography in faeces. Bacterial infections of the respiratory, urinary and gastrointestinal systems were confirmed microbiologically by culturing the pharyngeal swab, tracheal aspirate, and urine and faeces samples.

Statistical analysis

Statistical analyses were performed using Statistica v.13 (Dell Inc., 2016, Tulsa, OK, USA). The results of analyses pertaining to the quantitative variables were presented as mean and standard deviation, median (*M*) of the lower and the upper quartile (interquartile range, IQR). The quantitative variables were checked to see if they followed the Gaussian curve, and due to a lack of normal distribution for many groups, the analysis was performed using a non-parametric Kruskal–Wallis ANOVA test. Where differences were found, a multiple comparisons test was applied. The chi-square test and the test for two population proportions were used to compare the differences in terms of the sex of the participants. The results of the analyses were considered statistically significant for $p < 0.05$.

Parameter	Number	Mean ± *SD*	*M* (IQR)
Age [months]	–	41.41 ± 37.47	29 (17–48)
Sex – F/M	55/66	–	–
WBC [G/L]	–	10.39 ± 5.61	8.65 (6.48–12.98)
Neu [G/L]	–	5.51 ± 5.08	3.79 (2.15–7.04)
Lymph [G/L]	–	3.67 ± 2.26	2.99 (2.05–5.03)
ESR [mm/h]	–	13.48 ± 12.83	10 (6–17)
CRP [mg/dL]	–	1.43 ± 2.58	0.24 (0.2–1.3)
PCT [ng/mL]	–	0.63 ± 1.94	0.09 (0.03–0.36)
IgG [mg/dL]	–	624.74 ± 250.58	598 (439.5–778.5)
IgA [mg/dL]	–	63 ± 55.77	45 (29–72)
IgM [mg/dL]	–	79.33 ± 36.02	72.5 (51.5–98)

CRP – C-reactive protein; **ESR** – erythrocyte sedimentation rate; **F** – female; **IgA** – immunoglobulin A; **IgG** – immunoglobulin G; **IgM** – immunoglobulin M; **Lymph** – lymphocytes; **M** – male; ***M* (IQR)** – median (interquartile range); **Neu** – neutrophils; **PCT** – procalcitonin; **WBC** – white blood count; **SD** – standard deviation.

Tab. 1. Characteristics of the study group, n = *121*

The Bioethics Committee at the Poznan University of Medical Sciences approved the study on 6 December 2018 (Approval No. 1281/18). The legal guardians of the patients provided written informed consent before the study. The characteristics of the study group are presented in Tab. 1.

RESULTS

Patients

In the study group of 75 patients with seizures, the median age was 21.5 months in FS patients, and 124 months in GE patients. The composition of the study groups in terms of the distribution, number, age, and sex of the participants is presented in Tabs. 2–5. In the FS group, there were 48/64 (75%) patients with first-time (FT) seizures, with a median age of 18 months. 16/64 (25%) patients were hospitalised following subsequent (SS) seizures, with a median age of 28.5 months. In all FS groups, FT seizure cases were the most common – SFS 29/43 (67.4%); SFS+ 9/10 (90%); CFS 10/11 (90.9%). 14/43 (32.6%) of SFS patients experienced SS seizures – a second episode was observed in 7 patients, third in 4, fourth in 1, and fifth in 2 subjects. In the SFS+ and CFS groups, individual patients experienced SS seizures – the second and third episode, respectively. In the GE group, SS seizures developed in all patients.

Laboratory findings

Patients with CFS and FT seizures had significantly higher Neu and the lowest Lymph compared to the CG. GE patients presented lower Lymph compared to the CG. The highest ESR was observed in FT SFS subjects, in comparison to CG. The highest CRP was found in SS SFS patients compared to the CG. The highest PCT was observed in patients with FT SFS+ as compared to CG.

