

# Total Cerebral Volume Is Reduced in Patients With Localization-Related Epilepsy and a History of Complex Febrile Seizures

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**Context:** Febrile seizures may lead to later epilepsy. They have been associated with hippocampal atrophy but their effect on total cerebral volume is unknown.

**Objective:** To compare total cerebral volume in patients with mesial temporal lobe epilepsy with and without a history of complex febrile seizures (CFS).

**Design:** Survey.

**Setting:** Epilepsy monitoring center.

**Subjects:** Forty patients with localization-related epilepsy and temporal lobe onset determined by video electroencephalogram and 20 controls.

**Intervention:** Magnetic resonance imaging measurement of cerebral volume.

**Main Outcome Measure:** Total cerebral volume.

**Results:** Patients with a history of CFS had significantly reduced total cerebral volume compared with patients without CFS. In addition, male patients with CFS had significantly lower total cerebral volume than male normal controls. There was no significant difference between patients without CFS, or all patients, and controls.

**Conclusion:** Complex febrile seizures may have a global effect on brain development.

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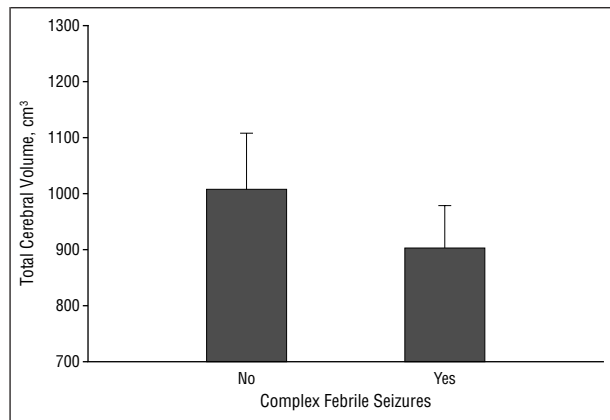
**H**IPPOCAMPAL formation (HF) atrophy is a common finding on magnetic resonance imaging in patients with complex partial seizures (CPS), and is one of the imaging hallmarks of mesial temporal sclerosis. The presence of atrophy is a reliable marker of the epileptogenic zone and is associated with a history of complex or prolonged febrile seizures (CFS), seizures associated with fever occurring before the onset of afebrile seizures and lasting longer than 15 minutes, with focal features or followed by transient or persistent neurologic abnormalities.<sup>1-5</sup> Epilepsy duration, the total number of generalized tonic-clonic seizures (GTCS), and perhaps complex partial seizures, are also significantly associated with increasing HF, but CFS appears to be the strongest factor.<sup>1,3,4</sup> These are much more likely to be associated with later epilepsy as well, as some studies have shown.<sup>5</sup>

Animal and human evidence suggest persistent effects of childhood febrile seizures on the brain. In immature rats, CFS induce transient structural changes in hip-

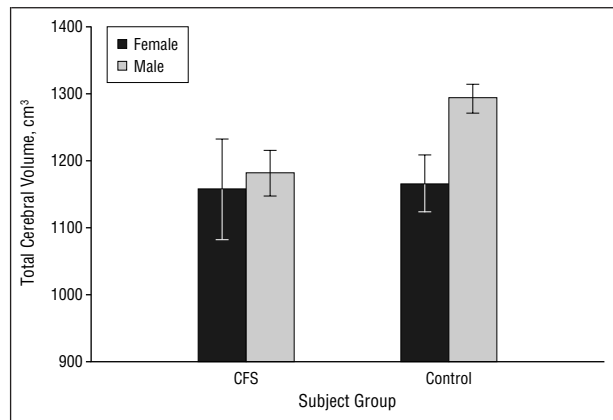
poampal pyramidal neurons and long-term functional changes of hippocampal circuitry.<sup>6</sup> Some clinical studies suggest that febrile seizures may have behavioral and neuropsychologic consequences in addition to epilepsy. In the National General Practice Study of Epilepsy, children in the febrile seizure cohort, particularly those with multiple or a first CFS, were more likely than controls to develop neurologic sequelae as well as nonfebrile seizures.<sup>7</sup> Children with CFS had lower nonverbal intelligence and more behavioral problems than those with simple febrile seizures or controls; multiple febrile seizure recurrences reduced overall neuropsychologic test performance.<sup>8</sup> A study that found no difference in performance at age 10 years between patients with and without a history of febrile seizures reported that special schooling was required for more children who had febrile convulsions in the first year of life than for those who had them later in life.<sup>9</sup>

Some studies have not found a strong effect of febrile seizures on HF atrophy or a specific association with temporal lobe seizures as opposed to epilepsy in gen-

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**Figure 1.** Comparison of total cerebral volume in patients with and without a history of complex febrile seizures.



**Figure 2.** Comparison of total cerebral volume between patients with a history of complex febrile seizures and controls.

eral.<sup>7,10-13</sup> It is possible that CFS may have a more global deleterious influence, extending beyond the HF. To investigate this potential effect, we used magnetic resonance imaging to measure total cerebral volume in 40 patients with uncontrolled seizures and 20 controls.

## METHODS

### SUBJECTS

We determined the history of CFS, epilepsy duration, frequency, and lifetime number of seizures for CPS and GTCS, separately, by reviewing medical records for multiple hospitalizations and follow-up outpatient visits. All of the patients had epilepsy of temporal lobe onset confirmed by ictal video-electroencephalogram telemetry and appropriate clinical imaging studies. Ten patients had a right, and 30, a left, temporal focus. Twenty right-handed controls (13 were male) with normal physical and neurologic examination results and no history of chronic illness were studied as well. Nineteen patients were female and 21, male. The mean ± SD age of patients with and without a history of CFS and controls did not differ ( $35.0 \pm 6.9$  years vs  $34.7 \pm 11.2$ ,  $36.1 \pm 8.8$  years, respectively).

