

Spectrum, Evolution, and Clinical Relationship of Magnetic Resonance Imaging in 31 Children with Febrile Infection-Related Epilepsy Syndrome

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Abstract

Objective Describing spectrum, evolution, and clinical relationship of brain magnetic resonance imaging (MRI) findings in a large case series of children with febrile infection-related epilepsy syndrome (FIRES).

Methods This retrospective study included 31 children with FIRES. Clinical data and MRI findings of the brain were evaluated. Poor clinical outcome was defined as severe disability, persistent vegetative state or stupor, very low intelligence quotient (<80), or death (modified Rankin scale 4–6 and Glasgow Outcome Score 1–3).

Results Seventeen (54.8%) children with FIRES showed no abnormalities in the initial MRI, whereas 28 (90.3%) children showed MRI abnormalities at follow-up. The most frequent abnormalities were brain atrophy (74.2%) and T2/fluid-attenuated inversion recovery changes (64.5%), mostly hippocampal (45.2%). Generalized brain atrophy was the most frequent type of atrophy (58%). The earliest atrophy was recorded 9 days after the onset of disease. It progressed even beyond the acute phase in most children (51.6%). The exploratory data analysis revealed nominal significance between all MRI abnormalities considered together and poor outcome ($p=0.049$) and between generalized brain atrophy and anesthesia ($p=0.024$). After adjustment for multiple testing, the p -values were not significant. The outcome in four (12.9%) children was not poor despite generalized brain atrophy.

Keywords

- FIRES
- status epilepticus
- magnetic resonance imaging
- anesthesia
- brain atrophy
- children

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Conclusion In contrast to the uniform clinical course, MRI demonstrated a broad spectrum of findings. Initially, these were mostly normal and therefore indicative of FIRES but then changed rapidly and were mostly progressive despite the stable chronic course. The cause may be ongoing disease, treatment intensity, or both. Future studies should focus on what process underlies the onset and the progression of brain atrophy. However, brain atrophy was not always related to poor outcomes in children despite FIRES.

Introduction

According to the latest definition, febrile infection-related epilepsy syndrome (FIRES) is a subtype of new-onset refractory status epilepticus and a rare epilepsy syndrome that can occur in both healthy children and adults.¹ The clinical picture is characterized by refractory status epilepticus (SE) which is preceded by a febrile infection occurring 2 weeks to 24 hours prior to onset of SE.¹ The refractory SE quickly turns into a superrefractory status epilepticus (SRSE).² The following chronic phase is characterized by refractory epilepsy with rare seizure-free intervals and a poor general outcome.^{3,4} In cryptogenic cases, the cause remains unknown after extensive work-up.¹ An important diagnostic tool in the acute phase is magnetic resonance imaging (MRI). Although the first MRI findings are usually normal,^{5,6} a number of patients may show MRI abnormalities mostly in the insula, temporal area, and basal ganglia.^{3,7} MRI findings with generalized brain atrophy have been reported during the chronic phase.^{5,8}

Here, we describe the long-term timeline of MRI findings, and its relationship between clinical course, anesthesia, and outcome, based on the data of a large case series of children with FIRES.

Methodology

This is a retrospective observational study. The ethics committee of the Faculty of Medicine at the Kiel University (CAU) approved this study (D 470/20), and written informed consent was obtained. The collected data include information about demographics, clinical course, brain MRI findings, use of anesthetics, and clinical outcomes. The inclusion criteria used were published by van Baalen et al 2012⁹: previously healthy children with an acute febrile illness 2 to 28 days prior to the onset of recurrent seizures or SE and with no evidence of infectious agents in cerebral spinal fluid.

The clinical course was categorized into two phases: the acute and the chronic phase. We defined the acute phase as the period of time from seizure onset to end of SE or significantly fewer recurrent seizures. The chronic phase was defined as the subsequent follow-up time.

Serial MRI brain imaging was performed at variable timing for each child, from the acute phase after seizure onset to the chronic phase of outpatient follow-up. The MRI

scans were either performed at our clinic or were gathered from outside facilities. One neuroradiologist (J.H.) reviewed all images.

The functional outcome in the follow-up period was categorized as (1) good outcome or (2) poor outcome. Children with a good outcome either returned to their baseline status, had an IQ > 80 (Glasgow Outcome Score 4–5), or showed an incomplete recovery with only mild residual disability (modified Rankin Scale 0–3). This included children with aphasia who were still able to walk. Children with a poor outcome had either a severe disability, a persistent vegetative state or stupor, an intelligence quotient < 80 (Glasgow Outcome Score < 1–3), or had died during the clinical course (modified Rankin Scale 4–6).

