THEORETICAL ARTICLE

# Hypothesis: Febrile infection-related epilepsy syndrome is a microglial NLRP3 inflammasome/IL-1 axis-driven autoinflammatory syndrome

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**Abstract**

FIRES (febrile infection-related epilepsy syndrome) is a protracted neuroinflammatory condition of obscure cause. It mainly afflicts school-age children and often leads to permanent neurological sequelae. Most treatments to date have been of limited efficacy, while ketogenic diet and anti-interleukin-1 therapy appear beneficial for some patients. Research into this clinical entity is hampered by its rarity and complexity. Nonetheless, accumulating evidence derived from basic investigations and clinical observations converges to implicate the autoinflammatory nature of this syndrome. A closer analysis of current literature suggests that microglia and the NLRP3 inflammasome might be the pivotal cellular and molecular players in FIRES pathogenesis, respectively. Through evidence synthesis, herein we formulate the working hypothesis of overactivation of microglial NLRP3 inflammasome/ interleukin-1 axis as the driving event in FIRES by creating a proinflammatory and proconvulsive milieu. The reverberation between neuroinflammation and seizure forms a vicious cycle. The unique properties of microglia might also contribute to unopposed IL-1 signalling and incessant sterile neuroinflammation in this context. The potential therapeutic relevance of the proposed conceptual framework is discussed.

**Keywords:** autoinflammatory, febrile infection-related epilepsy syndrome, inflammasome, interleukin-1, microglia

## INTRODUCTION

FIRES, the acronym of febrile infection-related epilepsy syndrome, is characterised by new-onset refractory status epilepticus preceded by a febrile illness 24 h to 2 weeks earlier.[1] This neuroinflammatory syndrome usually develops in school-age children without a clear identifiable cause, and the exact pathogenetic mechanisms remain to be elucidated. Clinical care for patients with FIRES is challenging, and the neurological prognosis is often dismal.[2] The effects of anti-seizure medications and first-line immunomodulatory therapies are usually disappointing, while some promising results have been reported regarding ketogenic diet and anti-cytokine therapies.[3–6] Systematic research into this clinical entity is difficult owing to its rarity and complexity. On the basis of current literature, herein we formulate a unifying theory of FIRES as

an autoinflammatory syndrome of the central nervous system (CNS), in which danger signalling is pathologically amplified in the brain. We will present an overview of threads of evidence that converge on this hypothesis.

## THE ROLE OF IL-1 SIGNALLING IN FIRES

The role of interleukin-1 (IL-1) signalling in seizure and epilepsy is well established in animal models and human patients.[7–9] Elevated IL-1 signalling has been consistently shown to be proconvulsive. Endogenous IL-1 receptor antagonist (IL-1Ra) encoded by *IL1RN* serves as the counter-regulatory mechanism, keeping IL-1 signalling activity in check. Augmented IL-1Ra has been shown to confer seizure resistance in mice.[10]

However, IL-1 is also one of the major endogenous pyrogens. Hence, it is reasonable to consider the components of IL-1 signalling cascade as potential molecular players in seizures developing in a febrile context. Through a candidate gene approach, a significant association between *IL1RN* haplotype containing RN2 and FIRES was detected in Japanese children.[11] Although cerebrospinal fluid (CSF) IL-1Ra was elevated in patients with FIRES, it was found to be functionally deficient in a patient,[12] which might be related to *IL1RN* gene polymorphism. Intrathecal overproduction of IL-1β and related cytokines in FIRES was demonstrated in several human studies.[12,13] CSF IL-1β levels were consistently elevated in patients with FIRES, while serum IL-1β levels were elevated only in some patients in a recent study.[12] Perhaps the most compelling evidence for overactive or unopposed IL-1 signalling in the brain in FIRES came from mounting reports of positive clinical responses to anti-IL-1 therapy in these patients (summarised in Table 1),[14–19] which can be viewed as proof of the concept. Dramatic responses to anti-IL-1 therapy were reported in single-case studies,[15,16,18] and the use and discontinuation of therapy appeared to be correlated with the ebb and flow of disease activity in some patients.[16,17] A retrospective cohort study involving 25 patients suggested that an earlier use of anti-IL-1 therapy was associated with improved outcomes.[19] It is notable that all of these studies use anakinra (a recombinant IL-1 receptor antagonist), which might have better brain penetration because of its smaller molecular weight (17.3 kDa) than canakinumab

(a recombinant anti-IL-1β monoclonal antibody, 145 kDa) and rilonacept (an IL-1α and IL-1β cytokine trap, 251 kDa).

