Original Article

Risk factors for secondary epilepsy in children with complex febrile seizures and their effect on growth and development—a retrospective cohort study

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Background: Complex febrile seizures are prolonged and can cause neurologic abnormalities, leading to secondary epilepsy and affecting growth and development. At present, the mechanism of secondary epilepsy in children with complex febrile seizures is not clear, and this study aimed to explore the risk factors for secondary epilepsy in children with complex febrile seizures and analyze its effects on the growth and development of children.

Methods: The data of 168 children with complex febrile seizures admitted to the Ganzhou Women and Children's Health Care Hospital between January 2018 and December 2019 were collected retrospectively and divided into a secondary epilepsy group (n=58) and control group (n=110) according to whether the children had secondary epilepsy or not. The differences in clinical features between the 2 groups were compared, and logistic regression analysis was used to explore the risk factors for secondary epilepsy in children with complex febrile seizures. A nomogram prediction model for secondary epilepsy in children with complex febrile seizures was established and verified using the R 4.0.3 statistical software, and the effect of secondary epilepsy on the growth and development of children was analyzed.

Results: Multivariate logistic regression analysis showed that family history of epilepsy, generalized seizures, number of seizures, and duration of seizures were independent influencing factors of secondary epilepsy in children with complex febrile seizures (P<0.05). The dataset was randomly divided into a training set and a validation set, with a sample size of 84 in the training set and 84 in the validation set. The area under the receiver operating characteristic (ROC) curve of the training set was 0.845 (95% confidence interval: 0.756–0.934), and the area under the ROC curve of the validation set was 0.813 (95% confidence interval: 0.711–0.914). Compared with the control group, the Gesell Development Scale score in the secondary epilepsy group was significantly reduced (77.84±8.86 *vs.* 85.64±8.65, P<0.001).

Conclusions: The nomogram prediction model could better identify complex febrile seizures children at high risk of secondary epilepsy. Strengthening intervention in such children may be beneficial for improving their growth and development.

Keywords: Complex febrile seizures; epilepsy; predictive models; children

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Introduction

Children with complex febrile seizures have systemic convulsions lasting more than 15 minutes, and convulsions can also take place when low-grade fever occurs. Seizures can be partial seizures or systemic seizures, they can occur multiple times, and there may be abnormal neurological signs such as temporary paralysis syndrome after convulsive seizures (1,2). Some children may still have electroencephalogram (EEG) abnormalities after fever, and the prognosis is worse than that of simple febrile seizures. Children with a family history of epilepsy or organic brain lesions are more likely to develop epilepsy (3,4), and secondary epilepsy can affect the growth and development of the child. Studies of the relevant factors of secondary epilepsy in children with complex febrile seizures is encouraging for prevention and treatment of secondary epilepsy, but unfortunately there is a lack of relevant research. Thus, we designed this study to explore the risk factors for secondary epilepsy in children with complex febrile seizures and their impact on the growth and development of children, so as to provide bias for further prevention and treatment of secondary epilepsy. We present the following article in accordance with the TRIPOD reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-203/rc).

Highlight box

Key findings

- The nomogram predictive model could better identify children at high risk of secondary epilepsy.

What is known and what is new?

- Children with complex febrile seizures have a higher incidence of secondary epilepsy.
- Family history of epilepsy, generalized seizures, number of seizures, and duration of seizures were independent risk factors for secondary epilepsy in children with complex febrile seizures.

What is the implication, and what should change now?

- The nomogram prediction model could better identify high-risk children with secondary epilepsy, and strengthening intervention in such children may be beneficial for improving their growth and development.