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Parameter	SFS – *n* = 43 *M* (IQR)	SFS+ – *n* = 10 *M* (IQR)	CFS – *n* = 11 *M* (IQR)	GE – *n* = 11 *M* (IQR)	CG – *n* = 46 *M* (IQR)	*p*	*p* for multiple comparisons
Age [months]	22 (15–38)	17 (12–32)	22 (13–42)	124 (72–156)	37 (22–68)	0,00008*	SFS vs. GE 0.0004 SFS+ vs. GE 0.002 CFS vs. GE 0.02
Sex – F/M	20/23; 46.5%/53.5% *p* = 0.509	2/8; 20%/80% *p* = 0.007	9/2; 81.8%/18.2% *p* = 0.003	8/3; 72.7%/27.3% *p* = 0.035	16/30; 35%/65% *p* = 0.004	0.007*	–
WBC [G/L]	9.38 (6.18–16.48)	7.34 (5.1–12.52)	13.9 (7.09–18.54)	8.68 (6.16–10.97)	8.29 (6.77–11.32)	0.463	–
Neu [G/L]	6.18 (1.87–2.70)	3.32 (1.17–7.62)	7.05 (5.01–13.12)	4.30 (3.37–6.56)	2.69 (2.14–4.28)	0.005*	CFS vs. CG 0.01
Lymph [G/L]	2.43 (1.99–4.54)	3.62 (1.37–5.82)	1.58 (1.28–2.58)	2.05 (1.62–3.01)	4.44 (3.01–5.41)	0.000056*	SFS vs. CG 0.005 SFS+ vs. CG 0.001 CFS vs. CG 0.02
ESR [mm/h]	13 (8–24)	11 (7–12)	17 (11–24)	8 (4–12)	6 (4–9)	0.00001*	SFS vs. CG 0.000006 CFS vs. CG 0.0006
CRP [mg/dL]	1.07 (0.37–4.75)	1.01 (0.28–3.52)	0.53 (0.2–2.92)	0.2 (0.2–1.35)	0.2 (0.2–0.2)	0.00001*	SFS vs. CG 0.0000001 SFS+ vs. CG 0.001 CFS vs. CG 0.04
PCT [ng/mL]	0.32 (0.13–0.67)	0.27 (0.09–1.82)	0.17 (0.05–0.22)	0.03 (0.02–0.10)	0.03 (0.02–0.05)	0.00001*	SFS vs. CG 0.0000001 SFS+ vs. CG 0.0002 CFS vs. CG 0.008 SFS vs. GE 0.007
IgG [mg/dL]	556 (384–652)	546.5 (390–599)	538 (329–660)	955 (757–1128)	683.5 (449–873)	0.0003*	SFS vs. GE 0.0009 SFS+ vs. GE 0.01 CFS vs. GE 0.02
IgA [mg/dL]	43.5 (28–58)	40 (34–43)	37 (26–57)	134 (37–236)	54 (28–100)	0.02*	SFS vs. GE 0.04
IgM [mg/dL]	74 (56–96)	54.5 (51–63)	74 (51–121)	87 (59–130)	72.5 (49–98)	0.21	–

* $p < 0.05$.
CFS – complex febrile seizures; **CG** – control group; **CRP** – C-reactive protein; **ESR** – erythrocyte sedimentation rate; **F** – female; **GE** – generalised epilepsy; **IgA** – immunoglobulin A; **IgG** – immunoglobulin G; **IgM** – immunoglobulin M; **Lymph** – lymphocytes; **M** – male; ***M* (IQR)** – median (interquartile range); **Neu** – neutrophils; **PCT** – procalcitonin; **SFS** – simple febrile seizures; **SFS+** – simple febrile seizures plus; **WBC** – white blood count.

Tab. 2. Clinical and laboratory characteristics of the study groups

Given our laboratory reference values for Ig according to age, decreased Ig levels were observed in some patients, more frequently IgA and IgG than IgM. In SFS patients, lower Ig levels compared to the reference values were found in 31/43 (72.1%) subjects, in SFS+ in 8/10 (80%), in CFS in 6/11 (54.5%), in GE in 4/11 (36.4%), in the CG in 24/46 (52.2%). Lower Ig levels were more commonly observed in FS patients than in GE subjects, and were also more prevalent in SFS patients (48.4%) and SFS+ (12.5%) than in CFS participants (9.4%). Due to the small size of the groups in our study, a uniform standard for the Ig parameter was adopted. IgG levels were significantly lower in FS patients compared to GE, with the lowest found in CFS – 538 mg/dL. The IgA level was significantly lower in SFS patients compared to GE. In FT SFS, the IgG level was significantly lower compared to CG. The results are presented in Tabs. 2 and 3.

