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Cognitive functioning one month and one year following febrile status epilepticus

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ABSTRACT

Objective: The objective of this study was to determine early developmental and cognitive outcomes of children with febrile status epilepticus (FSE) one month and one year after FSE.
Methods: One hundred ninety four children with FSE were evaluated on measures of cognition, receptive language, and memory as part of the FEBSTAT study and compared with 100 controls with simple febrile seizures (FSs).
Results: Children with FSE did not differ dramatically on tasks compared with FS controls at one month after FSE but demonstrated slightly weaker motor development ($p = 0.035$) and receptive language ($p = 0.034$) at one year after FSE. Performances were generally within the low average to average range. Within the FSE cohort, non-White children performed weaker on many of the tasks compared with Caucasian children. At the one-year visit, acute hippocampal T2 findings on MRI were associated with weaker receptive language skills ($p = 0.0009$), and human herpes virus 6 or 7 (HHV6/7) viremia was associated with better memory performances ($p = 0.047$).
Conclusion: Febrile status epilepticus does not appear to be associated with significant cognitive impairment on early developmental measures, although there is a trend for possible receptive language and motor delay one year after FSE. Further follow-up, which is in progress, is necessary to track long-term cognitive functioning.

1. Introduction

Febrile seizures (FSs) are relatively common seizures that occur, in association with a febrile illness (temperature greater than 38.4 °C) without concurrent central nervous system infection or acute electrolyte imbalance, in 2–4% of children [1–5]. Simple FSs are isolated, brief, generalized seizures, and complex FSs are focal, prolonged (greater than 10 or 15 min depending on definition) or multiple (more than one seizure during a febrile illness) [1–5]. Febrile status epilepticus (FSE) is a very prolonged FS lasting longer than 30 min [2–6]. Brief and/or simple FS is thought to be benign [3–5]. Febrile status epilepticus, however, can cause acute hippocampal injury leading to hippocampal sclerosis [6–9] and has also been causally linked to subsequent mesial temporal lobe epilepsy [6,9–11]. There is good evidence from epidemiological

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studies that complex FS and FSE are not associated with impairment of global intellectual function [12–14]. However, these studies did not specifically examine memory, a cognitive function subserved by the hippocampus, which is known to be impaired in mesial temporal lobe epilepsy [15,16].

The FEBSTAT study (Consequences of Prolonged Febrile Seizures in Childhood) is a prospective multicenter study following children from the time of their FSE episode with serial MRIs, EEGs, and neuropsychological testing [17,18]. It is designed to study the relationship between FSE and subsequent acute hippocampal injury, development of hippocampal sclerosis (HS), and later development of TLE. Memory and other cognitive functions are assessed, and a determination is made as to whether or not children are impaired even prior to the development of epilepsy [18]. In this report, we present the results of the cognitive testing at baseline and one year after FSE.

2. Methods

2.1. Participants

Two hundred and fourteen children met criteria for FSE and were enrolled in the FEBSTAT (N = 199) and the Columbia Study of Febrile Seizures (N = 15) studies. Characteristics of the overall samples can be found in Table 1. Comparison children with a first simple febrile seizure (SFS: N = 102) were drawn from the Columbia Study.

Of those enrolled, 187 FSE and 100 SFS children completed cognitive evaluations at one month, and 155 FSE and 89 SFS children completed evaluations at one year. Some children within the FEBSTAT cohort who did not complete one-month cognitive evaluation completed the one-year evaluation (12 children), while a percentage of the group completed one-month but not one-year evaluation (35 children). A small portion of the children were administered incorrect or inappropriate measures, and those were excluded from the analysis. As a result, a total of 182 one-month and 151 one-year FSE visits were used in this analysis. As some children were only able to complete one of the measures because of age or other limitations, individual numbers analyzed for each measure are included in each table as appropriate. We could not find any demographic or neurological differences between those children who had testing at one time point versus those who were seen for both one-month and one-year visits.

Briefly, the FEBSTAT study prospectively recruited 199 children with FSE from June 2003 through March 2010 from five academic medical centers across the United States. Eligible subjects were children aged 1 month to 5 years who presented with a first episode of FSE. Febrile status epilepticus was defined as a FS [3,19] lasting 30 min or longer, or repetitive FSs lasting at least 30 min without regaining alertness [20]. Children with prior afebrile seizures, acute CNS infection/insult, and/or known severe neurologic disability were excluded. The detailed methodology of assembling the cohort is described elsewhere [17,18].

