

Developmental evaluation in children experiencing febrile convulsions

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ABSTRACT

Background. The objective of this study was to determine the effect of febrile convulsion (FC) on neuromotor development.

Methods. Data of 325 patients, who were followed up at our outpatient clinic and diagnosed with FC between January 2012 and December 2018, were retrospectively evaluated. Of these patients, 203 underwent the Denver Developmental Screening Test II (DDST II) and were included in the study as the patient group and 100 healthy children as the control group.

Results. Of the study group, 84 (41.4%) were girls and 119 (58.6%) were boys (B/G: 1.4). Of all patients, 163 (80.3%) were diagnosed with simple FC, 22 (10.8%) with complicated FC, and 18 (8.9%) with FC+. There was no significant relationship found between FC subtypes and gender, family history of FC, family history of epilepsy, iron (Fe) deficiency, and Fe deficiency anemia. DDST II subtest points were significantly lower in all developmental areas in the patient group when compared to the controls ($p<0.001$), while suspected and abnormal test results were higher in all developmental areas in the patient group compared to the controls ($p=0.01$). It was also determined that the language points were lower as the age of first seizure increased ($r=-0.319$, $p<0.01$).

Conclusions. Although FC is known to usually having a good prognosis, the low DDST II test results measured in this study indicated that the FC may pose a developmental risk and patients with FC should be followed up in terms of developmental features. Because of the retrospective nature of the study, there was no "pre-convulsion" developmental evaluation. This is a major limitation of our study.

Key words: DDST II, febrile convulsion, neuromotor development, prognosis.

Febrile convulsions (FCs) are the most commonly seen age-related seizures in childhood usually with a good prognosis. These seizures have been defined by the International League Against Epilepsy (ILAE) as convulsions observed in the febrile conditions in children who had not experienced an afebrile convulsion previously, without having a cause such as a central

nervous system infection, electrolyte imbalance, metabolic disorder, trauma, and intoxication or any other cause.¹ The age range of FCs has been reported between 1 month and 8 years though the highest incidence occurs between 18-22 months.^{2,3} FCs have been reported higher in boys than in girls (B/G: 1:1-1.7:1).⁴ Although its pathogenesis is not fully understood, the association of the FC with numerous factors has been reported, including infections related to inflammatory mediators, cytokines, iron (Fe) deficiency anemia, mineral deficiencies, high fever, and genetic predisposition.^{5,6}

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FCs are known to have a good prognosis. However, there are limited studies reporting the language, motor, behavior, attention, cognitive functions, and developmental disorders in patients with the FC.⁷⁻⁹ Denver Developmental Screening Test (DDST II) is a test that is used to detect the developmental status of healthy children in the personal-social, language, fine and gross motor areas by comparing them with their healthy peers of the same age.

In this study, we aimed to determine the neurodevelopmental status of children diagnosed with FC by comparing them with healthy controls using the DDST II in order to determine the effect of the FC on neuromotor development.

Material and Methods

In this study, the patients, who were diagnosed with FC at Mersin University Medical Faculty, Pediatric Neurology Outpatient Clinic and underwent the DDST II between January 2012 and December 2018, were evaluated retrospectively. The study was conducted in accordance with the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of Mersin University (2020:2020/221). The inclusion criteria for the patient group were being between the ages of one month and six years, being monolingual, observing an increase in the body temperature above 38°C, not having a central nervous system infection, ruling out the other factors causing convulsions, not having any other chronic disease, and complying with the DDST II test application and determined according to the ILAE criteria for the FC diagnosis.¹ The exclusion criteria were included being out of the specified age range, being bilingual, fever and/or central nervous system infection during the seizure, the presence of other secondary causes that may affect neurodevelopment and/or lead to convulsions, those diagnosed with epilepsy later, patients with missing data and incompliance to the test application. According to the inclusion and exclusion criteria, a study

flow diagram has been given in Figure 1. Of the participants, 122 patients were excluded from the study group due to incompliance with the DDST II test. Incompliance to the DDST II was described as a refusal of the test at least two times. An additional 14 (11.5%) patients were excluded from the study since they had afebrile seizures and 46 (37.7%) patients were excluded due to missing data. The number of patients who did not complete the DDST II test was 42 (34.4%) whereas the numbers of patients diagnosed with epilepsy later and having other secondary causes that may affect neurodevelopment and/or lead to convulsions were 13 (10.7%) and 7 (5.7%), respectively. As a result, 122 patients who met the aforementioned exclusion criteria were excluded from the study. The control group was comprised of 100 healthy children, whose age and gender-matched to children with FC and who had no systemic or neurological problems that could affect their neurodevelopment, and showed compliance to the test application. These participants were selected among the children regularly followed at the healthy children outpatient

