Research progress of febrile seizures in children

Abstract: Febrile seizures (FS) are common neurological diseases in childhood. It is age-dependent and often occurs in children from 6 months to 5 years old. The etiology of FS is diverse and the mechanism is complex, which is not completely clear, but most children have a good prognosis. Through timely identification, symptomatic treatment and health guidance to patients' families, we can get a good prognosis. In the treatment of FS, we should pay attention to finding the cause, and do a good job in the health education and guidance for children's families. At present, the long-term use of antiepileptic drugs is not recommended to prevent the recurrence and secondary epilepsy of FS. In the future, through the development of traditional Chinese medicine, the combination of Chinese and Western medicine can be considered in order to improve the therapeutic effect of FS. This paper reviews the relevant literature about the research progress of FS in recent years in China and abroad, to provide new ideas for the diagnosis and treatment of FS in children.

【Key words】Febrile seizures; Children; Etiology; Treatment; Prognosis

Introduction

What are febrile seizures?

Convulsion is one of the most common acute and critical diseases in children. Timely identification and early reasonable symptomatic management are very important for the treatment and prognosis of this disease. Febrile seizures (FS) is the most common type of convulsions and the most common neurological disease in children[1]. FS is age-dependent, mostly occurring between 6 months and 5 years old, and it also can occur repeatedly. The prevalence rate of FS is 3%-5% in children all over the world, and about 4.4% in children in China, and the data is still increasing year by year[2]. According to the standards of the American Academy of Pediatrics (AAP) in 2011, FS can be defined as a seizure in the course of one heat stroke (anal temperature ≥38.5℃, axillary temperature ≥38℃), excluding central nervous system infection and other causes of convulsion, and without history of convulsion in the past[3]. The clinical manifestations of FS are mainly mandatory or clinic convulsions of systemic or local muscle groups. The general process is self-limited and the prognosis is good. According to clinical symptoms, FS are divided into simple and complex. Simple FS attack time is not more than 15 min show the comprehensive attack, the prognosis is relatively good, and without obvious abnormal changes of the nervous system.After modalities FS onset time sustainable 15 ~ 30 min can show the comprehensive or focal seizures, and attack more than once to each of the thermal process, even after abnormal nervous system evidence, such as Todd´s paralysis[4]. The

duration of FS can exceed 30 min and the onset has no obvious rules. Complex FS and FS duration may even develop into epilepsy or more critical conditions, such as brain injury[5]. This paper reviewed the published data in recent years about the FS related basic and clinical research literature, children FS with athogenesis, auxiliary examination, clinical diagnosis and the final outcome of research were reviewed, in order to improve the public and clinical doctors for children to have a comprehensive understanding of FS, to guide reasonable prevention, early detection and treatment.

What causes febrile seizures?

Etiology. FS seizures, often quickly and without clinical symptoms if not handled in time, is likely to influence the outcome of each organ function and even life, provide for symptomatic treatment in time and looking for the cause is the important factor of prognosis.Valton et al.(2020), according to a study, in the almost half of all cases, through causes were been identified and dealt with in a timely manner,They can effectively prevent the progression of the disease[6], so it is very important to identify the etiology in the early stage of the disease. According to the research results of domestic and foreign scholars, the etiology can been roughly summarized into two categories: infection and non-infection. Studies have found that the common causes of FS include acute upper respiratory tract

infection (66.4%), viral enteritis (10.94%), bronchitis (9.38%), pneumonia (7.81%), herpetic angina (5.47%), otitis media or rash diseases, etc[2,**Error! Reference source not found.**]. Among them, virus infection is the main reason. Respiratory onditions with enterovirus exists in 75% of FS children and the viruses most closely related to FS are influenza virus, respiratory syncytial virus, parainfluenza virus, human coronavirus and rotavirus[7]. Influenza virus is considered to the virus most commonly associated with FS. It is also most often detected when other viruses are not present at the same time[9]. A Norwegian nationwide study by Bakken et al.(2015) examined the association between influenza A (H1N1) vaccination and infection and the onset of FS, suggesting that pandemic influenza infection was associated with a significantly increased risk of FS[10]. Studies indicate that respiratory syncytial virus (RSV) is found in nearly 11% of FS episodes (95% confidence interval: 7-16%); Upper respiratory tract infection is usually the first clinical symptom of respiratory syncytial virus infection in children. More than 75% of FS patients with positive respiratory syncytial virus have upper respiratory tract infection, and the lower respiratory tract will been affected 3 to 5 days after onset. Fever usually occurs at the beginning of the disease, which is also consistent with the occurrence of FS[7]. Some studies have shown that, although very rare, FS can also occur in the acute phase of Kawasaki disease, presenting as systemic convulsion accompanied by persistent disturbance of consciousness and increased

