Artikel Penelitian

Differences in Risk Factors between Simple Febrile Seizures and Complex Febrile Seizures

Annisa Muhyi[1], Muhammad Harbiyan Acikdin[2], Iskandar Muda[3]

Abstrak

Pendahuluan: Kejang demam merupakan bangkitan kejang akibat terjadi peningkatan suhu tubuh di atas 38^{o}C dan bukan karena proses infeksi intrakranial. Kejadian kejang demam sering dilaporkan pada anak laki-laki dan 2-5% terjadi di usia 6-60 bulan. Kejang demam sederhana (KDS) merupakan kejang umum tonik dan atau klonik serta tanpa gerakan fokal terjadi kurang dari 15 menit serta dapat berhenti sendiri. Kejang demam komplek (KDK) dicirikan dengan kejang fokal atau fokal menjadi umum, berulang dalam 24 jam dan berlangsung lebih dari 15 menit. Beberapa faktor risiko yang dapat menyebabkan terjadi kejang pada anak seperti umur anak, jenis kelamin, penyakit penyerta, suhu tubuh, riwayat kejang pada keluarga, status gizi, jumlah leukosit dan kadar hemoglobin. **Metode:** Penelitian observasional analitik dengan uji analisis menggunakan *Mann-Whitney U Test* untuk melihat perbedaan dua sampel yang independen antara kejang demam sederhana dengan kejang demam komplek. Sampel diambil secara purposive sampling dengan kriteri inklusi dan eksklusi. **Hasil:** Pada penelitian ini diperoleh hasil tidak terdapat perbedaan faktor risiko antara kejang demam sederhana dan kejang demam komplek dengan nilai p > 0.05. **Simpulan:** tidak terdapat perbedaan faktor risiko antara kejang demam sederhana dan kejang demam komplek, tetapi faktor risiko memiliki pengaruh untuk terjadinya kejang pada anak dengan usia 0-60 bulan.
Kata kunci: Kejang Demam, Kejang Demam Sederhana, Kejang Demam Komplek

Abstract

Introduction: *Febrile seizures are seizures caused by an increase in body temperature above 38^{o}C and not due to an intracranial infection. The incidence of febrile seizures is frequently reported in boys and 2-5% occur at the age of 6-60 months. Simple febrile seizures (SFS) are generalized tonic and/or clonic seizures without focal movement lasting less than 15 minutes and can stop on their own. Complex febrile seizures (CFS) are characterized by focal or focal seizures becoming generalized, recurring within 24 hours and lasting more than 15 minutes. Several risk factors can cause seizures in children such as the child's age, gender, comorbidities, body temperature, family history of seizures, nutritional status, leukocyte count and hemoglobin level*. ***Methods:*** *Analytical observational study with analysis test using Mann-Whitney U to see the difference of two independent samples between simple febrile seizures and complex febrile seizures. Samples were taken by purposive sampling with inclusion and exclusion criteria.* ***Results:*** *In this study, the results showed that there was no difference in risk factors between simple febrile seizures and complex febrile seizures with a p-value > 0.05. In this study, the results showed that there was no difference in risk factors between simple febrile seizures and complex febrile seizures with a p > 0.05.* ***Conclusion:*** *There is no difference in risk factors between simple febrile seizures and complex febrile seizures, but risk factors have an influence on the occurrence of seizures in children aged 0-60 months.*
Keywords*: Febrile Seizure, Simplex Febrile Seizure, Complex Febrile Seizure*

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Affiliasi penulis : 1. Laboratory of Pediatrics, Mulawarman University, Abdoel Wahab Sjahranie Hospital, Samarinda, Indonesia, 2. Medical Study Program, Faculty of Medicine, Mulawarman University, Samarinda, Indonesia, 3. Laboratory of Biomedicine, Faculty of Medicine, Mulawarman University, Samarinda, Indonesia
Korespondensi : "Annisa Muhyi" annisa.muhyi@gmail.com Telp: +6281351555123

