Original Article

Analysis of cytokines and trace elements in children with febrile seizures

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Background: Febrile seizure (FS) is a common neurological condition in children and affects 2–5% of cases of fever. FS occurs with temperature >38 ℃ without symptoms of central nervous system infection, severe electrolyte imbalance, or clear cause.

Methods: From June 2018 to December 2019, 65 children with FS, and 60 children with acute upper respiratory tract infections without seizures who were admitted to the pediatric department, and 60 healthy children as the control group were selected for the study. The serum iron (SI), serum calcium (SC), interleukin (IL)-6, IL-10 and procalcitonin (PCT) levels in the two groups of children were detected. The FS group was further divided into simple FS (SFS) and complex FS (CFS).

Results: The duration of fever in the FS group was significantly longer than in the control group (P<0.05). The SC and SI levels of the FS group were significantly lower than those in the control group (P<0.05). The SC and SI levels of the CFS group were also lower than those of the SFS group (P<0.05), and the IL-6 levels of the CFS group were significantly higher than in the SFS group (P<0.05).

Conclusions: A decrease in the levels of SI, and SC and an increase of IL-6 were closely related to the occurrence of FS, suggesting that clinical attention should be paid to monitoring changes of SI, SC and IL-6 levels in children with FS. As the levels of SI and SC decrease, the frequency of possible seizures may increase. Care should be taken to correct electrolyte disorders in time.

Keywords: Children; cytokines; febrile seizures (FS); interleukin-6 (IL-6); trace elements

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Introduction

According to the 2011 American Academy of Pediatrics standards (1), febrile seizures (FS) occur in infants or children aged 6 months to 5 years with fever (real temperature ≥38.5 ℃, axillary temperature ≥38 ℃) but no evidence of central nervous system infection or other causes of seizures, and no history of FS. The incidence of FS is about 2–5%, and the highest incidence is at 18 months of age (2). FS usually occur within 24–48 h after fever, and are classified as simple FS (SFS) and complex FS (CFS). SFS accounts for about 70–75% of cases, and CFS accounts for 20–25%; febrile status epilepticus refers to FS lasting ≥30 min, or repeated attacks, and interictal consciousness does not recover for ≥30 min, which accounts for about 5% of cases (3,4). SFS is a generalized seizure with a duration <15 min, occurs just once during the clinical course of fever, and there are no abnormal nervous system signs; CFS suggests a neurological abnormality before the onset, manifesting as a focal seizure or a generalized seizure lasting

>15 min or occurring more than once during the fever, and there are neurological abnormalities after seizures, but no history of afebrile seizures.

At present, the pathogenesis of FS is not fully understood, but is generally believed to be related to multiple factors such as genetic factors, infection, inflammatory factors, and trace elements (5-8). Cytokines also play a very important role. Studies (9,10) show that tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6 and other pro-inflammatory factors are closely related to FS in children. When the levels of TNF-α and IL-6 increase, the risk of FS increases, and the probability of recurrence increases accordingly. Some researchers have suggested that fever can cause changes in the ions of the cell microenvironment (11-13). During the onset of FS, abnormal concentrations of sodium, calcium, iron, and potassium ions are found and could be high-risk factors. Some studies have suggested that iron deficiency is a potential risk factor for FS (14-22). However, some studies have reported that the degree of iron deficiency in children with FS is lower than that in children with afebrile seizures. It is believed that iron deficiency can reduce the occurrence of FS (23-25). The level of procalcitonin (PCT) in plasma is related to the severity of bacterial infection and clinical recovery. Meanwhile, non-infectious factors, such as severe trauma, surgical trauma, burns, etc., can also cause its increase (26), as an important observation index of bacterial infectious diseases in children, its content is significantly increased in children with convulsion (27).

Therefore, it is of clinical significance for the diagnosis, treatment and prognosis of FS to determine the changes in the levels of relevant cytokines and trace elements.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tp-20-398).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Nantong Maternal and Child Health Care Hospital (No. 20140013) and informed consent was taken from all individual participants.

Subjects

The study data were derived from patients who attended Nantong Maternal and Child Health Care Hospital from June 2018 to December 2019.

Based on the following inclusion and exclusion criteria, the patients were allocated to the study group or the positive or negative control group.