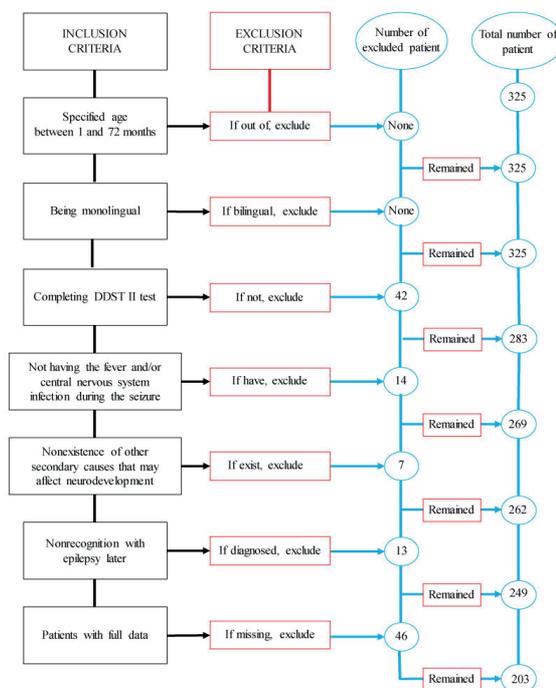


Fig. 1. Demonstrating the inclusion and exclusion criteria considered in this study.

clinic. The study and control groups were selected according to inclusion and exclusion criteria. The children included in the control group were similar to the study group in terms of socioeconomic and demographical features. Additionally, there were no bilingual children in this study.

The files of all patients were retrospectively evaluated from the time of the first seizure and recorded for the following: age, simple or complicated FC diagnosis, the number of convulsions experienced till the admission time, prenatal, natal and postnatal histories, FC and epilepsy histories in family, Fe deficiency and Fe deficiency anemia, and other factors that can influence the neuromotor development. The patients were classified according to the ILAE as simple and complicated FC and in addition to the ILAE criteria as the FC+ group. The patients having a simple FC repeating more than 3 times and a febrile status epilepticus (FSE) history and those having a complicated FC repeating more than 3 at different times were included in the FC+ group. The FC+ group was created in order to determine whether the specified factors caused a prognostic difference or not.

Denver Developmental Screening Test II (DDST II)

DDST II is a neurodevelopmental screening test developed to be carried out on healthy-appearing children between 0-6 years. The test compares the skills of children in subareas with their peers. DDST II has a significant role in screening possible developmental problems. The test can detect developmental deviations in the early screening of babies with suspected developmental delay, especially monitoring babies at risk. The test is easy to apply and interpret and only takes about 15 minutes to complete. Its other advantages are that it is easy to learn how to do and can be applied by non-physician professionals who receive training. However, it is not a test of intelligence, it cannot be employed to predict mental and adaptive ability in the future nor can it be utilized to identify learning difficulties, emotional

problems, and special education requirements. The patient may require further examinations since it is a screening test. The social and cultural differences leading to errors in the evaluation can be counted among its disadvantages.

The test compares the skills of the children in the following 4 subareas with their peers: personal-social (PS), fine motor skills (FMS), language, and gross motor skills (GMS). The test form involves 134 items. The validity and reliability of the Turkish version of the test used in this study were performed by Yalaz et al.¹⁰

DDST II tests of all children included in the study were performed by the same person, who was trained for the test and had 10-year experience in this area. In accordance with the test application rules, it was performed on all children by allocating at least 15 minutes after they had had enough sleep and on a full stomach. Moreover, the DSST II tests were conducted at least four weeks after experiencing the convulsion to exclude the possible unpleasant experience of the patient at the health center after the FC. Both the sub developmental areas and the overall score of the DDST II was evaluated. The test result was interpreted as normal in the case of no delay and at most one caution, abnormal in the case of two or more delays, and suspected in the case of one delay and/or two or more cautions. In order to state the scores in the DDST II test, firstly, the age scale is located and each mark on the scale form represents one month till the first 24 months. After the first 24 months, each mark means a 3-month interval. Then, the age of the child is calculated. The number of items to be tested is specified after determining the age of the child. The number of items depends on the age and ability of the child. Scoring in terms of pass-child (P), fail-child (F), no opportunity (NO), and for refusal (R) is carried out after specifying the number of items. Afterward, the advanced, normal, caution, delayed, and no opportunity items are determined in regard to the testing guidelines. According to the number of cautions and delayed items, the score is designated as normal, suspected, and abnormal. Each subtest