number of red blood cells in cerebrospinal fluid[11]. Panda et al.(2021) reported a case, in which an 18-month-old boy, clinically diagnosed as incomplete Kawasaki disease, had an outbreak of FS at the acute stage of the disease course[12]. In addition, foreign studies have found that vaccines are also a high risk factor for FS onset. The risk of FS within 7-10 days of vaccination with measles, mumps, rubella, and chickenpox vaccine is been increased by 2 times [13-14]. The cause may be fever after vaccination, which leads to convulsions, rather than a direct effect on the brain. Other scholars have proposed that low levels of iron, calcium, sodium, potassium and vitamin D are also high risk factors for FS, but such studies need to be confirmed by large sample and multi-center studies[15-17].

Mechanism. Currently, the pathogenesis of FS in children is still unclear, and it is generally believed that it is mainly caused by the comprehensive interaction of immature brain development, imperfect myelin sheath formation, inflammatory reaction, genetic susceptibility and fever in children[2,18]. Among them, genetic factors may play a major role in the pathogenesis of FS. If one parent has a history of FS, the risk of FS in children is about 33%, and the risk of FS among siblings with a history of FS is about 20%. At present, relevant genes have been identified as ion channel genes, receptor genes, cytokine genes and enzyme genes, etc. Various genes can play a role in FS through a variety of ways due to mutation or gene polymorphism. Polygenic or multifactorial inheritance

pattern is the most likely. Some studies have found that FS is related to gene coding mutation of γ -aminobutyric acid receptor 2 subunit[19]. Now, the development and improvement of new technological means such as gene base detection and sequencing can continuously provide new directions for FS diagnosis and targeted therapy[20]. At the same time, inflammatory factors such as IL-1 and IL-6 have also gradually attracted widespread attention, and were later confirmed to be closely related to FS[21]. Other scholars believe that arginine vasopressin (AVP) is also involved in the pathogenesis of FS, and in fever, AVP can be released as an endogenous antipyretic agent, which leads to produce FS after release[22]. This idea is been also supported by the fact that genetically deficient AVP homozygous rats do not convulse at the high core temperatures that normal rats experience convulsive episodes. This suggests that lack of AVP increases the threshold of tics[23].

How to identify febrile seizures?

FS is an exclusively diagnosed disease, which can be clearly diagnosed after being differentiated from convulsions caused by central nervous system infection, toxic encephalopathy, epilepsy, acute poisoning or metabolic diseases[2]. In order to clarify the etiology, after further exclusion of other diseases, the diagnosis and treatment plan are determined and the recurrence and prognosis are simultaneously assessed[3]. The following

examinations are often needed to be improved: (1) Routine laboratory tests, such as blood routine, urine and fecal routine, blood gas analysis, liver and kidney functional ions, lymphocyte subsets, etc. The average value of serum calcium in FS children is low, while calcium in urine will increase, and even lead to hypercalciuria. Children with frequent convulsions in summer can also identify toxic bacterial dysentery by routine stool tests and virus tests[24]. (2) Lumbar puncture for cerebrospinal fluid examination: if intracranial infection is highly suspected, lumbar puncture should be perfected as soon as possible, and the cause can be determined by looking for the source of fever[25-27]. (3) Electroencephalogram (EEG): EEG is recommended for children with recurrent or secondary risk factors of epilepsy, such as first-degree and second-degree relatives with FS history; Abnormal nervous system development; First onset <18 months of age; Pre-convulsive fever <39°C; The frequency of convulsions, etc[28]. EEG monitoring is also more conducive to the judgment of the condition and the grasp of drug courses. As for the timing of EEG examination, there is no clear regulation at present, but considering that both fever and convulsion can affect the background electrical activity of the EEG, and non-specific slow wave or abnormal discharge may occur, it is recommended to perform the examination at least one week after fever abatement, to exclude other effects[2]. (4) Neuroimaging examination: Such as cranial magnetic resonance imaging (MRI) and cranial computed tomography (CT)

are not recommended for routine inspection, if there are special circumstances, such as brain lesions can be carried out.Huang Jinying and others researchers had report in children with recurrent bouts of FS hippocampal volume will gradually increase with age, convulsions state will damage the hippocampus development continuously. Therefore, MRI can be used to understand the hippocampus, and timely intervention can be performed to avoid poor prognosis[29].