Data were analyzed with SPSS version 27. For comparison of the MRI abnormalities with anesthesia and MRI abnormalities with outcomes, we used Fisher exact test, chi-square test, and Mann–Whitney test. Results were regarded as nominally significant if *p* value was less than 0.05. The *p*-values were adjusted for multiple testing with the Bonferroni method.

Results

We evaluated a total of 31 children with FIRES. The clinical data are shown in ►Table 1 and ►Supplementary Table S1 (available in the online version).

The number of MRI scans and the timing in which these scans were carried out varied from patient to patient. The MRI findings are summarized in ►Table 2.

Magnetic Resonance Imaging Findings during the Acute Phase

Three children (9.7%) had normal MRI findings during acute and chronic phases despite refractory SE in all and anesthesia in two children. The initial MRI findings were normal in 17 (54.8%) children. However, nine of them (29.0%) developed MRI changes during the following acute phase. The most common MRI findings during this phase were T2/FLAIR changes in 12 (38.7%) children, with hippocampal signal abnormalities in 11 (35.5%) children. The hippocampal signal abnormalities were reversible in five (16.1%) children. Brain atrophy was the second most MRI finding during the acute phase (10 children, 32.3%), where two (6.5%) children developed focal atrophy and eight (25.8%) children generalized brain atrophy (►Fig. 1).

Table 1 Descriptive analysis of 31 children with febrile infection-related epilepsy syndrome

Demographics and clinical characteristics	
Age, median (range)	6 years (2-15)
Sex	
Male, n (%)	18 (58.1)
Female, n (%)	13 (41.9)
Status epilepticus	
Semiology, n (%)	
Generalized tonic-clonic	12 (38.7)
Focal motor	8 (25.8)
Nonconvulsive	1 (3.2)
Focal onset evolving into bilateral tonic-clonic	4 (12.9)
Unclassified	6 (19.4)
Treatments	
Duration, median (range)	14.5 days (29 minutes-153 days)
Use of anesthetics, n (%)	24 (77.4)
Use of thiopental, n (%)	16 (51.6)
Time to first use of anesthetics in days, median (range)	1 (1-14)
Use of steroids, n (%)	17 / 27 (63.0)
Use of intravenous immunoglobulins, n (%)	18 / 28 (64.3)
Use of anakinra, n (%)	2 / 28 (7.1)
Use of cannabidiol, n (%)	8 / 29 (27.6)
Use of ketogenic diet, n (%)	21 / 29 (72.4)
Neurostimulation, n (%)	5 / 26 (19.2)
Brain surgery, n (%)	0 / 26 (0.0)
Outcomes	
Functional outcome, n (%)	
Good outcome (mRS 0-3, GOS 4-5)	12 (38.7)
Poor outcome (mRS 4-6, GOS 1-3)	19 (61.3)
Seizure outcome, n (%)	
Seizure-free with or without ASM	3 / 28 (10.7)
Refractory seizures	24 / 27 (88.9)
Death, n (%)	8 (25.8)

mRS, modified Rankin Scale; GOS, Glasgow Outcome Score; ASM, antiseizure medication.

Regarding the timeline, the earliest brain atrophy was already observed at 9 days after disease onset. In 13 (41.9%) children, brain atrophy occurred during the first month after seizure onset.

Magnetic Resonance Imaging Findings during the Chronic Phase

The most common MRI finding during the chronic phase was brain atrophy, which was observed in 23 (74.2%) children. In six of them, focal atrophy was first noted in the chronic phase and then progressed to generalized brain atrophy. Overall, 18 (58%) children developed a generalized brain atrophy. The second most common radiologic findings during the chronic phase were T2/FLAIR changes which affected 12

(38.7%) children and were not present during the acute phase in half of them. Mostly frequent, T2/FLAIR changes occurred at the hippocampus in 9 (29%) children.