score of the patient were separately evaluated. In each subtest, firstly, in accordance with the age of the child, the number of items in which a 90% success should be achieved by the child was determined. Afterward, the percentile score was obtained by the following formula: Subtest score = $100 \times \frac{\text{the number of items/the number of items to succeed with respect to 90\%}}{100}$.¹¹⁻¹³ The 90%-reliability rate among the implementers and more than 85%-rate of yielding similar result for the repetitive measurements have been reported by Yalaz et al.¹⁰

Statistical Analysis

The normality of the values was analyzed using the Shapiro-Wilk test. Independent samples t-test or Mann-Whitney U test was used according to the results of Shapiro-Wilk. Spearman's correlation coefficient was calculated to determine the relationship between the continuous variables. The Chi-square test was conducted to examine the relationship among the categorical variables, and the exact test results were handled when the expected frequency percentage was lower than 25%. The comparison of the two ratios was done with the Z test when a meaningful relationship was established. Both mean \pm SD (standard deviation) and median (min-max) values for the continuous variables were presented whereas the categorical variables were summarized in terms of the number and percentage.

Differences were considered significant at $p < 0.05$. All statistical tests were performed using software named Statistica 13.3.1.

Results

The study group consisted of 203 patients, of which 84 (41.4%) were girls and 119 (58.6%) were boys and the boys/girl ratio was 1.4. The mean age of the first seizure was 19.5 ± 11.5 months. Of all patients, 163 (80.3%) were diagnosed with the simple FC, 22 (10.8%) with complicated FC, and 18 (8.9%) with FC+ (7 of them had the simple FC that repeated more than 3 times, 6 of them had the FSE, and 5 of them had complicated FC that

repeated more than 3 at different times). The demographic features of the patient group are presented in Table I.

No significant statistical relationship was determined between the FC type and the patient's gender ($p=0.133$), the family history of FC ($p=0.558$) and epilepsy ($p=0.708$) and Fe deficiency and Fe deficiency anemia ($p=0.237$).

In the patient group Fe deficiency was seen in 50/177 (28.2%) and Fe deficiency anemia was seen in 16/177 (9%) participants. But since the control group consisted of healthy children, blood samples were not obtained from these children due to ethical reasons, so the patient and control groups could not be compared in terms of Fe deficiency and Fe deficiency anemia.

The DDST II test, which was performed at least 4 weeks after the FC, was normal in 103 (50.7%) patients, whereas suspected in 87 (42.9%) and abnormal in 13 (6.4%) patients. There was a statistically significant difference between the patient and control groups in terms of DDST II test scores ($p < 0.001$).

When the patient and control groups were compared in regard to the DDST II subtest taking into consideration the normal, suspected, and abnormal scores; no significant difference was found between the two groups in terms of personal-social subtest scores ($p=0.100$). The rate of participants with suspected ($p < 0.001$) and abnormal ($p=0.024$) test scores in the language area were significantly higher in the patient group compared to the control group. In addition, the numbers of suspected patients both in fine and gross motor skills were significantly higher in the patient group compared to the control group ($p=0.001$, $p < 0.001$; respectively) (as indicated in Table II). There was a statistically significant negative correlation between the age of first seizure and language subtest scores in the patient group, and lower language scores were obtained as the age of the patient increased ($r=-0.319$, $p < 0.001$). No statistically significant difference was found between FC subtypes in terms of DDST II test

Table I. Demographic features of the patient and control groups.

		min-max	Mean±SD
First FC age (month)		3-65	19.5±11.5
		n	%
Gender	Girl	84	41.4
	Boy	119	58.6
FC subtype	Simple FC	163	80.3
	Complicated FC	22	10.8
	FC+	18	8.9
FC family history	Yes	69	34.0
	No	134	66.0
Epilepsy family history	Yes	38	18.7
	No	165	81.3
Treatment	Attack treatment	115	56.7
	Intermittent prophylaxis	26	12.8
	Continuous prophylaxis	61	30.0
	No treatment	1	0.5
Iron (Fe)	Deficiency	50	28.2
	Deficiency anemia	16	9.0
	Normal	111	62.7
		min-max	Mean±SD
Control group		4-74	27.8±15.1
		n	%
Gender	Girl	43	43
	Boy	57	57

FC: Febrile convulsion

Table II. The relationship between the patient and control groups in accordance with subtests; personal-social, fine motor skills, language, and gross motor skills scores.

