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RESEARCH ARTICLE

Investigations of clinical characteristics and inflammatory markers of febrile seizures induced by coronavirus infection

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ABSTRACT

The study of children who experienced with febrile seizures(FS) as a result of COVID-19 infection to gain insight into the clinical characteristics and prognosis of neurological damage, with the aim of improving prevention, diagnosis, and the treatment of neurological complications. This study investigated the clinical features of 53 children with FS who were admitted to Sanya Women and Children's Hospital from December 1, 2022, to January 31, 2023. The results indicated that the duration of convulsion in the case and control group was 7.90±8.91 and 2.67±1.23 (minutes) respectively. The analysis reveals that convulsions occurred within 24 hours in 39 cases (95.12%) of the case group, and in 8 cases (66.7%) of the control group. The difference was statistically significant (P<0.05). Additionally, the case group presented lower counts of WBC and NEU compared to the control group (p<0.05). The findings indicate that convulsions manifest at earlier stages of COVID-19 in children and the last longer than in the control group. It is therefore crucial for healthcare workers to remain attentive to patients with COVID-19 who report fever within 24 hours, and act promptly to implement preventive measures, particularly in cases of prolonged fever. It is essential to integrate the clinical manifestation, particularly convulsions, and the continuous numerical changes of inflammatory factors to assess COVID-19 linked with febrile seizures. In addition, larger-scale multi-center and systematic research are necessary to aid clinicians in monitoring neuropathological signals and biological targets, enabling more equitable diagnosis and treatment plans.

Keywords: COVID-19; febrile seizure; convulsion duration; drug prevention; inflammatory factors.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV-2). This virus belongs to the Coronaviridae family. The primary transmission routes of COVID-19 are respiratory droplets and contact transmission. Symptoms of COVID-19 include fever, fatigue, dry cough, dyspnea, and other symptoms. With ongoing research on COVID-19, scientific literature has reported on the effect of the Omicron variants (B.1.1.529) of the Coronavirus on the nervous system. Coronavirus can affect the human nervous system through neurotropic and neuroinvasive properties. Infected patients have exhibited various neurological problems, such as febrile seizures (FS), epilepsy, changes in mental status, encephalomyelitis and encephalitis, etc (Asadi-Pooya, 2020).

Understanding the clinical features and prognosis of nerve injury caused by COVID-19 can facilitate the prevention, diagnosis, and the treatment of neurological complications. A total of 53 patients with FS were admitted to Sanya Women and Children's Hospital between December 1st 2022 and January 31th 2023. Out of those, 41 cases of FS with COVID-19 were analyzed retrospectively and compared to 12 cases without COVID-19 in order to provide a clinical reference for the diagnosis and treatment of FS with COVID-19.

MATERIALS AND METHODS

Forty-one patients with FS and COVID-19 (the case group) were admitted to Sanya Women and Children's Hospital between December 1, 2022, and January 31, 2023, while 12 patients with FS but without COVID-19 (the control group) were analyzed retrospectively. The clinical data collected comprised demographic data, clinical symptoms and signs, laboratory inflammatory parameters, imaging findings and electroencephalography (EEG) results were assessed. Patients in the case group tested positive for coronavirus nucleic acids or antigens via real-time fluorescent RT-PCR of respiratory specimens. The diagnostic criteria aligned with guidelines for the diagnosis and treatment of coronavirus infection (Li *et al*., 2020), both groups met the diagnostic criteria of FS (Smith *et al*., 2019). The study compared clinical and laboratory parameters between two groups. These parameters included white blood cell (WBC), lymphocyte (LYM), neutrophil (NEU), serum amyloid A

(SAA), C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), creatine Kinase (CK) and isoenzyme (CK-MB). The study was approved by the Ethics Committee of Sanya Women and Children's Hospital.

Laboratory examination

Blood Cell Count: Samples of venous blood was obtained from patients and anticoagulated with EDTA-K2 was performed. Analysis of the blood was conducted via the impedance-laser method using the Sysmex XN-9000 XN-20(A1) automatic modular blood liquid analyzer.

Indicators of inflammation: The serum was obtained from 3ml of venous blood and detected using the Pumen eCL8000 automated chemiluminescence analyzer and electrochemiluminescence assay for IL-6, SAA, CRP and PCT.