Locations of Magnetic Resonance Imaging Findings during the Complete Clinical Course

The number of children with their different MRI findings and respective locations during the complete clinical course is listed in **Supplementary Table S2** (available in the online version). The most frequent observation and localization was generalized atrophy in 18 (58%) children. The second most common localization of MRI abnormalities was the hippocampus, where we found the largest number of children with T2/FLAIR changes (11 children, 35.5%), edema (7 children,

Table 2 Number of MRI findings during acute and chronic phase of FIRES

	Number of children during acute and chronic phases ^a	Number of children during the acute phase	Number of children during the chronic phase
No MRI abnormalities	3	11	4
MRI abnormalities	28	20	27
Diffusion restriction/cytotoxic edema	12	8	3
Enhancement	7	5	2
T2/FLAIR changes	20	12	12
Hippocampal signal abnormality	14	11	9
Amygdalae signal abnormality	4	2	2
Atrophy (focal and generalized)	23	10	23
Hippocampal atrophy	10	2	8
Hippocampal atrophy without initial restricted diffusion	5	0	5
Hippocampal sclerosis	7	1	6
Generalized atrophy	18	8	18
First MRI findings of atrophy (focal and generalized)	23	10	13
First MRI findings of hippocampal atrophy	5	1	4
First MRI findings of focal atrophy	8	2	6
First MRI findings of generalized atrophy	15	8	7
Insular involvement	8	4	3
Thalamus involvement	8	5	2

Abbreviations: FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

^aAll MRI findings during clinical course.

22.6%), diffusion restriction (5 children, 16.1%), and the second frequent location for atrophy (10 children, 32.3%), respectively.

Timelines and Outcome

Timelines and outcomes of 23 (74.2%) children with MRI findings describing brain atrophy and its long-term progression are summarized in **Fig. 2**. In six children with brain atrophy, we did not obtain follow-up MRI scans.

The atrophy progressed in most children (51.6%), even beyond the acute phase. The first MRI evidence of brain atrophy was very common between the first week and the first month after the first seizure (13 of 23 children, 56.5%). Most of these children showed progressive brain atrophy between the first month and first year after their first seizure (12 of 23 children, 52.2%). Even after the acute phase, the brain atrophy progressed in most children (15 of 23 children, 65.2%), progression carried on up to 5 years after the onset of FIRES. In total, 12 of 16 (75%) children with progressive brain atrophy (including five children with progressive brain atrophy already in the acute phase) presented a poor functional outcome.

Exploratory Data Analysis

Exploratory data analysis revealed nominal significance between all MRI abnormalities considered together and poor outcome ($p = 0.049$), and between generalized brain atrophy and anesthesia ($p = 0.024$). After adjustment for multiple testing, the p -values reached no significance.

Discussion

Our Main Results

This is one of the largest case series describing the spectrum, evolution, and clinical relationship of MRI findings in children with FIRES. In this study, we observed that, unlike the consistent and constant clinical course, MRI findings were inconsistent and progressive. FIRES seems not to be limited to a specific brain localization.

Acute Phase

In line with previous reports, the initial MRI in the majority of children, despite refractory SE, was normal.^{5,6,8,10,11} Therefore, a normal initial MRI is characteristic and not contradictory to a diagnosis of FIRES. The second most