Results obtained in patients following an epileptic seizure in the course of acute infection with/without fever

After ES in the course of acute infection, 4 patients with fever (GE/IWF) and 7 without fever (GE/IWoF) were hospitalised. Older patients with IWoF were more frequently hospitalised. Lymph was significantly lower in both groups, with the lowest level found in GE/IWF patients. CRP and PCT levels were significantly higher in GE/IWF patients. In both groups, Ig levels were higher than in the CG, though statistical significance was achieved only in IgG in the GE/IWoF group. No association was found between ES with fever and the levels of IgG, IgA, and IgM in GE patients. The results are presented in Tab. 4.

In the GE group, a single epileptic episode occurred in 8 patients, including 3 with fever. In the GE/IWoF group, 2 patients experienced cluster seizures (CS), including 1 patient with status epilepticus (SE). In the GE/IWF group, SE also occurred in 1 patient, and bacterial infections with *Streptococcus pyogenes* and *Staphylococcus aureus* were found in 2 patients. Clinically, one patient was diagnosed with acute tonsillitis, another with pneumonia with concomitant urinary tract infection – the patient was hospitalised at the Paediatric Intensive Care Unit due to SE. In 1 patient, an HHV-6 infection was confirmed; the clinical presentation was consistent with exanthema subitum (ExS). In 1 patient, the aetiological agent of infection was not identified, and the clinical presentation corresponded to upper respiratory tract infection (URTI). In the GE/IWoF group, viral infections were predominant and were confirmed in 3 patients: HHV-6, CMV, and EBV. HHV-6 infection progressed without a rash, with URTI. EBV and CMV infections were oligosymptomatic. In 4 patients, the aetiological agent of infection was not determined. URTI was found in 2 subjects, including 1 case where chronic rhinosinusitis was detected by computed tomography (CT) (CS patient), in 2 patients acute rhinosinusitis was diagnosed based on

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Parameter	SFS – *n* = 43		SFS+ – *n* = 10		CFS – *n* = 11		GE; SS – *n* = 11 *M* (IQR)	CG – *n* = 46 *M* (IQR)	*p*	*p* for multiple comparisons
	FT – *n* = 29 *M* (IQR)	SS – *n* = 14 *M* (IQR)	FT – *n* = 9 *M* (IQR)	SS – *n* = 1 *M* (IQR)	FT – *n* = 10 *M* (IQR)	SS – *n* = 1 *M* (IQR)				
Age [months]	18 (13.75–30.25)	33 (24–58)	17 (11.75–33.5)	29 –	23.5 (13–42)	22 –	124 (72–156)	37 (22–68)	0.00006*	SFS FT vs. CG 0.0001 GE SS vs. CG 0.02
Sex – F/M	15/14 $p = 0.76$	5/9 $p = 0.14$	2/7 $p = 0.02$	0/1 $p = 0.33$	8/2 $p = 0.007$	1/0 $p = 0.30$	8/3 $p = 0.035$	16/30 $p = 0.004$	0.033*	–
WBC [G/L]	9.11 (6.33–13.27)	12.75 (4.46–18.33)	7.41 (4.63–12.69)	7.27 –	12.23 (7.09–18.54)	17.37 –	8.68 (6.16–10.97)	8.29 (6.77–11.32)	0.679	–
Neu [G/L]	4.55 (2.04–7.79)	9.26 (1.87–15.55)	3.75 (1.62–7.92)	0.72 –	7.01 (4.81–13.06)	13.12 –	4.30 (3.37–6.56)	2.69 (2.14–4.28)	0.009*	CFS FT vs. CG 0.01
Lymph [G/L]	2.58 (2.15–5.51)	2.11 (1.51–2.57)	3.56 (1.31–4.81)	5.82 –	1.34 (1.27–2.61)	2.19 –	2.05 (1.62–3.01)	4.44 (3.01–5.41)	0.00004*	CFS FT vs. CG 0.002 SFS SS vs. CG 0.0002 GE SS vs. CG 0.01
ESR [mm/h]	18 (9–24)	12 (7–35)	10 (7–12)	12 –	17 (12–24)	11 –	8 (4–12)	6 (4–9)	0.00002*	SFS FT vs. CG 0.00001 CFS FT vs. CG 0.0004 SFS SS vs. CG 0.03
CRP [mg/dL]	0.92 (0.45–2.95)	1.98 (0.2–5.26)	1.25 (0.56–4.18)	0.2 –	0.66 (0.2–2.92)	0.2 –	0.2 (0.2–1.35)	0.2 (0.2–0.2)	<0.000001*	SFS FT vs. CG 0.0000001 SFS+ FT vs. CG 0.0001 CFS FT vs. CG 0.009 SFS SS vs. CG 0.002
PCT [ng/mL]	0.34 (0.14–0.54)	0.27 (0.07–2.11)	0.37 (0.14–1.82)	0.09 –	0.17 (0.05–0.22)	0.20 –	0.03 (0.02–0.1)	0.03 (0.02–0.05)	0.000001*	SFS FT vs. CG 0.0000001 SFS+ FT vs. CG 0.00009 CFS FT vs. CG 0.009 SFS SS vs. CG 0.00004
IgG [mg/dL]	530 (353.5–652)	595 (491.5–666.8)	519 (381.5–624)	576 –	559 (428–660)	329 –	955 (757–1128)	683.5 (449–873)	0.001*	SFS FT vs. CG 0.01
IgA [mg/dL]	36 (23.75–45.25)	55 (46–64)	44 (33–42)	58 –	42 (27–57)	22 –	134 (37–236)	54 (28–100)	0.07	–
IgM [mg/dL]	74 (54.75–89.25)	76 (57.75–117.75)	56 (50.75–64.00)	51 –	79.5 (66–121)	51 –	87 (59–130)	72.5 (49–98)	0.304	–