## THE ROLE OF INFLAMMASOME IN FIRES

The maturation and secretion of IL-1β are governed by inflammasomes, and IL-1β is one of the major downstream effectors of inflammasome activation.[20] Anti-IL-1 therapy has been shown to be efficacious in a multitude of autoinflammatory diseases, particularly those because of unrestrained activation of the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome.[21] Following in this vein, the partial control of FIRES achieved by IL-1 blockade suggests the possibility of excessive inflammasome activation in this condition. Notwithstanding, the involvement of inflammasome in the pathogenesis of FIRES has yet to be directly demonstrated.

Empirical evidence showed that ketogenic diet could be beneficial for FIRES in terms of seizure control and cognitive outcome.[4–6] β-Hydroxybutyrate (BHB) is one of the major circulating ketone metabolites in humans treated with ketogenic diet. It has been shown that BHB attenuates the NLRP3 inflammasome activity through preventing potassium efflux and reducing ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain) oligomerisation and speck formation.[22,23] BHB can be transported across blood–brain barrier, and its level in the brain appears to be highly correlated with that in the blood.[23] Therefore, it is plausible that ketogenic diet exerts its effect on FIRES through BHB-mediated suppression of inflammasome activation.

A further question would be about the putative inflammasome(s) and its cellular context in FIRES. Previous studies showed that several inflammasomes, including NLRP1, NLRP3, NLRC4 and AIM2, are involved in various acute and chronic CNS diseases,[24] with NLRP1 and NLRP3 particularly implicated in epilepsy.[25–27] The expression of inflammasome components is cell-type-specific, with NLRP1, NLRP3 and NLRC4 found in microglia, and AIM2, NLRP1 and NLRP3 in neurons.[24] Overall, the NLRP3 inflammasome is the most abundant inflammasome in the CNS, and it is the one that is specifically targeted by BHB. Activation of other inflammasomes, such as AIM2, NLRC4 and non-canonical inflammasome, could

**Table 1.** Empirical evidence for the efficacy of anti-IL-1 therapy[a] in FIRES

| Author and year of publication | Study Design | No. of patient(s) | Age and sex of patient(s) | Timing of treatment[a] initiation and duration | Main results and comments |
|---|---|---|---|---|---|
| Kenney-Jung et al. 2016[16] | Case study | 1 | 32 months, female | Days 6–23; days 54–190; days 191– | ▪ Well tolerated during 3 separate treatment epochs<br>▪ Starting anakinra (epochs 1 and 2) or reintroducing it at full doses (epoch 3) was associated with improved seizure control. |
| Dilena et al. 2019[17] | Case study | 1 | 10 years, male | Initiation: 1.5 years after FIRES onset; Duration: 7 months | ▪ No adverse effects<br>▪ Anakinra reduced the relapse of highly recurrent refractory seizures (only two clinical seizures occurred during the 7 months of anakinra treatment).<br>▪ After anakinra withdrawal, seizures and EEG epileptiform abnormalities increased. |
| Sa et al. 2019[14] | Case study | 2 | 9 years, male | Initiation: day 43; Duration: still on anakinra at 15 months after presentation | ▪ Seizure frequency decreased since day 51 and stopped on day 60.<br>▪ 15 months after presentation, he was having short focal seizures with an average of 2–5 seizures per month.<br>▪ After rehabilitation, the patient had good motor function and no significant cognitive impairment. |
| | | | 5 years, male | Initiation: day 22; Duration: 3 months | ▪ No apparent effect<br>▪ The patient remained in vegetative state |
| Westbrook et al. 2019[15] | Case study | 1 | 21 years, female | Initiation: day 32; Duration: still on anakinra (planned to continue for 1 year) | ▪ Well tolerated<br>▪ Termination of super-refractory status epilepticus within 24 h |
| Lai et al. 2020[19] | Retrospective cohort study | 25[b] | 8 years [IQR, 5.2–11 years], male (16) and female (9) | Initiation: median: day 20 [IQR, days 14–25]; Duration: 86 days [IQR, 13–257 days] | ▪ Adverse events: infections (n = 10, 40%); drug reaction with eosinophilia and systemic symptom syndrome (n = 3, 12%); and cytopenia (n = 2, 8%).<br>▪ Only one child discontinued therapy because of infection.<br>▪ Earlier anakinra initiation was associated with shorter duration of mechanical ventilation, intensive care unit and hospital length of stay. |
| Yang et al. 2021[18] | Case study | 1 | 6 years, female | ▪ Initiation: four weeks after hospitalisation;duration: still on anakinra at one-year follow-up | ▪ Well tolerated<br>▪ Seizures stopped four days after anakinra use.<br>▪ The patient had infrequent seizures at one-year follow-up. |

IQR, interquartile range.
[a]Anakinra was used in all of these studies.
[b]Including the two patients reported by Sa et al.

not be inhibited by BHB.[22] Microgliosis, a pathological finding observed in the sample of patients with FIRES,[17,28] also appeared to be attenuated by BHB treatment in an Alzheimer's disease mouse model.[23] Microglia is the main source of IL-1 in the brain, and the association of epileptic seizure with microglial NLRP3 inflammasome/IL-1β axis has been observed in mice.[29] Taken together, the aforementioned findings suggest that microglial NLRP3 inflammasome would be the most likely candidate in FIRES pathogenesis.

