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Longitudinal assessment of skill development in children with first febrile seizure

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Abstract

To determine whether first febrile seizure (FS) has detrimental effects on development, 159 children (6 months to 5 years) with FS were compared to 142 controls on measures of cognition, motor ability, and adaptive behavior. Participants were identified through the emergency department in an urban, low income community. Children were evaluated within one month of the ED visit and one year later, and difference in performance over one year was examined. Performance did not differ between cases and controls on measures of cognition (baseline: p=0.5, one year: p=0.2, change over time: p=0.1) or motor skills (baseline: p=0.9, one year: p=0.7, change over time, p=0.6). The adaptive behavior composite score did not differ by FS case status at baseline (p=0.2) or one year later (p=0.6), however between group differences over time approached significance (p=0.05). Findings support that first FS does not pose more developmental or behavioral consequences than low socioeconomic environment.

Keywords

Febrile seizure; cognition; motor skills; adaptive behavior; children

Introduction

Febrile seizures (FS) are defined as “seizures occurring with a rectal temperature of 101°F (38.3°C) or higher in the absence of history of unprovoked seizures or concurrent central nervous system infection (1),” and occur in 2–5% of the population (2) between one month and six years of age. FS are defined as *simple*, brief non-focal convulsions lasting less than 15 minutes occurring once within a febrile illness (3), or *complex*, prolonged focal or recurrent convulsions lasting longer than 10 or 15 minutes within the same febrile illness (4) There is ongoing debate about the effects of a first FS on cognitive and motor development and adaptive behavior. Variations in study methodology, including population-based versus

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hospital-based studies, varying case definitions and inclusion/exclusion criteria, differences in outcome measures, timing of assessment after FS, or inadequate control for confounders, limit conclusive interpretations (5–12).

Major epidemiological studies of FS find no differences in intelligence, behavior, learning, or general abilities, including reading, comprehension, and arithmetic skill between children with and without FS (5–9), suggesting no adverse developmental consequences of a first FS. However, cases with reported abnormal development prior to FS were significantly different from their siblings in performance (5), indicating potential differences that preceded the first FS. Specifically, children with FS and prior abnormal development were more likely to have sleeping, hearing and speech problems compared to controls (6, 7). Studies comparing children with FS to controls reported worse behavior problems, and poorer visuomotor skills and arithmetic abilities in children with FS (10–12). Not all of these studies accounted for birth and medical history or for many environmental risk factors that may adversely affect the relationship between FS and subsequent development. Additionally, most of the studies assessed children a year or more after their first FS. The few with longitudinal designs (5–7, 9) assessed children years after their FS.

The Columbia Study of First Febrile Seizure examined cognitive, motor and adaptive behavior one month after the first FS and one year later in children with and without a first FS. We hypothesized that if FS has detrimental effects on long term development, we should see a decrease in performance on measures of cognition, motor and adaptive behavior compared to controls, from one month after the first FS to one year after, even after adjusting for risk factors for FS and poor developmental outcome.

Methods

A prospective cohort study of children with a first FS was conducted from March 1999 to April 2004 in the Morgan Stanley Pediatric Emergency Department at New York Presbyterian Hospital.

Subjects

Cases (N = 159) were identified through the ED as children who presented with a first FS, aged 6 months to 5 years. They were identified through screening logs in the ED and pediatric hospital discharge ICD-9 code 780.3. FS was defined as a “seizure occurring with a rectal temperature of 101°F (38.3°C) or higher in the absence of history of unprovoked seizures or concurrent central nervous system infection” (1). Controls (N = 142), aged 6 months to 5 years, who presented in the same ED with fever without a history of seizure and without devastating illness (e.g., cancer) were identified for study participation. Controls were frequency matched to cases by age, gender and time of year seen in the ED. We excluded one control whose family signed informed consent, because the family refused participation, and therefore did not receive any of the outcome measures.

Procedures

Once identified, the potential subject’s physician was notified and, with permission, families of FS patients were telephoned and offered participation in the study. Parents were consented and all children received a developmental evaluation one month after ED admission or after the presenting illness had resolved.

The institutional review board at Columbia University approved this study. Parents of enrolled children gave written informed consent.