Inclusion criteria: (I) aged from 3 months to 6 years; (II) seizures occurred after high fever with body temperature ≥38 ℃; (III) primary disease of acute upper respiratory tract infection, acute bronchitis, bronchial pneumonia, herpetic angina, acute tonsillitis, acute suppurative tonsillitis, etc.; (IV) normal results for cranial CT or MRI and EEG.

Exclusion criteria: (I) aged less than 3 months or more than 6 years; (II) received intravenous fluid treatment before hospital admission; (III) symptoms and signs of rickets; (IV) history of vomiting, diarrhea, seizures, epilepsy, and electrolyte disturbance; (V) intracranial infection or other organic and metabolic disorders that can cause seizures.

Study group: 65 children with FS were diagnosed according to the 2011 American Academy of Pediatrics criteria (1): age from 10 months to 6 years old, and temperature during seizure from 38.5 to 40.2 ℃. Cranial CT or MRI and EEG were normal, and infectious diseases of the central nervous system and other brain diseases were excluded.

Positive control group: 60 children with respiratory tract infection and fever in the same time period, aged from 12 months to 6 years old, temperature from 37.6 to 40.2 ℃ and no history of FS or epilepsy.

Negative control group: 60 healthy children who attended for physical examination during the same time period, aged from 12 months to 6 years old.

According to the frequency of seizures, the study group was divided into SFS and CFS groups. The SFS group had one seizure, and the CFS group had >1 seizure during the course of fever.

Parents or guardians gave signed consent for blood sample collection and data collection.

Specimen collection

A 6-mL peripheral blood sample was taken for all children, and serum was obtained by centrifugation at 3,500 rpm for 5 min at 4 ℃. The serum was immediately separated and stored at –70 ℃. In the FS group, blood samples were collected within 1 h after the occurrence of a seizure. The sex, age, number of seizures, duration of seizures, body temperature and fever course were recorded in the study group; sex, age, and fever temperature were recorded in the control group.

Table 1 Comparison of baseline clinical data

Variables	Group		
	FS (n=65)	Positive control group (n=60)	Negative control group (n=60)
Age, months	20.6±6.3	21.2±5.9	20.7±6.5
Sex			
M (%)	36 (55.38%)	33 (55%)	
F (%)	29 (44.62%)	27 (45%)	
Maximum temperature (℃)	39.41±0.37	39.35±0.44	36.6±0.32
Duration of fever (days)	3.76±0. 89	2.59±0.72*	–

*, compared with positive control group P<0.01. FS, febrile seizures.

Specimen evaluation

The levels of serum iron (SI) and serum calcium (SC) were determined using the Hitachi 7600-020 automatic biochemical analyzer.

The concentrations of pro-inflammatory cytokines (IL-6) and anti-inflammatory cytokines (IL-10) were measured using a commercially available enzyme-linked immunosorbent assay kit [Milliplex MAP (ELISA) kit, human cytokine/chemokine magnetic bead panel-immunology multiplex assay, Cat. #HCYTOMAG-60 K, EMD Millipore Corp., Burlington, MA, USA].

The serum procalcitonin (PCT) was determined with the Swiss Roche Cobas E601 electrochemiluminescence immunoassay analyzer. The calibration solution, reagents, and quality control products were all provided by Roche.

Quality control

Management of quality control for this study is summarized. (I) Concurrent selection of the three groups of children, with guaranteed randomness and continuity. (II) Strict application of the criteria for diagnosis, inclusion and exclusion of research subjects to ensure reliability of the samples. (III) Similar age and sex balance of the three groups (P>0.05). (IV) All samples measured in duplicate to improve accuracy.

Statistical analysis

Data were entered into a spreadsheet (Excel; Microsoft China Co., Ltd., Beijing, China), and SPSS (V.22.0; SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Normally distributed measurement data are expressed as mean ± standard deviation ($\bar{x}\pm s$), the two independent samples *t*-test was used for comparison between groups, a paired *t*-test was used for comparison within groups, and count data are expressed as percentage. Comparison of count data between groups was analyzed with χ^2, and statistical significance of difference was set as P<0.05 for all tests.