The Columbia Study of Febrile Seizures [21] recruited 159 children with a first febrile seizure who received almost the same work-up as the FEBSTAT cohort at baseline and at one year. The seizure semiology and classification were all reviewed by the FEBSTAT phenomenology core and classified [18,21]. The majority of the Columbia cohort (90.6%) did not meet criteria for FSE but rather presented with a first simple FS (SFS) (64.2%) or a first complex FS that was not FSE (26.4%). The children with first SFS from the Columbia cohort have been used as controls for the FEBSTAT study for phenomenology and imaging [8,18] and are the controls in this analysis.

There was no significant difference in age or gender between the FSE and SFS groups, but the SFS group was significantly more Hispanic (89%) than the FSE population (29%; $p < 0.001$).

Table 1
Description of the FSE cohort at baseline.

	FSE cases (N = 214)	Simple FS controls (N = 102)
Mean age (months) (SD)	20.2 ± 12.7	22.0 ± 10.6
Median age (months) (IQR)	15.8 (12.0–23.2)	19.7 (15.8–25.03)
Sex (%)		
Male	111 (51.9)	59 (57.84)
Female	103 (48.1)	43 (42.16)
Mean duration of febrile seizure (min)	87.7 (70.1)	22.0 ± 10.6
Median duration of febrile seizure (IQR) (min)	70.0 (45.0–105.0)	3.00 (2.00–5.00)
Type of seizure (%)		
Continuous	121 (56.5)	102 (100.00)
Intermittent without full recovery	69 (32.2)	0 (0.00)
Intermittent with drug therapy	24 (11.2)	0 (0.00)
Focal seizure (%)		
Definitely	148 (69.2)	0 (0.00)
No (generalized)	66 (30.8)	102 (100.00)
Definite cerebral lateralization (%)		
Left	38 (17.8)	0 (0.00)
Right	29 (13.6)	0 (0.00)
No definite cerebral lateralization	147 (68.7)	102 (100.00)
Seizure classification (%)		
Generalized tonic–clonic	66 (30.8)	102 (100.00)
Complex partial only	4 (1.9)	0 (0.00)
Partial with secondary generalization	144 (67.3)	0 (0.00)
Prior development (%)		
Normal	183 (85.5)	100 (98.04)
Suspect	13 (6.1)	2 (1.96)
Abnormal	18 (8.4)	0 (0.00)
Baseline MRI findings (%)		
Any definite abnormality	140 (73.7)	79 (89.77)
Increased T2 signal in the hippocampus	50 (26.3)	9 (10.23)
HIMAL (%)		
No	140 (89.2)	79 (97.53)
Yes	17 (10.8)	2 (2.47)
HHV6 and HHV7 (%)		
No	111 (65.7)	NA
Yes	58 (34.3)	NA
Acute T2 signal		
No	140 (88.6)	102 (100.00)
Yes	18 (11.4)	0 (0.00)
Baseline EEG findings (%)		
Any abnormality	108 (54.3)	NA
Epileptiform abnormality	91 (45.7)	NA

NA — not applicable.

2.2. Procedures

Once identified, the children and their parents were recruited within 72 h. Written informed consent was obtained from the parents in all cases. Clinical data was collected, and the child received a neurological evaluation, EEG, MRI, and blood work (including serum to assay HHV6/HHV7 centrally for viremia or reactivation). One month later, the child was scheduled for a neuropsychological assessment and was once again evaluated by a neurologist. At that time, additional blood work and parental behavioral rating scales were completed. Neuropsychological assessment, EEG, MRI, neurological evaluation, blood work, and behavioral rating scales were repeated one year after initial evaluation. The children in the Columbia cohort also received imaging at baseline and one year using a similar imaging protocol as well as cognitive testing at baseline and one year but did not have EEGs or virology testing [18,21].

All procedures were approved by institutional review boards for the protection of human subjects at all the participating institutions.

2.3. Measures

Given the young age of the children at their one-month visit (median age 17 months) and one-year visit (median age 29 months), the test battery was designed to assess general development and