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Clinical Analysis of the Relationship between Convulsion and Blood Electrolyte in Children

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Abstract

Objective: Febrile convulsion in children is age-dependent and genetic predisposition. However, mild electrolyte disturbances are not uncommon in such children. This study was to investigate the effect of electrolyte disturbance on febrile convulsion and to screen for febrile convulsion-related genes. **Methods:** This retrospective cohort study included children who admitted to the Pediatric Emergency Department of Guangzhou Women and Children's Medical Center due to fever and febrile convulsion between May to December 2020. Clinical manifestations and serum electrolyte levels were recorded and analyzed by binary logistic regression on risk factors of convulsion, and children with family histories were screened for febrile convulsion-related genes. **Results:** This study included 322 children with fever: 161 in the febrile convulsion group (FC Group) including 71 in the single convulsion group (SC Group) and 90 in the multiple convulsion group (MC Group), and the control group consisted of 161 children with fever without convulsion and nervous system disease. Serum sodium, potassium and calcium in FC Group were lower than those in the control group ($p < 0.05$), but blood glucose was higher (5.7 mmol/L vs. 5.2 mmol/L, $p = 0.01$); meanwhile, the threshold of serum sodium level in convulsion was 133 mmol/L [Sensitivity: 70.2%, Specificity: 62.1%, AUC: 0.694, $p < 0.001$]. In the FC Group, there were no significant differences in serum sodium, calcium and chlorine between SC Group and MC Group, but lower level of blood glucose in the MC Group (5.6 mmol/L vs. 5.9 mmol/L, $p = 0.008$). Although univariate analysis showed that serum sodium, potassium, calcium, and sugar levels were associated with febrile convulsion, only serum sodium was below normal values. There was no pathogenicity variation related to disease phenotype was found in 5 FC patients with family histories, but four of them found other mutations. **Conclusion:** Hyponatremia may be a relative risk factor in febrile convulsion, and

for children with a family history of febrile convulsion and serum sodium lower than 133 mmol/L, related gene analysis can be performed.

Keywords

Febrile Convulsion, Electrolyte, Recurrence of Convulsion, Hyponatremia, Family History, Gene

1. Introduction

Febrile convulsions are common in children with a febrile state (T ≥ 38˚C), without central nervous system diseases and metabolic disturbances that can cause convulsions, and most of them without history of febrile convulsions [1]. Febrile convulsions are divided into simple and complex febrile convulsion based on clinical features. The former mostly occurs in 6 months to 5 years old, with generalized seizures, duration less than 15 minutes, one attack in a febrile course, and no abnormal neurological signs; and the latter occurs in less than 6 months or more than 5 years, and the symptoms are focal or generalized seizures, neurological abnormalities before onset, seizure duration ≥ 15 min, or seizure duration ≥ 2 times in a febrile course, and neurological abnormalities after seizure, such as Todd's palsy [1] [2]. Febrile convulsions are believed to be the result of multiple factors, including the vulnerability of the developing central nervous system to fever and potential risk factors (including environmental and genetic factors) [1] [3] [4] [5]. The prognosis of febrile convulsion is good generally, but convulsion happens repeatedly can cause organic pathological changes or functional abnormality in brain, especially in persistent convulsions [6] [7] [8] [9]. Therefore, it is very important to find out the risk factors in time, which may help to predict the progress of the disease such as recurrent convulsions.

Febrile convulsions are an age-dependent phenomenon. Although the most commonly identified risk factors of febrile convulsions include age, high fever, infection, recent immunization, and a family history of febrile convulsions [10] [11], some patients also have mild electrolyte disturbances, especially in children with complex febrile convulsions [3] [12] [13]. Whether electrolyte disturbances are a risk factor for febrile convulsions and recurrent convulsions still not clear. In addition, studies have shown that the direct effect of heat on ion channels [14], such as voltage-gated sodium channel [15], localized to the site of action potential initiation potentially causes a profound increase in neuronal excitability [14], which is likely to contribute to abnormal serum sodium levels and febrile convulsions genesis.