Biochemical testing: 3ml of venous blood was collected, and serum was separated. The reagent of Beckman-kurt Company and Beckman-Kurt AU5800 series automatic biochemical analyzer was used. The LDH, CK, CK-MB, ESR levels were measured using the rate method (lactate-pyruvate), enzyme coupling rate method, immunosuppression-rate method and manual method respectively.

All procedures were strictly operated in accordance with operating procedures and instrument and reagent instructions, and quality control testing is conducted daily to ensure testing quality.

Normal Range of Parameters

Normal reference range of Parameters: WBC: (4.3~14.2)×10^9/L; LYM:(2.4~9.5)×10^9/; NEU: (0.6~7.5)×10^9/L; SAA: 0.00~10.47(mg/L); High-sensitive CRP: <1mg/L; PCT: 0.00~0.5 (ng/mL); IL-6: 0.00~6.60 (pg/mL); ESR: 0.00~20.00 (mm/h); LDH: 180~430 (U/L); CK: 19~288 (U/L); CK-MB: 2.0~19 (U/L). The results of each parameter were collected for the corresponding statistical analysis.

Statistical Analysis

SPSS 26.0 software was utilized for statistical analysis. The measurement data underwent a normality test and test for homogeneity of variance. Normally distributed measurement data were expressed as mean ± standard deviation (x ± s), and an independent sample t-test was used for the comparison of quantitative data between two groups. Count data were expressed as the number of cases and percentages (%), and X^2 test was used for comparison between group data. A value of P<0.05 was considered statistically significant.

RESULTS

Clinical General Data

In this study, 41 cases were collected in the case group, age (2.05±1.28) years, male: female=29:12; 12 cases in the control group, age (1.88±0.83) years, male: female=10:2. 11 cases (26.83%) in the case group had a history of previous FS and 7 cases (17.07%) had a history of FS in the patient's immediate family; 5 cases (41.67%) in the control group had a history of previous FS and 4 cases (33.33%) had a history of FS in the patient's immediate family. The number of convulsions during this disease course was 1.15±0.36 and 1.42±0.52 in the two groups, respectively, and the average hospitalization days were 3.68±1.79 and 3.75±1.66 (days), respectively. The average hospitalization costs were 3501.06±2097.34 and 3436.44±1864.06 (yuan). The duration of convulsions was 7.90±8.91 and 2.67±1.23 (min) in the case group and the control group, respectively, and the analysis of interval between fever and convulsions showed that there were 39 cases (95.12%) of convulsions followed within 24h of fever and 2 cases (4.88%) within 48h in the case group, and 8 cases (66.7%) within 24h and 4 cases (23.3%) within 48h in the control group. and the differences were statistically significant (P<0.05). Detailed data were shown in Table 1.

In the case group, 14 cases underwent pre-hospital emergency (including the local hospital and our outpatient clinic), 6 cases were treated with midazolam intramuscularly or intravenously, 4 cases with diazepam intravenously, and 4 cases with phenobarbital intramuscularly; 4 cases in the control group were treated with midazolam intramuscularly, 1 case with diazepam intravenously. These treatment measures successfully controlled the convulsions.

Comparison counts of WBC, LYM and NEU in Each Group

The WBC and NEU counts were 6.67±2.33 and 4.25±2.28 (×10^9/L) in patients of the case group and 9.18±5.41 and 6.27±4.64 (×10^9/L) in patients of the control group, respectively. WBC and NEU counts were lower in patients of the case group than in the control group (P<0.05). The LYM counts were 2.84±7.56 and 2.09±1.42 (×10^9/L) in the case and the control groups, respectively, and the differences were not statistically significant. The specific data can be seen in Table 2.