Measures

Data collected at baseline included demographic, neurological, developmental, and behavioral dimensions of children with a first FS and controls. All interviews were conducted with at least one or both of the child's parents/guardians, mostly mothers (95.3%). Interviews were conducted in either English (41%, n =123) or Spanish (59%, n=177) depending on the participant's primary language. Seizure type was classified as simple or complex by a consensus of epileptologists, according to definitions presented above.

Outcomes—Outcome measures of cognition, motor skills, and adaptive behavior were obtained during developmental evaluation of the child at baseline and one year later. The Bayley Scales of Infant Development–Second Edition (Bayley-II) was given to children aged 1 month to 3 years. The Bayley-II measures mental and motor development and is individually administered with items suitable for the child's age. Two scores are derived; the mental scale and the motor scale (13). The Developmental Indicators for the Assessment of Learning–Third Edition (DIAL-3) was administered to children older than 3 years. The DIAL-3 is an individually administered assessment of language, concepts and motor skills (14). To assess cognitive development across all ages, we combined standard scores on the Bayley-II mental scale, with the average of the DIAL-3 concepts and DIAL-3 language scales. To assess motor development, we combined standard scores on the Bayley-II motor and DIAL-3 motor scales. For children born prematurely, standard scores on the Bayley-II were adjusted to reflect gestational age for children under 2 years of age at testing. Adaptive behavior was measured by parent report on the Vineland Adaptive Behavior Scales (VABS). This semi-structured interview assesses adaptive behavior across four domains including communication, daily living skills, socialization, and motor skills. The adaptive behavior composite was calculated from the standard scores of these four domains to obtain an overall measure of adaptive behavior (15). Standardized scores on all instruments have a population mean of 100, standard deviation of 15.

All measures were administered in either English or Spanish by a trained research assistant fluent in the language of administration, whose work was overseen by the study neuropsychologist (VJH). Data were collected and then double scored by a second independent rater to ensure reliability. Differences were resolved by consensus.

Potential confounders—Information on factors known to be strongly associated with developmental and behavioral outcome were collected during the interview with the child's mother. These variables were examined to see whether they were confounders. Additionally, mothers were administered the Peabody Picture Vocabulary Test (PPVT) or the Spanish version of the test, Test de Vocabulario en Imagenes Peabody (TVIP), to obtain a verbal IQ estimate (16, 17). In addition to the maternal estimated verbal IQ, the following factors were examined: FS, socioeconomic status (indexed by the family's income and household crowding defined as the number of people per room), mother's verbal intelligence on the PPVT/TVIP, breastfeeding duration, poor home environment (indexed by hours per week the child watched television and number of books in the home), Spanish as a primary language, delay in sitting, walking or talking, and neurological abnormality present since birth.

Statistical Analysis

Frequencies and percentages were used to summarize demographic characteristics and seizure phenomenology among children with a first FS and controls. Chi-squared tests were used for categorical variables and T-tests/ANOVA were used for continuous variables. Univariate linear regression models were used to assess factors known to be strongly

associated with outcome of developmental and adaptive functioning. An adjusted model was constructed using multivariable linear regression. For retention purposes, each variable significant at $\alpha = 0.10$ was included in the initial multivariable model. FS case status was retained in each model. Breastfeeding duration was log transformed as values were not normally distributed. All analyses were conducted via SAS 9.2 (SAS Institute, Cary, NC, U.S.A.).

Results

Of the 300 children included in this analysis, 159 were children with a first FS (cases) and 141 were children with fever and no prior history of seizure (controls). Median age of the 159 children with a first FS was 18.0 months (IQR=11.0) and 8.3% were born prematurely. Of the cases, 54.7% (N=87) were male and 84.3% (N=134) were Hispanic. Simple FS occurred in 65.8% (N=104) and complex FS occurred in 34.2% (N=54). Of those with a complex first FS, 51.9% (N=28) experienced seizure duration of greater than 15 minutes and 14.6% (N=23) had focal seizures. Median age of the 141 control children with fever and no prior history of seizure was 19.0 months (IQR=11.0) and 8.5% were born prematurely. Of the controls, 56.7% (N=80) were male and 90.1% (N=127) were Hispanic. More than 62.6% of the families in this study live below poverty level (defined as $23,050 for a family of four). There was no difference in demographic characteristics between cases and controls. Potential confounders were not associated with case status but were strongly associated with outcome, and therefore were retained in the model. Additionally, demographics did not differ from the children included in the cognitive and motor analyses and the VABS analysis (Table 1).