* $p < 0.05$.
CFS – complex febrile seizures; **CG** – control group; **CRP** – C-reactive protein; **ESR** – erythrocyte sedimentation rate; **F** – female; **FT** – first-time seizures; **GE** – generalised epilepsy; **IgA** – immunoglobulin A; **IgG** – immunoglobulin G; **IgM** – immunoglobulin M; **Lymph** – lymphocytes; **M** – male; ***M* (IQR)** – median (interquartile range); **Neu** – neutrophils; **PCT** – procalcitonin; **SFS** – simple febrile seizures, **SFS+** – simple febrile seizures plus; **SS** – subsequent seizures; **WBC** – white blood count.

Tab. 3. Clinical and laboratory characteristics of the study groups with first-time, subsequent febrile seizures, subsequent epileptic seizures in generalised epilepsy

Parameter	GE – *n* = 11 IWF – *n* = 4 *M* (IQR)	CG – *n* = 46 *M* (IQR)	*p*	GE – *n* = 11 IWoF – *n* = 7 *M* (IQR)	CG – *n* = 46 *M* (IQR)	*p*
Age [months]	65 (14.5–126)	37 (22–68)	0.681	140 (74–168)	37 (22–68)	0.000*
Sex – F/M	3/1	16/30	0.147	5/2	16/30	0.077
WBC [G/L]	7.81 (5.53–16.28)	8.29 (6.77–11.32)	0.844	8.68 (7.07–10.97)	8.29 (6.77–11.32)	0.864
Neu [G/L]	4.79 (3.84–5.74)	2.69 (2.14–4.28)	0.179	4.3 (1.97–8.16)	2.69 (2.14–4.28)	0.151
Lymph [G/L]	1.5 (1.27–1.74)	4.44 (3.03–5.24)	0.022*	2.62 (1.99–3.62)	4.44 (3.03–5.24)	0.007*
ESR [mm/h]	8 (4–24)	6 (4–9)	0.488	8 (4–12)	6 (4–9)	0.591
CRP [mg/dL]	0.78 (0.2–1.55)	0.2 (0.2–0.2)	0.049*	0.2 (0.2–1.3)	0.2 (0.2–0.2)	0.052
PCT [ng/mL]	0.46 (0.10–0.91)	0.03 (0.02–0.03)	0.004*	0.03 (0.02–0.04)	0.03 (0.02–0.03)	0.51
IgG [mg/dL]	859 (676–1038)	683.5 (449–873)	0.260	1104 (757–1128)	683.5 (449–873)	0.013*
IgA [mg/dL]	85 (28–151)	54 (28–100)	0.734	142 (80–287)	54 (28–100)	0.16
IgM [mg/dL]	84 (66–156)	72.5 (49–98)	0.371	87 (52–130)	72.5 (49–98)	0.207

* $p < 0.05$.
CG – control group; **CRP** – C–reactive protein; **ESR** – erythrocyte sedimentation rate; **F** – female; **GE** – generalised epilepsy; **IgA** – immunoglobulin A; **IgG** – immunoglobulin G; **IgM** – immunoglobulin M; **IWF** – infection with fever; **IWoF** – infection without fever; **Lymph** – lymphocytes; **M** – male; ***M* (IQR)** – median (interquartile range); **Neu** – neutrophils; **PCT** – procalcitonin; **WBC** – white blood count.