Results

General clinical data

The 65 children in the study group, comprised 36 males and 29 females, with an average age of 20.6 months and an average temperature of 39.41 ℃. As the primary disease, 11 children had acute upper respiratory tract infection, 10 had acute bronchitis, 14 had bronchial pneumonia, 7 had herpetic angina, 16 had acute tonsillitis, and 7 children had acute suppurative tonsillitis. In the positive control group, there were 60 children with respiratory tract infection and fever during the same time period, comprising 33 males and 27 females, with an average age of 21.2 months, and an average temperature of 39.35 ℃. The primary diseases included 9 cases of acute upper respiratory tract infection, 6 cases of acute bronchitis, 11 cases of herpes angina, 20 cases of bronchial pneumonia, 10 cases of acute tonsillitis, and 4 cases of acute suppurative tonsillitis. In the negative control group, there were 60 children comprising 33 males and 27 females with an average age of 20.7 months. The differences were not statistically significant (P>0.05). The average duration of fever in the FS group was 3.76 days, and 2.59 days in the positive control group (P<0.01). The duration of fever in the FS group was significantly longer than that of children in the positive control group (*Table 1*).

Table 2 Comparison of indexes of study group and positive control group

Group	n	SI (μmol/L)	SC (mmol/L)	PCT (ng/mL)	IL-6 (ng/L)	IL-10 (ng/L)
FS	65	11.97±5.49	2.04±0.27	0.98±0.41	12.08±26.39	4.40±0.99
Positive control group	60	21.07±5.85	2.55±0.21	0.83±0.43	7.76±13.70	5.69±1.49
t		–8.9	–11.6	1.2	1.13	2.85
P		0.001	0.000	0.098	0.049	0.005

FS, febrile seizures; IL, interleukin; PCT, procalcitonin; SC, serum calcium; SI, serum iron.

Table 3 Comparison of indexes of study group and negative control group

Group	n	SI (μmol/L)	SC (mmol/L)	PCT (ng/mL)	IL-6 (ng/L)	IL-10 (ng/L)
FS	65	11.97±5.49	2.04±0.27	0.98±0.41	12.08±26.39	4.40±0.99
Negative control group	60	21.53±6.42	2.55±0.20	0.62±0.33	1.18±3.10	6.35±1.98
t		–8.96	–12.05	1.72	3.17	5.12
P		0.000	0.000	0.07	0.02	0.000

FS, febrile seizures; IL, interleukin; PCT, procalcitonin; SC, serum calcium; SI, serum iron.

Table 4 Comparison of indexes of positive and negative control groups

Group	n	SI (μmol/L)	SC (mmol/L)	PCT (ng/mL)	IL-6 (ng/L)	IL-10 (ng/L)
Positive control group	60	21.07±5.85	2.55±0.21	0.83±0.43	7.76±13.70	5.69±1.49
Negative control group	60	21.53±6.42	2.55±0.20	0.62±0.33	1.18±3.10	6.35±1.98
t		–0.42	–0.176	1.94	3.62	2.21
P		0.678	0.861	0.04	0.001	0.04

Table 5 Comparison of indexes of SFS and CFS groups

Group	n	SI (μmol/L)	SC (mmol/L)	PCT (ng/mL)	IL-6 (ng/L)	IL-10 (ng/L)
SFS	44	12.14±5.9	2.12±0.23	0.96±0.41	7.25±11.28	5.75±1.43
CFS	21	10.31±3.67	1.87±0.25	1.06±0.61	22.19±42.39	2.31±0.21
t		0.352	3.859	–1.63	–2.19	1.43
P		0.726	0.000	0.177	0.03	0.156

CFS/SFS, complex/simple febrile seizures; IL, interleukin; PCT, procalcitonin; SC, serum calcium; SI, serum iron.

Comparison of trace elements

In the FS group the levels of SI and SC were lower than in the positive group (*Table 2*), and the negative group (*Table 3*), and the difference was statistically significant (P<0.05).

There was no significant difference between the positive and negative groups in the levels of SI and SC (P>0.05) (*Table 4*).

The level of SC in the SFS group was higher than in the CFS group, and the difference was statistically significant (P<0.05). There was no significant difference in the level of SI between the SFS and CFS groups (P>0.05) (*Table 5*).

Comparison of cytokines

Compared with the positive control group, the level of

IL-6 was higher, and the level of IL-10 was lower in the FS group, and the difference was statistically significant (P<0.05). There was no significant difference between the two groups in the level of PCT (P>0.05) (*Table 2*).

Compared with the negative control group, the levels of IL-6 and PCT were higher in the FS group, with a statistically significant difference (P<0.05) (*Tables 3*,*4*).

The level of IL-6 in the SFS group was higher than in the CFS group, and the difference was statistically significant (P<0.05). There was no significant difference in the level of IL-10 between the SFS and CFS groups (P>0.05) (*Table 5*).