	Group		p-value
	Patient (n=203)	Control (n=100)	
	Mean ± SD	Mean ± SD	
	Median [min - max]	Median [min - max]	
Personal-social	89.2±4.3	90.0±0.0	0.045
	90.0 [60.0 - 90.0]	90.0 [90.0 - 90.0]	
Fine motor skills	88.2±6.2	90.0±0.0	0.002
	90.0 [51.0 - 90.0]	90.0 [90.0 - 90.0]	
Language	85.6±8.5	90.0±0.0	<0.001
	90.0 [51.0 - 90.0]	90.0 [90.0 - 90.0]	
Gross motor skills	87.3±6.8	90.0±0.0	<0.001
	90.0 [64.0 - 90.0]	90.0 [90.0 - 90.0]	

results.

There were statistically significant differences between the patient and control groups in terms of all subtest scores and the results are shown in Table II. In the patient group, it was determined that only attack treatment was recommended to 115 (56.7%) children, intermittent prophylaxis to 26 (12.8%) children, and continuous prophylaxis to 61 (30.0%) children and no treatment was given to 1 (0.5%) child.

As there is a possibility that it can have an effect on developmental delay those patients with Fe deficiency and Fe deficiency anemia who were on continues Fe prophylaxis were removed from the group step by step and the statistical analysis was repeated. When the patients, who received continuous antiepileptic drug prophylaxis, were excluded from the patient group, this group still showed a statistically significant difference in the field of fine motor skills (p=0.001), gross motor skills (p<0.001), personal-social (p=0.038) and language (p<0.01) when compared with the control group (Table III). When the patients with

Fe deficiency and Fe deficiency anemia were excluded from the patient group, the results were similar (fine motor skills (p=0.009), gross motor skills (p<0.001), personal-social (p<0.086), and language (p<0.001) (Table IV). When both groups were excluded from the study group, the test results of the fine motor skills (p=0.003), gross motor skills (p<0.001), personal-social (p=0.148), and language (p<0.001) fields were still statistically significant compared to the control group (Table V).

Discussion

FCs are the most commonly observed seizures in children and seen more frequently seen in boys.⁴ In our study, the DDST II test and subtest results of 203 FC patients, of which 84 (41.4%) were girls and 119 (58.6%) were boys, were compared with the control group. The boy/girl ratio was reported as 1.⁴ by Knudsen¹⁴, and 1.3 in a study by Okumura et al.¹⁵ with 203 patients. In this study, boy/girl ratio was found as 1.4, which is consistent with previous

Table III. The relationship between the patient and control groups in accordance with subtests; personal-social, fine motor skills, language, and gross motor skills scores: excluding the continuous prophylaxis case.

	Group		p-value
	Patient (n=142) Mean ± SD (Median)	Control (n=100) Mean ± SD (Median)	
Personal-social	89.1±4.2 (90.0)	90.0±0.0 (90.0)	0.038
Fine motor skills	87.9±6.6 (90.0)	90.0±0.0 (90.0)	0.001
Language	85.1±9.1 (90.0)	90.0±0.0 (90.0)	<0.001
Gross motor skills	87.2±7.1 (90.0)	90.0 0.0 (90.0)	<0.001

Table IV. The relationship between the patient and control groups in accordance with subtests; personal-social, fine motor skills, language, and gross motor skills scores: excluding the Fe deficiency and Fe deficiency anemia case.

	Group		p-value
	Patient (n=137) Mean ± SD (Median)	Control (n=100) Mean ± SD (Median)	
Personal-social	89.4±3.6 (90.0)	90.0±0.0 (90.0)	0.086
Fine motor skills	88.6±5.6 (90.0)	90.0±0.0 (90.0)	0.009
Language	85.7±8.5 (90.0)	90.0±0.0 (90.0)	<0.001
Gross motor skills	87.7±6.3 (90.0)	90.0±0.0 (90.0)	<0.001

Table V. The relationship between the patient and control groups in accordance with subtests; personal-social, fine motor skills, language, and gross motor skills scores: excluding both the continuous prophylaxis and Fe deficiency and Fe deficiency anemia case.

