Potential of Early Hippocampal Magnetic Resonance Imaging Findings in Prediction of The Long-Term Consequences of Febrile Status Epilepticus : A Retrospective Study

by

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ABSTRACT

Background: Febrile seizure (FS) occurs in childhood around the ages of greater than 1 (3-6) month(s) of age [1-3], associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures [1]. FSs are common in children, with incidence rates up to 14% in developing countries; febrile status epilepticus accounts for roughly 5% of all febrile seizure cases. The Neurocritical Care Society guidelines from 2012 revised the definition of status epilepticus (SE) to a seizure with 5 minutes or more of continuous clinical and/or electrographic seizure activity, or recurrent seizure activity without recovery between seizures [4]. FSs lasting longer than 5 minutes with a variety of complex signs are called febrile status epilepticus (FSE). Yearly, approximately 20 children per 100,000 population suffer from convulsive SE and in 22-25% of cases, it is febrile status epilepticus (FSE) [3]. Both SE and FSE are life-threatening conditions that put children at risk of future epilepsy and that require timely diagnosis and care. FSE can be associated with hippocampal sclerosis and/or development of temporal lobe epilepsy [5]. Not all patients with FSE develop further complications and the specific characteristics of patients in the risk group for developing epilepsy remain unclear. Even though some brain MRI features occurring in the acute phase and over long-term follow-up have been studied in both children and animals, the causal relationships between these findings and risk of adverse seizure outcomes still need clarifying.

Hypothesis 1: FSE patients with T2 signal increase in the hippocampal area on acute MRI after the first episode of FSE do not develop epilepsies more frequently than those without.

Hypothesis 2: FSE patients with asymmetry between the right and left hippocampal volumes on initial MRI after the first episode of FSE develop epilepsies more frequently than those without.

Methods: Patients aged between 1 and 60 months with FSE admitted to the Stollery Children's hospital PICU from August 2002 to December 2007 were studied. The study was approved by the U of A HREB (Pro00101017). List of patients was created from PICU MetaVision database. Demographics and long-term seizure outcomes were studied via chart reviews. Brain MRI scans performed within 30 days of FSE were extracted from PACS and reviewed by experienced neuroradiologist, who was blinded to clinical and follow-up data. We evaluated hippocampal T2 signals and presence/absence of hippocampal volume asymmetry in FSE patients. Hippocampal T2 signal intensity (T2Score) on coronal MRI sections was rated from 0 to 4 (0=normal, 1=equivocal, 2=mildly abnormal T2 signal on >1 slices, 3=moderately abnormal, 4=markedly abnormal throughout hippocampus) [6], and only T2Scores ≥ 2 were considered abnormal. Hippocampal volume was calculated using the RadiAnt DICOM Viewer software (version 2020.2. Jul 19, 2020, Medixant). The right and left hippocampus volumes of each participant were acquired separately to determine the presence or absence of hippocampal volume asymmetry. A computer mouse and a closed polygon function of the software for measurement of area and perimeter were used to manually trace the ROI. The total hippocampus volume (cm3) was calculated by multiplying the whole area by the slice thickness + gap. To assess the association between right-to-left volume asymmetry and subsequent development of epilepsy, volume ratios between 0.95 and 1.05 were considered symmetric, volume ratios <0.95 and >1.05 were considered asymmetric. Patients' follow-up data on whether they developed epilepsy or not was obtained from Connect Care, NetCare, and e-clinician systems (patient clinical information systems) 14-19 years later (February 2021).

The univariate and multivariate logistic [odds ratio (OR); 95%CI] regressions, and t-tests were used to evaluate the association of MRI findings with further development of epilepsy. Descriptive

statistics are given in absolute values, percentages, means and standard deviations (SD). We present data as mean ± SD, median and 25 and 75 interquartile range (IQR). Univariate and multivariate analysis comparison with p-values <0.05 were considered significant. Statistical analysis was performed by using the SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp)

Results: Out of 309 patients, 54 met the inclusion criteria. The mean age of our FSE patients was 17.19 months (SD=15.22), 30 (56%) subjects were males, median length of seizure was 32.5 minutes (5.0 – 240.0), and patients had a mean body temperature of 38.4 °C (SD=.623). The median interval between admission to PICU and MRI examination was 4 days (0 -30). Twenty-one (39%) MRI examinations were done within the first 3 days of admission, 41 (76%) - within first 7 days. Fourteen (26%) patients had an early hippocampal T2score ≥ 2, and 23/54 (42%) developed epilepsy in the long term. Of the patients with an early MRI hippocampal T2score ≥ 2, 9/14 developed epilepsy in the long term. Twenty-two (66.7%) of 33 measured patients had hippocampal asymmetry and it made up to 41% (22/54) of all FSE patients, 11/33 (33.3%) patients' hippocampal volumes were evaluated to be within the ranges of symmetry. Nine (41%) out of 22 patients with hippocampal asymmetry developed subsequent epilepsy (figure 9), 4/11 (36%) of patients without hippocampal asymmetry developed epilepsy.

The odds ratio of patients with a T2Score ≥ 2 of developing epilepsy was 2.143 [95% CI (0.46, 9.984)], adjusted odds ratio (aOR) was 4.056 [95% CI (0.520 – 31.660)]. The odds ratio of patients with hippocampal volume asymmetry developing epilepsy was equal to 1.35 [95% CI (0.211 – 8.617)], and aOR was 0.838 [95% CI (0.054 - 13.054)].

Conclusion: This small study shows that FSE patients with early T2 signal hyperintensities may have increased odds of developing future epilepsy. MRI done within first 3-7 days would be

preferred for more accurate detection and interpretation of imaging findings. Substantial variety in imaging protocols leading to the differences in thickness and number of slices visualizing the hippocampus was a limitation. Dedicated thin section coronal T2 imaging of the hippocampus, which would improve visualization, may increase MRI detection of hippocampus abnormalities in these patients. Systematically accurate coding of diagnoses, recording of exact length of seizure and body temperature immediately after the seizure are crucial.

Future directions: Detailed attention to the hippocampus, in larger studies, may prove helpful in finding MRI changes that predict long term outcomes in children with FSE.

PREFACE

This thesis is an original work by Nozima Avazbek Kizi Fayzieva. The research project included in this thesis received research ethics approval from the University of Alberta Health Research Ethics Board, Project Name: "Potential of magnetic resonance imaging in prediction of short term and long-term consequences of febrile status epilepticus: A Retrospective Study", No. Pro00101017, Date of approval: Thursday, August 20, 2020.

Chapter 1 consists of an introduction with the literature review for this research, a brief history of status epilepticus and febrile status epilepticus, and merits and limitations of neuroimaging studies both in FSE pediatric population and animal models. The research hypotheses and objectives are also given in this chapter. Tables 1 and 2 are given in the 1st chapter.

Chapter 2 includes the first and second hypotheses tested in this study along with their objectives. Also, materials and methods including, search, inclusion/exclusion criteria for research subjects, methods of evaluating hippocampal T2 signal and detailed explanation of the measurement of hippocampal volumes in our sample is highlighted in this chapter. Additionally, the examples of various hippocampal T2 signals, along with the illustration of hippocampal volume measurements can be found in the second chapter. Figures 1 and 2 are given in this chapter.

Chapter 3 consists of the detailed information on the results of this study. It includes demographic, clinical, imaging findings along with the results of statistical analyses, such as univariate and multivariate logistic regressions, and t-tests. Tables 3 - 6, and Figures 3-9 are given in the 3rd chapter.

Chapter 4 includes discussion section, where we tried to compare and contrast the results of our study with the results of previously published studies and acknowledge the limitations of our study.

Finally, in **Conclusion** section we summarize the results of literature review and our study, and mention possible future directions.

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LIST OF COMMON ABBREVIATIONS

ADC - Apparent diffusion coefficient

aOR – adjusted odds ratio

CFC – Complex febrile convulsion

CFS - Complex febrile seizure

CI – confidence interval

CNS – Central nervous system

CT – Computed tomography

DWI – Diffusion weighted imaging

EEG – Electroencephalography

eFSE – experimental Febrile status epilepticus

FC – Febrile convulsion,

FLAIR – Fluid-attenuated inversion recovery

FS - Febrile seizure

FSE – Febrile status epilepticus

HS – Hippocampal sclerosis

ILAE – International league against epilepsy

MRI – Magnetic resonance imaging

MRS – Magnetic resonance spectroscopy

MTS – Mesial temporal sclerosis

OR – odds ratio

PFC – Prolonged febrile convulsion

PFS – Prolonged febrile seizure

SE – Status epilepticus

TLE – Temporal lobe epilepsy

Chapter 1

Introduction

Febrile seizures (FS) are defined as seizures occurring in febrile children aged between 6 and 60 months who do not have an intracranial infection, metabolic disturbance, or history of afebrile seizures [1]. FS are common, affecting 2-5% of children in the United States and Western Europe, 6% to 9% of children in Japan, and 14% of children in India and Guam [2]. Status epilepticus (SE) affects ~20 children per 100,000 each year and is defined by the 2012 Neurocritical Care Society as a seizure with 5 minutes or more of continuous clinical and/or electrographic seizure activity, or recurrent seizure activity without recovery between seizures [3]. Of children suffering from convulsive SE, about a quarter have febrile status epilepticus (FSE) [4], a medical emergency that can be defined as a seizure of prolonged duration (>30 minutes) in a febrile child. FSE develops in 5% to 9% of patients who experience an initial FS [5].

However, there are issues with these definitions, particularly with respect to the length of seizure duration, age of onset, and brain maturity. For instance, there have been different definitions of SE over the last 40 years, the most widely recognized, based on animal studies, as being a 30-minute period of seizures [6]. Later, the literature has popularized new terms like early or impending SE, which introduce the concept of 5-7-minute-long seizures and allows earlier medical intervention [7-11]. Similar timing-related issues apply to FSE. While a decrease in seizure duration from 30 to 5 minutes as a definition for FSE could make the definition more clinically practical, it creates additional complexity in understanding the difference between a simple versus complex seizure, which still includes a 15-minute threshold.

With respect to age and brain maturity, the minimum age of seizure onset for a definition of FS differs according to definition and is either 1 or 3 or 6 months of age [1, 2, 7, 12]. The six months threshold is problematic since, if seizures occurring before 1 month of age are considered neonatal seizures and FS start at 6 months, this creates uncertainty about seizures occurring between 1 and 6 months. Moreover, in children younger than 6 months, a seizure event can be associated with an infectious etiology such as viral meningitis, so work-up and management are different [13, 14].

While FSE is thought to represent the extreme end of the complex FS spectrum [15], it is apparent that seizure duration is not the only factor to consider. The young age of seizure onset, immaturity

of the brain, and prolonged seizure activity are the aspects of concern in regards to further seizure consequences.