Table 1. Comparison of basic information of patients in two groups (* differences are statistically significant)

	The Case Group (n=41)	The Control Group (n=12)	t /X^2	P
Age (year old)	2.05±1.28	1.88±0.83	0.43	0.67
Gender (Male/Female)	29/12	10/2	0.25	0.61
Previous history of FS (%)	11 (26.83%)	5 (41.67%)	0.39	0.53
History of FS in immediate family (%)	7 (17.07%)	4 (33.33%)	0.67	0.41
Duration of convulsions (min)	7.90±8.91	2.67±1.23	2.01	0.04 *
Number of convulsions in present course	1.15±0.36	1.42±0.52	-1.70	0.11
Type of FS (cases, %)	SFS: 28 (68.29%) CFS: 13 (31.71%)	SFS: 7 (58.33%) CFS: 5 (41.67%)	0.09	0.77
Interval between fever and convulsions (h)	39 cases within 24h (95.12%) 2 cases within 48h (4.88%)	8 cases within 24h (66.7%) 4 cases within 48h (23.3%)	4.92	0.03 *
Time of hospitalization (days)	3.68±1.79	3.75±1.66	-0.12	0.91
Average hospitalization cost (¥)	3501.06±2097.34	3436.44±1864.06	0.10	0.92
3 months of follow-up	1 case of recurrent FS	1 case of recurrent FS	/	/

Table 2. comparison of laboratory parameters and various inflammatory factors in two groups (* differences are statistically significant)

	The Case Group (n=41)	The Control Group (n=12)	t	P
WBC ('10^9/L)	6.67±2.33	9.18±5.41	-2.35	0.02 *
LYM ('10^9/L)	2.84±7.56	2.09±1.42	0.34	0.73
NEU ('10^9/L)	4.25±2.28	6.27±4.64	-2.08	0.04 *
SAA (mg/L)	79.41±70.71	178.72±185.26	-1.67	0.13
CRP (mg/L)	3.64±4.34	27.10±35.36	-2.29	0.04 *
PCT (ng/mL)	0.58±1.34	1.02±1.61	-0.98	0.33
IL-6 (pg/mL)	33.22±45.16	51.32±44.50	-1.23	0.23
ESR (mm/h)	8.06±3.74	15.90±11.36	-2.15	0.06
LDH (U/L)	314.73±65.93	297.24±45.01	0.83	0.41
CK (U/L)	288.51±310.68	463.51±584.81	-1.35	0.18
CK-MB (U/L)	24.95±11.61	23.97±8.93	0.26	0.79

Comparison of Serological Levels of SAA, CRP, PCT, IL-6, ESR, LDH and CK in Patients

The levels of SAA, CRP and PCT were 79.41±70.71 (mg/L), 3.64±4.34 (mg/L) and 0.58±1.34 (ng/mL) in patients of the case group, respectively. The levels were lower than those in patients of the control group. The serological levels of IL-6, ESR, LDH, CK and CKMB were 33.22±45.16 (pg/mL), 8.06±3.74 (mm/h), 314.73±65.93 (U/L), 288.51±310.68 (U/L) and 24.95±11.61 (U/L) in patients of the case group, respectively. The differences had no statistically significant. The specific data can be seen in Table 2.

Imaging and Electroencephalography

During hospitalization, a cranial CT or MRI was performed on 17 out of 41 patients in the case group. Among these cases, 2 presented left choroidal fissure cysts while 1 case had bilateral relative enlargement of lateral ventricles with large cisterna magna. The remaining 14 cases showed normal results, 16 cases underwent Electroencephalography (EEG), 2 cases that suggested borderline EEG, 14 cases had normal EEG, and 2 cases had a normal cerebrospinal fluid examination. Seven cases in the control group had cranial imaging examination, 1 case had a fornix cavity, while the remaining six were normal. Of the two cases that underwent EEG testing, both exhibited normal results.

Outcomes of Follow-up

Fifty-three patients were followed up for 3 months after being discharged from the hospital and their mental behavior was deemed ordinary. In each of the two groups, one child experienced a recurrence of FS. Patients were recommended to take a short-course prophylactic medication if they had: (i) FS within a short period (≥3 within 6 months or ≥4 within 1 year); or (ii) a persistent state of convulsions. Prophylactic medication was required when the body temperature was at or above 37.5°C. Diazepam tablets at a dose of 0.3–0.5mg /kg every 8 hours three times orally or levetiracetam at a dose of 10mg/kg every 12 hours orally should be administered. The dose should be stopped once the fever subsides.

