



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 (aged 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 the idea that first FS does not pose developmental or behavioral consequences in a low socioeconomic environment.

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1. Introduction

Febrile seizures (FSs) 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. Febrile seizures are defined as *simple*: brief, nonfocal convulsions lasting less than 15 min occurring once within a febrile illness [3], or *complex*: prolonged, focal or recurrent convulsions lasting longer than 10 or 15 min 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 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 studies with longitudinal designs [5–7,9] assessed children years after their first 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.

2. 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.

2.1. 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

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ICD-9 code 780.3. Febrile seizure was defined as a “seizure occurring with a rectal temperature of 101 °F (38.3 °C) or higher in the absence of a 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 as seen in the ED. We excluded one control because the family refused participation even though they signed the informed consent, and therefore, did not receive any of the outcome measures.

2.2. Procedures

Once identified, the potential subject's physician was notified and, with permission, families of patients with FS were telephoned and offered participation in the study. Parents 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 the enrolled children gave written informed consent.

2.3. 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 the definitions presented earlier.

2.3.1. 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 the 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 semistructured 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, with a 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.

2.3.2. Potential confounders

Information on factors known to be strongly associated with developmental and behavioral outcome was 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 Imágenes 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 presence of neurological abnormality since birth.

2.4. Statistical analysis

Frequencies and percentages were used to summarize demographic characteristics and seizure phenomenology among children with a first FS and controls. Chi-square tests were used for categorical variables, and T-tests/ANOVA was 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. Febrile seizure 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.).

3. 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). The 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 min, and 14.6% (N = 23) had focal seizures. The 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 the 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).

4. Between-group primary analysis

4.1. 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 than in children with simple FS ($p = 0.03$); however, motor performance over time did not differ by FS type

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