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Warming Up to the Notion That Febrile Seizures Can Be Associated With Cognitive Impairment

Cognitive Impairment Following Experimental Febrile Seizures Is Determined by Sex and Seizure Duration

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Background: Febrile seizures are the most common type of seizures in children. While in most children the outcome is favorable, children with febrile status epilepticus may exhibit modest cognitive impairment. Whether children with other forms of complex febrile seizure, such as repetitive febrile seizures within the same illness are at risk of cognitive deficits is not known. In this study, we used a well-established model of experimental febrile seizures in rat pups to compare the effects of febrile status epilepticus and recurrent febrile seizures on subsequent spatial cognition and anxiety. Methods: Male and female rat pups were subjected to hyperthermic seizures at postnatal day 10 and were divided into groups of rats with continuous seizures for $\geq$40 min or recurrent febrile seizures. They were then tested as adults in the active avoidance and spatial accuracy tests to assess spatial learning and memory and the elevated plus maze to measure anxiety. Results: Febrile status epilepticus rats demonstrated impaired spatial cognition in active avoidance and spatial accuracy and exhibited reduced anxiety-like behavior in the elevated plus maze. Rats with recurrent febrile seizures did not differ significantly from the controls on any measures. There were also significant sex-related differences with females with FSE performing far better than males with FSE in active avoidance but demonstrating a navigational learning impairment relative to CTL females in spatial accuracy. However, once learned, females with FSE performed the spatial accuracy task as well as CTL females. Conclusion: There is a duration-dependent effect of febrile seizures on subsequent cognitive and behavioral outcomes. Febrile status epilepticus resulted in spatial cognitive deficits and reduced anxiety-related behaviors whereas rats with recurrent febrile seizures did not differ from controls. Sex had a remarkable effect on spatial cognitive outcome where males with FSE fared worse than females with FSE. The results demonstrate that sex should be considered as a biological variable in studies evaluating the effects of seizures on the developing brain.

Commentary

Febrile seizures (FS) are the most common seizure type in children.[1] Febrile seizures usually occur only in the context of fever during an age-specific window early in life—typically 1 to 5 years of age. Febrile seizures are divisible into 2 types: simple and complex. Simple FS are generalized from onset, brief (<15 minutes), and occur once during a febrile illness. An FS is termed complex if it has a focal onset, if more than one FS occurs during a febrile illness (recurrent FS [RFS]), or if it is prolonged (>15 minutes).[2] Febrile status epilepticus (FSE) comprises a subset of prolonged FS when seizure duration exceeds 30 minutes.[3] It is presumed that most FS are benign and incur no lasting neurological or cognitive sequelae but complex FS carry a higher risk for the later development of epilepsy and long-term cognitive impairments, especially following FSE.[4] Febrile status epilepticus also portends a higher risk of temporal lobe epilepsy.

In principle, any seizure, even a FS, could adversely affect brain development and neuronal circuit function.[5] Numerous animal studies have investigated whether experimental FS are associated with subsequent cognitive or behavioral impairments.[6] While several aspects of human FS can be mimicked in animal models, some questions remain unanswered.[7] Most studies of experimental FS, including the present one[8] utilize hyperthermia as a surrogate for actual fever, which can be difficult to induce in a rodent. Yet, even in humans, it is not clear whether fever itself or the illness-induced signaling changes or inflammation "cause" the FS.[9] In addition, it is unknown whether the number, duration, or cumulative seizure burden in FS might lead to subtle sequelae that cannot be assessed adequately in animals. Tests used by investigators to examine cognitive consequences of FS vary widely, and some are not sufficiently sensitive, being limited in rodents to non-language cognitive domains. Spatial learning and memory have

Table 1. Results of Cognitive Testing in Experimental Groups Compared With Controls.

Experimental group	Active avoidance test	Elevated plus maze	Spatial accuracy test (females only)
Febrile status epilepticus (FSE)	Impaired spatial cognition (males worse)	Decreased anxiety (especially females)	Impaired spatial cognition; FSE females learned task slower but once learned, did not differ from controls
Recurrent febrile seizures (RFS)	No difference	No difference	No difference

most often been assayed using hippocampus-based tests such as the Morris water maze. Other cognitive domains are harder to assess in both animal models and humans. In children, FS occur at an age when neuropsychological assessments are limited, and more accurate and comprehensive cognitive tests (especially verbal and language-based tests) need to be performed at older ages.[4]

Kloc and colleagues[8] investigated whether outcomes differed between normothermic control rats versus those that had undergone FS. At postnatal day (P)10, experimental rats underwent 60 minutes of hyperthermia induced by a heated air stream in an enclosed chamber, during which the semiology (freezing/chewing), duration, and number of seizures were recorded. Based on those observations, the rats were allocated post hoc into a continuous seizure group (FSE) in which rats experienced FSE for an average of 31 minutes or an intermittent recurrent seizure group (RFS) in which seizures were short and distinct but repetitive. As adults (starting around P50), animals underwent cognitive testing.