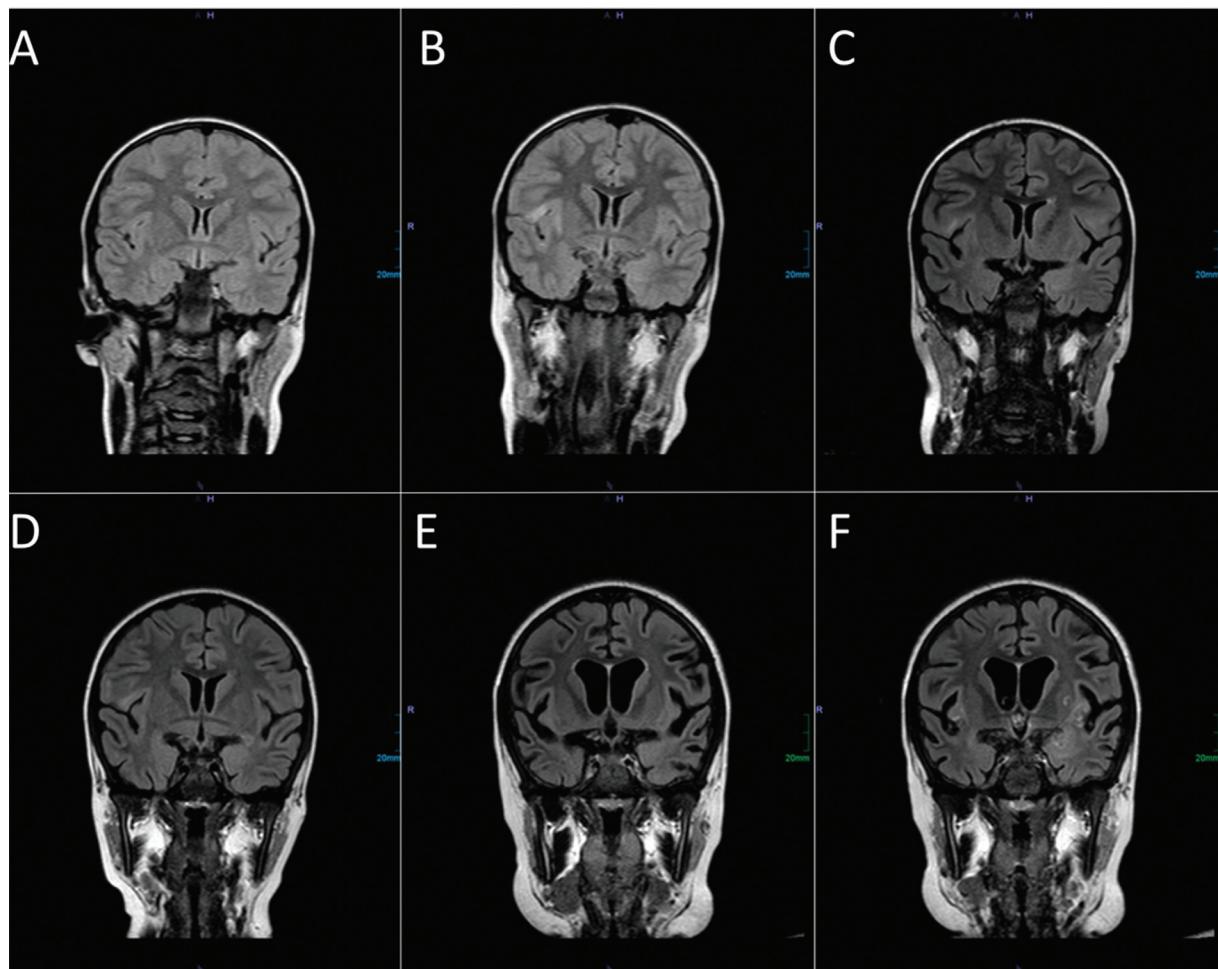


Fig. 1 T2w-FLAIR coronal MRI (Philips Achieva 3T, TE 160, TR 12000) of a 7-year-old girl with FIRES. (A) start, (B) 10th day, (C) 23rd day, (D) 39th day, (E) 6th month, and (F) 11th month with severe generalized atrophy, starting 10 days after diagnosis and being constant after 6 months.

common finding during the acute phase was T2/FLAIR changes, mostly located in the hippocampus. Previously, the hippocampus and temporal lobe were described as the most affected areas during the acute phase.^{6,11} Reliable data, whether these changes are due to the persistent epileptic activity or the underlying epileptogenic process itself, are still missing.¹⁰⁻¹²

Chronic Phase

Lee and Chi¹⁰ also described focal unusual high signal intensity at bitemporal cortical areas and bilateral hippocampi emerging not only on the first but also on follow-up MRI. The number of our children with T2/FLAIR changes was constant in the acute and in the chronic phase. Lee and Chi¹⁰ reported that 34.5% of the children showed generalized brain atrophy on follow-up MRI. In contrast, we observed that most children (58%) developed generalized brain atrophy.

Brain Atrophy: Onset

Additionally, already during the acute phase, 32.3% of our children developed focal or generalized brain atrophy. We found the earliest brain atrophy at 9 days after disease onset, which may reflect the severity of this condition. In most children, however, first proof of brain atrophy was more

likely between the first week and first month after disease onset. Rivas-Coppola et al¹¹ similarly reported the earliest MRI evidence of brain atrophy at 2 to 3 weeks after disease onset.

Brain Atrophy: Localization

Regarding the localization of brain atrophy, 58% of our FIRES cohort developed a generalized brain atrophy. In agreement, Culleton et al,⁶ who comprehensively reviewed the reported literature, described the most common finding during the chronic phase to be generalized brain atrophy (49.4% of the children). This was also confirmed by other studies with similar results.^{5,11}

Brain Atrophy: Progression Despite Stable Chronic Course

In contrast to the small case series of Rivas-Coppola et al,¹¹ we were able to follow-up the progression of brain atrophy in a large number of children in relation to the acute and chronic phase. Interestingly, most children (16 out of 23 children, 69.6%) showed a progression of brain atrophy despite a stable chronic course. Implying, that either the underlying pathogenic process may be ongoing even after SE, the treatment intensity may contribute, or both are the case.