Methods

General information

This was a retrospective cohort study. The data of 168 children with complex febrile seizures admitted to the Ganzhou Women and Children's Health Care Hospital between January 2018 and December 2019 were collected retrospectively and divided into a secondary epilepsy group (n=58) and control group (n=110) according to whether the children had secondary epilepsy or not. The inclusion criteria were: (I) complex febrile seizures; (II) age 1–17 years old; and (III) complete data. The exclusion criteria were: (I) prior central nervous system disease; (II) congenital diseases; (III) malignant tumors; and (IV) lost to follow-up. The present study was conducted in accordance with the 2013 edition of the Declaration of Helsinki and approved by the Ethics Committee of the Ganzhou Women and Children's Health Care Hospital (No. 20220901002). Informed consent was waived in this retrospective study. A flowchart of the inclusion of complex febrile seizure patients is shown in *Figure 1*.

Data collection

Data collection included age, number of convulsions, body temperature, duration of seizures, sex, family history of epilepsy, seizure type, time from fever to first convulsions, EEG abnormalities, blood pressure abnormalities, and Gesell developmental scale score.

Diagnostic criteria

Diagnostic criteria included the following: (I) complex febrile seizures: there may have been neurological abnormalities during the onset of febrile seizures, manifested as focal seizures or generalized seizures, the duration of the seizures ≥15 minutes or ≥2 seizures in a febrile seizures course, and there may have been neurological abnormalities after the seizures. (II) Secondary epilepsy: if the children developed the following events (including major seizures, minor seizures, simple partial seizures, complex partial seizures, and autonomic seizures), the secondary epilepsy was diagnosed. (III) The

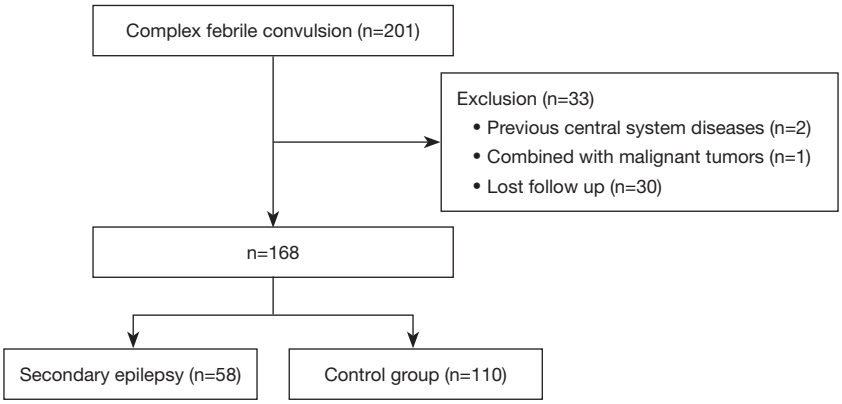

Figure 1 Flow chart of the inclusion of children with complex febrile seizures.

Gesell developmental scale: the Gesell developmental scale represents a child's developmental level based on developmental age and developmental quotient. According to the content of child development, it is divided into five functional areas. The lower the score, the more severe the developmental defect.

Statistical analysis

SPSS 26.0 (IBM Corp., Armonk, NY, USA) and R 4.0.3 statistical software were used to complete the data analysis. When P<0.05, the difference was statistically significant (bilateral). The measurement data of the 2 groups are expressed by mean ± standard deviation, and the independent sample *t*-test was used to analyze the difference in measurement data between the 2 groups. The count data of the 2 groups are expressed by n (%), and the chi-square test was used to analyze differences in count data between the 2 groups. Multivariate logistic regression analysis was used to explore the risk factors for secondary epilepsy in children with complex febrile seizures (variables with a P value <0.10 in univariate analysis were included in multivariate regression analysis). The receiver operating characteristic (ROC) curve was used to analyze the predictive value of different markers for secondary epilepsy in children with complex febrile seizures. According to risk factors identified by the multivariate regression analysis, the prediction model was constructed and verified by the R 4.0.3 statistical software, and the dataset was randomly divided into a training set and a validation set, with a sample size of 84 in the training set and 84 in the validation set.