DISCUSSION

Due to adjustments of China's prevention and control policies for COVID-19, there is a tendency to increase the number of patients with COVID-19 at the end of 2022, with successive reports of the neurological syndrome in adult and pediatric infected populations at home and abroad. The neurological effects of COVID-19 are diverse and may be related to viral infection neurotropic and hematogenous routes, immune response, underlying chronic disease, associated treatment and rehabilitation-related complications and genetic susceptibility (Aghagoli *et al*., 2021). A retrospective study of 214 Chinese patients with COVID-19 in Wuhan found that 36.4% of patients had neurological symptoms, with dizziness (16.8%) and headache (13.1%) being the most common neurological manifestations (Mao *et al*., 2020). Neurological symptoms can also occur after coronavirus infection in children, and the most common neurological symptoms were headache, convulsions, encephalopathy, and myalgias (Valderas *et al*., 2022). 1060 of 15137 children (7.0%) with COVID-19 had neurological complications, and the most common neurological complications were FS (3.9%), non-febrile convulsions (2.3%) and encephalopathy (2.2%). Death and readmission were also more common in patients with neurological complications (Antoon *et al.*, 2022). However, a study of 3707 pediatric patients found that 16.7% presented with mild and nonspecific neurological symptoms and only 1% had severe neurological complications (Panda *et al*., 2021). Research also noted that convulsions are the most common neurological manifestation in the acute phase of coronavirus in children. Approximately 20% to 30% of hospitalized children with neurological symptoms complicated by coronavirus infection present with convulsions (Ray *et al*., 2021; Tso *et al.*, 2022).

The pathogenesis of neurological symptoms associated with coronavirus infection remains incompletely understood, with hypotheses encompassing two main categories: direct viral invasion through neural pathways or indirect entry via angiotensin-converting enzyme 2 (ACE2) receptors that damage neuronal cells, vascular endothelial injury, inflammatory cytokines, and autoimmune injury (Lin *et al*., 2021). Children with coronavirus disease may have hypoxia, metabolic disturbances, organ failure or brain damage, all of which may lead to a lowered threshold for seizures. Viral infections, especially those associated with high fever, have been shown to increase neuronal excitability and lower the threshold of seizures, especially in the developing central nervous system (Smith *et al*., 2019). However, the etiology, treatment, and management requirements for FS with COVID-19 remain poorly understood.

A total of 543 patients were admitted in pediatric wards of Sanya Women and Children's Hospital from December 2022 to January 2023, including 158 (29.10%) patients with coronavirus. A total of 66 patients with convulsions. The clinical data of 53 patients diagnosed with FS were collected, including 41 with coronavirus infection and 12 with non-coronavirus infection. The clinical data and manifestations were presented in Table 1. There were no statistically differences between the two groups in age, gender, time of hospitalisation and hospital costs. Previous history of FS in the case group accounted for 26.83% and history of FS in immediate family members accounted for 17.07%, and the difference between the two groups was not statistically significant. The type of complex

febrile seizures (CFS) is defined as focal seizures, seizures lasting ≥ 15 minutes and/or more than once in 24 hours, accounted for 13 patients (31.71%) of the case group and 5 patients (41.67%) of the control group. According to the study, a total of 8854 pediatric patients aged 0-5 years were diagnosed with COVID-19 in 34 healthcare facilities, 44 (0.5%) were diagnosed with FS, 30 (68.2%) were simple febrile seizures (SFS) and 14 (31.8%) were CFS, the proportions of the data were similar to our data (Cadet *et al*., 2022). The interval between fever and convulsions was within 48h in both groups, but 95.12% occurred within 24h and 4.88% within 48h in the case group, whereas only 66.7% occurred within 24h in the control group. The duration of convulsions in the case group was 7.90±8.91 minutes, with a longer duration of convulsions than in the control group (2.67±1.23 minutes). The difference was statistically significant($P<0.05$). It reminds us that the onset of convulsions in children with coronavirus infection is earlier, mostly occurring within 24h after fever, and the duration of convulsions is longer. We need to pay more attention to children with coronavirus infection at an early stage and take preventive measures, especially in children with persistently high temperatures during the first 24h, and 24h is a timely warning window for coronavirus infection with convulsions. The first-line drugs midazolam and diazepam are commonly used to control seizures. However, in the community and secondary hospitals phenobarbital intramuscularly still was used as an emergency drug, which is not consistent with the principles of treatment of status convulsions in children (Glauser *et al.*, 2016; Kapur *et al*., 2019), and there is still a long way to strengthen the training of convulsions management in the community and secondary hospitals.