## AUTOINFLAMMATION *VERSUS* TRIGGERED INFLAMMATION

The clinical course of FIRES is protracted. Although it is conventionally divided into acute and chronic phases, the boundary between these two phases is indistinct, and relapse during chronic phase is not uncommon. The relapses were similarly responsive to ketogenic diet or anti-IL-1 therapy.[5,16,17] These clinical features argue against an incidentally triggered inflammatory event, which is expected to be temporally circumscribed. Instead, a trivial trigger may elicit self-perpetuating neuroinflammation in the presence of specific host factors, such as functional defect of endogenous IL-1Ra discussed above. Once activated, inflammasome-induced IL-1β secretion may be more persistent in microglia as compared to haematopoietic macrophages, because negative regulation of pro-IL-1β (but not IL-1Ra) transcript seems lacking in the former.[30] The unopposed IL-1 signalling creates a proinflammatory and proconvulsive milieu. Furthermore, the reverberation between inflammation and seizure forms a vicious cycle,[31] thereby sustaining inflammation in the CNS. The picture depicted above also provides a potential explanation for the fact that inflammation in FIRES is largely restricted to the brain. Overall, the aberrant activation of innate immunity is consistent with the notion of autoinflammation.

## LACK OF EVIDENCE FOR OTHER COMPETING HYPOTHESES

### Lack of evidence for self-directed adaptive immune response

It has been well established that autoimmune response, either autoantibody- or cell-mediated, could also ignite neuroinflammation. Patients with FIRES were often extensively tested for autoantibodies related to CNS diseases, yet positive findings were only reported in a minority of cases.[6,28,32,33] Serum and CSF analyses showed that proinflammatory cytokines and chemokines were selectively up-regulated, while most T-cell-associated cytokines were not.[13] Pathological examination revealed infiltrations of neutrophils and activated microglia, with few CD8$^+$ and no CD4$^+$ cells.[17,28] No risk allele was identified by HLA sequencing study.[34] Taken together, these findings argue for a predominance of innate immune activation in the generation and maintenance of FIRES.

### Lack of evidence for genetic predisposition to fever-provoked seizures

Several monogenic epilepsies, such as epilepsies related to SCN1A, PCDH19 or POLG mutations, are characterised by seizures associated with elevated body temperature. Seizures in these contexts are often prolonged or clustered, mimicking FIRES at the outset. Therefore, one could reason that FIRES may be the presenting manifestation of these genetic epilepsies. Indeed, patients with FIRES were often tested for these genes for clinical or research purposes, yet so far, the results were rarely positive.[11,16,17,34–36]

## STRENGTHS AND LIMITATIONS

Our hypothesis of microglial inflammasome overactivation as the driving event in FIRES, if validated, has clear therapeutic implications (Figure 1). In addition to the biologics targeting IL-1 signalling, several novel small molecules (e.g. MCC950) or repurposed agents (such as type I interferons and proton pump inhibitor) have been identified as potential inhibitors or modulators of inflammasome (NLRP3, in particular) activity.[37–39] The explanatory power of our theory also extends to account for the potential utility of cannabidiol in FIRES,[40] as cannabidiol has been shown to suppress NLRP3 inflammasome activation.[41,42] More studies are needed to clarify the efficacy of cannabidiol in this condition.

Herein, we are unaware whether microglia is primed before or during the initiating event in FIRES.[43] We also have no ready answer as to the nature of the prime mover that initiates the inflammatory cascades in the brain. One