How are febrile seizures treated?

The treatment of FS can be divided into acute episode treatment and long-term preventive treatment. The former can been divided into systemic treatment, antipyretic treatment and anticonvulsive treatment. In the acute phase, most FS are transient and generally last 1-3 minute, so there is no need to rush for anticonvulsive treatment[2]. The respiratory tract of the child should be kept unobstructed, and the secretions from the mouth and nose should be cleaned up in time to prevent falls and injuries, and avoid further injury to the child.To ensure the normal heart and lung function, when necessary, can be sputum suction and oxygen inhalation, establish venous access. After remission of convulsion, the primary task is to determine the root cause of the fever and symptomatic treatment. This can be done by encouraging children to drink water to ensure adequate hydration, or by taking acetaminophen or ibuprofen to relieve discomfort

caused by infection[30]. If the convulsion of children is difficult to control in a short time, anticonvulsive drugs should be timely intervention.

Phenobarbital is a long-acting sedative and hypnotic drug, which is widely used because of its short onset time and long acting time of anticonvulsion.Meanwhile, diazepam,as a benzodiazepine,has the effects of anti-convulsion, sedation, hypnosis and muscle relaxation. Combined use with phenobarbital can play a synergistic effect to further reduce the excitatory effect of glutamate, inhibit the single synaptic and multi-synaptic transmission between central nerves, and enhance the effect of anti-convulsion[31]. In some cases, benzodiazepines, such as rectal diazepam or oral midazolam, can even be used as a first-aid method for parents to stop convulsions in children[32-33].

In terms of long-term prevention, in order to prevent recurrence, it can be divided into intermittent short-term treatment and long-term continuous treatment. After hospitalization, children identified with risk factors for recurrence should receive short-term intermittent antiepileptic drug therapy, such as oral diazepam, which is not used at ordinary times. If fever recurs in this course, preventive treatment should be given in time.Once fever occurs, it can be used immediately until fever is cured[34-35]. In terms of long-term continuous medication, domestic and foreign scholars agree that oral phenobarbital and sodium valproate are the most effective, and there are still objections to this. Offringa et al.(2017) reported that although

intermittent diazepam or continuous phenobarbital treatment in children with FS may reduce the recurrence rates,but both drugs cause mild to moderate adverse reactions in up to 30 percent of subjects. At the same time, due to the favorable long-term prognosis of children with FS, treatment may only bring short-term benefits regardless of whether their FS is successfully prevented or not, and we should weigh possible drug-related adverse events before giving treatment[36]. Therefore, another point of view is that long-term use of antiepileptic drugs should not generally be used as preventive drugs for FS, as they have been shown not to reduce the risk of seizures and their potential side effects outweigh their potential benefits[37-39]. In recent years, Traditional Chinese medicine (TCM) has made some progress in the treatment of FS, but it is still in the preliminary research stage. Ye Xueying and others have conducted controlled experiments on 60 cases of children with febrile convulsion to observe the safety and effectiveness of various first -aid methods of traditional Chinese medicine in the treatment of febrile seizures. Treatment group was given acupuncture combined with Xingnaojing Injection, Dachengqi Decoction granules enema. Experimental results show that the various first-aid methods of traditional Chinese medicine in the treatment of febrile seizures can shorten the anticonvulsion and cooling time, reduce seizure recurrence rate within 24 hours, which is worthy of clinical promotion[40].Combined with the advantages and limitations of Western

medicine and Traditional Chinese medicine in the application of pediatric FS, the combined application should be considered in the future to improve the therapeutic effect. In short, rather than long-term preventive treatment, what we can do is to focus on health education and guidance of the parents of the children, reduce the anxiety and tension of the children's family members, and avoid inappropriate treatment due to their eagerness to seek medical treatment, and even lead to a poor prognosis.

Conclusion and Outlook

FS is one of the common diseases in pediatric emergency. Most simple FS can achieve a good prognosis through timely identification of causal factors, symptomatic treatment and health guidance for family members. Children with risk factors for recurrence, the etiology can be further clarified through blood routine and biochemical examination, cerebrospinal fluid examination, video EEG monitoring, etc., so the identification of other complex diseases that may cause seizures, and a better prognosis can be obtained through appropriate and efficient treatment. At the same time, health education and guidance for the family members of children should also been done well. At present, long-term use of antiepileptic drugs is not recommended to prevent the recurrence and secondary epilepsy of FS. In the future, through the development of Traditional Chinese medicine, the combined treatment of Traditional Chinese and western medicine should been considered to improve the

therapeutic effect of FS.

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