Discussion

The onset of FS is related to the age of the child. It is more common in children aged less than 3 years, with a small number of children showing onset after 5 years of age. In this study, patients younger than 3 years old (n=35) accounted for 53.82% of cases, those aged 3–5 years old (n=28) accounted for 43.1%, and those aged more than 5 years (n=2 cases) accounted for3%. In children aged 6 months to 3 years old, the anatomy, physiology, and biochemistry of the brain are in a state of rapid development. The structure of the brain cells is simple, with incomplete functional differentiation and branching of the axons and dendrites, myelination is not perfect, and the chemical components and enzyme activities are different from those of the mature brain. The dynamic balance of the excitatory and inhibitory systems is in unstable, and the seizure threshold is low, so FS is more likely to occur (28). Studies have found that SI and SC levels are also reduced and may be an important predisposing factor for FS (29). The normal calcium ion concentration can maintain the selectivity and permeability of the nerve cell membrane to sodium and potassium ions and regulate the release of nerve mediators. When calcium ions decrease, the permeability of nerve axons and muscle membranes to sodium ions increases, which increases the sensitivity of the brain to various stimuli, leading to seizures. Iron is an essential trace element for the human body. The total amount in a normal human body is 3–5 g, stored in the form of ferritin and hemosiderin. Iron is absorbed in the duodenum and upper jejunum in the form of Fe^{2+}. After the absorbed iron enters the circulation, Fe^{2+} is converted to Fe^{3+}, and then combined with transferrin to form plasma iron, which is transported to bone marrow, liver, spleen and other tissues for use or storage (30). Iron is related to the metabolism of neurotransmitters and plays an important role in the formation and maintenance of nerve myelination. When the body is iron-deficient, it can affect the myelination of nerve fibers; monoamine oxidase and aldehyde oxidase are reduced and their activity decreases. Thus, the balance of neurotransmitters in the body is disturbed and brain function is abnormal (31). In recent years, studies have found that during infectious diseases, iron consumption increases, intake decreases, and utilization disorders occur. Iron-deficiency anemia can cause damage to nerve development and myelination, leading to increased neuromuscular excitability and being more prone to seizures (29).

Daoud *et al.* found that the level of plasma ferritin in children in their FS group was significantly lower than that of the control group; the incidence of iron-deficiency anemia was also higher than that in the control group, suggesting that the iron status was a risk factor for FS (32). Another report (33) showed that among 88 children with FS in the observation group, the incidence of iron-deficiency anemia was 61.36% and that of the control group was 43.42%, with a statistically significant difference between the two groups. In the observation group, the incidence of iron-deficiency anemia in CFS was 85.0% and that of SFS was 54.41%, suggesting that the SI level may be closely related to the occurrence of FS in children. Some researchers believe that the concentration of serum 25-(OH)D in children with iron deficiency is reduced, which leads to disorders of calcium absorption and metabolism, causing a calcium deficiency in the body and increased neuromuscular excitability (34). Iron supplementation can promote the absorption of vitamin D in the intestines, increase serum vitamin D levels, and improve SC deficiency.

The blood calcium level in the human body is mainly divided into ionized calcium and complex calcium. The physiological role of electrolyte calcium ions in the body is very important. It is the main factor in nerve excitement and conduction. It will affect the change in cell membrane potential and the release of nerve mediators. If the concentration of calcium ions is within a certain normal range, the selectivity and permeability of the human nerve cell membrane to potassium and sodium ions is stably maintained and the release of nerve mediators is also regulated. Therefore, if the level of electrolyte calcium in patients is lower than normal, it will affect depolarization of potentials and affect the release of sodium ions in neuronal axons. Thereby, the excitability of nerve cells in normal

children is increased, which leads to the occurrence and development of FS (35). When the body is in a state of fever, hypoxia, etc., cells will be destroyed, resulting in an imbalance of the Na–K pump on the cell membrane, resulting in changes in the cell membrane potential, and the opening of calcium channels to an influx of Ca^{2+}, while the Ca^{2+} in plasma decreases, and the permeability of Na^{+} simultaneously increases, which depolarizes the cells, increases neuromuscular excitability, and reduces the convulsive threshold. At the same time, the damaged cells release of phosphorus, which can increase blood phosphorus level, reduce the blood calcium level, and facilitate seizures (36). A study by Wang and Zhu found that compared with the control group, the electrolyte calcium level of children with FS was significantly lower than that of the control group (37). However, Peng *et al.* (38) showed no significant difference in SC levels between children with FS and the control group. They concluded that the level of SC in children with FS and after treatment did not change significantly. It is suspected that the physiological function of calcium is mainly exercised by serum free calcium, and the change in serum free calcium is less affected by the change in the serum total calcium (38).