FSE is a subtype of both FS and SE. FSE appears to have worse outcomes than simple FS but better outcomes than CSE [16]. The clinical sequelae of FSE are heterogeneous but it is unlikely to result in death or serious morbidity [17]. There is some evidence of hippocampal and memory deficits in FSE [16]. Neuroimaging would be useful to both diagnostically and prognostically if salient features could be defined. The objective of this review is to provide an overview of FSE and review the acute and chronic imaging changes seen in FS and FSE patients.

Historical aspects of SE, FSE.

The history of SE shows that it was not recognized until the early 19th century[18-20]. It started to be diagnosed more frequently with the introduction of anticonvulsant treatment in the second half of the 19th century. Few of the many case reports of epilepsy published in the 16th, 17th, and 18th centuries may be considered status epilepticus in retrospect. Morgagni (1761) in his great work reported several patients who died following a series of convulsions which may have been SE. Cases more closely resembling SE began to be documented around the end of the 18th century. Due to the exclusion of severely ill patients from hospitals, a large concentration of epileptic patients in newly built asylums in Europe gave the opportunity of long-term direct and continuous observation to the time of death and often post-mortem examination. Calmeil (l824) first used the term "état de mal" to describe SE in his doctoral thesis of Paris University based on his experience in asylums. Delasiauve in 1854 differentiated *état de mal* from serial epilepsy and other forms of repeated seizures, and noted that the most danger was due to the inability of regaining consciousness between seizures, rather than the frequency or intensity of seizures. In 1868 the term status epilepticus first appeared in the English language in Bazire's translation of Trousseau's "Lectures on clinical medicine". Afterward, several researchers such as Bourneville, Obersteiner, Charcot, and Westphal in their works mentioned hyper-pyrexia in patients with SE and tried to explain that it was not the consequence of infection, and they linked higher body temperature with worse prognosis. At the beginning of the 20th century, Clark and Prout described the pathology and treatment of SE. They believed that the SE was "the maximum development of epilepsy" and the most common cause of death in epileptic patients. Bourneville, Clark, and Prout differentiated SE into the convulsive and the stuporous stages, and moderately severe cases thought to last not

less than 30 hours, with the majority lasting between 2 and 9 days. The scientists believed that possible causes for death after SE were underlying brain pathology, an acute inflammatory disorder, or sudden withdrawal of antiepileptic drugs. However, there were controversial theories about patients being relieved of epileptic seizures during fever and hence, there were suggestions of fever induction, and even the establishment of malaria or erysipelas to cure epilepsy. In 1909 The International League Against Epilepsy was founded, and the 20th century was, for epilepsy, the century of this league. However, until the period after World War II, not much work had been done on SE. Since the mid-1970s SE gained greater importance due to the realization of its greater incidence, experimental potential, and promising therapeutic advances. Xth Marseille Colloquium (1962) was the first meeting dedicated to SE, and EEG findings along with clinical reports on SE were presented. SE was redefined in this meeting, however, Gastaut (the President of the ILAE, ILAE Secretary-General and Editor of Epilepsia at that time) added 60 minutes duration to the definition later on. 1973 was in many ways the end of a period of relative obscurity for status epilepticus [18-20].

In 1970 Aicardi and Chevrie conducted research on SE in children (<15) and reported about the group of children in their cohort who did not have any reason for seizure except fever and emphasized the importance of this type of SE, even though they did not necessarily use the term FSE. Aicardi was the first to request that febrile type of SE in children should be treated with great urgency [18-20]. However, apart from that data on FSE is missing in the historical literature, and FSE appears to be the young diagnostic entity with the continuing attempts of its redefinition.

Animal models of FSE and neuroimaging findings

Animal models of FSE are only an approximation of the human FSE. Research into the temporal relationship between FSE and the development of epilepsy has also been undertaken in rats, mice, and primates [21-26]. FSE has been modeled in rodents and primates via different heating methods to study its clinical features, EEG findings, and subsequent development of afebrile seizures. Studies of imaging features predicting risk of seizure consequences were mainly conducted in rats [21-23, 25]. While the results from animal models were promising, the use of ultrahigh field strength scanners, initial imaging within an ultrashort time (<2 h) after FSE, serial imaging within a short time interval, similar age and baseline conditions of case subjects within the group and with

controls, and the short latency period between FSE and the development of adverse consequences have made it difficult to replicate the same results in humans.

Nevertheless, imaging findings such as asymmetry in T2 relaxation times between the left and right hippocampus and amygdala and unilateral reduction of T2 relaxation times were observed in rats with FSE that became epileptic [22]. T2 values in the basolateral and medial amygdala and medial thalamus predicted epileptogenesis better than chance [22]. Several MRI scans repeated over time within 2 to 48 hours improved prediction of epileptogenesis compared with a single MRI scan [23]. The T2 difference in the medial amygdala was a better predictor of epilepsy than that in the basolateral amygdala [23]. According to the results of whole-brain T2 changes, rats with experimental FSE (eFSE) were classified as eFSE-vulnerable or eFSE-resilient; eFSE-vulnerable rats were found to have a minimal reduction in T2 relaxation times, which was significantly different to that observed for control or eFSE-resilient rats. The prolongation of T2 relaxation times in whole brains, the hippocampus, and the basolateral amygdala was also found to predict worse cognitive outcomes in rat models [21].

Neuroimaging literature on febrile seizures and febrile status epilepticus

Prolonged FS or FSE has been associated with the subsequent development of afebrile seizures, epilepsy, and/or hippocampal atrophy, and the nature of these associations remains ambiguous [15, 27-29]. While not all patients with FSE develop further complications, it remains unclear what specific characteristics define patients at risk for developing epilepsy.

Several studies have evaluated prognostic value of imaging, particularly MRI, to detect features that might identify children at a higher risk of adverse outcomes from FSE, such as afebrile epilepsies including temporal lobe epilepsy (TLE) and/or medial temporal sclerosis (MTS) (Tables 1 and 2). Wang et al. presented one of the first cases of MR imaging of a child with SE meeting the criteria for FSE [30]. In their report, while CT showed only a choroidal fissure cyst, MRI was more sensitive and detected increased T2 signal and enlargement of the entire right hippocampal formation. VanLandingham et al. attempted to identify signs of acute brain injury shortly after a seizure, particularly in the temporal lobe structures [31]. They reported that MRI abnormalities were only apparent in patients with focal or lateralized features. MRI changes suggestive of acute edema were observed in patients with significantly longer seizures, and two patients with initial MRI abnormalities showed hippocampal atrophy on follow-up MRI. A subsequent study re-

examined the patients recruited to the study prospectively and whose first imaging was within 72 hours of the initial seizure, with permanent brain injury the outcome of interest [32]. The initial MRI scans showed increased T2 signal shortly after prolonged FS and increased hippocampal volume. All abnormalities were unilateral and located in the hemisphere of seizure origin based on clinical localizing signs. Follow-up scans taken several months later showed that hippocampal volume decreased markedly and the T2 signal remained abnormal [32]. The same group went on to report a strong association between MRI evidence of a markedly hyperintense hippocampus in FSE children who subsequently developed MTS [33]. Conversely, Tanabe et al. revealed acute and follow-up MRI changes compatible with previous reports in only one patient out of 59 with FSE [34], concluding that the prevalence of hippocampal injury after FSE may be in the range of 0 to 10%.

A case report of sequential brain CT and MRI in a child with FSE and previously normal neuroimaging showed transient and harmless acute cytotoxic brain edema but irreversible delayed brain edema with hyperintense signal changes on T2-weighted images [35]. The patient subsequently developed atrophy and high signal on T2-weighted images, suggestive of gliosis.

FEBSTAT was a large prospective study to determine whether FSE generates acute hippocampal injury that develops into hippocampal sclerosis (HS) [5, 36-39]. In children with FSE, 22 out of 199 had acute increases in hippocampal T2 signal after FSE associated with increased volume; these changes were not observed in any of the 96 simple FS control subjects [5, 36]. Follow-up MRIs in 14 of these 22 patients showed that 10 and 12 patients had HS and reduced hippocampal volume, respectively. By contrast, follow-up of 116 children without acute hyperintensity revealed an abnormal T2 signal in only one patient, who had experienced another episode of FSE. Hippocampal malrotation was seen in 20 subjects in the FSE group compared with two control subjects [37, 39]. It was uncertain whether these MRI abnormalities were present before injury and predisposed for injury or whether they occurred after injury. Among the 22 patients with an abnormal T2 signal on the initial MRI, four had hippocampal malrotation. The percentages of extrahippocampal abnormalities in the two groups were similar. However, extrahippocampal abnormalities located in the temporal lobe were more common in the FSE group. Furthermore, compared to control subjects, FSE subjects with normal acute MRIs had abnormally low right-to-left hippocampal volume ratios, initially smaller hippocampi, and reduced hippocampal growth.

At the time of reporting, 16 patients with FSE had developed epilepsy, and mostly not TLE, while five of these patients were among the 22 subjects with initial T2 hyperintensity [5].

Yokoi et al. reported that the hippocampal hyperintensity on T2-weighted images was consistent with the hyperintensity of the same region on diffusion-weighted imaging (DWI) in children with FSE [40]. Unilateral hippocampal hyperintensity was present in 27% of patients evaluated on initial imaging, with follow-up data obtained between 9 and 13 years after initial imaging. All patients with hippocampal hyperintensity developed focal epilepsy and had signs of hippocampal atrophy, compared with only 1% without initial hippocampal hyperintensity. Suzuki et al. also found evidence of cytotoxic edema in the cortex on hyperacute diffusion-weighted imaging (DWI) before the appearance of any hippocampal abnormalities [41]. However, the authors concluded that edema was not associated with unfavorable short-term outcomes.

Hassan et al. used magnetic resonance spectroscopy (MRS) to determine hippocampal metabolic changes in patients with prolonged FS [42]. The authors found that MRS was a highly sensitive predictor of TLE, even in patients without any MRI abnormalities, and MRS revealed hippocampal injury more accurately and earlier than EEG. However, larger studies with longer follow-up are required to establish the association between these early metabolic changes and subsequent development of TLE.

Current bottlenecks to developing neuroimaging guidelines for FSE

There are currently no neuroimaging guidelines to help decide which FSE patients should be imaged, when they should be imaged, which imaging modality and protocols should be used, which areas of the brain should be particularly examined, what significant findings should be reported, who should have longitudinal imaging, and when follow-up imaging should occur. Retrospective studies have demonstrated that not all patients with FSE are routinely imaged, that different imaging modalities and protocols are used, and that the time of imaging is mostly based on either the clinical course of the disease or availability of imaging tools in individual centers. Moreover, imaging is often performed to exclude other pathologies rather than search for findings compatible with FSE, so the scans are usually reported as normal.