Although genetic susceptibility to febrile convulsions has received attention, the exact modes of inheritance are not fully understood. Susceptibility to febrile seizures has been linked to several genetic loci in different families, including the long arm of chromosome 8q13-21 (FEB1) [16], chromosome 19p (FEB2) [17]

and chromosome 2q23-24 (FEB3) [18], which is transmitted in an autosomal dominant pattern with reduced penetrance or as a polygenic or multifactorial model [19]. According to Yuxin Xu *et al.* [20], the series of genes controlling important nodes of neural signaling, including SCN1A, SCN2A, SCN1B, SCN9A, GABRG2, STX1B, and PCDH19, which are believed to be responsible for the early identification of generalized epilepsy with febrile seizures plus (GEFS+), Dravet syndrome (DS), and PCDH19 gene-related seizures. In some patients and families, the propensity for febrile convulsions is an early manifestation of GEFS+ [21] [22], and some with severe myoclonic epilepsy of infancy DS is another genetic epilepsy with a well-known preponderance for seizures with fever in early childhood [23]. Stefania Scalise *et al.* [11] also investigated the role of SCN1A mutations in encoding the voltage-gated sodium channel (VGSC) NaV1.1 gene in children with thermal convulsions, suggesting that SCN1A mutations lead to immature intracellular expression, which leads to normal neuronal transmission.

In this study, we investigated whether electrolyte balance disturbances were associated with convulsions during fever and which electrolytes were associated with recurrence of convulsions. Meanwhile, the genes related to febrile convulsions in children with a family history of convulsions were also analyzed.

2. Patients and Methods

2.1. Patients

Children with fever who visited the Pediatric Emergency Department (PED) of our hospital from May to December 2020 were selected as the research objects. Patients from convulsion to PED admission within 2 hours, including those were convulsing on admission, were classified as febrile convulsion (FC) group. And febrile patients without convulsion and neurological disease during the same period were selected as the control group. The criteria for febrile convulsion included: the presence of a seizure during fever (anal temperature ≥ 38.5˚C, axillary temperature ≥ 38˚C), no central nervous system infection or other cause of convulsion, and no history of febrile convulsion [24]; and the exclusion criteria included: gastrointestinal symptoms such as diarrhea and vomiting, central nervous system (CNS) infection or inflammation, acute systemic metabolic abnormality that may produce convulsions, history of previous afebrile seizures. The FC group was divided in single convulsion group (SC Group), and multiple convulsion group (MC Group) whose convulsions occurred more than once.

2.2. Ethics Approval

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. The study was approved by the ethics committee of Guangzhou Women and Children's Medical Center (No. [2022]199A01). Written informed consent was obtained from the legal guardians of the patients.

2.3. Method

Detailed demographic, convulsion characteristics and family histories, and blood electrolyte indicators of the patients were extracted from the structured electronic medical records system (EMRS). In addition, the first blood sample for measurement of electrolyte indicators was obtained from patients immediately after admission. The demographic and clinical data of the patients were collected, mainly including age, sex, form and numbers of convulsion, serum sodium, potassium, chlorine, calcium and blood glucose. Serum electrolyte indicators were measured by blood gas analyzer (instrument model: GEM Premier 4000; Manufacturer: American Instrumentation Laboratory; Instrument serial number: 19042043).

Genetic testing was performed for febrile convulsions children with family histories. Peripheral blood 2 ml was collected from the children and their parents respectively. Genomic DNA was extracted from blood samples using genomic DNA extraction kits. NextSeq 500 NGS was used for sequencing. The average depth of sequencing was 300×, and the average gene coverage was above 98.8%. The method of case analysis was used to screen the candidate mutation loci of each family. Firstly, gene mutation locus with frequency < 0.001 were screened from the frequency database. Secondly, potential pathogenic mutation sites were retained, including frameshift mutations, nonsense mutations, splicing mutations, and missense mutations predicted by various software to damage protein structure. Finally, the potential pathogenic loci in each family were analyzed in the following five patterns: 1) Epilepsy related gene pattern; 2) Dominant inheritance mode of emerging mutation; 3) Autosomal recessive inheritance pattern, including homozygous and compound heterozygous variants; 4) The model of X chromosome inheritance; 5) Family co-separation analysis model. All filtered rare variants were annotated according to the standards and guidelines recently recommended by the American Society of Medical Genetics and Genomics (ACMG [25]), and were divided into five categories: pathogenic, suspected pathogenic, benign, suspected benign, and of unknown clinical significance.

2.4. Statistical Analysis

Data were expressed as mean ± SD for normally distributed variables, median (IQR) for non-normally distributed variables, and number (percentage) for categorical variables. The normality of the data distribution was examined by using the Kolmogorov-Smirnov tests. Baseline characteristics were compared between different groups using Mann-Whitney U-Test and Chi-square/Fisher's exact test to detect any differences. Logistic regression models were used to estimate the odds ratio (OR) and 95% confidence intervals (CIs) for risk factors of febrile convulsions in different characteristics comparisons. The Receiver Operating Characteristic (ROC) Curve was also adopted to assess the predictive factors for electrolyte disturbances in patients with febrile convulsions. A two-sided p-value of <0.05 was regarded as statistically significant. Data management and statistical analyses were conducted using SPSS19.0 statistical software.

