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Review Article

Febrile Seizures, Ongoing Epileptiform Activity, and the Resulting Long-Term Consequences: Lessons From Animal Models

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ABSTRACT

Febrile seizures affect 2% to 14% of children. Prospective studies indicate that following a relatively prolonged febrile seizure there are long-term consequences. Although controlled experiments in children have ethical limitations, nonhuman animal models give us the ability to discover new phenomena, determine their mechanisms, and test treatments that can potentially translate to the human clinical population. Rat models of febrile seizures show two temporally distinct phases: (1); behavioral seizures and (2); ongoing epileptiform activity associated with hyperoxia. The behavioral seizures mimic those displayed by children including tonic-clonic convulsions and loss of postural control. Recordings show classic spiking discharges from cortical regions during the behavioral seizures. Following behavioral seizure termination electrical recordings in rodent models reveal that there is ongoing epileptiform activity that lasts longer than the duration of the behavioral seizures themselves. This ongoing epileptiform activity is also associated with hyperoxia—levels of brain tissue oxygen well above the normoxic zone (typical oxygen levels)—and can last more than an hour. When this hyperoxia, but not the epileptiform activity, is prevented in febrile rat pups the long-term learning impairments are also prevented. This leaves important questions unanswered, "Do children also have ongoing and long-lasting epileptiform activity and associated hyperoxia following termination of their febrile behavioral seizures and does this second phase have long-term consequences"? Here we discuss appropriate animal models of febrile seizures that replicate much of the human condition with special attention to the long-term effects of occult epileptiform activity following termination of a behavioral febrile seizure.

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Introduction

Febrile seizures are the most common childhood convulsive event, with anywhere from 2% to 14% of children having one in their lifetime, with the varying prevalence dependent on location in the world.[1-4] Febrile seizures typically occur in children aged six to 60 months, when a child has a viral or bacterial infection that typically causes a fever above 38°C (101°F).[5] By definition, febrile seizures are not due to a central nervous system infection, such as meningitis or an electrolyte imbalance, which in of themselves can cause a seizure.[1,6,7] Febrile seizures are clinically classified into simple, complex, or febrile status epilepticus; however, there is ongoing discussion regarding the usefulness of these definitions and the differentiation between the categories. The International League Against Epilepsy removed the terms simple and complex from their seizure terminology in 2010[8]; however, many febrile seizure researchers today still use this language. Simple febrile seizures are single, isolated events with generalized symptoms that can last up to 15 minutes.[2] Complex febrile seizures last anywhere from 15 to 30 minutes and are characterized by focal symptoms and/or more than one seizure occurring within 24 hours during the same infection, with or without the child regaining consciousness between seizures.[2] Febrile status epilepticus lasts longer than 30 minutes[9] and accounts for one quarter of pediatric status

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epilepticus and two thirds of status epilepticus cases in children under two years.[10]

Although it is understood that febrile seizures are precipitated by an infection,[5] the mechanism of seizure generation is likely multifactorial and not fully elucidated.[11] It is possible that febrile seizures result from a patient-specific, complex interplay of multiple factors such as genetic susceptibility, run-away inflammation, abnormalities in thermoregulation, fever-induced respiratory alkalosis, and the direct effect of fever on cerebral excitability, all occurring on the background of the hyperexcitability of the immature brain.[11]

Regarding genetic susceptibility, although 60% to 75% of children who express febrile seizures likely do not have a family history,[12] some genes related to febrile seizures have been identified. A large genome-wide study implicated genes involved in the febrile response and neuronal excitability, but this was rare.[13] Before this study, variants in SCN1A have been described in patients with generalized epilepsy with febrile seizure plus.[12] Genetics may exacerbate or potentiate febrile seizures, but it is clear that genes are not the only mechanism involved in febrile seizure genesis and, as such, further research is needed to appreciate other predisposing factors for the seizure and the long-term consequences following seizure termination.

Why do we need to study febrile seizures?