Results

Comparison of clinical features between the 2 groups

Compared with the control group, the number of seizures in the secondary epilepsy group was significantly increased (10.00±3.95 *vs.* 7.82±3.96, P=0.001). The duration of seizures was significantly prolonged in the secondary epilepsy group (25.09±9.61 *vs.* 18.01±7.51 minutes, P<0.001). Family history of epilepsy was significantly increased in the secondary epilepsy group (18.97% *vs.* 4.55%, P=0.002). The proportion of children with systemic seizure type was significantly increased in the secondary epilepsy group (67.24% *vs.* 33.64%, P<0.001). The proportion of children with fever to the first seizure time <24 hours was increased (46.55% *vs.* 20.91%, P=0.001; *Table 1*).

Risk factors for secondary epilepsy in children with complex febrile seizures

Multivariate logistic regression analysis showed that family history, systemic seizures, number of seizures, and duration of seizures were independent risk factors for secondary epilepsy in children with complex febrile seizures (P<0.05; *Table 2*).

Predictive value of number of convulsions and duration of seizures in children with complex febrile seizures

The number of convulsions and duration of seizures were valuable in predicting secondary epilepsy in children with

Table 1 Comparison of clinical features between the 2 groups

Variables	Secondary epilepsy group (n=58)	Control group (n=110)	t/χ^2 value	P value
Age (years), mean ± SD	9.38±4.51	8.15±4.98	1.575	0.117
Number of convulsions, mean ± SD	10.00±3.95	7.82±3.96	3.401	0.001
Body temperature (℃), mean ± SD	39.89±0.79	39.77±0.74	0.981	0.328
Duration of the seizures (min), mean ± SD	25.09±9.61	18.01±7.51	5.259	<0.001
Gender, n (%)			0.075	0.784
Male	33 (56.90)	65 (59.09)		
Female	25 (43.10)	45 (40.91)		
Family history of epilepsy, n (%)			9.164	0.002
Yes	11 (18.97)	5 (4.55)		
No	47 (81.03)	105 (95.45)		
Type of seizure, n (%)			17.312	<0.001
Generalized	39 (67.24)	37 (33.64)		
Partial	19 (32.76)	73 (66.36)		
Fever to the first seizure time, n (%)			11.945	0.001
<24 h	27 (46.55)	23 (20.91)		
≥24 h	31 (53.45)	87 (79.09)		
EEG abnormalities, n (%)			0.890	0.345
Yes	21 (36.21)	32 (29.09)		
No	37 (63.79)	78 (70.91)		
Abnormal blood pressure, n (%)			0.263	0.608
Yes	18 (31.03)	30 (27.27)		
No	40 (68.97)	80 (72.73)		

SD, standard deviation; EEG, electroencephalogram.

Table 2 Risk factors for secondary epilepsy in children with complex febrile seizures

Variables	B	Standard error	Wald	P value	Relative risk (95% confidence interval)
Family history of epilepsy	1.285	0.645	3.971	0.046	3.613 (1.021–12.784)
Generalized seizures	1.489	0.411	13.132	<0.001	4.434 (1.981–9.923)
Fever to the first seizure time <24 h	0.814	0.427	3.631	0.057	2.258 (0.977–5.218)
Number of convulsions	−0.162	0.055	8.700	0.003	0.851 (0.764–0.947)
Duration of the febrile seizures (min)	−0.085	0.024	12.449	<0.001	0.919 (0.877–0.963)
Constant	−2.117	1.694	1.562	0.211	0.120

complex febrile seizures, with an area under the curve of 0.642 (95% confidence interval: 0.556–0.727, P=0.003) and 0.703 (95% confidence interval: 0.617–0.790, P<0.001; *Figure 2*).

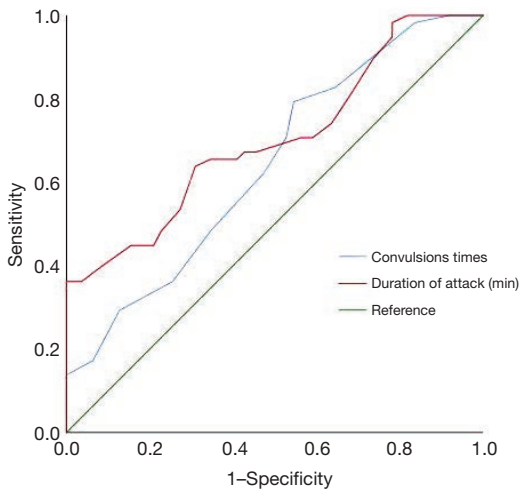

Figure 2 Predictive value of number of seizures and duration of seizures in children with complex febrile seizures.