3. Results

3.1. Clinical Characteristics of Enrolled Patients

A total of 322 children with fever were collected in this study, including 161 children in the febrile convulsions (FC) group and 161 children in the control group. In the FC group, 71 cases (44.10%) who had only convulsion once during the febrile course classified as SC Group, and 90 cases (55.90%) whose convulsions had more than once classified as MC Group. In this study, febrile convulsion was most common from 6 months to 3 years of age (80.75%), and there were no gender and age differences among the groups ($p > 0.05$) (Table 1). In febrile convulsion group, 159 cases (98.76%) had generalized tonic-clonic, 2 cases (1.24%) had focal onset, and 3 cases (1.86%) had prolonged convulsion (>30 minutes). There were fifteen cases (9.31%) had family history of convulsion, and 5 cases among them completed genetic testing.

Table 1. Patients' characteristics for all patients (n = 322).

Outcome	*FC Group		Control Group	P
	#SC Group	&MC Group		
Number of cases	71	90	161	
Sex				**0.37**
Male	43 (60.56%)	51 (56.67%)	86 (53.42%)	
Female	28 (39.44%)	39 (43.33%)	75 (46.58%)	
Age (month)				**0.081**
0 - 6	-	1 (1.11%)	0 (0%)	
6 - 36	56 (78.87%)	74 (82.22%)	143 (88.82%)	
36 - 72	12 (16.90%)	9 (10.00%)	16 (9.94%)	
>72	3 (4.23%)	6 (6.67%)	2 (1.24%)	
Forms of Convultions				
Generalized Convultion	70 (98.59%)	89 (98.89%)	-	
Focal Convultion	1 (1.41%)	1 (1.11%)	-	
Family history of convulsions				
Yes	5 (7.04%)	10 (11.11%)	-	
No	66 (92.96%)	80 (88.89%)	-	
Status epilepticus				
Yes	2 (1.86%)	1 (1.11%)	-	
No	69 (98.14%)	89 (98.89%)	-	

*FC Group: Febrile Convulsion Group; #SC Group: Single Convulsion Group; &MC Group: Multiple Convulsion Group. The numbers in bold in the p-value column in the table are the statistically different p-values.

3.2. Correlation between Electrolyte Disturbance and Febrile Convulsion

As shown in Table 2 and Figure 1, the serum sodium level of patients in each group was lower than the normal value of 138 mml/L, and the FC group was significantly lower than the control group (132 mmol/L vs. 134 mmol/L, p = 0.001), but among the FC group, there was no difference between SC group and MC group. Although Serum potassium and calcium in the FC group were significantly lower than those in the control group (both p = 0.001), but there was