WBC, LYM and NEU count can reflect the pathological process of the disease and the levels of all reflect the inflammatory response and immune status in infected person, which have an important reference value for disease diagnosis (Hildreth & O'Sullivan, 2019). Some studies have reported a negative correlation between the percentage of LYM in blood and the severity and prognosis of COVID-19 (Tan *et al*., 2020). However, the present study found a more significant decrease in WBC and NEU counts in patients with FS in the case group compared to the control group. Therefore, the decrease in WBC and NEU counts of COVID-19 with FS may also be a warning sign. Although no determined pathogenic microorganisms were found in the control group, the enrolled patients may be exposed to bacterial infection, which may also have an impact on WBC and NEU counts.

Both CRP and SAA are acute-phase proteins that are produced by hepatocytes stimulated by a large number of pro-inflammatory factors when viral infection (Mehta *et al.*, 2020; Zhang *et al*., 2020). PCT is a peptide precursor of calcitonin and is secreted by different cell types after stimulation by pro-inflammatory responses. Most COVID-19 have normal or slightly elevated serum PCT levels on admission, but they can be significantly increased when exacerbation or secondary to an infection, initiating a cascade amplification effect of cytokine storm (Huang *et al*., 2020). Cytokine storm is considered as a possible cause of neuronal damage in the most severe forms of coronavirus disease. COVID-19 can induce a hyperinflammatory state through cytokine storm and macrophage activation, and this immune dysregulation is associated with high levels of inflammatory biomarkers such as CRP, PCT, IL-6 and ESR (Lin *et al*., 2021). As an inflammatory factor, IL-6 contributes to the influence of inflammatory signaling on seizure threshold. Intranasal administration of IL-6 may exacerbate seizures in rat seizures model and increased IL-6 levels in mice cause seizures in those infected with encephalitis virus, as well as various clinical reports suggesting an association between elevated IL-6 levels and seizures (de Vries *et al*., 2016; Alapirtti *et al*., 2018). Coronaviruses are neuroinvasive and may produce cytokine storms and reduce the convulsive threshold (Kurd *et al*., 2021). However, our group compared the inflammatory factor data of two groups and found that the differences between the values of various data such as SAA, PCT and IL-6 were not increased in the case group, and the data of SAA, CRP, PCT, IL-6, CK and ESR were even lower than those of the control group, indicating that FS due to coronavirus infection is not caused by cytokine storm. Furthermore, we needed to continuous monitoring of inflammatory indicators for assessing the progression of the disease, and further large-sample multicenter research and animal model studies are needed to explore the mechanism of the occurrence of FS associated with coronavirus infection.

In the case group, cranial imaging was performed on 17 out of 41 cases and EEG was performed on 16 cases, which showed normal results. Additionally, 7 of 12 cases in the control group had normal cranial imaging findings and 2 cases had normal EEG findings. The common cranial imaging and EEG findings in coronavirus infection with FS were not different from those in patients in the control group. New-onset epilepsy is rare in coronavirus infections, and the high risk of epileptic seizure is in those with seizure-like events and those with pre-existing epilepsy or brain injury (Pellinen & Holmes, 2022). Both groups of patients were followed for 3 months, and only one patient in each group had one recurrence of febrile seizures. These findings suggest a favorable prognosis for individuals with coronavirus infections and febrile seizures; however, long-term follow-up observations are necessary. In this study, we analyzed the clinical data from 41 patients with COVID-19 induced febrile seizures (FS) who were admitted to the hospital and compared it with the control group. The results showed that, FS occurred earlier in the course of the illness for the case group, but seizures lasted longer and were more likely to develop into a status convulsion. Patients of coronavirus infections need early-stage preventive measures. Although immune response and cytokine storm may play an important role in the occurrence and development of coronavirus infections, this study did not find significantly higher inflammatory indicators in coronavirus infections with FS. Therefore, in evaluating the clinical characteristics of coronavirus infections with FS, it is essential to consider combining the clinical symptoms and the continuous variation of multiple inflammatory factors. Multi-center and systematic research is necessary to aid clinicians in identifying neuropathological indicators and biological targets, enabling the development of more effective diagnostic and treatment strategies to mitigate neurological damage induced by the coronavirus.

Conflict of interest statement

The author declares that they have no conflict of interests.

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