Tab. 4. Clinical and laboratory characteristics of patients with generalised epilepsy and infection with/without fever

the CT scan, including 1 with URTI (patient with SE preceded by CS). The history of epilepsy in 7 patients comprised a period from 7 months to 9 years of age. Antiseizure medications (ASMs) were initiated in 4 patients during hospitalisation, including 2 cases due to recurring ES. Valproic acid (VPA) was administered in 6 patients as monotherapy. In 2 patients, VPA was used with levetiracetam, and in 1 patient, with clobazam and stiripentol.

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Parameter	SFS(+) – *n* = 15 *M* (IQR)		SFS(–) – *n* = 27 *M* (IQR)	p_1	SFS+(+) – *n* = 5 *M* (IQR)	SFS+(–) – *n* = 5 *M* (IQR)	p_1	CFS(+) – *n* = 3 *M* (IQR)	CFS(–) – *n* = 8 *M* (IQR)	p_1	GE(+) – *n* = 2 *M* (IQR)	GE(–) – *n* = 9 *M* (IQR)	p_1	CG(+) – *n* = 6 *M* (IQR)	CG(–) – *n* = 38 *M* (IQR)	p^2	*p* for multiple comparisons
	ExS – *n* = 5	Wo ExS – *n* = 10															
Age [months]	14 (11–15)	25 (17–32)	23 (16–42)	0.17	29 (17–32)	12 (11–17)	0.20	21 (6–48)	24 (17–38.50)	0.68	39.5 (7–72)	140 (108–156)	0.08	52 (22–87)	37 (18–60)	0.003*	SFS(–) vs. GE(–) 0.0005 SFS+(–) vs. GE(–) 0.0006 CFS(–) vs. GE(–) 0.01 GE(–) vs. CG(–) 0.01
Sex – F/M	3/2	5/5	11/16		1/4	1/4		3/0	6/2		2/0	6/3		2/4	13/25	0.096	–
WBC [G/L]	**5.73 (5.16–9.11)**	**5.46 (3.90–12.88)**	**12.33 (6.85–17.66)**	**0.005***	7.41 (7.27–11.31)	6.48 (5.1–12.52)	0.99	7.64 (5.81–15.98)	15.64 (8.82–18.8)	0.36	6.79 (4.9–8.68)	9.46 (7.07–10.97)	0.29	10.11 (8.65–12.79)	8.23 (6.67–11.17)	0.99	–
Lymph [G/L]	5.47 (4.33–6.88)	2.27 (1.99–2.59)	2.39 (1.86–3.31)	0.23	3.56 (1.48–3.69)	4.32 (1.11–6.30)	0.83	1.33 (1.27–6.05)	1.82 (1.28–2.58)	0.99	3.62 (3.62–3.62)	2.02 (1.505–2.71)	0.99	4.75 (3.21–6.99)	4.47 (2.97–5.24)	0.0004*	SFS(–) vs. CG(–) 0.007 CFS(–) vs. CG(–) 0.005 GE(–) vs. CG(–) 0.02