Neuroimaging is an essential assessment in pediatric patients with epilepsy [43]. SE studies prioritize four non-mutually exclusive factors: diagnosis, localization, evaluation of

pathophysiology, and prognostication [43, 44]. CT and MRI are most often used to evaluate patients with SE, with CT used more widely than MRI due to shorter imaging times and wider availability [44]. However, MRI is believed to be more sensitive and specific for the detection of subtle changes in the hippocampus [30, 45]. Challenges to MRI in children include the need for sedation and difficulties in interpretation due to age. If a child cannot remain motionless long enough to obtain high-resolution images, the approved sedation method is general anesthesia [45]. Separately, ongoing myelination process over the first 2-3 years of life can make MRI interpretation difficult. Between 6 and 18 months of age, the phase of signal reversal may lead to false-negative results when detecting epileptogenic lesions [43, 45].

While 1.5 T field strength MRI is routinely used in clinical practice, a 3.0 T field strength is preferable to enhance the signal-to-noise ratio, spatial resolution, and reduce scan times [45]. Furthermore, 3.0 T scanners are superior to 1.5 T scanners for recognizing minute, hemosiderin-containing, or calcified lesions [43, 45]. However, 3.0 T MRI has some theoretical limitations, as high radiofrequency energy deposition can cause unpleasant heating of the patient's body, which can be partially overcome by parallel data acquisition [43, 45]. Parallel data acquisition techniques may appear noisier, but specific regions of interest may be better depicted due to a reduction in artifacts [45]. Additionally, higher field strength MRI machines are not readily available in every emergency unit due to their higher costs.

The Society for Pediatric Radiology Neuroradiology committee recommends that routine MRI sequences for brain seizures should include T1 3D in the sagittal plane, T2 fluid-attenuated inversion recovery (FLAIR) in the coronal plane, T2 fat-saturation fast spin echo in the coronal and axial planes, T2 axial fast spin echo, axial susceptibility-weighted imaging, and axial diffusion [46]. Optional sequences are available based on specific indications. In the late 1990s, The International League against Epilepsy recommended using temporal angulation for the examination of epileptic children, because patients primarily had temporal lobe epilepsies. The temporal angulation sequence is along or perpendicular to the hippocampal long axis, improving the visualization and evaluation of the hippocampus and temporal lobe [47]. More recently, an increase in the percentage of patients with subtle cortical abnormalities located primarily in the dorsal frontal and parietal lobes led to the recommendation of a FLAIR sequence with anterior–posterior commissure angulation [45].

Some brain structures such as the hippocampus and amygdala can be assessed scrupulously using quantitative MRI [48]. Some subtle changes, such as an increase/decrease in size or evidence of hippocampal asymmetry, may be detected using quantitative MRI, even in patients with FSE who show no apparent structural abnormalities. A decrease in hippocampal volume and an increase in hippocampal signal intensity on T2-weighted images are defined MRI parameters for HS [49, 50]. Additionally, changes indicating cytotoxic and vasogenic edema in children with SE have been identified utilizing DWI and the apparent diffusion coefficient (ADC) [6].

Table 1. Neuroimaging studies in patients with FSE included in the review.

#	Authors	Published year	Definitions used in the study	Number of patients	Imaging modalities
1	Wang T. et al. (Case report)	1996	CFS – focal FS lasting >30 minutes or occurs more than once over a 24-hour period. SE – a seizure persisting for >30 minutes or recurring seizures without regaining consciousness for at least 30 minutes.	1	Fast spin-echo MRI with and without contrast CT
2	Van Landingham K. E. et al.	1998	CFC – febrile convulsions with complex features of either duration >15 minutes, occurring more than once in 24 hours, or focality.	27	MRI
3	Scott R.C. et al.	2002	PFC – SE associated with a fever, not of CNS origin, occurring in developmentally normal children between 6 months and 5 years of age.	21	MRI
4	Lewis D.V. et al.	2002	FC - seizures occurring in childhood after 1 month of age associated with a febrile illness in the absence of a CNS infection or other acute cause and with no history of previous afebrile seizures.	30	MRI
5	Morimoto T. et al. (Case report)	2002	Term FSE is used; the definition is not given.	1	CT, MRI, MRA, SPECT
6	Provenzale J.M. et al.	2008	FSE – a prolonged seizure (i.e., at least 30 minutes in duration) or a series of seizures lasting >30 minutes without interictal recovery occurring in the context of a febrile illness.	11	MRI
7	Tanabe T. et al.	2011	PFS lasting longer than 15 minutes.	59	MRI FLAIR
8	The FEBSTAT study team	2012, 2013, 2014, 2015, 2016	FSE - a single seizure or a series of seizures without full recovery in between lasting ≥30 minutes that also met the definition of an FS.	199	MRI DWI
9	Yokoi S. et al.	2019	FSE - a seizure or series of seizures lasting for ≥30 minutes without return of consciousness between the seizures, with a temperature of 38°C or higher.	22	MRI DWI
10	Mohamed M.M. Hassan, et al.	2020	PFS >15 minutes	30	MRS
11	Suzuki T. et al.	2020	PFS - the presence of a febrile (>38.0 °C) seizure persisting for >15 min.	101	MRI FLAIR DWI

CFS – complex febrile seizure, FS – febrile seizure, SE – status epilepticus, CFC – complex febrile convulsion, PFC – prolonged febrile convulsion, CNS – central nervous system, FC – febrile convulsion, FSE – febrile status epilepticus, PFS – prolonged febrile seizure.

Table 2. Neuroimaging studies of chronic changes in patients with FSE included in the review. Acute studies include initial neuroimaging data acutely after FSE, mostly within first 72 hours (sometimes up to several days). Chronic studies include follow-up data, and usually follow-up imaging is performed within several months up to several years.

#	Authors	Type of study*	Number of followed-up patients	Length of follow-up period	Association with epilepsy**
1	Wang T. et al.	Acute	-	-	-
2	Van Landingham K. E. et al.	Acute, chronic	2	8-25 months	-
3	Scott R.C. et al.	Acute	-	-	-
4	Lewis D.V. et al.	Acute, chronic	8	6-30 months	+
5	Morimoto T. et al.	Acute, chronic	1	36 days	-
6	Provenzale J.M. et al.	Acute, chronic	11	3-23 months	+
7	Tanabe T. et al.	Acute, chronic	1	46 days and 1 year	-
8	The FEBSTAT study team	Acute, chronic	130	Ongoing	+
9	Yokoi S. et al.	Acute, chronic	15	9-13 years	+
10	Mohamed M.M. Hassan, et al.	Acute	-	-	-
11	Suzuki T. et al	Hyperacute, acute	-	-	-

*Studies researching acute, chronic, or both imaging findings

**Publication reported subsequent development of clinical afebrile seizures/epilepsy

Limitations of this review

The definitions of FSE are not used consistently in the published literature, and usually seizures meeting criteria for FSE are defined as something else. Only studies published in English were included in the review. Several studies claiming to include children with prolonged FS did not clearly indicate the length of seizures, which could bias the diagnosis and interpretation. Due to a lack of standardized neuroimaging guidelines and rapid changes in imaging techniques and technologies, various MRI protocols have been used over time, making comparisons difficult and compromising the generalizability of the results. Not all studies included long-term follow-up data, and there was a lack of high-quality evidence supporting an association between MRI findings and further seizure consequences.

Conclusions

Children admitted with FSE may show increased T2 signal intensity in the hippocampus by MRI, an increase in hippocampal size due to cytotoxic edema, and hippocampal malrotation. While acute brain edema seems to be transient and harmless, the significance of the association between increased T2 signal intensity and hippocampal malrotation and seizure activity remains unclear. Studies that included follow-up imaging showed persistent increases in T2 signal, which may be a sign of gliosis or HS; hippocampal atrophy or a decrease in hippocampus size; and delay in hippocampal growth compared to controls. Patients with increased T2 signal intensity will also have increased signal in hyperacute DWI. MRS seems to be a promising modality for the early detection of seizure-related metabolic changes, but larger studies with prolonged follow-up are necessary to evaluate the prognostic value of these findings. Animal studies have demonstrated the predictive value of asymmetry in T2 relaxation times in various brain areas and changes in the reduction in T2 relaxation times over time, but these findings need to be replicated clinically.

Future directions

Unified standardized neuroimaging guidelines are urgently needed for the evaluation of patients with FSE. These guidelines should include criteria defining the patients who need to be imaged, the optimal imaging modality, imaging protocols, timing, and the specific brain areas and structures to be evaluated and reported, along with their characteristics.

Studies reporting imaging findings in FSE and those comparing complex versus simple FS employed different inclusion/exclusion criteria, so comparing these results may not be appropriate. Larger prospective studies with detailed attention to the hippocampus are necessary to establish exactly which features in early MRI are associated with long-term outcomes in children with FSE. Moreover, due to changes in the definitions of SE and FSE, seizures lasting between 5 and 30 minutes should be accounted for in SE and FSE.

MR neuroimaging

MRI as inferred is the current modality of choice to assess brain pathology. Brain pathology can either manifest as a signal change (Ex. Increased T2 signal) or an architectural change (Ex. Rotation) [45]. To optimize the identification of these pathologies there are several choices that a radiologist can make. A volume of tissue, known as a voxel, is scanned by MRI and depicted onto a pixel. A pixel is an individual dot within an image, and the signal measured from the voxel is converted to a greyscale color ranging from black on one end to white on the other and assigned to the pixel [51]. To avoid interference from the radio waves in adjacent voxels most MRI sequences have a gap between voxels. If the lesion is small enough to fit into the gap its alteration in signal or architecture may not be depicted in the adjacent voxels and hence may be missed. Similarly, if a lesion within a voxel takes up a small portion of the voxel, then it may be obscured by the normal tissue within the same voxel, and thus to improve detection of the lesion thinner slices or improved spatial resolution within a slice is desired. All tissues contain T1 and T2 signals which are inherent properties of compounds. By altering TE (echo times) and TR (repetition times) one alters the weighting of T1 and T2 signals derived from each voxel [52]. Thus, choosing the optimal TE and TR to maximize the difference between normal and abnormal tissue is critical. Most pathology increases the T2 signal and thus by having a high TR and high TE one increases the T2 weighting of an image. To augment the difference between normal and abnormal tissue one could add additional pulse sequences such as fluid attenuation (Ex. FLAIR sequences), fat-saturation, an inversion recovery time to nullify the signal from certain tissues as it recovers after application of a radio pulse (Ex. STIR sequences), or magnetization transfer (Ex. MTC sequences). One can also change the type of sequencing from a spin-echo sequence to a gradient echo sequence to augment the detection of hemosiderin or calcium [52, 53].