Many children with febrile seizures will have a benign outcome, but the risk of subsequent epilepsy dramatically increases in those with recurrent (more than three) febrile seizures or with febrile seizures with atypical features including those with febrile status epilepticus.[14,15] Even a single febrile seizure, especially in infancy, can have a long-term cognitive impact, and data are mounting that febrile seizures lead to an increased risk of attention-deficit/hyperactivity disorder and other neuropsychiatric symptoms.[16-18]

Risk factors for subsequent epilepsy following febrile seizures include a family history of epilepsy, the presence of neurodevelopmental disabilities, and a febrile seizure with complex features.[15,19,20] The greater the number of complex features a febrile seizure has, the greater the chance of developing subsequent epilepsy.[19,20]

FEBSTAT, a large, mulicenter study of children with a history of febrile seizures and healthy controls, was conducted to expand upon the current literature of febrile seizures. These studies found a trend for weaker language and motor development[21] and an increased risk for a secondary febrile status epilepticus event after initial febrile status epilepticus.[22] A subset of febrile children also had impaired hippocampi growth one year after the febrile event[23] and hippocampal abnormalities five days following a prolonged febrile seizure.[13]

Prophylactic treatments for febrile seizures are limited, antipyretics are largely ineffective, and antiseizure drugs given for the initial febrile seizure do not prevent the later development of epilepsy.[24,25] Nonsteroidal anti-inflammatory drugs and conventional antiseizure drugs are also ineffective, although there is slight evidence to support the use of clobazam or levetiracetam as potential prophylactic treatments.[26] Benzodiazepines may be effective in preventing recurrences, but the adverse effects from benzodiazepines occur in up to one third of children, limiting the effectiveness and recommendation of widescale use.[14,26]

How do we best model febrile seizures in rodents?

Through the years rodent (rats and mice) models of febrile seizures have been refined to provide enhanced face validity. However, unlike children, rodent pups do not display spontaneous febrile seizures, and thus they must be induced. In early experiments febrile seizures were induced using exogenous heat.[27,28] The application of exogenous heat causes the internal temperature of the rodent to rise and induces a multiplicity of changes that can lower febrile seizure thresholds. Following upward of 10 minutes of heating rats typically show stereotyped behavior of mouth myoclonus, followed by hindlimb clonus, and then finally a fully generalized convulsion.[27-29] It is at this point that pups are removed from exogenous heat and returned to room temperature. During the behavioral seizure there is concurrent ictal electrographic activity.[29-31] Once the behavioral seizure terminates rats will locomote, although they are somewhat lethargic.

Rodents do not have febrile seizures upon exposure to an infectious agent naturally, and using exogenous heat to induce febrile seizures in rodents is an obvious confounder. As children with febrile seizures have an underlying immune challenge, more accurate rodent models of febrile seizures have been utilized that involve the administration of the endotoxin lipopolysaccharide (LPS) coupled with the application of heat or a chemoconvulsant to induce the seizures.[32,33] This method for inducing febrile seizure in rodents allows for studies to investigate the impact of the underlying proinflammatory state on the expression and mechanisms of febrile seizures, recognizing that febrile seizures occur most commonly following a viral or bacterial infection.[5,34]

LPS is a component of the cell wall of gram-negative bacteria and causes an immune response. In brief, LPS binds to LPS-binding protein, which shuttles it to Toll-like receptor-4 (TLR4).[35] TLR4 then forms a complex with CD14, which has many downstream targets, including the production of proinflammatory cytokines.[36] These immune pathways were reviewed in depth by Mosili and colleagues in 2020.[37] One of the most important actions of LPS is the downstream elevation of interleukin-1β. Interleukin-1β is a crucial molecule in febrile seizure initiation as well as the later development of epilepsy.[11,38] Through these downstream mechanisms LPS causes a slight increase in rodent body temperature[33] and allows pups to seize with less exogenous heat application.[39,40] The advantage of the LPS model is that it results in an inflammatory response involving crucial molecules without injecting a live pathogen and decreases the exogenous heat required to induce a febrile seizure, which allows the human condition to be more closely mimicked.[41]