INTRODUCTION

Febrile seizures are seizures caused by an increase in body temperature above 38^{o}C and not due to an intracranial infection.[1] Case of febrile seizures are frequently reported in boys and 2-5% occur at the age of 6-60 months.[2] Simple febrile seizures are generalized tonic and/or clonic seizures without focal movement lasting less than 15 minutes and can stop on their own and complex febrile seizures are characterized by focal or focal seizures becoming generalized, recurring within 24 hours and lasting more than 15 minutes.[3]

The pathogenesis of febrile seizures occurs due to the response of the brain to fever. An increase in body temperature will increase oxygen consumption and the body's basal metabolism will then be hyperexcited due to the depolarization of sodium ions into the cells due to an increase in ATP (Adenosine Triphosphate). Several studies

have shown that there is a sodium channel mutation so that febrile seizures continue until the child is over 60 months old. If febrile seizures continue, there will be a possibility of tonic-clonic seizures without fever in some cases of febrile seizures, which is called genetic epilepsy febrile seizure plus (GEFS+).[1,4,5]

Febrile seizures are a self-limited disorder and rarely occur with clinical manifestations of neurological disorders. The risk of recurring seizures and developing GEFS+ complex febrile seizures are a concern for medical personnel to determine initial prophylactic therapy and educate the family. So it is necessary to collect data on the characteristics of patients with complex febrile seizures based on demographics, clinical and laboratory parameters to determine the early prognosis of the first attack of seizures who are at risk of recurrence.[1,2,5] Because there is no research related to this, we wanted to know the differences between the comparison of risk factors in simple febrile seizures and complex febrile seizures.

METHODS

The research method is analytic observational with non-parametric analysis using Mann-Whitney U Test. Samples were taken from January until December 2022 at the Abdoel Wahab Sjahranie General Hospital, Samarinda. Samples were taken by purposive sampling with inclusion criteria being patients with febrile seizures aged 6 to 60 months who were hospitalized until the end of treatment and had complete medical record data, namely age, sex, body temperature during seizures, nutritional status, leukocyte count, hemoglobin and family history of seizures. Exclusion criteria were patients with febrile seizures who had developmental disorders (speech, motor, behavioral and social disorders), congenital abnormalities (microcephaly, hydrocephalus, tumor, spina bifida, myelocele), and a history of seizures without previous fever. The risk factors for febrile seizures studied were age, sex, body temperature, family history of seizures, nutritional status, leukocyte count, and hemoglobin level. Then, each risk factor for simple and complex febrile seizures was calculated for the difference. The results of the study were analyzed using the “Mann-Withney U Test”.

RESULTS

The results showed that 76 cases of febrile seizures met the inclusion criteria. Of the 76 cases, the number of cases of complex febrile seizures was 38 samples and 38 samples of simple febrile seizures. Following are the results of a comparison of risk factors for simple febrile seizures with complex febrile seizures (Table 1).

Table 1. Characteristic Risk Factors for Febrile Seizures.

Risk Factor	Simplex Febrile Seizure n (%)	Complex Febrile Seizure n (%)	N (%)
Age (Month)			
0-12	8 (21)	7 (18)	15 (20)
13-24	18 (47)	14 (37)	32 (42)
25-36	7 (18)	9 (24)	16 (21)
37-48	4 (10)	7 (18)	11 (14)
49-60	1 (2)	1 (2)	2 (3)
Gender			
Male	29 (76)	24 (63)	53 (70)
Female	9 (24)	14 (37)	23 (30)
Underlying Causes			
ARI	19 (50)	28 (74)	47 (62)
GEA	17 (45)	6 (16)	23 (30)
Urinary Tract Infection	2 (5)	2 (5)	4 (5)
Etc Other	0 (0)	2 (5)	2 (3)
Temperature (°C)			
38-38,9	28 (74)	27 (71)	55 (73)
39-39,9	6 (16)	8 (21)	14(18)
≥40	4 (10)	3 (8)	7 (9)
Family History of Seizure			
Yes	26 (68)	32 (84)	58 (76)
No	12 (32)	6 (16)	18 (24)
Nutritional Status			
Severe Thinness	2 (5)	2 (5)	4 (5)
Thinness	1 (3)	6 (16)	7 (9)
Normal	19 (50)	18 (47)	37 (49)
Risk Overweight	1 (3)	2 (5)	3 (4)
Overweight	9 (24)	5 (13)	14 (18)
Obesity	6 (16)	5 (13)	11 (15)
Leukocyte Count			
Normal	22 (58)	17 (45)	39 (51)
Leukositosis	11 (29)	19 (50)	30 (40)
Leukopenia	5 (13)	2 (5)	7 (9)
Hemoglobin			
Normal	29 (76)	29 (76)	58 (76)
Anemia	9 (24)	9 (24)	18 (24)