Neu [G/L]	**0.75 (0.62–1.87)**	**1.190 (0.93–4.29)**	**7.44 (3.21–12.8)**	**0.0006***	2.89 (0.72–7.62)	3.75 (1.77–3.93)	0.68	5.68 (4.21–7.01)	12.34 (5.01–15.23)	0.25	3.98 (3.98–3.98)	5.02 (2.905–7.095)	0.98	4.16 (2.21–4.36)	2.51 (2.12–3.58)	0.0002*	SFS(–) vs. CG(–) 0.00008 CFS(–) vs. CG(–) 0.01
ESR [mm/h]	17.5 (10.5–26)	9 (7–13)	18 (10–30)	0.20	9 (7–12)	11.5 (9–48)	0.45	40 (12–40)	15.5 (11–17.50)	0.18	3.5 (3–4)	9 (7–17)	0.08	5 (4–12)	6 (4–9)	0.0000*	SFS(–) vs. CG(–) 0.000008 CFS(–) vs. CG(–) 0.02 CFS(+) vs. CG(–) 0.02
CRP [mg/dL]	0.49 (0.37–0.92)	1.11 (0.65–2.89)	1.51 (0.37–5.66)	0.17	0.28 (0.20–0.76)	3.52 (2.24–6.14)	0.04*	0.79 (0.2–6.98)	0.43 (0.2–2.84)	0.61	0.2 (0.2–0.2)	0.24 (0.2–1.35)	0.25	0.2 (0.2–0.24)	0.2 (0.2–0.2)	0.0000*	SFS(–) vs. CG(–) 0.0000001 SFS+(–) vs. CG(–) 0.0009 SFS(+) vs. CG(–) 0.0003
PCT [ng/mL]	0.54 (0.37–0.70)	0.11 (0.07–0.52)	0.34 (0.16–1.73)	0.09	0.428 (0.06–0.15)	0.94 (0.37–4.43)	0.06	8.97 (0.05–17.9)	0.17 (0.1–0.21)	0.79	0.04 (0.04–0.04)	0.03 (0.02–0.1)	0.99	0.02 (0.02–0.05)	0.03 (0.02–0.05)	0.00001*	SFS(–) vs. CG(–) 0.0000001 SFS+(–) vs. CG(–) 0.0003 SFS(–) vs. GE(–) 0.01 SFS+(–) vs. GE(–) 0.03 SFS(+) vs. CG(+) 0.01 SFS(+) vs. CG(–) 0.00004
IgG [mg/dL]	474 (462–543)	484 (323–584)	581.5 (384–652)	0.14	556.8 (519–599)	390 (356–574)	0.29	538 (227–660)	556.5 (378.5–674.5)	0.76	**481.5 (465–498)**	**1,104 (863–1,128)**	**0.04***	875.5 (754–888)	653 (446–782)	0.0006*	SFS(–) vs. GE(–) 0.0004 SFS+(–) vs. GE(–) 0.004 CFS(–) vs. GE(–) 0.009 GE(–) vs. CG(–) 0.007
IgA [mg/dL]	36 (35–44	39 (28–58)	44.5 (23–63)	0.63	42 (37–41)	40 (30–43)	0.75	32 (15–46)	45 (26.5–57.5)	0.36	49 (18–80)	142 (133–236)	0.12	108.5 (42–121)	49 (24–89)	0.03*	SFS(–) vs. GE(–) 0.02
IgM [mg/dL]	93 (77–95)	54 (43–24)	74.5 (63–98)	0.23	56.8 (51–62)	56 (50–63	0.98	72 (25–95)	79.5 (58.5–125)	0.47	49 (39–59)	96 (80–130)	0.08	94.5 (58–105)	68.5 (47–98)	0.091	–