	Group		p-value
	Patient (n=96) Mean ± SD (Median)	Control (n=100) Mean ± SD (Median)	
Personal-social	89.7±2.4 (90.0)	90.0±0.0 (90.0)	0.148
Fine motor skills	88.3±6.0 (90.0)	90.0±0.0 (90.0)	0.003
Language	85.4±8.8 (90.0)	90.0±0.0 (90.0)	<0.001
Gross motor skills	87.5±6.7 (90.0)	90.0±0.0 (90.0)	<0.001

studies.⁴ Although it was reported that the male gender may be a negative factor in the prognosis of FCs¹⁶, in the current study, no relationship could be found between gender and FC subtypes ($p=0.133$). The age range of FC has been reported differently in studies, the highest incidence occurring between 18-22 months.^{2,3} In the study of Okumura et al.¹⁵, the average age of the FC patients was 28 months (range, 6 to 71 months), and the youngest patient of this study was a 6-month-old.

In the current study, 163 (80.3%) of the 203 patients were found to have the simple FC, 22 (10.8%) had complicated FC, and 18 (8.9%) had FC+. The rate of complicated FCs was found as 23.8% by Şen et al.¹⁷, 35% by Shinnar et al.¹⁸, and 27.2% by Verrotti et al.¹⁹ In this study group, the rate of complicated FCs was slightly lower than those reported studies. The reason for the lower rate of complicated FCs rate determined in this study was attributed to the inclusion of some of the complicated patients to the FC+ group. In the literature, FC history in the family was reported between 25% and 40%.²⁰ The FC history in the family in the first-degree relatives was reported as 17, 34, and 26.6% by Wallace⁴, Özaydın et al.²¹, and Ling²², respectively. In the current study, the FC history in the family was found as 34% and epilepsy history in the family as 18.7% of the total patients. In this study, no significant relationship was determined between the FC subtypes and the history of FC and epilepsy in the family ($p=0.558$ and 0.708 , respectively).

The prognosis of infants and children with FC is usually good, and they are mostly neurologically and mentally normal. In a study with 398 FC children, Verity et al.²³ found that the academic performance, mental and behavioral differences of children with FC were similar to healthy children.²³ In the study of Leaffer et al.²⁴, it was stated that 159 patients who had a first FC did not show any difference in cognitive, motor, and adaptive behaviors compared to the healthy control group one month and one year later. On the other hand, neurologic sequelae such as cerebellar ataxia, dyspraxia, pyramidal findings, and late speech were observed during the following-up of a very low proportion of children with FC.^{25,26} Learning difficulty, reading difficulty, attention deficit, and behavioral problems were more frequently accoutered in contrast to other children.^{25,26} Bertelsen et al.²⁷ showed that the frequency of ADHD increased in children diagnosed with FC compared to the healthy control group. Weiss et al.²⁸ showed a decrease in receptive language and motor skill abnormalities in children with FSE compared to children with simple FC. In the present study, the number of patients having suspected and abnormal test results was statistically significantly higher than the control group ($p=0.01$). The rate of persons with suspected ($p<0.001$) and abnormal ($p=0.024$) test scores in the language area were significantly higher in the patient group compared to the control group.

Similarly, the patient group showed a developmental delay in the language ($p<0.001$),

FMS ($p=0.002$) and GMS ($p<0.001$) subtests compared to the control group, while no significant difference was found between the patient and control groups in the personal-social subtest (see Table II).

It was reported in the literature that FCs at an early age increase the risk of cognitive impairment.^{25,26} In the current study, we found a statistically significant and negative relationship between the mean age of the first seizure and the DDST II language subtest score, and the severity of neuromotor delay increased as the seizure age increased ($r=-0.319$, $p<0.001$). Since the results from the current study indicated a direct relationship between the seizure age and neuromotor delay and it is known that the neuromotor delay can be one of the most significant signs of epileptic seizures, it can be stated that the FCs starting at older ages may be associated with epileptic (unprovoked) seizures triggered by the fever.²⁹ The oldest patient in the study herein was 65 months old. Epilepsy is a disease that can be seen at any age during childhood and in the patient group of this study there may be patients that have not developed epilepsy yet. Hermann et al.³⁰ reported cognitive and language anomalies even before the onset of seizures in patients with idiopathic generalized epilepsy.