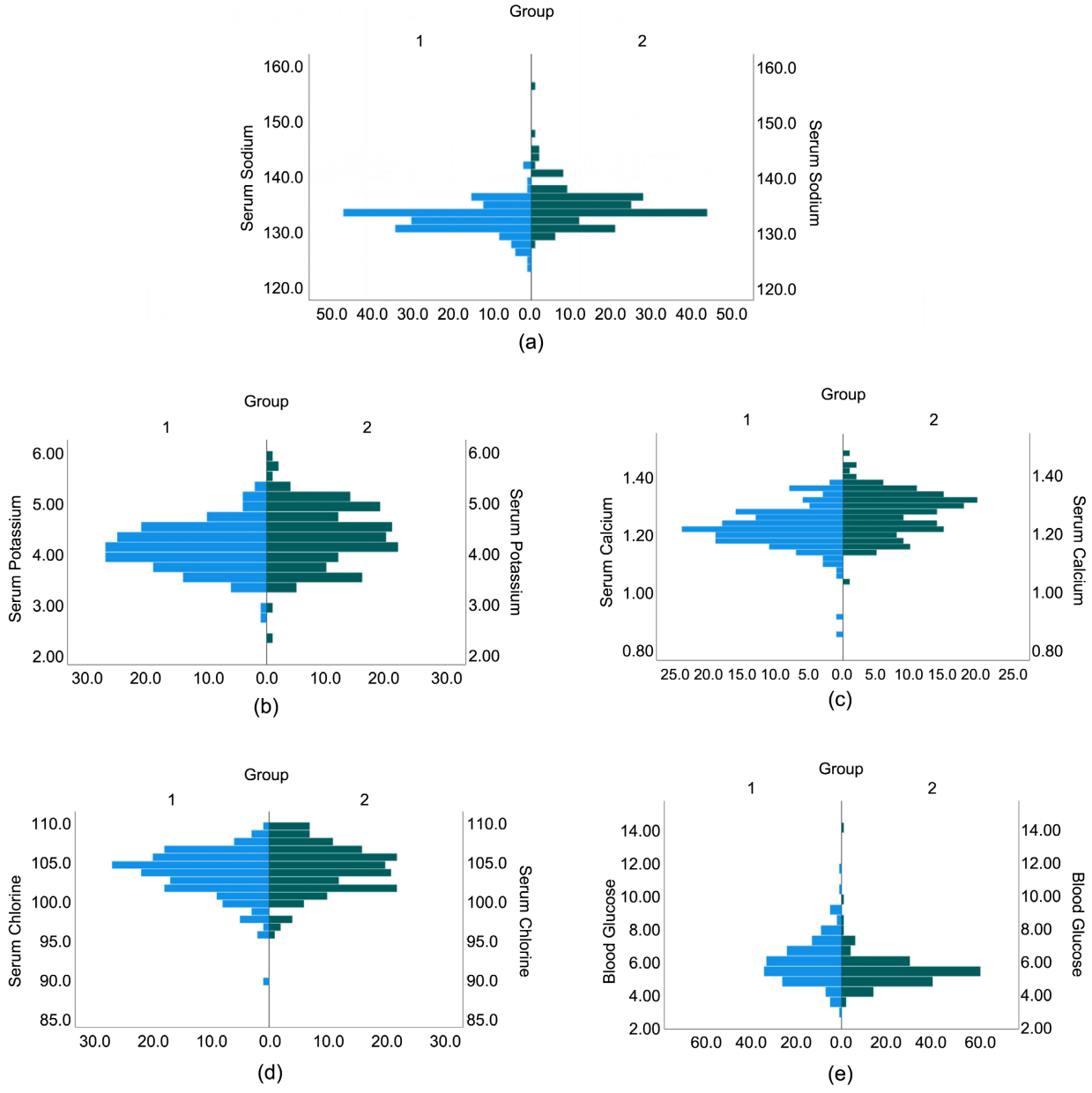

Figure 1. Frequency bar distribution of serum electrolyte in febrile convulsive group and control group. Group 1 is febrile convulsion group and group 2 is control group. (a) Frequency bar distribution of serum sodium. (b) Frequency bar distribution of serum potassium. (c) Frequency bar distribution of serum calcium. (d) Frequency bar distribution of serum sodiumchlorine. (e) Frequency bar distribution of blood glucose.

no difference between SC group and MC group ($p > 0.05$), and these two indicators in each group were within the normal range. In addition, the blood glucose level in the FC group was significantly lower than that in the control group (5.2 mmol/L vs. 5.7 mmol/L, $p = 0.001$), while there was no difference between the SC and MC groups, and the values in each group were within the normal range.

Further univariate analysis of risk factors showed that serum sodium (OR 0.803, 95% CI 0.731 - 0.881, $p = 0.001$), potassium, calcium and blood glucose were associated with febrile convulsion in children (Table 3). However, only serum sodium was below normal levels, and the rest of the indicators were within normal ranges. Therefore, mild hyponatremia may be a risk factor for febrile convulsions in our study.

In order to explore the sensitivity of hyponatremia level to the occurrence of febrile seizures in this group of patients, ROC curve analysis was further conducted. The threshold of serum sodium level in convulsion was 133 mmol/L [Sensitivity: 70.2%, Specificity: 62.1%, AUC: 0.694, $p < 0.001$] (Figure 2).

3.3. Genetic Analysis

There were 15 patients with febrile convulsions who had family history of convulsions, and 5 of them with their family members were tested for febrile convulsions related genes. Although all of them the genetic variants with highly

Table 2. Comparison of serum electrolyte levels in each groups.

Variable (Normal level, mmol/l)	Control Group	FC Group*				$p^{\S\S}$
		Total	SC Group$^{\#}$	MC Group$^{\#\#}$	$p^{\S}$	
Na^+ (138 - 144)	134.0 (3.5)	132.0 (3.0)	132.0 (4.0)	133.0 (3.0)	0.156	**0.001**
K^+ (3.4 - 5.7)	4.3 (0.9)	4.1 (0.7)	4.0 (0.6)	4.1 (0.6)	0.147	**0.001**
Ca^{2+} (1.1 - 1.5)	1.270 (0.105)	1.200 (0.085)	1.20 (0.07)	1.22 (0.09)	0.104	**0.001**
Cl^- (98 - 107)	104.0 (5.0)	103.0 (4.0)	103.0 (4.0)	103.0 (4.0)	0.962	0.107
Glu (4.1 - 5.9)	5.2 (1.0)	5.7 (1.6)	5.90 (1.25)	5.6 (1.43)	**0.008**	**0.001**

*FC Group: Febrile Convulsion Group; $^{\#}$SC Group: Single Convulsion Group; $^{\#\#}$MC Group: Multiple Convulsion Group; §p was SC Group vs. MC Group; §§p was FC Group vs. Control Group. The numbers in bold in the p-value column in the table are the statistically different p-values.