The results showed that the highest age for children to suffer from febrile seizures was 13–24 months, with 32 children (42%) consisting of 18 simple febrile seizures (47%) vs. complex 14 (37%).

The sex that most suffers from febrile seizures is male, namely 53 children (70%), respectively 29 (76%) vs 24 (63%) boys suffer from simple vs complex febrile seizures. The characteristics of the infection that accompanied the most febrile seizures were acute respiratory infections (ARI) 47 (62%), acute gastroenteritis (GEA) 23 (30%), urinary tract infections 4 (5%), and others. Children's body temperature experienced the most febrile seizures at temperatures of 38-38.9^{o}C, namely 55 children (73%) consisting of 28 SFS (74%) and 27 CFS (71%). There was a family history of seizures in 58 children (73%) consisting of 26 SFS children (68%) and 32 CFS children (84%).

Characteristics of nutritional status showed that 4 children (5%) were severely malnourished, 7 children (9%) were undernourished, 37 children (49%) were well nourished, 3 children (4%) were at risk of overnutrition, 14 children were overweight (18 %) and obesity 11 children (15%). Children with simple and complex febrile seizures were mostly children with good nutrition, 19 SFS children (50%), and 18 CFS children (47%). The number of leukocytes in children with SFS was highest in children with normal leukocyte counts, 22 children (58%), while children with CFS had the highest number of leukocytes, 19 children (50%). Characteristics of hemoglobin levels were found in children with SFS anda CFS, 9 children had anemia (24%), and 29 children with normal Hb (76%).

Table 2. Analysis of differences between simple febrile seizures and complex febrile seizures.

Risk Factor	Simplex Febrile Seizure n (%)	Complex Febrile Seizure n (%)	*p-value*
Age (Month)			
0-12	8 (21)	7 (18)	
13-24	18 (47)	14 (37)	0.315
25-36	7 (18)	9 (24)	
37-48	4 (10)	7 (18)	
49-60	1 (2)	1 (2)	
Gender			
Male	29 (76)	24 (63)	0.215
Female	9 (24)	14 (37)	
Underlying Causes			
ARI	19 (50)	28 (74)	
GEA	17 (45)	6 (16)	0.088
Urinary Tract Infection	2 (5)	2 (5)	
Etc Other	0 (0)	2 (5)	
Temperature (^{o}C)			
38-38,9	28 (74)	27 (71)	0.566
38-38,9	6 (16)	8 (21)	
≥40	4 (10)	3 (8)	
Family History of Seizure			
Yes	26 (68)	32 (84)	0.108
No	12 (32)	6 (16)	
Nutritional Status			
Severe Thinness	2 (5)	2 (5)	
Thinness	1 (3)	6 (16)	
Normal	19 (50)	18 (47)	0.174
Risk Overweight	1 (3)	2 (5)	
Overweight	9 (24)	5 (13)	
Obesity	6 (16)	5 (13)	
Leukocyte Count			
Normal	22 (58)	17 (45)	0.498
Leukositosis	11 (29)	19 (50)	
Leukopenia	5 (13)	2 (5)	
Hemoglobin			
Normal	29 (76)	29 (76)	1
Anemia	9 (24)	9 (24)	

The results of the study obtained the p-value using the Mann-Whitney U Test, namely age (p=0.315), gender (p=0.215), underlying causes (p=0.088), temperature (p=0.566), family history of seizure (p=0.108), nutritional status (p=0.174), leukocyte count (p=0.498), and hemoglobin (p=1.00). so it was concluded that the p-value > 0.05, which means that there is no difference in risk factors between simple febrile seizures and complex febrile seizures (Table 2).