Although the injection of LPS in rodents slightly raises their body temperature, the application of exogenous heat is not the same as a true fever in children. Clinical febrile seizures are not due to the external environment being too warm and the child unable to thermoregulate. Since both humans and rodents are endothermic (internally generated heat) homeotherms (relatively constant body temperature), they have a specific set point for optimal homeostatic and cellular functions (for in depth review see[42]). When environmental temperature increases, causing core body temperature to increase above the thermoneutral zone, various behaviors occur to decrease temperature and include escape behaviors, increased breathing rate (panting), and sweating in people or grooming in rodents.[42] These responses are fundamentally different than a fever in which the body is trying to raise the internal temperature to fight an infection. Children are considered to be less effective at thermoregulation than adults (reviewed in[43]), and this may be a modulating factor on the induction of febrile seizures. Although exogenous heat is still necessary to cause a febrile seizure in rodents, LPS creates an inflammatory environment and allows for the application of less exogenous heat, better modeling the human condition.

A suitable and ecologically valid nonhuman animal febrile seizure model needs to have low or no morbidity, a similar seizure threshold, internal temperature, and similar length of clinical

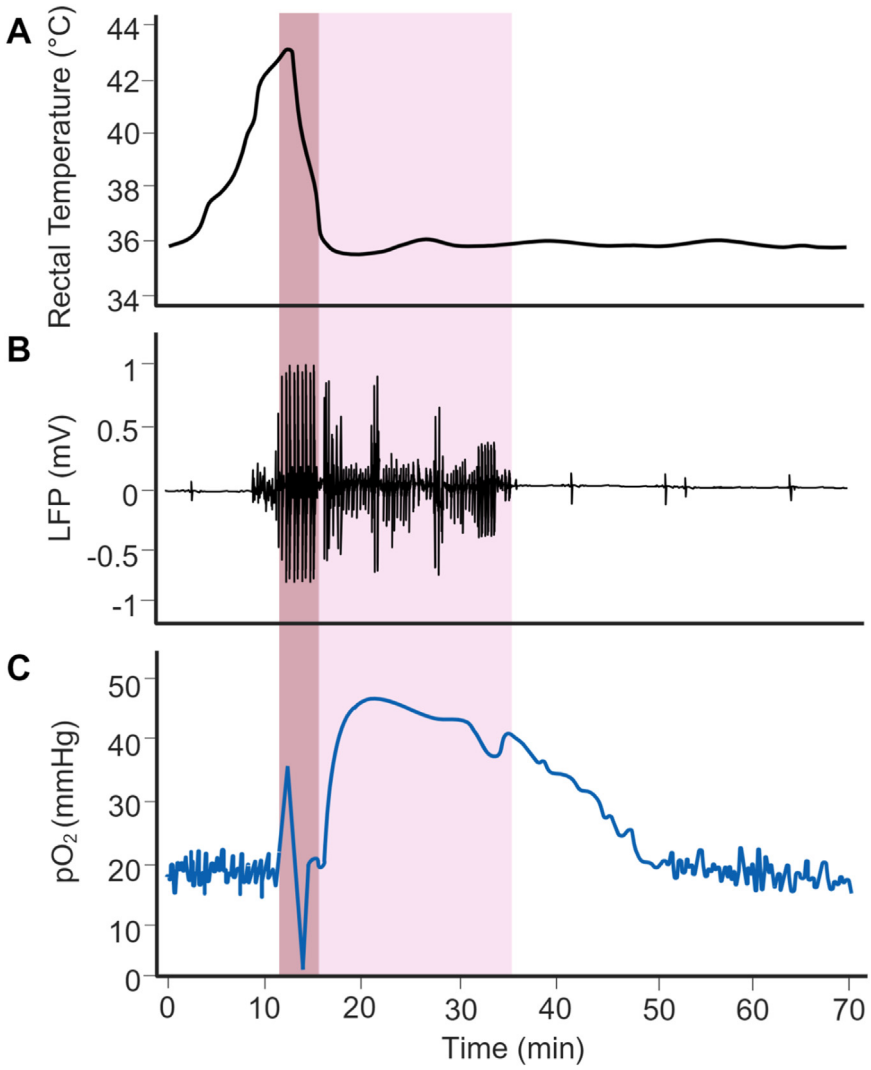

FIGURE. Stylized representation of (A) rectal temperature measured in degrees Celsius (°C), (B) local field potential (LFP) measured in millivolts (mV) in the hippocampus, and (C) partial pressure of oxygen (pO_2) measured in millimeters of mercury (mm Hg) in the hippocampus of Sprague Dawley rats over time measured in minutes (min) during external heating to induce a febrile seizure. Rats were injected with lipopolysaccharides for four days leading up to and including postnatal day 12. The heat started at time 0 minutes; rectal temperature increases from 36°C to approximately 43°C, electrographic activity increases at 10 minutes as the internal temperature of the pup increases, and oxygen is at a normoxic level (20 mm Hg). At 12 minutes, the behavioral seizure starts indicated by the dark pink background. Rectal temperature returns to normal, whereas the LFP shows regular and intense epileptiform activity. Oxygen levels increase briefly before decreasing and returning to normoxic level. With the end of the behavioral seizure, represented by the light pink background, electrographic epileptiform activity continues, whereas oxygen levels continue to rise to hyperoxic levels (above 30 mm Hg) and remain high. After the termination of epileptiform activity, electrographic activity appears like preseizure baseline and oxygen levels start to return to 20 mm Hg. The color version of this figure is available in the online edition.