Table 3. Binary logistic regression analysis of serum indexes in febrile children with convulsion.

Variable	OR (95% CI)	p
Na^+	0.803 (0.731 - 0.881)	**0.001**
K^+	0.426 (0.275 - 0.658)	**0.001**
Ga^{2+}	0.021 (0.001 - 0.817)	**0.039**
Glu	1.425 (1.133 - 1.792)	**0.002**

The numbers in bold in the p-value column in the table are the statistically different p-values.

Table 4. Results of genetic tests for febrile convulsions in 5 children with family history of convulsions.

Patient		*Gene*	*Chromosome location*	*Transcript exon*	*Nucleotide Amino acid*	*Homozygous/Heterozygous*	*Normal human frequency*	*Prediction*	*Pathogenicity analysis*	*Genetic pattern*	*Disease/Phenotype*	*Variation source*
Case A	1. Genetic variants with highly correlated clinical phenotypes and well-documented pathogenicity	not found										
	2. Large sample data support susceptible sites	*ATP7A*	chrX: 77301954	NM_000052; exon23	c.4390A > G (p.I1464V)	hemi	0.0166	-	-	1. XLR 2. XLR 3. XLR	1. *Menkes disease* 2. *Occipital Angle syndrome* 3. *X-linked distal spinal muscular atrophy type* 3	
	3. Other mutations with insufficient pathogenic evidence need to be further combined with clinical analysis, and the possibility of pathogenesis cannot be ruled out	*GABRG2*	chr5: 161524870	NM_000816; exon4	c.548 + 6C > A (splicing)	het	5.454E−5	-	Uncertain	1. AD 2. AD 3. AD	1. *Generalized epilepsy with febrile convulsion plus type* 3 2. *Familial febrile epilepsy 8* 3. *Epileptic encephalopathy in early infancy* 74	*Mother*
Case B	1. Genetic variants with highly correlated clinical phenotypes and well-documented pathogenicity	not found										
	2. Other mutations with insufficient pathogenic evidence need to be further combined with clinical analysis, and the possibility of pathogenesis cannot be ruled out	*SCN9A*	chr2: 167085398	NM_002977; exon22	c.3976A > C (p.I1326L)	*het*	0.00090	D	*Uncertain*	1. AD 2. AD 3. AR 4. AD 5. AD	1. *Systemic epilepsy with febrile convulsion type* 7 2. *Primary erythromelalgia* 3. *Congenital insensitivity to pain* 4. *Dravet syndrome, repair* 5. *Paroxysmal pain*	*Mother*

Continued

		MYH11	Chr16: 15818116	NM_002474; exon31	c.4267A > C (p.N1423H)	*het*	-	B	*Uncertain*	AD	*Familial thoracic aortic aneurysm and aortic dissection type* 4
	3. Other variation information	*CAD*	Chr2: 27456870	NM_004341; exon22	c.3400-6C > T (splicing)	*het*	0.00004	-	*Uncertain*	AR	*Congenital glycosylation disease Iz type*
		ARV1	Chr1: 231131724	NM_022786; exon4	c.667A > G (p.I223V)	*het*	0	B	*Uncertain*	AR	*Early infantile epileptic encephalopathy, type* 38
Case C	1. Genetic variants with highly correlated clinical phenotypes and well-documented pathogenicity	not found									
	2. Other mutations with insufficient pathogenic evidence need to be further combined with clinical analysis, and the possibility of pathogenesis cannot be ruled out	*SPTAN 1*	chr9: 131394760-131394760	NM_001130438; exon54	c.7010_7011insTAAG (p.F2337fs)	*het*	0.00060	-	*Uncertain*	AD	*Epileptic encephalopathy of early childhood type* 5	*Father*
	3. Other variation information	*RELN*	chr7: 103124262	*NM_005045; exon62*	*c.10019C > T (p.S3340L)*	*het*	0	*B*	*Uncertain*	1. *AR* 2. *AD*	1. *Anencephaly* 2. *Familial temporal lobe epilepsy 7*	
		MTOR	chr1: 11194424	*NM_004958; exon37*	*c.5230C > T (p.H1744Y)*	*het*	0.00020	*B*	*Uncertain*	*AD*	*Smith-Kingsmore syndrome*	
Case D	1. Genetic variants with highly correlated clinical phenotypes and well-documented pathogenicity	not found									
	2. Other variation information	*ARHGEF15*	chr17: 8216354	NM_173728; exon3	c.716G > A (p.R239H)	het	0.0000084	B	Uncertain	-	*Epileptic encephalopathy*	
		MAGI2	chr7: 78636530-78636531	NM_012301; exon2	c.302-9delT (splicing)	het	0.0039	-	Uncertain	AR	*Nephrotic syndrome type* 15	
Case E	Genetic variants with highly correlated clinical phenotypes and well-documented pathogenicity	not found									