Between-group primary analysis

Cognitive and motor development—We assessed cognitive and motor development in 159 cases and 141 controls at baseline; and 143 cases and 134 controls at follow-up. Only cases and controls with both evaluations were included in the analyses (Table 2). Performance in these domains did not differ between cases and controls at baseline (Cognitive: p=0.5; Motor: p=0.9), one-year later (Cognitive: p=0.2; Motor: p=0.7), or in change over time (Cognitive: p=0.1; Motor: p=0.6). Decline in cognitive performance over time was greater in children with complex FS compared to simple FS (p=0.03), however motor performance over time did not differ by FS type (p=0.465). The remaining analyses of cognition and motor skills focus on the change over time.

Cognition: Multivariable linear regression produced a five-variable model that explained 9.7% of the variance in change over time in cognition. Decline in cognition over time was associated with a neurological abnormality present since birth (p = 0.05). Improvement in cognition over time was associated with number of books in the home (p=0.04), hours spent watching television (p=0.02), and delay in developmental milestones (p=0.01). FS case status retained in the final model was not statistically significantly associated with change in cognition from baseline to one year (p = 0.06).

Motor skills: Multivariable linear regression produced a three-variable model that explained 4.1% of the variance in change over time in motor skills. Improvement in motor skills over time was associated with a delay in developmental milestones (p = 0.007) and higher scores on the mother's PPVT (p = 0.02). FS case status retained in the final model was not statistically significantly associated with change in motor skills from baseline to one year (p = 0.5).

Adaptive behavior—We analyzed adaptive behavior in 141 cases and 135 controls whose parents completed the VABS at both time points (Table 2). Parent report of communication skills was worse in cases compared to controls at baseline only (p=0.02); none of the indices differed between cases and controls at follow-up. Additionally, children with simple compared to complex FS did not differ on any indices of adaptive behavior including communication (p=0.7), daily living skills (p=0.4), socialization (p=0.2), motor skills (p=0.7), or the adaptive behavior composite score (p=0.5). Change in performance on overall adaptive behavior was not associated with any of the potential confounders we explored; including FS case status that was retained in the final model (p=0.052).

Contrary to our hypotheses, the decline seen over time was greater in controls compared to cases in communication skills (p=0.004), daily living skills (p=0.047) and overall adaptive behavior (p=0.052).

Raw scores on the Vineland communication, daily living and socialization scales were examined to determine whether children lost skills over time. In both cases and controls, the VABS scale scores increased over time.

Communication: Multivariable linear regression produced a two-variable model that explained 5.3% of the variance in change over time in the communication index. Improvement in communication skills was associated with presence of FS case status (p = 0.006) and a delay in developmental milestones (p = 0.01).

Daily living: Multivariable linear regression produced a two-variable model that explained 3.1% of the variance in change over time in the daily living index. Improvement in daily living skills was associated with the presence of a delay in developmental milestones (p = 0.03). FS case status retained in the final model was not statistically significantly associated with the change in daily living skills from baseline to one year (p = 0.07).

Socialization: Multivariable linear regression produced a one-variable model that explained 1.2% of the variance in change over time in the socialization index. Improvement in socialization skills over time was associated with a longer duration of breastfeeding (p = 0.08). FS case status retained in the final model was not statistically significantly associated with social outcome (p = 0.98).

Motor skills: Multivariable linear regression produced a two-variable model that explained 2.5% of the variance in change over time in the motor skills index. Decline in motor skills was associated with a delay in developmental milestones (p = 0.007). FS case status retained in the final model was not statistically significantly associated with motor outcome (p = 0.3).

Within-group secondary analysis

Cognitive and motor development—Within group differences were identified in both groups. Cognitive performance in the cases significantly declined over time (p=0.0003) and motor performance in the controls significantly improved over one year (p=0.02) (Table 2).

At baseline, more than one third of both the cases and controls had cognitive scores greater than or equal to one standard deviation below the mean and 10.5% fell at least two standard deviations below the mean, suggesting delayed cognitive development prior to the first FS. One year later, half of cases and controls scored greater than one standard deviation below the mean and 9.5% fall at least two standard deviations below the mean in the cognitive domain.