p_1 – *p*-value in a given group; p_2 – *p*-value between the groups; * $p < 0.05$.
(+) – HHV-6 positive; **(–)** – HHV-6 negative; **CFS** – complex febrile seizures; **CG** – control group; **CRP** – C-reactive protein; **ESR** – erythrocyte sedimentation rate; **ExS** – exanthema subitum; **F** – female; **GE** – generalised epilepsy; **IgA** – immunoglobulin A; **IgG** – immunoglobulin G; **IgM** – immunoglobulin M; **Lymph** – lymphocytes; **M** – male; ***M* (IQR)** – median (interquartile range); **Neu** – neutrophils; **PCT** – procalcitonin; **SFS** – simple febrile seizures; **SFS+** – simple febrile seizures plus; **WBC** – white blood count; **Wo** – without.

Tab. 5. Comparative analysis of the study groups with regard to HHV-6 infection

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One patient received lamotrigine, and in another subject, polytherapy with phenytoin, sulthiame, and rufinamide was applied.

Viral infections were predominant in the FS group: HHV-6, influenza virus type A and B, CMV, EBV, RSV, rotaviruses, varicella-zoster virus, human coronavirus HKU1. The HHV-6 infection was predominant. In the CG, 3 patients presented with asymptomatic EBV infections (1 co-infection with HHV-6), and 5 participants with HHV-6. In terms of bacterial infections, *Streptococcus pyogenes*, *Escherichia coli*, and *Campylobacter jejuni* were diagnosed.

Findings in view of HHV-6 – the most common aetiological agent of infection

WBC and Neu were statistically significantly lower in SFS patients with HHV-6 as compared to non-infected subjects. No statistical difference was observed in Ig levels in FS patients with HHV-6. In GE patients with HHV-6, IgG was significantly lower compared to non-infected patients. The study found no significant differences in age, sex and Lymph in FS and ES patients infected with HHV-6. The results are shown in Tab. 5.

DISCUSSION

The immune system plays a vital role in FS and epilepsy in children. In the 1980s, Eeg-Olofsson et al. investigated Ig levels in the CSF and blood of children following FS[24]. According to Korff and Dale, IS activation may precede, or be a consequence of ES. The researchers define various factors activating the IS, e.g. the CNS and extra-CNS infections, CNS trauma, autoimmune, cerebrovascular and metabolic diseases, ES and SE. The primary trauma may occur in or outside the CNS and, thus, the IS may be activated in one or both areas[2]. In 2017, ILAE recognised the involvement of immunological factors in the aetiology of epilepsy, as emphasised by Korff and Dale. Although FS and epilepsy are among the most common neurological disorders in children, evaluating the immune disorders constitutes a challenge. The findings are not always consistent and conclusive, as indicated by the researchers. In FS, characterised generally by a good prognosis, they point to the complex pathomechanism of the disease, including abnormalities in Ig levels.

The presented study assessed basic immunological parameters – Ig levels in children following FS and ES in GE during acute infection. Our analysis included the new SFS+ type proposed by Grill and Ng in 2013[6], and attempted to establish indications for extending the immunological diagnosis, even if patient history was not indicative of immune disorders. Isaacs et al. hypothesised that a low IgA level was associated with the development of FS[21]. Lenti et al., in turn, investigated serum levels of the IgG subclasses in children with FS and in first-degree relatives. They found lower IgG2 levels in FS patients, which may account for the increased susceptibility to infections occurring with FS[19]. Çaksen et al. analysed the serum levels of IgG, IgA, IgM, and IgE and the IgG subclasses in children following FS, and reported low IgG4 and IgG2 levels. The IgG and IgM levels were lower, whereas the levels of IgA and IgE were higher (not statistically significant). According to their findings, IgG2 and IgG4 deficiencies may account for frequent infections associated with FS, or may be involved in FS pathogenesis in some patients[20]. Eeg-Olofsson et al. investigated serum IgG, IgA, IgM and CSF levels in children following FS. They found no abnormalities in serum Ig levels and the blood–brain barrier function. Furthermore, they confirmed intrathecal Ig synthesis following FS, as well as 3–4 weeks afterwards, which – in patients without clinical signs of meningitis – may indicate an active immune response to e.g. viral antigens. This, in turn, is more common in fever complicated by seizures[24].

HHV-6 is a pathogen frequently associated with the development of FS. Primary HHV-6 infection may present with ExS symptoms or without a rash, which renders the infection diagnosis in FS children more difficult. HHV-6, like other pathogenic herpesviruses, is characterised by latency in the infected organism. Pantry and Medveczky emphasise the unique latency mechanism of HHV-6, which involves integration with host telomeres[25]. HHV-6 displays a primary tropism for T lymphocytes (CD4, CD8, natural killer cells), and infects macrophages, astrocytes, and fibroblasts[26]. In their papers, Barone et al. and Bertolani et al. analysed haematological parameters, inflammatory markers, as well as IgG, IgA, and IgM levels following FS in children with/without HHV-6 infection. Barone et al. found significantly lower WBC and Neu in patients with FT FS and HHV-6 infection as compared to non-infected patients[27]. Bertolani et al. observed significantly higher WBC, Neu, and lower blood IgM in FT SFS patients compared to febrile patients without seizures. Nevertheless, they reported no significant differences in Lymph, ESR, IgA and IgG levels, and CRP. FS patients with HHV-6 were reported to present significantly lower IgA and IgM levels. No significant differences in WBC, Neu, Lymph, ESR, CRP, and IgG levels were observed[28].