Our study found that the SC and SI levels of children in the FS group were significantly lower than in the two control groups (both $P<0.05$), and we also found that during FS, the blood calcium level of children with CFS was lower than that of children with SFS, with a statistically significant difference ($P<0.05$), suggesting that hypocalcemia may be one of the causes of multiple seizures in the same febrile course. It can be seen from the results of this study that, on the one hand, the reduction in electrolyte SC levels may cause seizures in children with high fever, and they are also more likely to have FS than children with normal SC levels. On the one hand, the occurrence of FS may also further reduce the level of SC ions. Therefore, a decrease in the SC ions can be the result of FS, and it can also lead to a reduction in the seizure threshold. Therefore, in clinical practice, if we find that a child has both high fever and decreased SC level, we must be alert to the occurrence of FS. For children who have already developed FS, we must pay attention to monitoring changes in SC ion levels, and give timely corrections with appropriate calcium supplements to maintain the stability of the internal environment, and avoid further aggravation of hypocalcemia and aggravation of the child's condition.

A member of the nerve cytokine family, IL-6 is a lymphokine produced by activated T cells. It can promote and activate T cells, stimulate B cells and immunoglobulins to secrete other growth factors, and it can participate in a variety of cell growth processes. However, overexpression of IL-6 can lead to pathological changes in nerve cells (39). Studies by Li *et al.* have shown that IL-6 gene polymorphism is significantly related to the onset of FS in children (40). The results of our study showed that the serum IL-6 level of children with CFS was significantly higher than in the SFS group and the control group, suggesting that serum IL-6 level may be related to the severity of FS in children.

IL-10 is an anti-inflammatory factor, which can participate in the biological regulation of immune cells and inflammatory cells. It plays a role in downregulating inflammation and antagonizing inflammatory mediators in various diseases such as autoimmune diseases and infectious diseases (41). Xia has shown that the level of IL-10 in hippocampal neurons of epileptic rats is significantly lower than that of normal rats (42), indicating that IL-10 may have anti-epileptic effects. Liang's (43) research showed that the levels of IL-10 in the peripheral blood of children with *Mycoplasma pneumoniae* wheezing and non-wheezing groups were significantly lower than those of normal children, indicating that IL-10 has a negative regulatory effect on inflammation. Our study showed that the serum IL-10 levels of children with FS were significantly lower than in the control groups. IL-10 may have a certain anti-inflammatory effect, and thus affect the process of FS.

The etiology of FS is complex and diverse. Repeated seizures and convulsion status will affect the development of cognitive function and language function. Since most of the children are admitted to the hospital after the seizure, it is very important to establish a family-based intervention strategy. Recommendations: (I) let the child sleep on his side, keep the throat clean, and ensure that secretions such as saliva and vomit flow out smoothly. (II) Call the emergency call promptly in the following situations: the seizure duration is longer than 5 minutes; serious injury occurs during the seizure; severe breathing difficulties or skin bruising after the seizure; repeated seizures or unable to wake up after convulsions. (III) Children with recurrent attacks should take preventive measures to reduce or avoid injury. For example, move the patient away from potentially dangerous places (such as stoves, furniture, baths, stairs, vehicles, etc.); instruct children to avoid riding alone and sliding in traffic jams; avoid activities at high places to prevent seizures Fall injuries; family supervision is required when playing by the water; children with epilepsy need

to keep a good sleep, take medicines on time, and wear a necklace or wristband with drug identification. (IV) When the child has risk factors for the recurrence of febrile seizures, a dose of diazepam can be given through the rectum at home to prevent the seizures.

Study limitations

(I) The outcome and prognosis of children with FS were not followed up. (II) The body mass of each child was not recorded in detail. (III) The number of children included in the experiment was small. These shortcomings will be improved in future research, and clinical data mining will be carried out in more detail, to discover patterns that will lead to improvements in the outcome and prognosis of FS.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/tp-20-398

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tp-20-398). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Nantong Maternal and Child Health Care Hospital (No. 20140013) and informed consent was taken from all individual participants.

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