DISCUSSIONS

Febrile seizures associated with the presence of fever that occurs in a child accompanied by no intracranial infection, electrolyte imbalance, hypoglycemia that occurs in children aged 6 months to 6 years.[4] The results showed that there was no significant difference between simple and complex febrile seizures on gender indicators and age. The highest incidence is in boys ages 13 to 24 months. The age group of children most prone to febrile seizures is the age of 6 months to 3 years with the most occurrences at the ages of 16 and 22 months [7,8] This situation is when the child is in a developmental window, where the child is in a period of brain development where if there is a trigger it will be easy for the child to have seizures.[9] The developmental window is a condition in the brain system where excitation is more dominant than the inhibition system, when a child receives a stimulus in the form

of fever during that phase, the child will be prone to seizures when compared to a mature brain.[10] The etiology of fever in febrile seizures is often caused by a viral infection, namely ARI, otitis media, gastroenteritis, and urinary tract infections. Acute respiratory infections that are often found in children are pneumonia, acute pharyngitis, and the common cold which clinically manifests as fever, cough, sore throat, and shortness of breath. Many studies have stated that the cases of febrile seizures that often occurs in boys is associated with the cause of fever and the slower maturation of neuron cells compared to girls. The immune system of boys against infections is more vulnerable than girls because of the hormone testosterone. The hormone testosterone can suppress the immune system, namely reducing the secretion of Interferon-gamma (IFN-γ) and Interleukin 4 (IL-4) through T lymphocyte cells. When an infection occurs, a fever will increase the body's basal metabolic needs and oxygen consumption. Furthermore, cell membrane hyperexcitability occurs as a result of prolonged depolarization. This situation gives rise to febrile seizures.[11,12]

Research conducted by Gourabi states that infections of the upper respiratory tract and digestive tract that cause febrile seizures are due to a viral infection in the system.[13] ARI was the most common disease in children and ARI caused by a viral infection was most often associated with febrile seizures. ARI is most commonly found in influenza A viruses, which are neurotropic and closely related to febrile seizures.[6,8] Apart from influenza viruses, other types of viruses are most often associated with febrile seizures, namely HHV-6 (human herpes virus 6), adenovirus, and parainfluenza. Viral infections, especially those associated with high fever, increase the risk of febrile seizures because high fever has been shown to increase nerve excitability and the seizure threshold.[2] In children with fever attacks, body temperature increases (temperature above 38ºC). This is because a child whose temperature rises 10 degrees in a state of fever can increase the basal metabolic rate by 10% until 15% and oxygen demand by 20%. So, the increase in temperature can cause depolarization and changes in the permeability of the neuron membrane.[14,15]

Febrile seizures are thought to be genetically inherited in an autosomal dominant manner. The condition of these genetic factors is one of the risk factors for recurring and long-lasting febrile seizures. This is related to genetic mutations in DNA that regulate the amino acids that make up the gate of Na+ ion channels. Mutations at the gate of the Na+ ion channel, namely the alpha subunit (SCN1A) and the beta subunit (SCN1B). Mutations of the two voltage gates of Na+ ion channels result in excessive Na+ influx so that plasma sodium levels decrease and intracellular sodium levels increase. The result will be prolonged depolarization and convulsive seizures. Other studies have also shown that there is a genetic predisposition to febrile seizures, with the risk of febrile seizures in affected siblings increasing to 33% in affected parents. Genes associated with chromosomes 2q23-34, 5q14-15, 6q22-24, 8q13-21, 18p11.2, 19q, and 19p13.3 have been associated with an increased risk of febrile seizures in polygenic or multifactorial conditions. It is also likely that studies have associated febrile seizures with multiple mutations in the gene encoding the γ2 subunit of the γ-aminobutyric acid receptor type A (GABA-A).[16,17,18]