Predictive value of nomogram for secondary epilepsy in children with complex febrile seizures

R 4.0.3 statistical software was used for statistical analysis. The dataset was randomly divided into a training set and a validation set, with a sample size of 84 in the training set and 84 in the validation set. Family history of epilepsy, generalized seizures, number of convulsions, and duration of seizures were included in the prediction model, and the nomogram, clinical decision curve, calibration curve, and ROC curve were produced. The area under the curve of the training set was 0.845 (95% confidence interval: 0.756–0.934), and the area under the curve of the validation set was 0.813 (95% confidence interval: 0.711–0.914). In the validation set, the model was evaluated using Hosmer-Lemeshow goodness-of-fit test, with a chi-square value of 10.22 and a P value of 0.250 (*Figures 3-6*).

Effect of secondary epilepsy on growth and development in children with complex febrile seizures

Compared with the control group, the Gesell Development

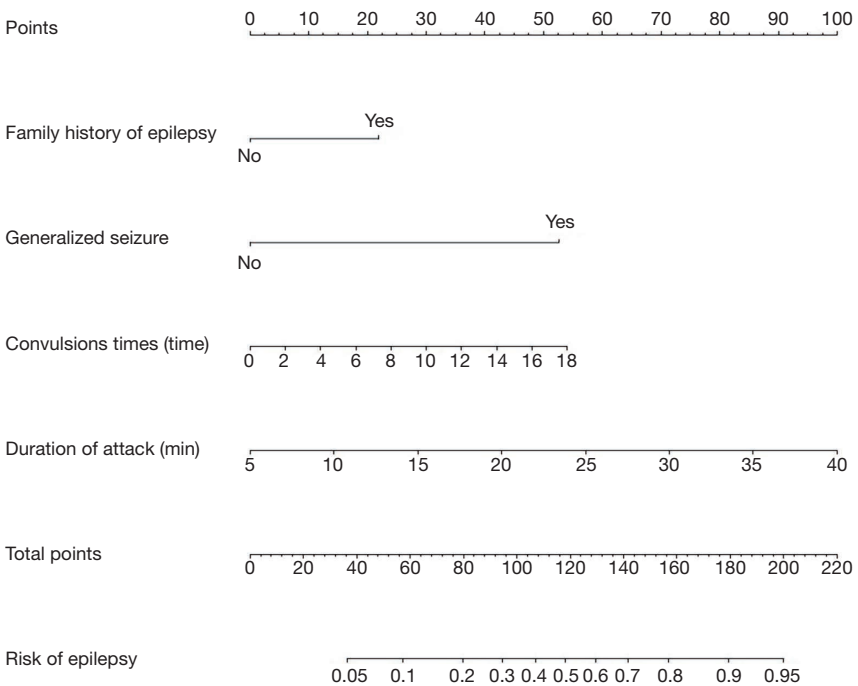

Figure 3 Nomogram predictive model for secondary epilepsy in children with complex febrile seizures.

Scale score in the secondary epilepsy group was significantly reduced (77.84±8.86 *vs.* 85.64±8.65, P<0.001; *Figure 7*).

Discussion

Children with complex febrile seizures are prone to secondary epilepsy, which can seriously affect their growth and development (5-7). This study was designed to explore risk factors for secondary epilepsy in children with complex febrile seizures. The results showed that family history of epilepsy, generalized seizures, number of seizures, and duration of seizures were independent influencing factors of secondary epilepsy in children with complex febrile seizures (P<0.05).