The specific list of tested genes is shown in the attachment.

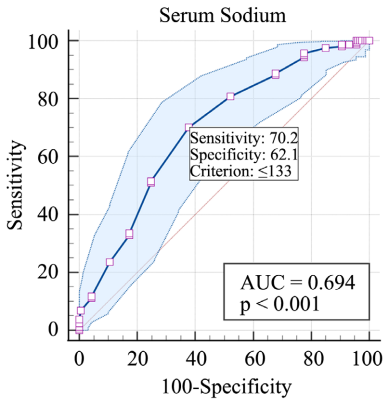

Figure 2. ROC curve of the influence of serum sodium on febrile convulsion.

correlated clinical phenotypes and well-documented pathogenicity were not found, four cases found other mutations (**Table 4**), including in the list of analyzed genes (Supplementary table), with insufficient pathogenic evidence need to be further combined with clinical analysis. On the other hand, three of the families underwent household analysis (**Figure 3**). One case found a mutant gene ARHGEF15, a gene known to have functional roles that are plausibly relevant to epilepsy [26]. One case found mutant gene ATP7A, which is the pathogenic gene of Menkes kinky-hair syndrome and X-linked Distal spinal muscular atrophy [27] [28], and GABRG2 mutation, c.548 + 6C > A (splicing) from mother associated with generalized epilepsy with febrile seizures plus type 3 (OMIM: 611277) [29], familial febrile epilepsy 8 (OMIM: 607681) [30], and early infantile epileptic encephalopathy 74 (OMIM: 618396) [31]. One case found SCN9A mutation, c.3976A > C (p.I1326L) from mother associated with generalized epilepsy with febrile seizures type 7 (OMIM: 613863) [32], and a modifier gene in Dravet syndrome (OMIM: 607208) [33]. One case found SPTAN1 mutation, c.7010_7011insTAAG (p.F2337fs) from father associated with early-onset childhood epileptic encephalopathy type 5 (OMIM: 613477) [34].

4. Discussion

Febrile convulsion is the most common disease in Pediatric Emergency Department, usually occurring between 6 months and 5 years old [1]. Age, infection, vaccination, trace element deficiency, maternal states and genetic predisposition are the commonly known risk factors for febrile convulsion. [10] [11]. Studies have shown that various electrolyte disturbances occur in patients with febrile convulsion [12] [35] [36] [37]. Similarly, in our study, significant hyponatremia was found in the febrile convulsion group compared with the febrile-only group within 2 hours after the onset of convulsions. However, hyponatremia levels in children with febrile convulsion did not reach levels of severe hyponatremia that could trigger convulsion, and there was no different between Single Convulsion Group and Multiple Convulsion Group. In addition, some mutations genes with insufficient pathogenic evidence were found, which need to be further combined with clinical analysis.