febrile seizures. Although clinical febrile seizures can lead to the later development of epilepsy or cognitive deficits, they almost never result in death.[44,45] Thus, it is important that animal models do not die from the application of exogenous heat, and reducing the heat required by challenging the animal immune system with LPS aids this goal. Furthermore, since human febrile seizures result from a fever and not exogenous heat, it is important that the exogenous heat required in animal models does not burn or upregulate immune factors.[46] Burns on animals can result in behavioral deficits in adulthood that are not from the febrile seizure and not present in the human population.[47,48]

Studies indicate that the height, not the rate of the rise, of temperature is a determining factor in the onset of febrile seizures.[28] However, in some patients and in rodent models, febrile seizures may occur when the temperature is still rising (Fig A), especially in the context of a pre-existing structural brain abnormality.[29,30] Furthermore, a shorter duration of fever before the onset of a febrile seizure is indicative of worse outcomes and subsequent seizures in human children.[15,49]

Temperature has an intimate relationship with cell excitability; indeed *in vitro* models show that postnatal day (P) 13 to 20 rat pup hippocampal slices show ictal-like spiking when temperature is increased.[50] Moreover, hyperthermia also reduces inhibitory transmission in hippocampal neurons.[51,52] Heightened brain temperature is damaging and can exacerbate cerebral injuries, whereas the opposite, brain hypothermia, has been found to be neuroprotective against excitotoxicity.[53] Prolonged increased brain temperature through a fever or exogenous heat may further drive ongoing epileptiform activity even as the behavioral seizure terminates[29,30] and increase the likelihood for the later development of seizure-induced brain damage[54] and temporal lobe epilepsy; however, the latter has yet to be fully investigated.

When developing an animal model, it is also important to age match rats and mice to a developmentally relevant human age. Children can have a febrile seizure anywhere from age three months to five years, but the peak susceptibility is around age two to three years.[3] Ages of rodents do not directly translate to children, thus developmental timelines need to be considered. The peak age for febrile seizures in rats is P10 to 11.[47] When correlating brain developmental milestones such as peak brain growth,[55] peak gliogenesis,[56,57] oligodendrocyte maturation,[58,59] and peak excitatory amino acid receptor expression (*N-methyl-d-aspartate* and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid),[60] translating brain developmental stages in rodents to humans is fraught with difficulties. Broadly, a P10 to 11 rat corresponds to a human neonate at full term to approximately a one-year-old, depending on the factors and brain regions being compared.[60,61] Thus, the peak age for febrile seizures (P10 to 12) for rats occurs before the peak age of febrile seizures (two years) but still within the broad range in which febrile seizures occur in humans. By the time a rat is developmentally similar to a two- to three-year-old child, at P20-21,[62] febrile seizures are increasingly hard to evoke and are often associated with mortality.[47,61,63]