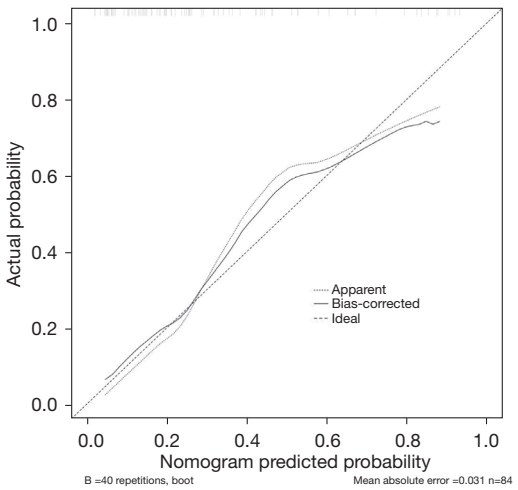

Figure 4 Calibration curve of the nomogram prediction model for secondary epilepsy in children with complex febrile seizures.

Secondary epilepsy refers to epilepsy secondary to other diseases, also known as "symptomatic epilepsy". It can be caused by diseases within the brain or outside the brain. People with a family history of epilepsy have increased susceptibility to epilepsy. Therefore, people with a family history of epilepsy should try to avoid predisposing factors such as high fever, brain trauma, fatigue, cold, and flash stimulation to reduce the probability of epilepsy (8-10). Febrile seizures can be divided into systemic seizures and partial seizures. With systemic seizures, the child's central nervous system will also be in a state of excessive excitement. This "excitement" affects the thalamus, causing it to produce intense electrical discharges that are transmitted to other parts of the brain, eventually leading to epilepsy (3,11-13). Convulsions mostly occur within 24 hours of fever. Complex febrile seizures tend to occur multiple times and last for a long time, and metabolism, oxygen consumption, and blood flow of nerve cells change during the seizure, resulting in central nervous system lesions and secondary epilepsy (14). The above studies support the present study, which also showed that family history of epilepsy, systemic seizures, number of seizures, and duration of seizures were independent risk factors for secondary epilepsy in children with complex febrile seizures (P<0.05).

In addition, to better identify children at high risk of epilepsy secondary to complex febrile seizures, we

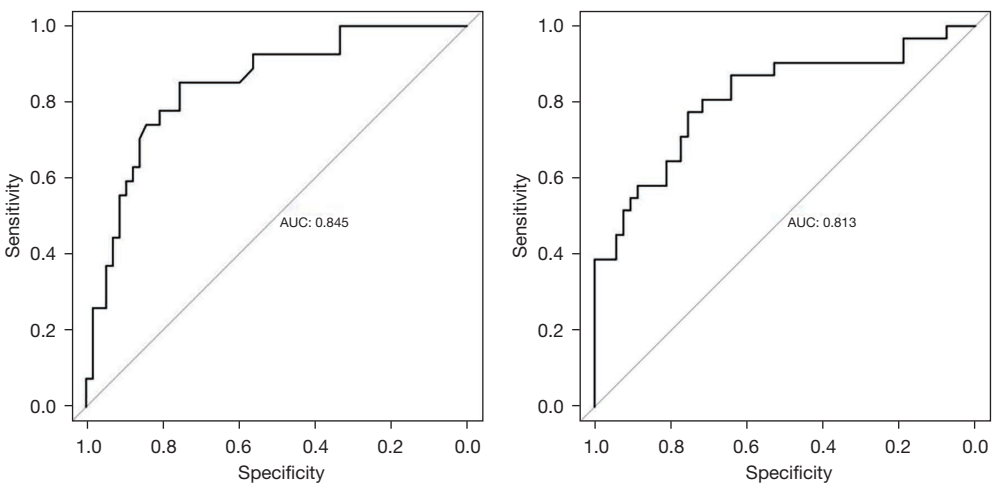

Figure 5 Predictive value of the nomogram for secondary epilepsy in children with complex febrile seizures (the figure on the left was the training set, the figure on the right was the verification set). AUC, area under the curve.