Zubiel et al. showed that immune abnormalities were more common in children with a single episode of FS than in those with recurring FS[9]. In turn, Callenbach et al. demonstrated that the humoral immunity in patients with newly diagnosed epilepsy was altered at the onset of the disease, before the initiation of ASMs. The researchers also considered the possible effect of infection and the interaction between the CNS and the IS, and found that ASMs affected the Ig levels[29].

Compared to the results obtained by other researchers, the presented study revealed some promising findings concerning the analysis of haematological parameters and Ig levels, particularly in FS patients with HHV-6, as well as in terms of inflammatory markers. In addition, our study assessed basic immunological parameters in FT/SS FS and GE. FT SFS patients were the youngest subjects in the study

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group, while SS GE patients were the oldest. We did not find a significant difference in age in patients with HHV-6 infection after FS and ES. Similarly, in their studies, Barone et al. and Bertolani et al. showed no age difference in patients with HHV-6 infection after FS episodes[27,28]. Contrary to the findings reported by Bertolani et al., no difference in WBC was observed in the current study. Our research also showed a significant increase in Neu in patients with CFS and FT seizures, whereas in the study by Bertolani et al. this was reported in patients following SFS. Additionally, in the current study, significantly lower Lymph was found in FS and GE patients, while the lowest Lymph was demonstrated in patients with CFS and FT seizures. In contrast to the findings obtained by Bertolani et al., in the presented study FS patients showed statistically significant differences in ESR, CRP and PCT, particularly in FT/SS SFS and FT SFS+[28]. The Ig levels were also different from those observed by the above-mentioned researchers. Lower IgG levels were noted in FS patients compared to GE patients, with the lowest shown in CFS subjects. IgA level was lower in SFS patients. Considering the type of seizures, a statistically significantly lower IgG level in FT SFS patients was noted, as compared to CG[20,21,24,28].

Ig levels in GE were higher than in CG, with a visible impact of past infections. Similarly to Barone et al. and Bertolani et al., the presented study assessed the impact of HHV-6 infection on the immunological parameters in FS patients, and additionally in GE individuals, during acute infection. Our results differed from the previous findings[27,28]. In our study, a relationship was found between WBC, Neu (lower) and HHV-6 infection in SFS patients. Inflammatory markers were higher in both CFS and SFS. There was no association between IgG, IgA, and IgM levels and HHV-6 infection in FS patients. Similar results were obtained with respect to Lymph. In GE patients infected with HHV-6, no significant differences were demonstrated in the haematological parameters, inflammatory markers, or age and sex. However, a statistically significantly lower IgG level was observed compared to the non-infected patients.

Additional data would be useful for the assessment of Ig concentrations in epilepsy patients, such as baseline Ig levels prior to epilepsy diagnosis and ASMs administration, as well as during and after infection. Furthermore, the caregivers of epilepsy patients should be encouraged to keep a diary and observe the course of the infection. The need to monitor infection in children with epilepsy and to determine Ig concentrations was indicated by Callenbach et al.[29]. Ig levels should also be measured in patients hospitalised following FS episodes, while follow-up tests should be recommended if abnormal results are found. Importantly, the diagnosis of the IS should start with the most basic screening tests[30]. Our study demonstrates that CBC+DIFF, as well as determining the Ig level are effective in assessing IS function in patients with seizures. These tests are easily accessible to both general practitioners and clinicians.

The reported study has certain limitations: sample size analysis was not performed, there was no data regarding Ig concentrations in GE patients before and during the administration of ASMs, and the size of the studied subgroups was small. Consequently, follow-up research on a larger patient population appears necessary.

CONCLUSIONS

Monitoring basic haematological parameters and immunoglobulin concentrations is effective in the diagnosis of seizure disorders in children. Screening tests provide an initial quantitative assessment of the humoral and cellular responses, as well as phagocytes. The level of lymphocytes was found to be the lowest in patients with FT CFS and GE, while the level of neutrophils - in patients with SFS and HHV-6 infection. Lower IgG and IgA levels were observed in FS patients; a lower IgG level was observed only in GE patients with HHV-6 infection.

Conflict of interest

The authors report no financial or personal relationships with other individuals or organisations that could adversely affect the content of the publication and claim ownership of this publication.

Author contributions

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

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