Adaptive behavior—From baseline to one year later, declines were observed in both cases and controls on all indices of adaptive behavior ($p<0.0001$) (Table 2).

Discussion

Among these urban, low SES children residing in Northern Manhattan, New York City, we found no differences in cognition, motor skills and overall adaptive behavior between cases with a first FS and controls at baseline. Cognition, motor skills, and adaptive behavior were also comparable between cases and controls one year after their first FS. Moreover, there were no between group differences in change scores over time on any of the outcome measures. Thus, the findings do not support the hypothesis that there is a detriment in development following a first FS. Rather, these data indicate that the cases and controls performed similarly on developmental measures of cognitive, motor and adaptive behavior, both at the time of the first febrile event and over time. These findings are consistent with previous studies of first FS, documenting that a first FS does not pose increased risk for poor outcome in the developing child (5–9) and extend the period of time to one year after the first FS.

Over one year, performance for both groups declined in the cognitive domain and improved slightly in the motor domain. No between group differences were identified in the change over time analyses in these domains, again supporting the hypothesis that FS is not associated with an adverse developmental outcome. Within group differences were found in cognition in both cases and controls with declines in performance over time, however only the decline found in cases reached significance. Although the poor performance in cognition seen in both groups was greater than expected, the percentage falling two standard deviations below the mean did not change from baseline to follow up, demonstrating that the children with serious delays remained impaired over time. We found that change in cognition over time was the only outcome measure that was statistically significantly different by febrile seizure type, suggesting the mean decline over time in cognition was greater in children with complex FS compared to simple FS. From baseline to one year, greater decline in communication skills, daily living skills, and overall adaptive behavior was found in controls compared to cases. Analysis of raw scores showed that children do not lose skills over time but rather declined in performance on scaled scores. Significant within group differences were found on all indices of adaptive behavior with declines in both groups over time. Although we had hypothesized a greater developmental decline among cases compared to controls, the observed declines among controls were unexpected.

Compared to other studies which have shown delay in developmental milestones most strongly associated with decline in cognition (5, 18, 19), we failed to find this relationship. However, presence of delay was associated with the decline in communication, daily living and motor skills on the VABS, a parental report. Paradoxically, we found that delays in developmental milestones were associated with decline in motor skills assessed on the VABS, but they were associated with improvement in motor skills assessed by parents on the Bayley and DIAL. We have no explanation for the difference in relationship between developmental delay and direct testing of children versus parent report.

Our findings support prior studies that have demonstrated increased hours of television viewing, fewer number of books, and the presence of neurological abnormality present since birth may negatively affect cognitive outcome (5, 6, 20–29). We also found a strong association between breastfeeding duration and socialization in cases and controls, consistent with prior studies reporting more personal and social delay in children who were never breastfed compared to children who were breastfed for more than six months (30).

Performance on measures of cognition and adaptive behavior declined in both groups from baseline to one year, accounting for the absence of an effect of FS on these outcomes over time. We were able to identify other factors that were associated with change in function over time, including delay in developmental milestones, hours of television watching per week, number of books in the child's home, neurological abnormality present since birth, mother's verbal intelligence, and breastfeeding duration. These observations likely reflect the detrimental consequences of the impoverished, urban environment in which these children live. We also found that income was the only potential confounder that significantly differed by FS type, suggesting that children with complex FS are more likely to come from lower income households, which has been demonstrated in other studies (31). Extensive research has documented that low SES is associated with poorer developmental outcome (32–35), and it is possible that rate of skill acquisition among our population is slower than among the standardization samples for the measures used, as a consequence of their low SES. Our findings support the conclusion that contributing factors of SES may explain a greater proportion of the variance in cognition, motor skills and adaptive behavior than a first FS.

Our study was the first to look at risk factors for developmental outcome at one month and one year after a febrile episode with or without a first seizure. We identified potential risk factors for impaired development and adaptive behavior, suggesting an effect due to the impoverished community where these children live. This study provides further supporting evidence that FS does not place the child at increased risk for poor developmental and behavioral outcome in the year after the first FS in children from low SES communities.