In the study of Kolfen et al.³¹, it was observed that a significant decrement was observed in the non-verbal intelligence of patients with prolonged FC compared to the patients with simple FCs and the control group. In patients with recurrent FC, poor performance was observed in all neuropsychological tests. In the study of Tsai et al.³² in patients with complicated FC, it was emphasized that these children had lower intelligence scores than the healthy control group. In our study, no significant neurodevelopmental difference was detected between the simple FC, complicated FC, and FC+ groups. However, DDST II is a neurodevelopmental screening test and in this study, no comparison was made with the control group with other neuropsychological tests.

It is suggested that low serum iron decreases the convulsion threshold, however, fever further increases this adverse condition and facilitates the occurrence of convulsion. Daoud et al.⁵ emphasized that the first FC was associated with low iron levels. In our study, we also found 28.2% Fe deficiency and 9% Fe deficiency anemia in the patient group. But the investigation and statistical evaluation related to the Fe deficiency and Fe deficiency anemia of the control group could not be performed due to ethical reasons. On the other hand, in the patient group included in our study, approximately 40% of Fe deficiency or Fe deficiency anemia indicates a possible relationship between Fe deficiency and FC. However, no statistically significant relation was found between Fe deficiency or Fe deficiency anemia and FC subtypes ($p=0.237$). Fe deficiency and Fe deficiency anemia are reported to affect neuromotor development negatively.^{33,34} Therefore, patients with Fe deficiency and Fe deficiency anemia were excluded from the study group and the statistical analysis was performed again. It was observed that there was a statistically significant difference between the groups in the areas of FM ($p=0.009$), GM ($p<0.001$), Language ($p<0.001$), and PS ($p=0.086$).

The use of continuous prophylaxis was determined as 30% in the patients of the current study group. In order to exclude the possibility of antiepileptic drug use affecting neurodevelopmental test results, patients who received continuous prophylaxis were excluded and statistical analysis was re-performed. It was determined that the patient group was lower in the FM ($p = 0.001$), GM ($p<0.001$), PS ($p=0.018$) and Language ($p<0.001$) subtypes than the control group.

Due to the fact that our study was retrospective, the patients included in the study were selected among the patients who applied to the hospital, and the lack of neuropsychological tests that could make more detailed comparisons reduced the strength of the study. Because our study subgroups had a smaller number of patients, the case selection bias risk cannot

be determined totally. On the other hand, in order to eliminate case selection bias, statistical analysis was performed again after excluding patients who received both Fe deficiency, Fe deficiency anemia, and continuous prophylaxis that could affect DDST II test results. According to the results obtained, it was revealed that the difference in PS ($p=0.148$) subtype scores disappeared. In addition, it was determined that p values of FM ($p=0.003$), Language ($p<0.001$) and GM ($p<0.001$) scores increased but statistically significant difference continued. Therefore, it was concluded that neuromotor development delay was due to FC rather than iron deficiency, iron deficiency anemia, or antiepileptic use.

The weaknesses of our study were 1) the fact that the DDST II is a developmental screening test, not a neurodevelopmental evaluation test, 2) lack of detailed neuropsychological test battery for neurodevelopmental evaluation, 3) retrospective and hospital-based study design, and 4) case selection bias risk due to a smaller number of patients in study subgroups. The strengths of our study were 1) although DDST II has normative data to interpret the patient's neurodevelopmental status we had a large control group for statistical analysis, 2) the total number of patients included in the study and 3) in order to eliminate the case selection bias risk, we used large exclusion criteria and detailed statistical analysis including exact test.

In conclusion, we found that patients with FC scored significantly lower in all subtest scores than the control group. In addition, we found that patients with FC had more suspicious and abnormal test results than the control group. Although FCs are generally known to have good prognosis, our study shows that they may pose a developmental risk, and children having FCs require the necessity for close clinical and developmental follow up. On the other hand, our study had a major limitation primarily being the retrospective nature of the study, and that there was no "pre-convulsion" developmental evaluation. To make a more definite decision about the developmental risk of FC, further

prospective long-term follow-up studies are needed with a detailed neuropsychological test battery.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: Rİ, MK, ÇÖ; data collection: Rİ, BGP, MÇD; analysis and interpretation of results: Rİ, KM, DDY, ÇÖ; draft manuscript preparation: Rİ, MK, ÇÖ. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of Mersin University (2020:2020/221).

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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