Noise (information that is not part of the desired signal) competes for signal and originates from a number of sources including electronic interference [51-53]. Noise in MRI comes from two main sources; charged particles in the human body creating electromagnetic noise, and resistance from the electronic components of the MRI system. By measuring multiple times from the same structure, done by increasing the number of signal averages (NSA), the effect of noise on the inherent signal is diminished. This reduction in the effect of noise increases the signal-to-noise ratio (SNR), improving the image. A number of factors used to improve lesion detection however will lower the SNR such as increasing the spatial resolution. As sequence time increases it is more likely a patient will move producing a different type of noise, movement artifact. There are also several anatomic structures one cannot control that produce artifacts for example phase encoding artifact from flowing vessels that produce unintended signal from adjacent voxels where vessels lie into voxels where brain structures are being studied. Some of this can be overcome for example by flipping the frequency and phase encoding gradients so that phase encoding artifacts are depicted in other voxels away from the area of interest.

The time taken to acquire an MRI sequence (acquisition time) is dependent on several factors. Spin echo sequences which are the basic imaging sequence have an acquisition time defined as

Acquisition time = Repetition time * Phase encoding steps * Number of Signal averages

In addition to these variables one can control sequence design which can dramatically change acquisition times for example, increasing the repetition time by 10% may allow enough time to read two phase encoding rows instead of one which results in an acquisition time decrease to 55% of the original acquisition time.

Acquisition time = (1.1 * Repetition time) * (½ * Phase encoding steps) * NSA =.55 * Original acquisition time

Each MRI slice covers a part of the body, known as the field of view. Most brain MRIs encompass a field of view ranging from 18-30 centimeters depending on the size of the patient's head.

Each MRI image has a top and bottom, and a left to right orientation. With reference to image acquisition, these are known as the phase encoding and frequency encoding directions and are chosen by the radiologist. As mentioned above movement from structures in the slice such as from arterial pulsations results in artifacts in the adjacent voxels to the vessel in the phase encoding direction. In addition to the phase encoding direction, the radiologist can choose the number of phase encoding steps. Spatial resolution is a measure of the smallest object that can be resolved by the scanner. Spatial resolution in MRI is defined as

Spatial resolution = Field of view / phase encoding steps

The choice of direction of phase encoding and frequency encoding steps may be done to optimize spatial resolution of the structure being scanned as very few body parts are equidistant in all directions. For example, most people's heads are not equidistant cubes. The choice of the phase encoding direction thus has a major effect on spatial resolution depending on the plane being scanned.

The spatial resolution formula also shows to improve lesion detection, to detect it when it is early and small, one needs to improve spatial resolution by either decreasing the field of view or increasing the number of phase-encoding steps. This of course leads to tradeoffs, as it is in all MRI sequence choices, where in this example increasing phase encoding steps leads to an increase in acquisition time which has its own deleterious effects. Another example of choice is increasing repetition time to increase T2 weighting which not only increases acquisition time, which has its own problems, but due to radiofrequency decay with time the signal diminishes the longer the repetition time which decreases the signal and decreases the signal to noise ratio.

Anatomic structures may best be depicted in specific planes and as MRI has an infinite number of orientations to depict images this leads to another choice in sequence design. The hippocampus is best depicted in images acquired in the coronal plane, but what precise angulation in the coronal

plane relative to other structures (E.g., the base of skull, a line joining the anterior and posterior aspect of the corpus callosum) offers the optimal plane to view the hippocampus? Architectural change, causing patient symptomatology, and thus plane choice may be in the plane that shows a normal structure best but on occasion, a perpendicular plane may be better to show the full extent of a lesion or improves its detection.

The hardware chosen can have dramatic effects on signal, for example, the use of optimized head coils to transmit and received radio signals improve the signal measured in the brain.

The strength of the magnetic field (Ex. 3 Tesla) can alter signal, where in theory the signal to noise ratio increases linearly with magnetic field strength as the square of the field strength, this gain in signal to noise can improve visualization of the signal or maybe utilized in decreasing the acquisition time, increasing the resolution by increasing the phase encoding steps, or combinations of both.

As discussed, there are a number of MRI factors the radiologist can choose to improve lesion detection (E.g., Decreasing slice thickness, improving spatial resolution, using parallel imaging techniques) however, this comes at a cost namely decreasing the SNR and/or increasing acquisition time. A drop in SNR is also seen with decreasing the TR and increasing the TE, changes which will alter the T1 and T2 weighting of the image. Changes in TR may also be necessitated by minimizing the gap in between slices which will require more slices to cover the same volume. Similarly, an increase in TR may be required by having more slices when using thinner slices to cover the same volume [51-53]. Thus, optimizing imaging parameters requires balancing what is being gained and what is being lost, as both occur simultaneously, with each sequence parameter change.

Ongoing developments in hardware and software result in improved depiction of pathology and choosing ideal imaging parameters also changes regularly to take advantage of these new innovations. This of course results in another limitation of our study, as it is in all imaging research, namely the MRI acquisitions in our study will become out of date with engineering advances as well as concurrent research into sequence parameter changes.

Rationale:

The literature review demonstrated that there is uncertainty about the character of the association between early hippocampal MRI findings and further development of epilepsy, and the predictive value of these MRI abnormalities in the FSE patients. The researchers who studied the character of acute and chronic MRI changes in FSE patients most frequently evaluated the association of early MRI changes with the appearance of the signs of HS/MTS on follow-up images, and not the actual development of clinical epilepsy. The most frequently mentioned and promising findings were the increase of hippocampal signal intensity in T2 coronal images and changes in the volume of the hippocampus. Therefore, we decided to research the character of early MRI findings in the hippocampal area and their association with subsequent development of epilepsy in patients with FSE. With the purpose of assessing the predictive value of hippocampal MRI signal and volume changes separately we formed two hypotheses.

Objective 1

The first objective of this study was to understand the association between early hippocampal MRI signal changes and long-term seizure outcomes of FSE patients. The results of the Consequences of Prolonged Febrile Seizures in Childhood (FEBSTAT) study – a recent prospective multicenter study with the highest number of recruited subjects led to the first hypothesis [5]. The FEBSTAT is an ongoing study, and by 2014 16 out of 199 patients with FSE had developed epilepsy, and the majority (68,75%) of patients who developed epilepsy were subjects without initial T2 hyperintensity [5].

Hypothesis 1

FSE patients with T2 signal increase in the hippocampal area on acute MRI after the first episode of FSE do not develop epilepsies more frequently than those without.

Objective 2

The second objective of this study was to understand the association between early hippocampal volume changes and long-term seizure outcomes of FSE patients. The literature review showed that hippocampal volume may increase due to cytotoxic edema hyper acutely within a couple of hours after the episode of FSE, however, this edema is transient and prognosis in this case seems

to be favorable [35, 41]. Because of the retrospective character of our study and inclusion of the patients with initial MRI within 30 days after the episode of FSE, we had more chances of witnessing delayed secondary edema, which from the literature seems to be the sign of more serious conditions and unfavorable prognosis [35]. Also, there was a knowledge gap on the association of hippocampal volume changes in initial MRI scans of patients with FSE and further development of epilepsy, and it led to our interest in researching this problem.

Hypothesis 2

FSE patients with asymmetry between the right and left hippocampal volumes on initial MRI after the first episode of FSE develop epilepsies more frequently than those without.

Chapter 2

Methods

Our search criteria for creating patients' list from MetaVision (iMDsoft, Tel Aviv, Israel) system included patients admitted to the pediatric intensive care unit (PICU) of the University of Alberta hospital between the 1st of August, 2002 and the 31st of December, 2007; aged between 1 month and 5 years; who had febrile seizures lasting longer than 5 minutes. Our date range was chosen as there were no electronic database of PICU patients prior to the 1st August of 2002. Our cut-off date of December 31st, 2007 was chosen as we needed a minimum of 11 years of follow-up to be able to adequately assess the development of seizure consequences.

Exclusion criteria comprised infants younger than 1 month, children older than 5 years, seizures lasting less than 5 minutes, epilepsy, seizures associated with suspected intracranial infection, seizures in which the patient's axillary temperature was less than 38.0°C, and patients with previous histories of FSE or unprovoked seizures.

Our sample size included all patients who met our eligibility criteria, who had brain T2 coronal MRI performed within 30 days after the episode of FSE. To include only the first admissions of the patients we deleted duplicates and repeated visits of the same patients. The resultant list of patients was searched in the institutional PACS (Agfa, Impax) to assess availability of brain MRI scans done within 30 days of admission to the PICU and had T2 coronal images assessing the hippocampi.

Imaging

We analyzed patients' first brain T2 coronal MRI, acquired within 30 days after the first episode of FSE, to assess the signal intensity on the hippocampal areas. The T2 hyperintensity criteria were adapted from the FEBSTAT study [5]. Hippocampal T2 signal (T2Score) was rated from 0 to 4 (0=normal, 1=equivocal, 2=mildly abnormal T2 signal on >1 slices, 3=moderately abnormal, 4=markedly abnormal throughout hippocampus). T2Scores of ≥2 were considered as increased T2 signal intensity. T2Scores were evaluated by a pediatric neuroradiologist with 25 years' experience. Pediatric neuroradiologist was informed of the subject's age at the time of the examination but was blinded to all other clinical parameters and follow-up data. Examples of

patients' MRI with hippocampal T2Scores varying from 0 to 4 on the right or left or bilaterally are given on the figure 1.

The total area for the region of interest (ROI) - right and left hippocampi was analysed and calculated using the RadiAnt DICOM Viewer software (version 2020.2. Jul 19, 2020, Medixant). The whole hippocampus was measured according to each slice where the hippocampus was visible, slices posterior to and including the anterior commissure were summed for each hippocampal volume [37, 54]. The right and left hippocampus volumes of each participant were acquired separately to determine the presence or absence of hippocampal volume asymmetry. A computer mouse and a closed polygon function of the software for measurement of area and perimeter were used to manually trace the ROI (fig. 2).

For each slice, each ROI was traced three times and the mean area of the hippocampus on each slice was calculated. The total area was calculated by adding all of the areas (cm2) from each slice together. The total hippocampus volume (cm3) was calculated by multiplying the whole area by the slice thickness + gap [54, 55]. The right to left volume ratio for each subject was calculated by dividing the volume of the right hippocampus by the volume of the left hippocampus [37]. Comparisons of the mean right-to-left volume ratios were made between the group of patients with FSE who developed epilepsy later on (excluding those with abnormal T2 signal intensity in the hippocampus) and the group of patients with FSE who did not develop epilepsy later on. To assess the association between right-to-left volume asymmetry and subsequent development of epilepsy, volume ratios between 0.95 and 1.05 were considered symmetric, volume ratios <0.95 and >1.05 were considered asymmetric.

Figure 1.