The process of having a fever caused by an infection is also related to the process of immunity in the body, the body's immune system can be formed due to a good nutritional status in a child. Nutritional status describes a person's nutritional balance consisting of macro and micronutrients. These components play a role in the formation of the immune system, such as proteins (macronutrients) that are absorbed by the body to form amino acids, an amino acid that plays a role in the immune system, namely arginine. Arginine influences the function of T lymphocytes, stimulates T cell

proliferation, increases the function of macrophages and NK (Natural Killer) cells, and forms a nitric oxide which is cytotoxic to antigens.[19.20] Micronutrients such as zinc play an important role in the development of cellular immunity, especially T lymphocytes, and maintain the normal function of macrophages and natural killer cells.[21] The process of immunity in the body involves rather than leukocyte cells, leukocytes are an integral part of the body's immune system, leukocytes are formed in the bone marrow and some are formed in the lymphatic system, which after being formed are distributed and transport to other areas of the body through the circulatory system, especially leukocytes to areas where there is an infection or where microorganisms are found.[22] Exogenous pyrogens originating from outside the body can stimulate leukocytes, macrophages and other immune cells to produce endogenous pyrogens resulting in a fever in a person. Bacterial and fungal infections cause leukocyte counts to be high and increase.[23] Febrile seizures are diseases caused by clinical manifestations in the form of fever, in people with a fever they are usually caused by infection. One symptom of infection in humans is a high white blood cell count, which is affected by the increased production of infection-fighting cells. When an infection occurs, leukocytes automatically carry out phagocytosis or destroy microorganisms that cause infection.[24] IL-1β, IL-6, IL-10, IL-1Rα, and TNF-α are endogenous mediators or cytokines that arise as a result of a response from exogenous pyrogens and cytokines involved in the process of fever. The cytokines most frequently associated with febrile seizures are IL-1β and tumor necrosis factor alpha (TNF-α), which affect directly or indirectly on neurons and are the neurotoxic neurotransmitters released during inflammation or excitation. Inflammation is a mechanism of the innate immune system, in which condition there are subtypes of immune cells that work, namely neutrophils, eosinophils, basophils, lymphocytes, monocytes, macrophages, dendritic cells and mast cells. Immune system activation is especially important in patients with febrile seizures. During infection, immune cells such as macrophages and lymphocytes are stimulated and consequently secrete pro-inflammatory cytokines such as IL-6, IL-1β and TNF-α. Double-stranded RNA (Ribonucleic Acid) induces leukocytes to produce large amounts of IL-1β in children with febrile seizures. IL-1β can also stimulate cortisol secretion, cortisol causes leukocytosis, neutrophilia, and lymphopenia.[25,26]

Febrile seizures are also related to the presence of oxygen supply to the brain, oxygen supply is affected by hemoglobin in red blood cells. An indicator indicating that a patient is anemic can be seen from the degree of hemoglobin value. In Indonesia, the most common anemia found is iron deficiency anemia. If anemia is caused by iron deficiency, brain iron levels decrease. this is closely related to the occurrence of febrile seizures in a child due to iron deficiency anemia, where there is an imbalance between unstable intake and increased demand. Lack of hemoglobin in the blood is also in line with a decrease in the binding of oxygen to red blood cells, while oxygen is involved in the process of metabolism, including the function and development of cells in the brain.[27,28]

Seizures caused by iron deficiency anemia result in hypoxemia in the brain area, this hypoxemia causes changes in nerve cell metabolism in the brain and impaired myelination. Iron levels in the body also have a function on monoamine oxidase and aldehyde enzyme activity, these enzymes are important in the stability of neurotransmitter degradation.[29] Iron deficiency anemia also affects neurotransmitter systems such as GABA (Gamma Amino Butyric Acid), glutamic acid, serotonin, dopamine, and norepinephrine.[30] The mechanism by which seizures occur is due to an imbalance in the inhibitory and excitatory neurotransmitters. a child who has anemia, there is a disturbance

in the binding of oxygen by red blood cells, it is this oxygen that plays a role in stabilizing the nerve membrane by acting on the active transport system of Na-K ions. if this is disturbed, there is an increase in the concentration of sodium ions in the brain cells resulting in an increase in depolarization and a change in the permeability of the nerve membrane which triggers seizures in children.[9,26]

CONCLUSION

There is no difference in the risk factors between simple febrile seizures and complex febrile seizures, but boys, family history of seizures, body temperature >38ºC, nutritional status, leukocyte count, and hemoglobin level have a synergistic effect on the occurrence of seizures in children with age 0-60 months.

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