Another key factor of febrile seizures that needs to be considered in nonhuman animal models is the length of the febrile seizure. As stated above, the delimitation between simple and complex febrile seizures occurs at 15 minutes.[2] The probability of future seizures increases with a shorter duration of the fever before the seizure, and with complex febrile seizures compared with short, simple febrile seizures.[19,49,64] To model febrile seizures and examine lasting effects some studies only include rat pups if their seizure lasts beyond a certain cutoff time, for example, only seizures longer than 15 minutes.[65,66] However, behavioral febrile seizures in animal models are highly varied and are reported to last anywhere from less than 10 minutes[67-69] to more than 20 minutes,[70] or, in some cases, more than 45 minutes.[71] Possibly more important and more indicative of seizure outcome, than the length of the behavioral seizure, is the length of the epileptiform activity. Following termination of the behavioral seizure in rodents there is ongoing epileptiform ictal activity that can last up to twice as long as the behavioral seizure.[29,30] It is currently unclear if this phenomenon is seen in clinical febrile seizures in the human population, and depth, rather than just surface, electrographic recordings need to be performed to determine whether there is ongoing epileptiform activity following behavioral seizure termination in children.[72] Once this is done, the effect of epileptiform activity with and without behavioral seizures on long-term deficits and the development of temporal lobe epilepsy can be closely examined.

Is the postictal period really postictal following febrile seizures?

As mentioned earlier in this review, a few animal studies that have examined febrile electrographic activity found that even after a rat recovers behaviorally from a febrile seizure, there is a period of ongoing epileptiform activity (Fig B).[29,30] This electrographic activity is not postictal electroencephalographic (EEG) depression, seen as a characteristic flattening of EEG following termination of an electrographic seizure,[73] which does occur in rat pups immediately following a febrile seizure,[29,74] but rather is continuing epileptiform spiking despite recovery from the behavioral seizure.[29,30] Currently, febrile seizures in human children are classified based on their behavioral seizure duration; however, it may be more indicative of consequences if length of epileptiform activity is considered.[29,30,54] Differences in electrographic seizure length may be obscuring whether or not deficits are reported following febrile seizures in some studies. Ongoing epileptiform activity in the brain likely also drives brain hyperoxia and the long-term negative consequences associated with it (discussed in the next section of this review).[30] Monitoring electrographic seizure length could provide insight to why some children have only a single febrile seizure, whereas in other children the seizures are reoccurring. In addition, examining ongoing epileptiform activity following the termination of the behavioral seizure may be paramount in elucidating causal mechanisms of long-term consequences following febrile seizures, such as learning deficits and the development of TLE.

Postictal hyperoxia following febrile seizures

Regarding brain oxygenation, brief, self-terminating afebrile seizures in adulthood result in what is known as postictal hypoxia, a severe reduction in brain oxygenation similar to a stroke,[75,76] whereas longer, traumatic seizures have an increase in brain oxygen that continues to rise during epileptiform activity[30,77-79] and then returns to around baseline as the electrographic seizure terminates. Postictal hypoxia has been linked to many behavioral comorbidities that can be prevented if postictal hypoxia is prevented.[75]

Febrile seizures in the immature brain, as in prolonged or traumatic seizures in adulthood, result in increased brain oxygenation that does not start to decline until all epileptiform activity in the brain has subsided (Fig C).[30,77-79] Hyperoxia can lead to oxidative damage in the brain, which may result in hippocampal sclerosis, decreased seizure thresholds, and deficits in learning in adulthood.[80,81] In fact, learning deficits can be prevented through normalizing ictal and postictal brain oxygen, through the inhibition of TRPV1 receptors.[30]

Brain oxygen dynamics can facilitate assessment of the extent of prolonged epileptiform activity. Postictal hypoxia and hypoperfusion has been imaged in adult patients with seizures using both arterial spin-labeling magnetic resonance imaging[82] and computed tomographic perfusion,[83] thereby assisting clinicians in locating the seizure onset zone. As stated above, ongoing epileptiform activity following a seizure in rats leads to hyperoxic brain conditions,[30,77-79] and the oxygenation remains above baseline until all ictal spiking has terminated. Using this correlation, it is possible that arterial spin-labeling magnetic resonance imaging, ictal single-photon emission computed tomographic perfusion scans, and near-infrared spectroscopy could be used to measure hyperoxia in the brain and give insight into seizure length and ongoing epileptiform activity despite recovery from a behavioral seizure. Given that it is currently not recommended to perform EEG on children following simple seizures,[84] these noninvasive imaging techniques would be useful in classifying and monitoring seizure length and recovery. Examining the length of electrographic seizures and hyperoxia during febrile seizures will give further insight into the prognosis of a febrile seizure. Understanding febrile seizure length with consideration of electrographic and not just behavioral seizures may facilitate in differentiating between a benign seizure and when interventions should be implemented to prevent the development of epilepsy or cognitive deficits. As postictal hypoxia and hypoperfusion is being examined and quantified in adults following a brief seizure,[75,82,83,85,86] brain oxygen dynamics should also be thoroughly investigated and related to ongoing epileptiform activity following febrile seizures in the pediatric population.