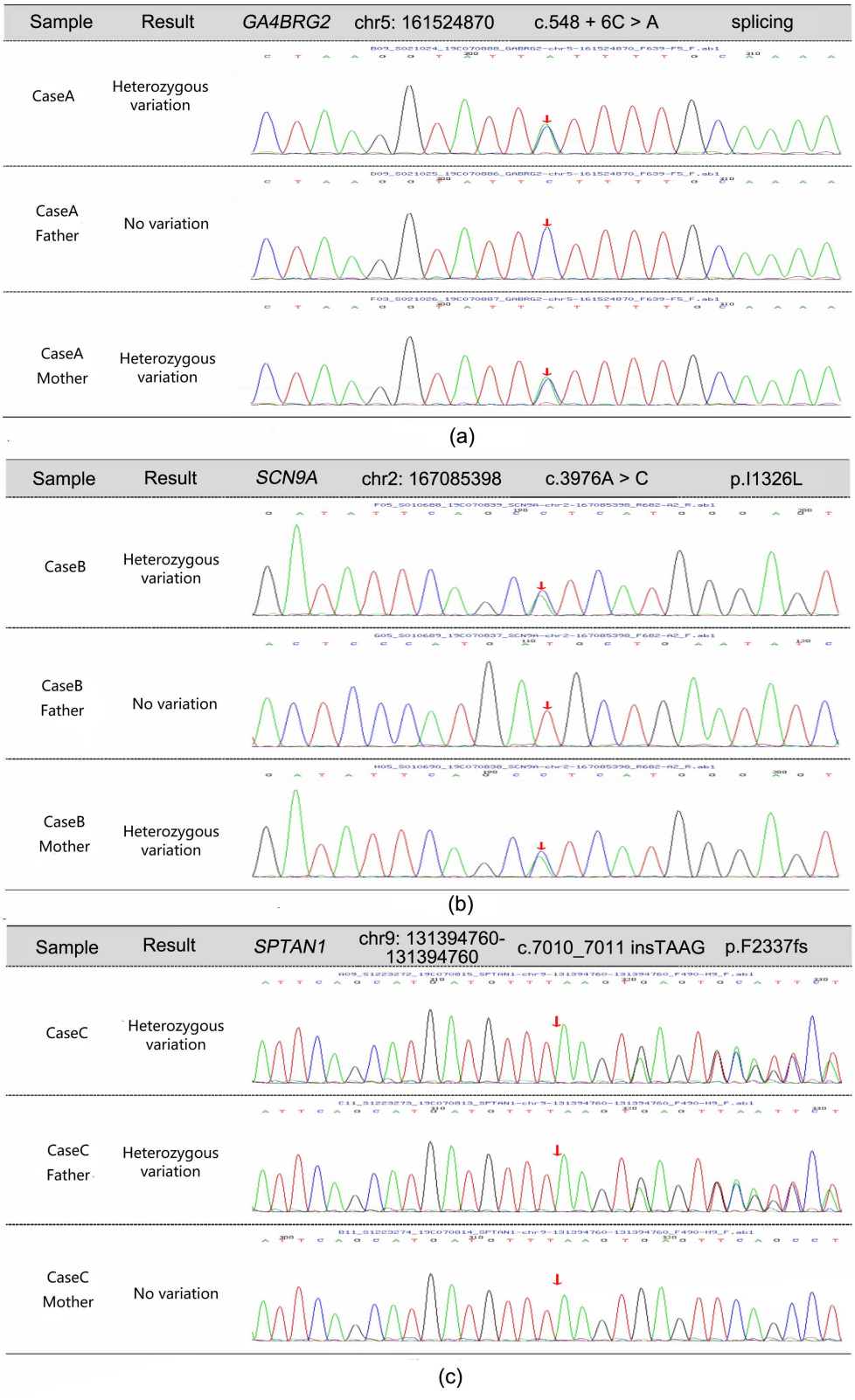

Figure 3. The pedigree analysis of variant genes in case A, B and C. (a) GABRG2 mutation, c.548 + 6C > A (splicing). The mother was heterozygous at this site. (b) SCN9A mutation, c.3976A > C (p.I1326L). The mother was heterozygous at this site. (c) SPTAN1 mutation, c.7010_7011ins TAAG (p.F2337fs). The father was heterozygous at this site.

In this study, the children in this study were all febrile patients, and most of them had hyponatremia, which may be related to hyponatremia caused by inappropriate ADH secretion syndrome in infected patients [38] [39] [40]. The serum sodium of the children in the febrile convulsion group was mostly lower than 133 mmol/L, and ROC curve analysis suggested that serum sodium had a certain predictive effect on febrile convulsion (serum sodium AUC0.694), and determined the critical value (serum sodium < 133 mmol/L, sensitivity 70.2%, specificity 62.1%). However, there was no correlation between serum sodium and recurrence of febrile convulsions. The additional gating defects for both R859H and R865G mutants were detected at 40˚C, and the GEFS+ mutant R859H showed a loss of function in the voltage dependence of inactivation and an increased channel use-dependency at 40˚C with no reduction in peak current density [41]. Meanwhile, the DS mutant R865G exhibited reduced peak sodium currents, enhanced entry into slow inactivation, and increased use-dependency at 40˚C [41]. These studies explain that patients with defects of R859H or R865G mutants had higher levels of hyponatremia triggering febrile convulsions than patients with nonfebrile convulsions [42], but had not shown that this mechanism was associated with repeated convulsions.