The sophisticated cognitive tests employed by Kloc and colleagues[8] assayed unique aspects of spatial cognition or anxiety. First, the hippocampus-dependent "active avoidance test" pairs an aversive stimulus (mild shock) with the animal's location in a defined region on a rotating disk. Rats are trained to avoid this vulnerable region. The authors found that animals that had undergone FSE performed significantly worse (spent more time in the shock zone) than controls or those with RFS. Notably, males performed significantly worse than females across groups on this test.

Because anxiety could have played a role in the active avoidance test results, the authors next utilized the elevated plus maze test of anxiety. Interestingly, they found that FSE rats demonstrated significantly *less* anxiety than control and RFS rats. The anxiety level of female FSE rats was significantly lower than males. The authors concluded that the lower anxiety level in female FSE rats contributed to their better post-FSE spatial cognition performance.

Finally, a third task, the "spatial accuracy test," pairs appetitive operant reward with a circumscribed region of space in a stationary arena. This test has the advantage of having both hippocampus dependent and independent components. Only female rats completed this task; as males avoided participation by remaining motionless along the chamber wall (thigmotaxis), precluding analysis. Among females that completed the test, those with FSE took significantly longer than controls to learn the task, but once they learned it, there were no differences between the FSE group and controls. Thus, the spatial accuracy test uncovers a subtle, sex-specific learning impairment that could be overcome with training and was not revealed by the earlier active avoidance task.

Results are summarized in Table 1. Rats that underwent FSE had significantly impaired performance on the hippocampus-dependent active avoidance task, and this effect was more notable in male rats. Female rats had less anxiety in the elevated plus maze and demonstrated deficits on the spatial accuracy test compared to controls that could be overcome with training. Therefore, these results add to the accumulating literature that FS duration has a profound impact on cognitive deficits, in a sex-specific manner. Strengths of this study include the unique quantitation of spatial cognition that correlates, to some extent, with cortical region. The post hoc assignment of rats to the FSE or RFS groups must be interpreted with caution, as this allocation was not based on EEG seizure data and number of subjects was relatively modest. The inability of males to participate in the spatial accuracy task, whether from anxiety, fear, or another reason, leaves open the question of whether FS are more impairing in males as a function of FS duration.

Some important questions emerge from these results. Why would a rat (or a child) develop FSE as opposed to RFS, and is this distinction significant clinically? If so, is it attributable to genetic, developmental, or environmental factors? As the authors caution, the choice of test matters! The conclusion as to whether FS lead to cognitive impairments depends on whether the test focuses on spatial cognition, social interaction, memory, language, and so on.[4] Recurrent febrile seizures might cause subtle cognitive effects even though the cognitive tests employed here failed to reveal deficits. Indeed, in a previous study of cognition in rats that had only RFS, there were no deficits on the active avoidance test but signaling efficacy abnormalities were found in the CA1 region.[10] In studies of FSE sequelae, in both humans and animals, a wide range of behavioral tests needs to be employed. An unresolved question is whether the order of cognitive and anxiety testing plays a role, especially with regard to the poorer performance of males.

These results must be considered in the context of human research on FSE, particularly those emerging from the FEBSTAT study, in which initial hippocampal signal changes could be detected on MRI scans, indicating a substrate for future cognitive or epileptogenic changes.[11] In data not yet published in full, visual memory scores 5 to 10 years after FSE appear to be higher in females.[4] In concept, even brief seizures, whether induced by fever or not, could disrupt neuronal circuit function in adverse manner.[5,10] The work by Kloc and colleagues aims

to elucidate the network circuit dysfunction following FS, that is, what degree or type of hippocampal pathophysiology is sufficient to engender cognitive deficits?

Ultimately, the clinical question is whether treatment, either acutely or prophylactically, would alter the consequences of the various forms of FS. While this study does not directly address that issue, it does provide further evidence that subtle cognitive impairments can occur following FS, underscoring the urgency of averting prolonged FS. However, even briefer FS could portend neurological consequences. Fortunately, the vast majority of children outgrow FS without overt significant sequelae. Findings such as those of Kloc and colleagues suggest that even those children who appear to have escaped negative consequences of FS might benefit from neuropsychological testing or even intervention trials if scholastic or behavioral concerns arise.

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Declaration of Conflicting Interests

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