What are the long-term consequences of febrile seizures that are replicated in animal models?

Nonhuman animal research has confirmed and expanded upon our current understanding of febrile seizures. The many

consequences of febrile seizures seen in animal models were briefly discussed above, but here we provide a more in-depth discussion on the development of temporal lobe epilepsy and reduced seizure threshold,[66,70,74,87] and learning deficits later in life.[30,69,88] Discovering these consequences, the causal mechanisms, and the relationship to ongoing epileptiform activity, preventing them from developing is instrumental in animal and human febrile seizure research. Extensive research in rodent models of experimental febrile seizures provides evidence that febrile seizures lead to decreased seizure threshold and the development of temporal lobe epilepsy. Febrile seizures likely result in long-term potentiation and increases in hippocampal excitability through Hebbian plasticity.[88-91] Furthermore, febrile seizures lead to increased suppression of gamma-aminobutyric acid release, altering the balance between excitation and inhibition in the brain.[92] These mechanisms may increase seizure length and work synergistically to precipitate temporal lobe epilepsy in adulthood.

Following a febrile seizure there is a decrease in seizure threshold when a chemoconvulsant is given later in life[93,94] due to an imbalance of the excitation/inhibition in the brain leading to increased excitability.[66] Spontaneous recurrent seizures have been reported following experimental febrile seizures, but robust and in-depth studies are lacking.[74,88] No study, in animal models or human children, is yet to examine the length of electrographic ictal spiking in febrile seizures and how it relates to reduced seizure thresholds later in life.

It is currently unknown why some febrile seizures are relatively benign, whereas others can lead to cognitive deficits. However, multiple clinical investigations involving large patient populations indicate that febrile seizures, even when simple, are not as benign as once was thought.[16,18] Research on children with febrile seizures indicates that learning deficits may occur if there are more than two febrile seizures in childhood (which would also be typical for brief afebrile seizures) or if the behavioral febrile seizure is prolonged.[21,95] However, animal studies indicate that memory is impaired even after a single febrile seizure when tested under specific conditions. One study shows that rats with a febrile seizure had reduced memory when tested on some aspects of the Morris water maze but performed at control levels on other aspects.[94] Learning and memory deficits were also reported in rats with febrile seizures harboring a small preexisting brain abnormality.[88] More recent studies have been able to rescue a learning deficit despite the occurrence of a febrile seizure. In these studies, administration of either a TLR4 antagonist[69] or a TRPV1 antagonist[30] before the febrile seizure rescued learning deficits with novel object recognition in adulthood. Further studies evaluating the effect of treatments on the length of ongoing epileptiform activity may give insight to discerning learning and memory outcomes in adulthood.

Conclusions

Febrile seizures have detrimental effects in a large proportion of our population. Both simple and complex febrile seizures can lead to negative lifelong consequences such as cognitive deficits, brain abnormalities, and the development of temporal lobe epilepsy in a subset of children. Recent research indicates there is hyperoxia coupled with ongoing epileptiform activity in the brain following recovery from a behavioral febrile seizure. Using advanced imaging techniques, hyperoxia and ongoing epileptiform activity in febrile seizures could be examined in children, thus allowing for the development of treatments to improve the prognosis for children with febrile seizures.

CRediT authorship contribution statement

Sydney A. Harris: Writing – review & editing, Writing – original draft, Conceptualization. **Emily E. Gordon:** Writing – review & editing, Writing – original draft, Visualization. **Karlene T. Barrett:** Writing – original draft, Conceptualization. **Morris H. Scantlebury:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **G. Campbell Teskey:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of Competing Interest

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