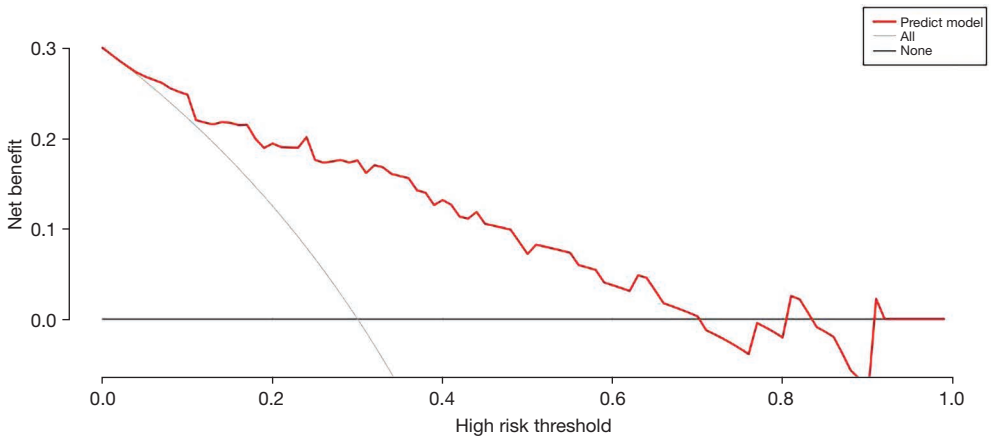

Figure 6 Clinical decision curve of the nomogram predictive model for secondary epilepsy in children with complex febrile seizures.

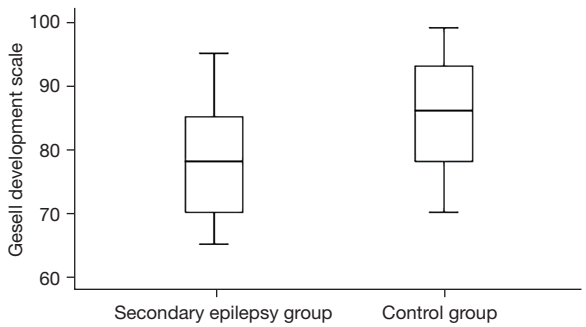

Figure 7 Effect of epilepsy secondary to complex febrile seizures on growth and development of children.

established a nomogram predictive model. Nomogram prediction models combine multiple risk factors to form a new indicator that can better predict prognosis and are widely used in the diagnosis and treatment of multiple diseases (15-20). In the present study, the prediction model established had a high predictive value for secondary epilepsy in children with complex febrile seizures, with an area under the curve of 0.845 (95% confidence interval: 0.756–0.934) in the training set and an area under the curve of 0.813 (95% confidence interval: 0.711–0.914) in the validation set. In the validation set, the model was evaluated with Hosmer-Lemeshow goodness-of-fit test, and the chi-square value of 10.22 and P value of 0.250 indicated that the model had high predictive value and credibility.

Finally, the Gesell Development Scale score reflects the growth and development status of the child, and this study showed a significant decrease in Gesell Development Scale score in patients with secondary epilepsy, indicating that strengthening intervention in such children may be beneficial for improving their growth and development (21).

Limitations

This was a retrospective clinical study, and we failed to explore the molecular mechanism of secondary epilepsy in children with complex febrile seizures. Moreover, in the FEBSTAT study, magnetic resonance imaging abnormality was related with the development of secondary epilepsy. However, we failed to study this in the present study.

Conclusions

The nomogram predictive model could help clinicians accurately identify high-risk children with epilepsy secondary to complex febrile seizures, and strengthening intervention in such children may be beneficial for improving their growth and development.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-203/rc

Data Sharing Statement: Available at https://tp.amegroups.

com/article/view/10.21037/tp-23-203/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-203/coif). 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 present study was conducted in accordance with the 2013 edition of the Declaration of Helsinki and approved by the Ethics Committee of the Ganzhou Women and Children's Health Care Hospital (No. 20220901002). Informed consent was waived in this retrospective study.

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