### MAGNETIC RESONANCE IMAGING

Cerebrospinal fluid–corrected total cerebral volume was measured on a 1.5-T Signa scanner (GE Medical Systems, Milwaukee, Wis), using previously described methods.<sup>14,15</sup> Contiguous 2-mm thick slices were acquired using repetition time, 24; echo time, 5; and flip angle, 45. Images were analyzed using the Medical Imaging Retrieval Analysis and Graphics package (National Institutes of Health, Bethesda, Md). The brain was outlined at the pia-arachnoid junction in successive slices to the level of the cervicomedullary junction. Gray-white matter subsegmentation was not performed. Systat (SSPS Inc, Chicago Ill) was used for statistical comparisons. Data are given as mean ± SD unless otherwise indicated.

## RESULTS

Patients with CFS had reduced total cerebral volume compared with patients without CFS ( $901 \pm 71$  cm<sup>3</sup> vs  $1007 \pm 99$  cm<sup>3</sup>;  $P < .002$ ) (**Figure 1**). As expected, males had larger brains than females ( $1021 \pm 96$  cm<sup>3</sup> vs  $941 \pm 97$  cm<sup>3</sup>;  $P < .02$ ). There were 4 females and 5 males in the CFS-positive group, and 15 females and 16 males in the CFS-

negative group. In an analysis of variance, CFS remained a significant factor ( $F = 10.49$ ,  $P = .003$ ), but not sex ( $F = 2.81$ ) or the interaction term ( $F = 1.18$ ). There were no significant differences between patients with and without a history of CFS in GTCS number, duration of epilepsy, age at onset, or age at scan.

There was a trend ( $.05 < P < .06$ ) for patients with a history of CFS to have smaller brains than controls. This was significant for male patients in comparison with male controls ( $913 \pm 52$  vs  $1001 \pm 58$ ;  $P < .02$ ) (**Figure 2**) but not female patients vs female controls. There was no significant difference between patients without CFS, or all patients, and controls. The number of GTCS or CPS did not correlate with total cerebral volume, nor did epilepsy duration or the number of years since the first GTCS, the age at GTCS onset, or the age at epilepsy onset.

We also measured right and left lateral temporal, hippocampal, and thalamic volumes. Patients with CFS had significantly smaller left lateral temporal and left hippocampal regions. There were nonsignificant trends toward reduced right lateral temporal, hippocampus, and right and left thalamus.

As in our previous study, there was a significant relationship between ipsilateral HF volume and epilepsy duration ( $P < .02$ ). Patients with CFS had significantly smaller HF ipsilateral to the electroencephalogram–indicated focus than patients without CFS ( $2.16 \pm 0.45$  vs  $2.84 \pm 0.60$ ;  $P < .003$ ).

Neuropsychologic evaluation showed no difference in Wechsler memory and intelligence verbal or performance scale results between patients with and without CFS. There was a significant interaction between CFS history and side of focus for the Boston Naming test ( $F = 3.16$ ;  $P < .05$ ): patients with CFS with a right temporal focus had lower test scores than patients without CFS with a right temporal focus. Overall, patients with a left temporal focus had significantly lower Boston Naming scores than patients with a right temporal focus.

## COMMENT

We found that patients with a history of CFS had lower total cerebral volume than those who did not. We did not find an effect of epilepsy duration or of GTCS his-

tory on total cerebral volume. It is possible that separation into gray and white matter moieties or correction for intraventricular volume might reveal an effect. Moreover, the mean number of lifetime GTCS among our patients was only 8, which might account for the failure to find an effect that others have detected for the HF.<sup>1,4</sup> Our study was retrospective and sample size may have affected the results as well. However, it is more likely that epilepsy duration and seizure number would have only a small influence on the total adult cerebral volume in contrast with the HF ipsilateral to the epileptic focus.

Extrahippocampal temporal lobe, frontal, and thalamic volume reduction has been reported previously in patients with HF seizure onset. Moran et al<sup>16</sup> found no effect of febrile seizures on extra HF temporal atrophy but may not have distinguished between simple and CFSs.<sup>17,18</sup> We did not find a significant effect on the thalamus in our previous study, possibly owing to the smaller number of subjects studied.<sup>15</sup> It is possible as well that the effect of CFS outside the epileptic HF is small and only appears when the entire brain is studied.

Lee et al<sup>18</sup> reported that total brain size was lower in patients with temporal lobe epilepsy than in controls but did not note an effect of febrile seizure history. A recent study of a large group of children with a mean age of 8 years found a nonsignificant effect of simple febrile seizure but not CFS on total brain volume.<sup>19</sup> Szabo et al<sup>20</sup> did not report any effect of febrile seizure on the whole brain in children younger than 6 years. Reduced brain size may more likely be a consequence of CFS rather than a characteristic present at the onset of CFS. It is possible that the effect we found might not become apparent until patients have attained full growth.

One study reported that men might be more vulnerable to hippocampal damage from seizures than women.<sup>21</sup> Our results are consistent with that finding, since only men with CFS had significantly lower total cerebral volume than controls. Our finding of reduced whole brain volume in patients with CFS needs to be confirmed by additional studies. The presence of a correlation does not provide evidence of a causal relationship. In our study, patients with a history of CFS did not have lower scores on neuropsychologic tests except for the Boston Naming. These tests can be influenced by several factors, such as seizure frequency and antiepileptic drug therapy. However, our results do suggest a possible global effect of CFS on brain development that is consistent with some reports of impaired cognitive function and forms of epilepsy in addition to complex partial seizures of temporal lobe origin.

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