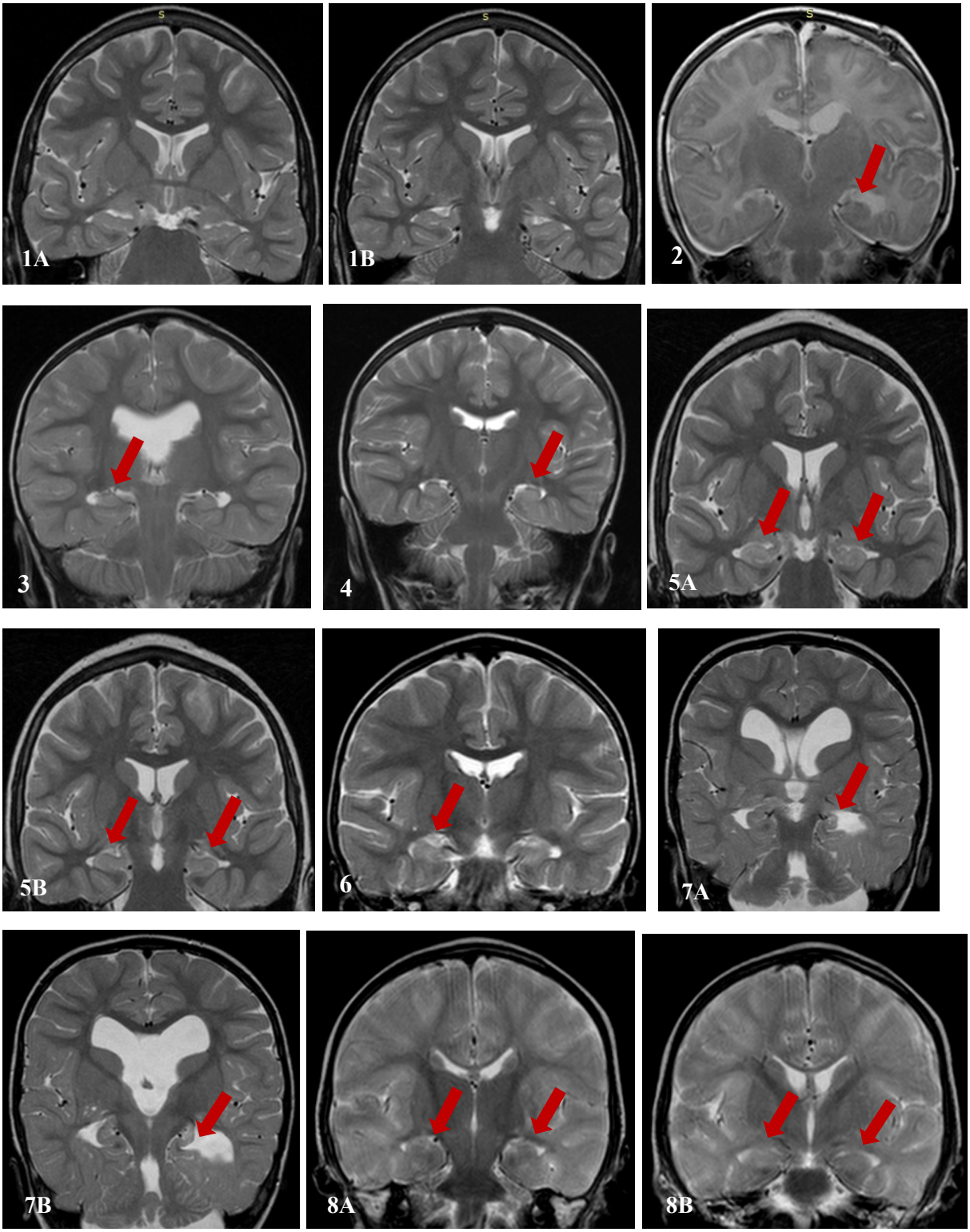

Fig.1. Examples of patients' MRI with normal and increased hippocampal T2Scores. 1A,1B – normal (T2Score=0), **2**- equivocal (T2Score=1) on the left, **3** - mildly abnormal (T2Score=2) on

the right, **4**- mildly abnormal (T2Score=2) on the left, **5A,5B** - mildly abnormal (T2Score=2) bilaterally, **6** - markedly abnormal (T2Score=4) on the right, **7A,7B** - markedly abnormal (T2Score=4) on the left, **8A,8B** - markedly abnormal (T2Score=4) bilaterally.

Figure 2.

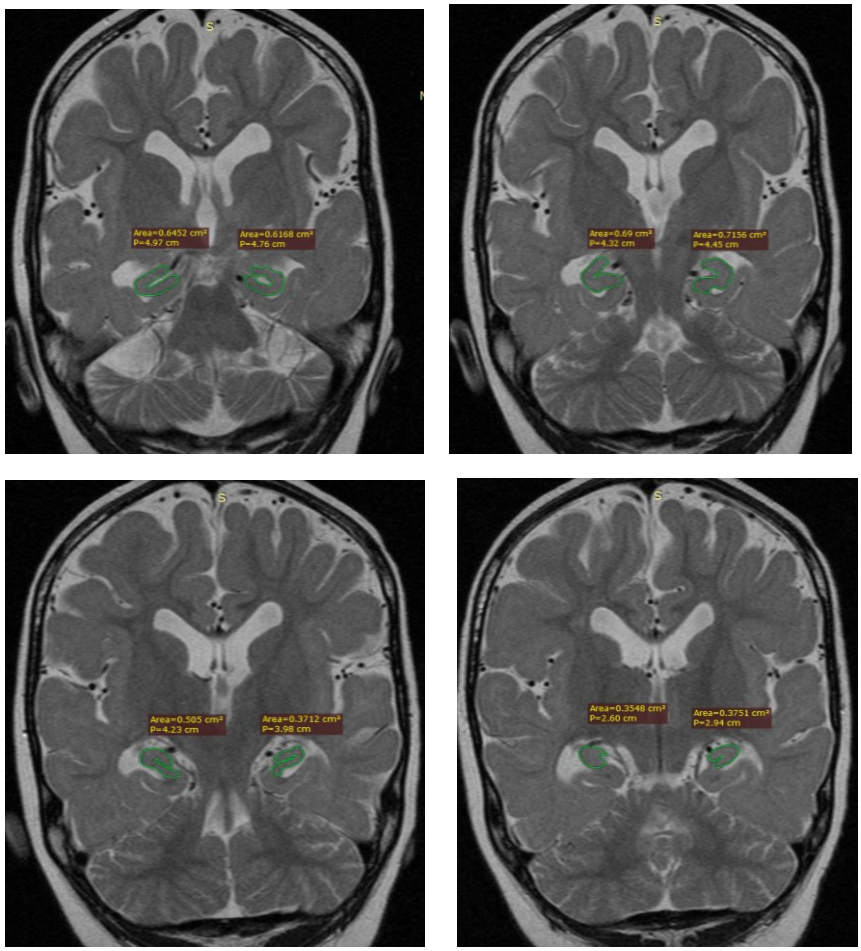

Fig.2. **ROI measurement.** The process of tracing and measuring the areas of the right and left hippocampus on the consecutive T2 coronal slices of the patient's brain.

Demographics

Medical records of the patients were reviewed to obtain patient demographics, clinical course, and EEG reports after all the MRI data was obtained. Thus, while assessing the patients' brain MR images researchers were blinded from clinical and follow-up data. Demographic data included age, gender, and postal codes of patients. The postal code allowed access to the patients' city, and province of residence by a search of the postal code database (can.postcodebase.com) website.

Clinical data

Clinical data obtained included body temperature upon admission, clinical signs and symptoms of seizures, duration of seizures, clinical and discharge diagnoses, EEG reports, brain MRI reports and brain CT reports, where available.

Then we searched through Connect Care, and e-clinician systems (patient clinical information systems) for further follow-up information on patients. Follow-up data were gathered in February, 2021. The evaluation of patients' follow-up data with regards to the development of epilepsy was performed by a pediatric epileptologist with 3 years' experience. Patients with established diagnosis of epilepsy were marked as "developed epilepsy". Patients with available information without any further mentions of seeing neurologist or epileptologist, or not taking any anti-epileptic drugs were marked as "did not develop epilepsy". Patients whose follow-up information was not available in the systems were marked as "lost for follow-up". Patients who had died were marked as "deceased".

Statistical analysis

To build the model for the multivariate regression analysis we included variables that were assumed to be the risk factors for developing further complications, and previously hypothesized and tested somewhere else [56, 57], in addition to considering the relevant results of our univariate analysis. We included the following independent variables: age in months, gender, and length of the FSE episodes in minutes. Positive family history of seizures and/or epilepsies was also considered to be one of the possible confounding factors, mentioned in other papers [17]. However, due to the retrospective character of the study this piece of information was not available. We chose only the previously known clinical predictors with the highest reported effect size to avoid

overfitting. We did not correlate highly interdependent variables to reduce risk of multicollinearity because it complicates the interpretation of the results from the regression analysis [58, 59].

Associations between potential predictor variables and outcomes were determined using univariate and multivariate logistic [odds ratio (OR); 95%CI] regressions, and t-tests were used to assess statistical significance of any difference of the means of different independent (predictive variables) between the epilepsy and no-epilepsy groups. Descriptive statistics are given in absolute values, percentages, means and standard deviations (SD). We present data as mean ± SD, median and 25 and 75 interquartile range (IQR). Univariate and multivariate analysis comparison with p-values <0.05 were considered significant. We used a complete-case approach in the multivariate logistic regression analysis to manage missing data.

Statistical analysis was performed by using the SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp)

Chapter 3

Results

A review of the MetaVision database using the search criteria of patients admitted to the PICU of the University of Alberta hospital between the 1st of August, 2002 and the 31st of December, 2007; aged between 1 month and 5 years; who had febrile seizures lasting longer than 5 minutes, identified 309 patients. There were 170 duplicate patients as well as 47 patients who had repeated (not first episode of FSE) visits. The remaining 92 patients had their images reviewed on the PACS system, 26 patients were removed from the list due to the absence of brain MRI and 12 – due to the absence of T2 coronal images. 54 patients met our eligibility criteria and were recruited in the study (fig.3).

Figure 3.