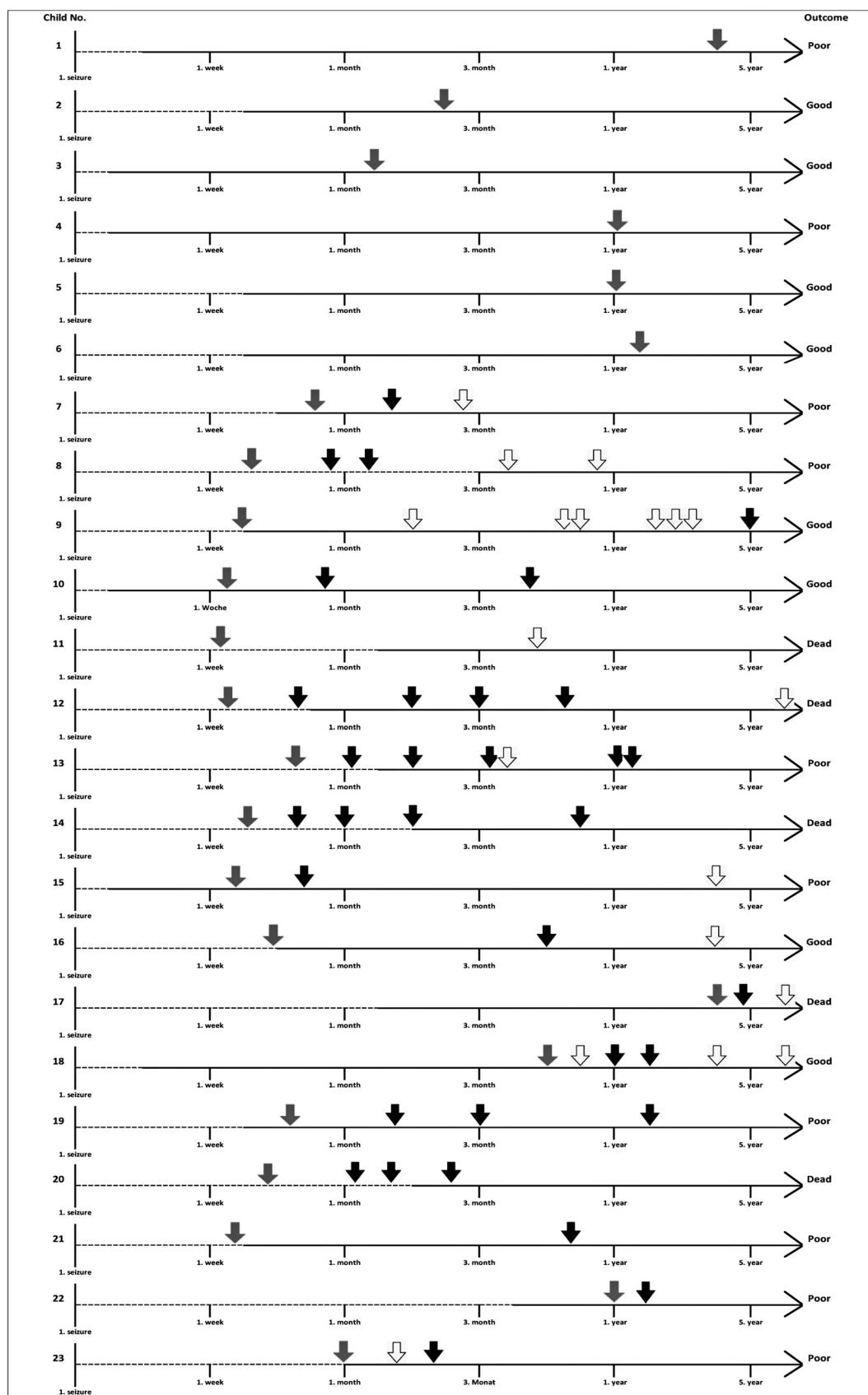


Fig. 2 Outcome, first MRI evidence and progression of brain atrophy. - - - = acute phase. — = chronic phase. ↓ = first MRI evidence of an atrophy. ↓ = progressive atrophy. ↓ = constant atrophy. Abbreviations: Child No.: child number.