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Highlights

- Development and behavior was examined in children with and without febrile seizure.
- Performance was examined at baseline, one year, and in change over time.
- No significant between group differences were found in cognition or motor skills.
- Between group differences in adaptive behavior over time approached significance.
- Findings support that a first FS does not pose immediate consequences in low SES communities.

Table 1

Demographics and seizure phenomenology in children with FS and controls.

	Total Enrolled Sample		Cognitive & Motor Analyzed Sample		Adaptive Behavior Composite Analyzed Sample	
	Cases (N=159)	**Controls (N=141)**	**Cases (N=143)**	**Controls (N=134)**	**Cases (N=141)**	**Controls (N=135)**
Age (in months)						
Median (IQR)	18.0 (11.0)	19.0 (11.0)	18.0 (11.0)	19.0 (11.0)	18.0 (10.0)	19.0 (11.0)
Range	6.0 – 57.0	7.0 – 56.0	6.0 – 57.0	7.0 – 56.0	6.0 – 57.0	7.0 – 56.0
Sex: N (%)						
Male	87 (54.7)	80 (56.7)	76 (53.2)	75 (56.0)	74 (52.5)	77 (57.0)
Female	72 (45.3)	61 (43.3)	67 (46.9)	59 (44.0)	67 (47.5)	58 (43.0)
Race/Ethnicity: N (%)						
Hispanic	134 (84.3)	127 (90.1)	124 (86.7)	120 (90.0)	122 (86.5)	121 (90.0)
Non-Hispanic	25 (15.7)	14 (9.9)	19 (13.3)	14 (10.5)	19 (13.5)	14 (10.4)
Income: N (%)						
Under $15,000	65 (43.0)*	60 (42.9)**	59 (43.7)†	55 (41.4)††	57 (42.9)‡	56 (41.8)‡‡
$15,000 & Over	86 (57.0)	80 (57.1)	76 (56.3)	78 (58.7)	76 (57.1)	78 (58.2)
Seizure Type: N (%)						
Simple	104 (65.8)***	NA	95 (66.4)	NA	95 (67.4)	NA
Complex	54 (34.2)	NA	48 (33.6)	NA	46 (32.6)	NA

*Income in cases N=151

**Income in controls N=140

***Seizure type N=158

†Income in cases N=135

††Income in controls N=133

‡Income in cases N=133

‡‡Income in controls N=134

Table 2

Cognition, motor skills and adaptive behavior in FS and controls on the Bayley, DIAL, and Vineland.

		Baseline: Mean (SD)	Follow-Up: Mean (SD)	Change over time: Mean (SD)
Febrile Seizure	**Development**	N = 143	N = 143	N = 143
	Cognition	90.0 (14.3)	84.6 (13.4)	−5.4 (17.4)
	Motor Skills	92.7 (14.8)	95.4 (14.0)	2.7 (17.8)
	Adaptive Behavior	N = 141	N = 141	N = 141
	Communication	96.3 (12.1)	90.3 (11.9)	−6.0 (13.0)
	Daily Living	99.2 (13.5)	93.0 (13.3)	−6.2 (14.2)
	Socialization	100.0 (12.7)	89.0 (13.9)	−11.0 (15.7)
	Motor Skills	100.6 (13.6)	92.2 (13.8)	−8.4 (14.3)
	Adaptive Behavior Composite	98.5 (13.8)	88.3 (12.7)	−10.1 (13.4)
No Febrile Seizure	**Development**	N = 134	N = 134	N = 134
	Cognition	88.7 (15.1)	86.5 (13.3)	−2.2 (16.6)
	Motor Skills	92.3 (14.4)	96.1 (15.7)	3.7 (17.7)
	Adaptive Behavior	N=135	N=135	N=135
	Communication	100.1 (15.9)	89.3 (15.0)	−10.8 (14.2)
	Daily Living	101.5 (14.4)	91.9 (12.4)	−9.6 (13.8)
	Socialization	101.0 (14.1)	90.3 (12.1)	−10.7 (14.5)
	Motor Skills	100.2 (12.1)	90.2 (14.8)	−10.0 (15.3)
	Adaptive Behavior Composite	100.7 (15.6)	87.6 (13.5)	−13.1 (12.7)