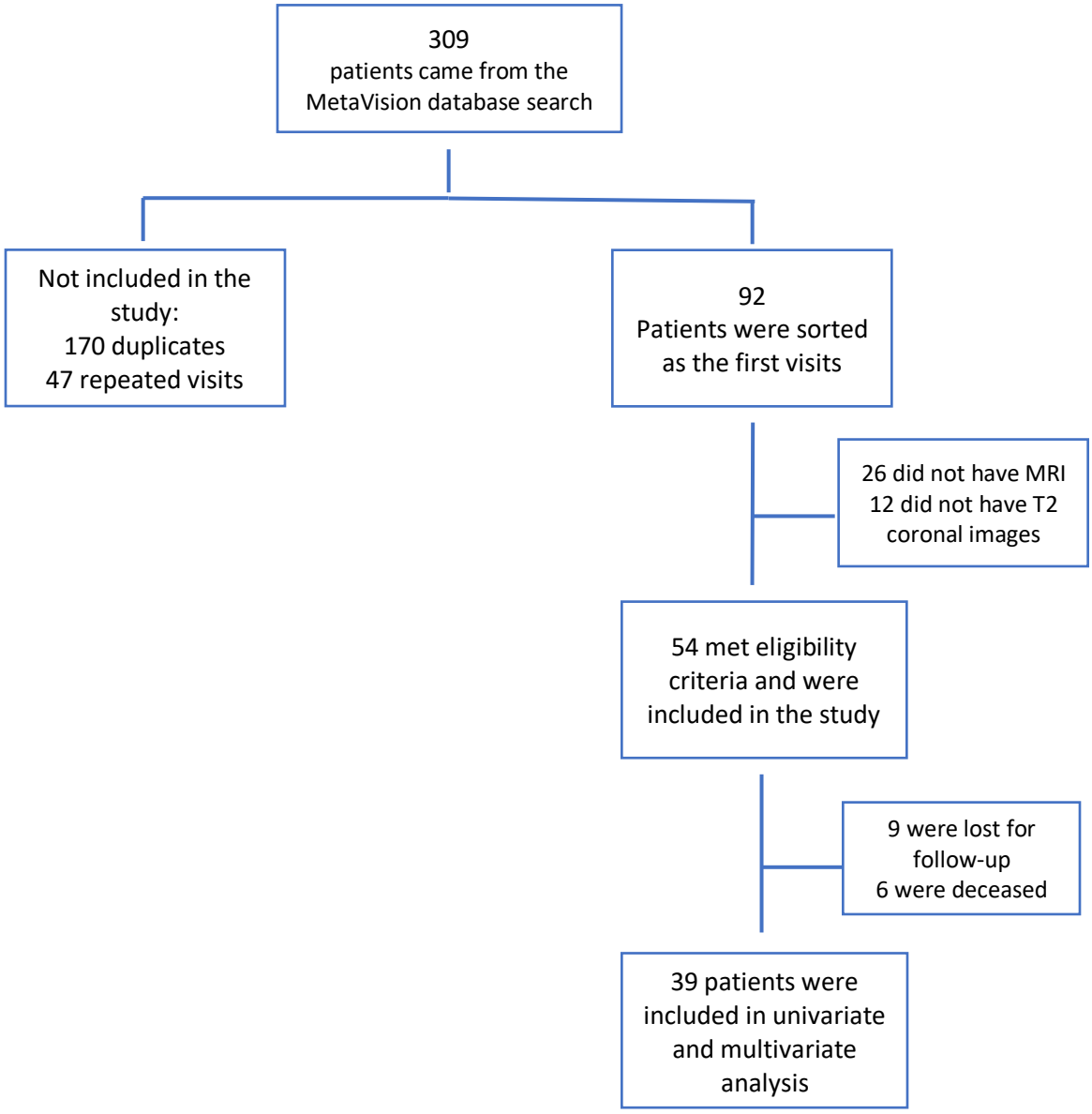

Fig.3. Process of sorting subjects according to the eligibility criteria

Our sample of FSE patients had a mean age of 17.19 months (SD=15.22), 30 (56%) subjects were males, median length of seizure reported upon admission was 32.5 minutes (5.0 – 240.0), and patients had a mean body temperature of 38.4 °C (SD=.623). The median interval between admission to PICU and MRI examination was 4 days (0 -30), 21 (39%) MRI examinations were done within the first 3 days of admission, 41 (76%) - within first 7 days, and 44 (81.5%) - within first 10 days.

In the postal code database information about territories within Canada was sorted in 3 levels: 1) region 1 – provinces, 2) region 2 – large centered areas within provinces, 3) city – cities and/or divisions within region 2. Territorially the majority of our patients 48/54 (88.9%), were from the province of Alberta, the site of our hospital. The remaining patients were from the Northwest territories 4/54 (7.4%) and the adjacent province of Saskatchewan 2/54 (3.7%); Within Alberta the highest number of subjects 34/48 (70.8%) were from the region of Edmonton, the site of our hospital. Within the Edmonton region the majority of patients 20/34 (58.8%) were from the city of Edmonton. Equal number of patients were from Inuvik - 2/4 (50%), and Fort Smith - 2/4 (50%) regions of the Northwest territories, and all of the patients from Saskatchewan were from Lloydminster region - 2/2 (100%). More detailed information on the territorial distribution of patients is illustrated on figures 4 and 5.

Figure 4.

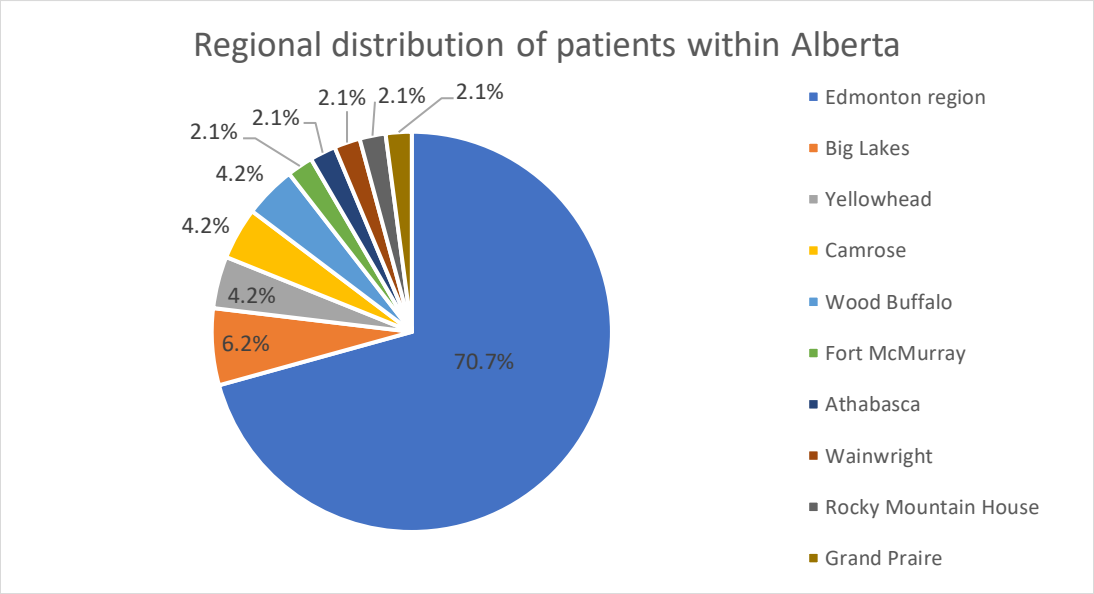

Fig4. The pie-chart illustrating the regional distribution of Albertan patients.

Figure 5.

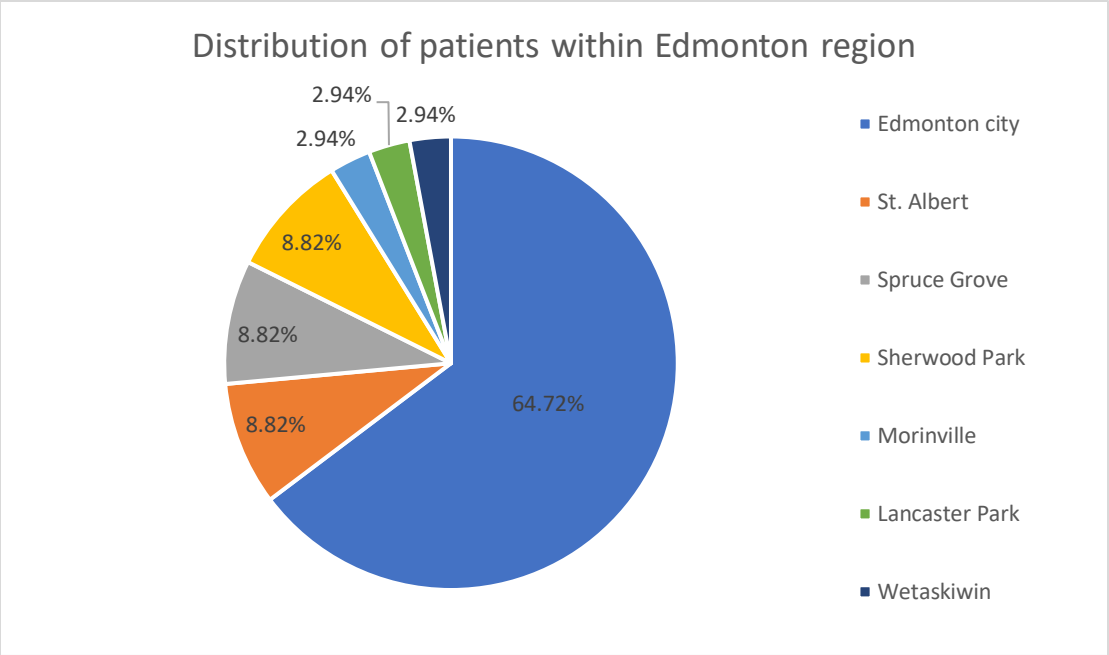

Fig.5. The pie-chart illustrating the distribution of the patients residing within Edmonton region.

Based on the clinical data acquired from medical charts, patients were interpreted as having focal versus generalized seizures or focal onset seizures with secondary generalization. Nineteen (19/54, 35.19%) patients had focal seizures, 11/54 (20.37%) - generalized seizures, and 7/54 (12.96%) – seizures with focal onset with secondary generalization. In some patients' (17/54, 31.48%) medical charts, seizures were not categorized as either focal or general, and details needed for assigning them into one versus another group were not available. Prior to the episode of FSE patients had several additional clinical manifestations, including cough, cold and flu-like symptoms - 15/54 (27.78), gastroenteritis type illness including vomiting and/or diarrhea - 13/54 (24.07). Some patients were supposedly well prior to the seizure episode -7/54 (12.96%), and some patients' conditions prior to the episode of seizures were not clearly reported in the medical charts – 19/54 (35.19%). A number of anti-epileptic drugs (AED) such as Phenobarbital, Midazolam, Diazepam, Clobozam, Dilantin, Ativan, Depakene, Topomax, Keppra, and Valium were used in the emergency department or PICU to stop and control seizures. In majority of cases (37/54, 68.5%) Phenobarbital was the first choice of AED, and in 24/54 (44.4%) cases more than one AED was required and medicines were chosen individually to treat each patient.

EEG results obtained from medical chart reports were not specific and in the majority of cases, no active seizure activity, or no abnormal epileptiform discharges, waves or spikes were reported. Twelve (22.2%) patients' EEG results were reported as within normal limits; 31/54 (57.4%) – diffuse background slowing due to sedation or more prominent asymmetric focal slowing correlating with postictal state. Only 1 (1.9%) patient's EEG result was reported as mildly abnormal due to excessive sharp wave activity in the right hemisphere, which was non-specific though out of keeping for age and there were no convincing epileptiform abnormalities or seizure tendencies and 10/54 (18.5%) patients' EEG data were not found in medical charts.