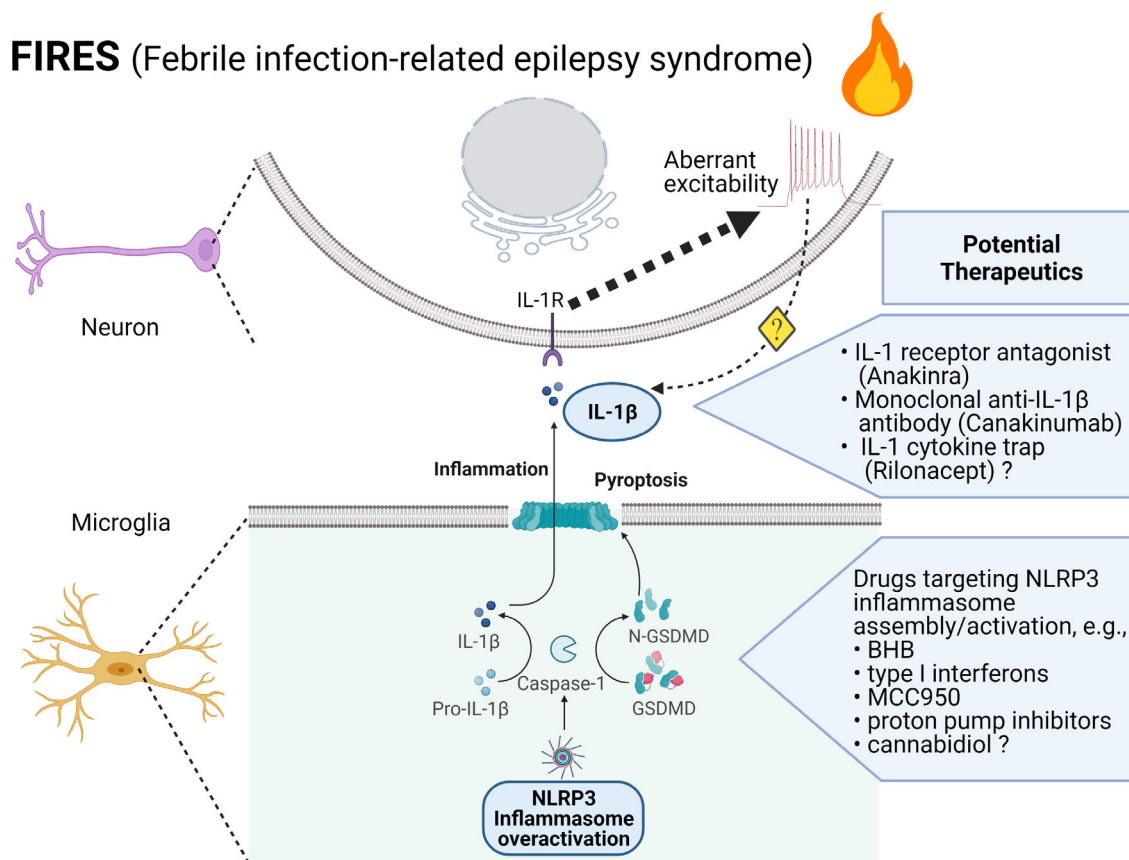## FIRES (Febrile infection-related epilepsy syndrome)



**Figure 1.** Working hypothesis of FIRES (febrile infection-related epilepsy syndrome) as an autoinflammatory syndrome of the CNS driven by overactive NLRP3 inflammasome/IL-1 axis, and its therapeutic implications. BHB, β-hydroxybutyrate; FIRES, febrile infection-related epilepsy syndrome; (N-)GSDMD, (N-terminal) gasdermin D; IL-1, interleukin-1; IL-1R, IL-1 receptor; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3. The figure was created with BioRender.com.

possibility is that seizure itself at the very beginning of the illness could assume the role to spark the fire,[31] which is then propagated by damage-associated molecular patterns released from cell pyroptosis following inflammasome overactivation. This positive feed-forward loop ultimately culminates in widespread and long-lasting sterile neuroinflammation. Our hypothesis is theoretically testable by examining the biofluids and tissue samples for evidence of inflammasome priming and activation, as well as for its downstream effectors. Given the rarity of FIRES and its ever-changing course, however, such investigations may be practically difficult. This is further complicated by technical and methodological issues. For example, quantification of IL-1β, one of the main read-outs of inflammasome activation, is affected by its minute amount and labile nature, its existence within

extracellular vesicles, and the interference by soluble type II IL-1 receptor and other plasma proteins.[9,12,16,44] Actually, the levels of serum and CSF IL-1β have been documented to be elevated in only a minority of patients with FIRES, including the anakinra-responsive cases.[19]

## CONCLUSION

In summary, our synthesis of current evidence suggests that it is reasonable to hypothesise FIRES as an autoinflammatory process in the CNS. We propose that excessive activation of microglial inflammasome/IL-1 axis might represent the pivotal event in FIRES, which creates a proinflammatory and proconvulsive milieu. The reverberation between inflammation and seizure forms a vicious cycle, resulting in smouldering neuroinflammation. The conceptual

framework presented above could stimulate further research that ultimately leads to better care for patients suffering from this devastating condition.

## ACKNOWLEDGMENTS

## CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

## AUTHOR CONTRIBUTIONS

**Wei-Sheng Lin:** Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Visualization; Writing-original draft; Writing-review & editing. **Ting-Rong Hsu:** Resources; Writing-review & editing.

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