Hocker et al¹³ presented a retrospective study demonstrating the evolution of generalized brain atrophy in a series of adults with SRSE despite seizure control.¹³ Therefore, the question of what process underlies the brain atrophy acquired during treatment and progresses beyond the acute phase must be answered.¹⁴ Future studies with this focus are important to facilitate our understanding of the balance between treatment intensity and seizure control.¹³

Anesthesia, Brain Atrophy, and Clinical Outcome

The high number of generalized brain atrophy has raised concerns about the poor outcome of FIRES after anesthesia; however, in contrast to other case series,^{10,11} four (12.9%) of our children with generalized brain atrophy had a good but not completely normal outcome. For example, one studied at a university despite refractory epilepsy, one had an IQ of 86 and was able to walk and another one worked at a sheltered workshop. The already mentioned retrospective case series in adults with SRSE confirmed that the development of brain atrophy was associated with the duration of anesthetic use but not with functional outcomes.¹³

Limitations

The limitation of our study is the retrospective design; therefore, the timing of the MRI was variable and the exact onset of the brain atrophy could not be specified. On the contrary, due to the exact timing of serial MRI during the clinical course, we were able to describe the progressive changes and classify these in the acute or chronic phase in a large number of children with FIRES.

Conclusion

This retrospective study confirmed that, although children with FIRES developed a uniform clinical course, the MRI findings were variable and frequently progressive despite a stable chronic course. The cause may be an ongoing disease, the treatment, or both. The observation that generalized brain atrophy was most prevalent early during anesthesia and their unclear causal relationship, making prospective studies necessary to assess this primarily and, hopefully, to improve the outcome, even if brain atrophy was not related to poor outcomes in all children despite FIRES.

Conflict of Interes

None declared.

References

- Hirsch LJ, Gaspard N, van Baalen A, et al. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. *Epilepsia* 2018;59(04):739–744
- Farias-Moeller R, Bartolini L, Staso K, Schreiber JM, Carpenter JL. Early ictal and interictal patterns in FIRES: the sparks before the blaze. *Epilepsia* 2017;58(08):1340–1348
- van Baalen A, Häusler M, Boor R, et al. Febrile infection-related epilepsy syndrome (FIRES): a nonencephalitic encephalopathy in childhood. *Epilepsia* 2010;51(07):1323–1328
- Caraballo RH, Reyes G, Avaria MF, et al. Febrile infection-related epilepsy syndrome: a study of 12 patients. *Seizure* 2013;22(07):553–559
- Kramer U, Chi CS, Lin KL, et al. Febrile infection-related epilepsy syndrome (FIRES): pathogenesis, treatment, and outcome: a multi-center study on 77 children. *Epilepsia* 2011;52(11):1956–1965
- Culleton S, Talenti G, Kaliakatsos M, Pujar S, D'Arco F. The spectrum of neuroimaging findings in febrile infection-related epilepsy syndrome (FIRES): a literature review. *Epilepsia* 2019;60(04):585–592
- Kim HJ, Lee SA, Kim HW, Kim SJ, Jeon SB, Koo YS. The timelines of MRI findings related to outcomes in adult patients with new-onset refractory status epilepticus. *Epilepsia* 2020;61(08):1735–1748
- Byler DL, Grageda MR, Halstead ES, Kanekar S. Rapid onset of hippocampal atrophy in febrile-infection related epilepsy syndrome (FIRES). *J Child Neurol* 2014;29(04):545–549
- van Baalen A, Häusler M, Plecko-Startinig B, et al. Febrile infection-related epilepsy syndrome without detectable autoantibodies and response to immunotherapy: a case series and discussion of epileptogenesis in FIRES. *Neuropediatrics* 2012;43(04):209–216
- Lee H-F, Chi C-S. Febrile infection-related epilepsy syndrome (FIRES): therapeutic complications, long-term neurological and neuroimaging follow-up. *Seizure* 2018;56:53–59
- Rivas-Coppola MS, Shah N, Choudhri AF, Morgan R, Wheless JW. Chronological evolution of magnetic resonance imaging findings in children with febrile infection-related epilepsy syndrome. *Pediatr Neurol* 2016;55:22–29
- Fatuzzo D, Giuliano L, Mainieri G, Sortino G, Sofia V, Zappia M. Febrile infection-related epilepsy syndrome (FIRES) in an adult patient: an early neuroradiological finding. *Neurol Sci* 2019;40(11):2407–2410
- Hocker S, Nagarajan E, Rabinstein AA, Hanson D, Britton JW. Progressive brain atrophy in super-refractory status epilepticus. *JAMA Neurol* 2016;73(10):1201–1207
- Cole AJ. Status epilepticus and brain atrophy: shrinkage is a growing problem. *JAMA Neurol* 2016;73(10):1182–1183