Early hippocampal T2score ≥ 2 on coronal MRI sections was seen in 14/54 (26%) patients, 8/14 (57%) of them had a T2score = 2 (mildly abnormal), 1/14 (7%) - T2score = 3 (moderately abnormal), and 5/14 (36%) - T2score = 4 (markedly abnormal). Two (14%) patients with signal abnormalities were assessed as having atrophy on visual evaluation. Equal number of patients had T2 signal abnormality either on right or left – 6/14 (43%), and only 2/14 (14%) patients had bilateral increase of T2 signal intensity. Forty (74%) patients' T2 coronal MRI signal was

evaluated as normal (T2Score < 2), and only 2/40 (5%) had a T2Score=1 (equivocal), both on the left hippocampal area.

Twenty-three (42.6%) patients developed epilepsy in the long term (our study outcome). Of the patients with an early MRI hippocampal T2Score ≥ 2, 9/14 (64.3%) developed epilepsy in the long term. Sixteen (29.6%) patients with the first episode of FSE did not develop epilepsy in the long term, and 3/14 (21.4%) patients with the early hippocampal T2Score ≥ 2 did not develop epilepsy. Examples of head MRI scans of the patients with early hippocampal T2Score ≥ 2 who did and did not develop epilepsy later on are demonstrated on figures 6 and 7. Nine (16.7%) patients were lost for follow-up, and 6/54 (11.1%) subjects were deceased till the time of gathering follow-up data. Of the patients with an early MRI hippocampal T2score ≥ 2, 2/14 (14%) were lost for follow-up.

Figure 6.

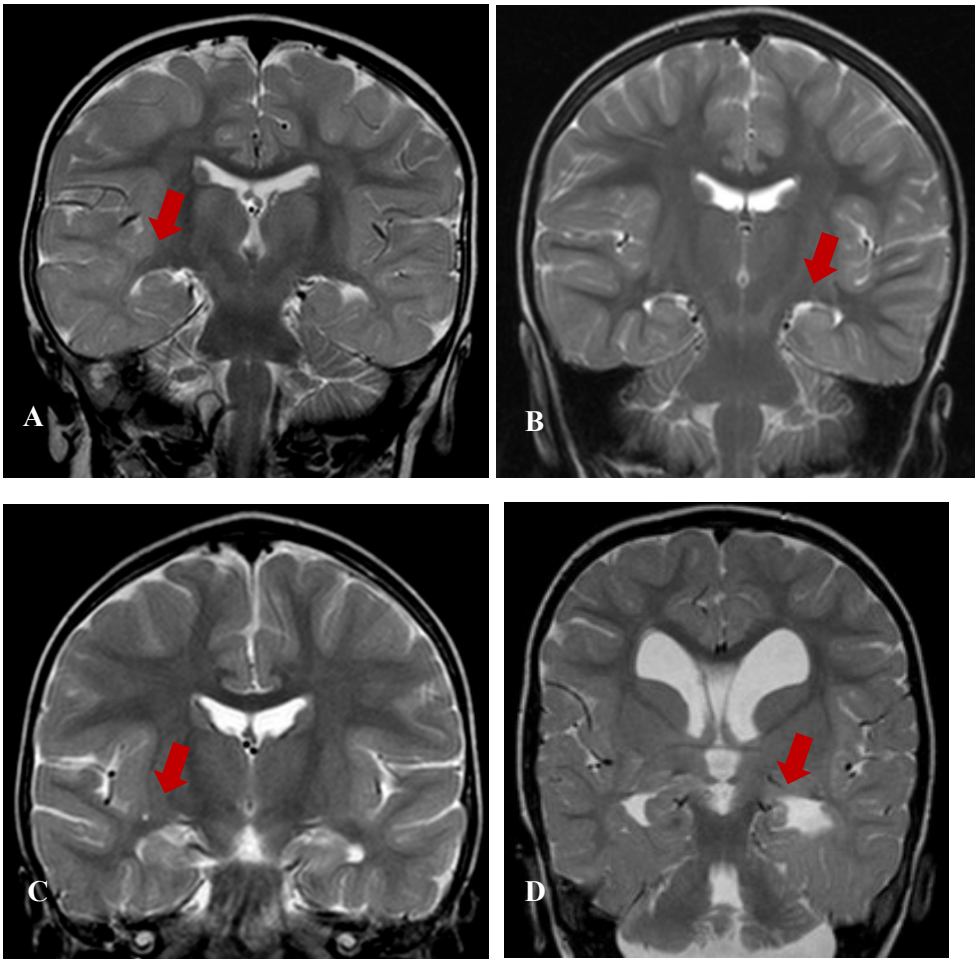

Fig.6. Examples of head MRI scans of patients with initial increase of hippocampal T2Scores, who developed epilepsy later on. A- 11 months old girl with recurrent generalized seizures without regaining consciousness between them (T2Score = 2 on right), **B**-19 months old girl with 20-30 minutes long focal seizures (T2Score = 2 on left), **C**- 2 years old boy with 30 minutes long generalized tonic-clonic seizure (T2Score = 4 on right), **D**-2 years old girl with 20 minutes long secondary generalized seizure (T2Score = 4 on left)

Figure 7.

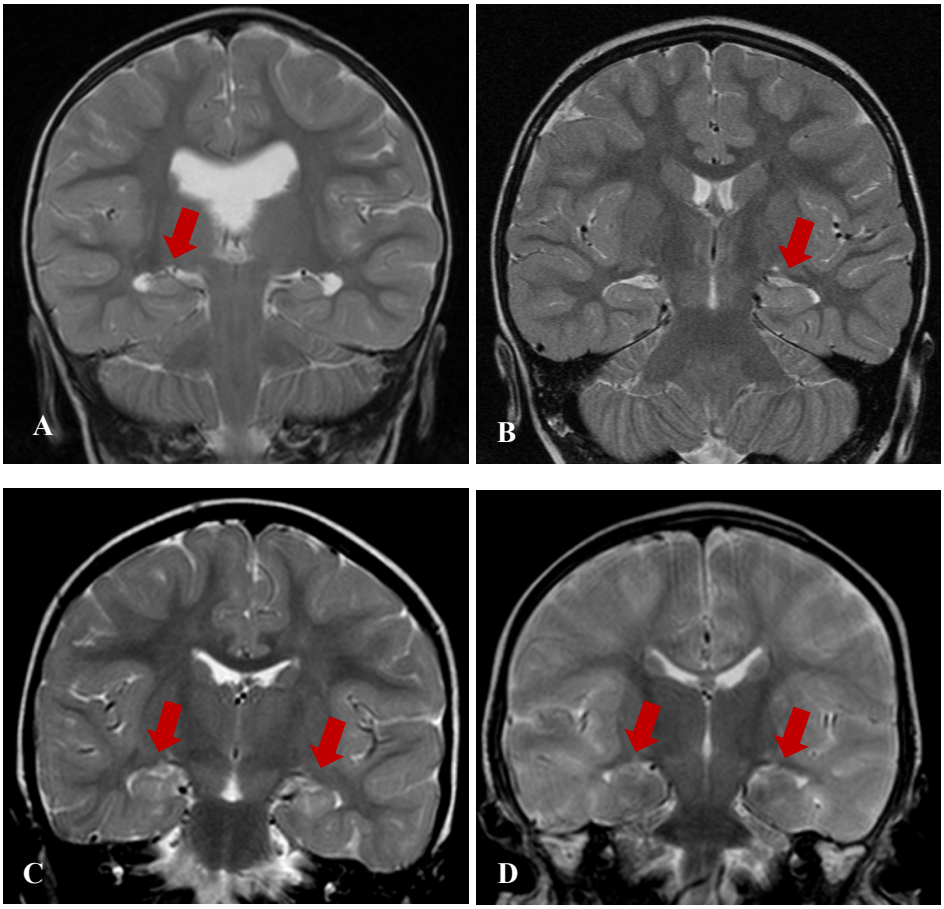

Fig.7. Examples of head MRI scans of patients with initial increase of hippocampal T2Scores, who did not develop epilepsy. A- 2 years old boy with 6 minutes long recurrent focal seizures (T2Score = 2 on right), **B**- 4 years old girl with 8 minutes long recurrent tonic-clonic seizure (T2Score = 2 on left), **C**-22 months old girl with 40 minutes long seizure (T2Score = 2 bilaterally), **D**- 5 months old boy with 90 minutes long right-sided tonic- clonic seizure (T2Score = 4 bilaterally)

Hippocampal volumes were calculated in 33/54 (61%) subjects, with exclusion of 14/54 (26%) patients with an early hippocampal T2score ≥ 2 to avoid the compounding effect of two variables and assess the predictive value of hippocampal signal hyperintensity and hippocampal volume asymmetry separately. This methodology, for making comparisons of the mean right-to-left volume ratios between the groups of patients who did and did not develop epilepsy, was similar to previously published data [37]. Further, 7/54 (13%) patients' MRI included whole head and neck images, which created obstacles to measure hippocampal area due to the imaging factors such as slice thickness and resolution of the images, and thus accurate and comparable measurements could not be made. Due to the young age and hence physiologically small size of hippocampus of our subjects, thick slices (>5mm) create obstacles for accurate detection and measurement of the borders of hippocampal area when the hippocampus is visible only on 1 slice. The resolution of the image is equal to the division of the field of view by the number of pixels in this field, and good resolution is necessary for accurate detection and delineation of the hippocampal area, avoiding blurriness caused by volume averaging with normal tissue.

Twenty-two (66.7%) of 33 measured patients had hippocampal asymmetry which comprised 41% (22/54) of all FSE patients. Eleven of 33 (33.3%) patients' hippocampal volumes were evaluated to be within the ranges of symmetry. Nine (41%) out of 22 patients with hippocampal asymmetry developed subsequent epilepsy (figure 9), while 4/11 (36%) of patients without hippocampal asymmetry developed epilepsy.

Figure 8.