On the other hand, potassium, and calcium concentrations were lower and blood glucose concentrations higher than those in the control group, both of which were associated with febrile convulsion. However, these indicators are within the normal range and have no effect on clinical judgment. In a study of 1199 children, febrile seizures and trauma were found to be more likely to cause stress hyperglycemia than fever alone, and none of the children in the study went on to develop diabetes [43]. Raluca Maria Costea *et al.* suggested that the duration of febrile convulsions was longer (>15 min), repeated febrile convulsion\, focal convulsion, body temperature ≥ 39.5˚C, and higher lactate values are significantly associated with stress hyperglycemia, and stress hyperglycemia can be a predictor of recurrence of febrile convulsions [44]. In this study, although blood glucose in the MC group was significantly lower than that in SC group, the mean blood glucose in the two groups was still within the normal range, and the effect of hyperglycemia on recurrent convulsion was not reflected in this study.

Children with a family history of convulsions are more likely to develop febrile convulsions, which may be associated with multiple genes. Studies have shown that mutations in sodium channel and GABA receptor genes are found in families with syndromes associated with febrile convulsions [45]. In this study, 5 of the 15 family members of children with a family history of convulsion agreed to be tested for gene related to febrile convulsion. 189 gene loci, such as AARS, were detected, and no obvious gene mutations related to clinical phenotype of febrile convulsion were found, but mutations at other gene loci were reported in 4 of them, such as ARHG EF15, MAG12, ATP7A, GABRG2, SCN9A, SPTAN, RELN, MTOR. Patient A tested a large sample of data supporting the predisposition locus ATP7A (a gene that encodes an inherited or acquired predisposition

to a disease in response to appropriate environmental stimuli). ATP7A is an important gene encoding copper pump, and its clinical phenotypes are Menkes disease, occipital Angle syndrome, and X-linked distal spinal muscular atrophy type 3 [46]. At the same time, GABRG2 mutation was also detected. Although the evidence of pathogenicity was insufficient, the possibility of pathogenicity was not excluded in combination with the clinical practice of febrile convulsion in children, which needs further follow-up. The gene GABRG2 was derived from the mother, and the disease phenotypes were generalized epilepsy with febrile seizures plus type 3 (OMIM: 611277), familial febrile epilepsy 8 (OMIM: 607681), and early infantile epileptic encephalopathy 74 (OMIM: 618396) [47]. The SCN9A mutation was detected in patient B, which originated from his mother. Combined with clinical analysis, the possibility of pathogenesis was not excluded. The clinical phenotypes consistent with clinical manifestations were generalized epilepsy with febrile convulsion type 7 (OMIM: 613863) and Dravet syndrome (OMIM: 607208) [8] (. SPTAN1 mutation was detected in Patient C. The variant originated from the father and had the clinical phenotype of early onset infant epileptic encephalopathy type 5 (OMIM: 613477), it has also been reported that SPTAN1 encephalopathy is a unique clinical syndrome caused by SPTAN1 specific mutations [31]. Although the current history of febrile convulsion in the child is not supported by clinical evidence, it is not excluded that the child will later develop corresponding epileptic encephalopathy, and need further followed up. In patient D, genetic variants of ARHGEF15 and MAGI2 were detected, both of which were of undetermined pathogenicity and of non-parental origin, and ARHGEF15 was reported to be a mutation associated with epileptic encephalopathy [26].

5. Conclusions

Hyponatremia may be a relative risk factor for febrile convulsions, which may also be a reflection of patient carrying genes involved in sodium channel regulation in febrile seizure-related genes such as R859H or R865G mutants in patients. Therefore, for children with a family history of febrile convulsion and serum sodium lower than 133 mmol/L, related gene analysis can be performed to clarify the etiological diagnosis and predict subsequent neurological diseases.

Furthermore, Gene mutations of various ion channels are closely related to the occurrence of febrile convulsions. It is expected to be further investigated by multicenter randomized controlled studies in future.

Limitations

The current study has some limitations that should be noted. One of the limitations is that blood samples were collected within 2 hours after febrile convulsions and blood electrolyte indicators were measured, which could not be evaluated before the occurrence of convulsions. Future prospective cohort studies or long-term clinical follow-up studies are needed to reveal the intrinsic link between electrolytes and febrile convulsions. In addition, due to economic and

family reasons, many families did not agree to complete febrile convulsions related genes, resulting in a small quantity of genetical cases. In the future, education and promotion of the conclusions in this study can be conducted to obtain more clinical data conducive to research.

Acknowledgements

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Data Availability Statement

The data reported in this paper have been deposited in the OMIX, China National Center for Bioinformation/Beijing Institute of Genomics, Chinese Academy of Sciences. The information record number is BF2022083012025. (https://ngdc.cncb.ac.cn/omix: accession No.OMIX807).

Conflicts of Interest

All authors declare no conflict of interest.

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