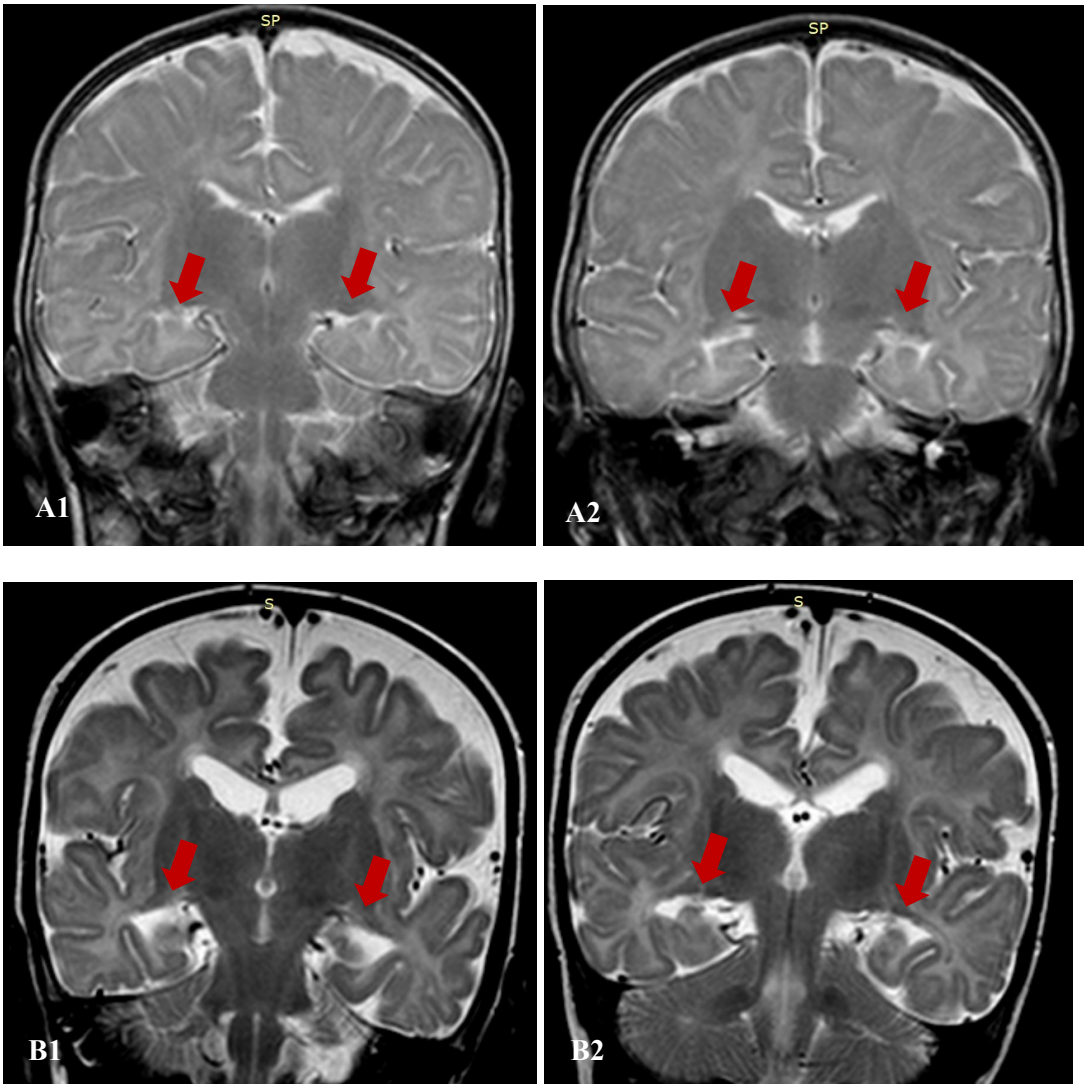

Fig.8. Examples of head MRI scans of patients, whose T2Scores were <2, but because of the thick slices and poor resolution of images the measurement of hippocampal volumes was impossible. A1,2 – 1 month old boy 15 minutes long recurrent generalized seizures, developed epilepsy later on, **B1,2** – 6 months old boy prolonged generalized tonic-clonic seizure, developed epilepsy later on.

Figure 9.

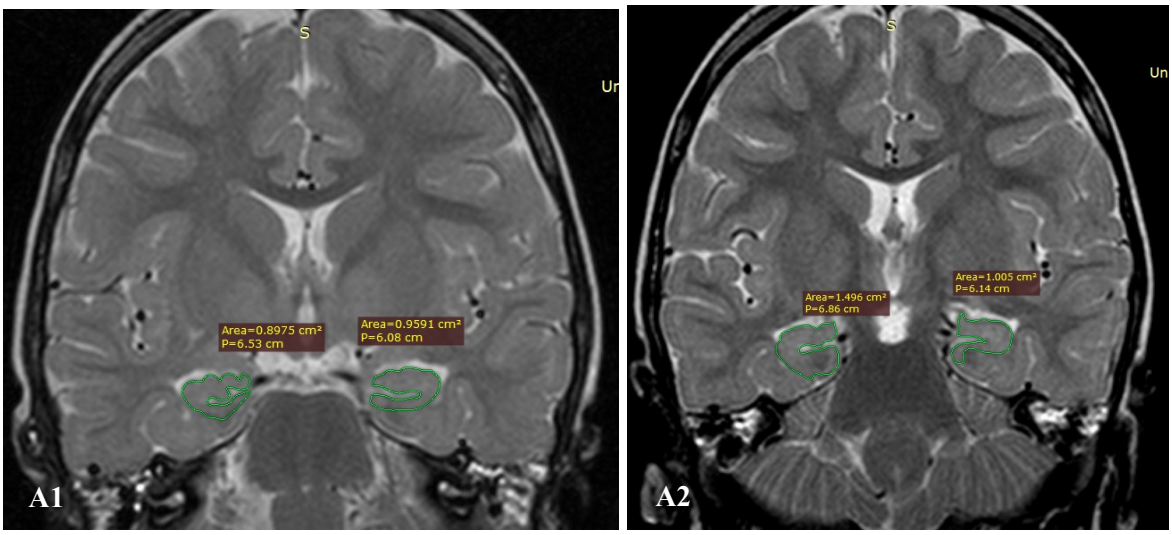

Fig.9. An example of head MRI scans of patients with hippocampal volume asymmetry, who developed epilepsy later on. A1,2 – 2 years old boy with 15 minutes long focal clonic seizure with secondary generalization.

Univariate analysis

The patients with a hippocampal T2Score ≥ 2 had approximately twice the odds of developing subsequent epilepsy. The odds ratio of patients with hippocampal volume asymmetry developing epilepsy was equal to 1.35 [95% CI (0.211 – 8.617)]. Overall, according to the results from the univariate analysis (table 3) there was no clinical or MRI parameter that predicted the development of subsequent epilepsy better than chance.

Also, a bivariate t-test was performed to compare the means of risk factors (continuous variables) and analyze the existence of any statistically significant difference between the groups of subjects who developed epilepsy later on versus those who did not develop epilepsy by the time of gathering follow-up data (February, 2021). Based on the results of these t-tests there was no statistically significant difference in the means of baseline, clinical, and MRI characteristics between the two groups (table 4). Only, the period of time between the admission of the patients and MRI examination showed borderline significance (p=.058), where it's mean was 8.43 (SD=8.891), and 4.31 (SD=2.626) in epilepsy and no-epilepsy groups, respectively.

Table 3.

Risk factors	**OR**	**95% CI**
Gender	0.786	0.201 - 3.075
Age (months)	0.998	0.946 - 1.054
Seizure length (minutes)	1.037	0.977 - 1.102
Body temperature	0.818	0.219 - 3.047
Interval between admission and MRI	1.123	0.954 – 1.322
Hippocampal T2Score ≥ 2	2.143	0.46 - 9.984
Hippocampal volume asymmetry	1.35	0.211 – 8.617

Table 3. The results of univariate binary logistic regression analysis. OR – odds ratio, 95% CI – 95% confidence interval.

Table 4.

Risk factors	**Epilepsy group Mean (SD)**	**No-epilepsy group Mean (SD)**	**P-value**
Gender	56%M:44%F	50%M:50%F	.738
Age (months)	15.52 (12.784)	15.77 (12.995)	.956
Body temperature (°C)	38.462 (.634)	38.533 (.572)	.774
Seizure length (minutes)	40.00 (21.985)	27.17 (18.498)	.233
Interval between admission and MRI (days)	8.43 (8.891)	4.31 (2.626)	.058
T2Scores (0 to 4)	.91 (1.345)	.46 (.877)	.286
Right hippocampal volume (cm^3)	8.575 (3.030)	7.616 (2.184)	.447
Left hippocampal volume (cm^3)	8.091 (2.987)	7.383 (1.964)	.560
Right/Left hippocampal volume ratio	1.069 (.126)	1.055 (.067)	.753

Table 4. The results of bivariate t-tests. SD – standard deviation, M-male, F-female.

Multivariate analysis

The multivariate logistic regression analysis was performed twice - separately for testing both hypotheses, however in both cases the analyses included same baseline (gender, age) and clinical (body temperature, interval between the admission and MRI) independent variables for adjustment. The first analysis showed that after the adjustment for gender, age, body temperature, and number of days between the first episode of seizure and performed MRI, the patients with early hippocampal T2 hyperintensity had 4 times the odds of developing subsequent epilepsy though this was not statistically significant (table 5). The adjusted odds ratio of hippocampal volume asymmetry was 0.838, also not significant (table 6). Seizure length was not included in the multivariate analysis, because statistically this variable was not a good fit for the model (possibly due to high number of missing values).

Table 5.

Risk factors	**aOR**	**95% CI**
Gender	0.970	0.143 – 6.573
Age (months)	0.977	0.900 – 1.062
Body temperature	1.440	0.287 - 7.241
Interval between admission and MRI (days)	1.181	0.954 – 1.461
Hippocampal T2Score ≥ 2	4.056	0.520 – 31.660

Table 5. The results from the first multivariate binary logistic regression. aOR – adjusted odds ratio, 95% CI – 95% confidence interval.

Table 6.

Risk factors	**aOR**	**95% CI**
Gender	0.939	0.093 - 9.539
Age (months)	1.105	0.940 - 1.299
Body temperature	0.715	0.070 - 7.274
Interval between admission and MRI	1.173	0.858 - 1.603
Hippocampal volume asymmetry	0.838	0.054 - 13.054

Table 6. The results from the second multivariate binary logistic regression. aOR – adjusted odds ratio, 95% CI – 95% confidence interval.

Chapter 4

Discussion

The association of FSE with subsequent development of epilepsy in children has been debated since SE began to be diagnosed and FSE was considered to be a substantial part of SE population among children. The prognostic value of early MRI changes in hippocampal signal intensity and volume in patients with FSE, though being researched repeatedly, remains unclear due to the existence of conflicting results of the studies.

The mean or median age of FSE patients, reported in other studies ranged between 15-25 months [31, 33, 36], the mean age of the patients in our study (17 months) was compatible with the results of these studies. Gender variability in our study was 56% males: 44% females, and it was close to the results of the earlier reported studies: 52%M:48%F [31]; 68%M:32%F [40]; 51%M:49%F [38].

We gathered the information about body temperature of patients recorded upon admission either before, during or after the episode of seizure independently on the method of temperature measurement due to the retrospective character of this study, and a mean body temperature of 38.4 °C (SD=.623) complies with the requirements for definition of FS and hence FSE. Among previous studies the prospective ones designed their research with specific type and timing of temperature measurement [33, 38], and some retrospective studies included body temperature recorded in the medical charts not accounting for the way of measuring the body temperature.

In patients recruited in the FEBSTAT study seizures lasted a median of 68.0 minutes [60], in another study, where patients with seizures lasting longer than 5minutes were included, the mean seizure duration was 12.2 minutes (SD=26.9) [10]. In our cohort the median length of seizure was 32.5 minutes (5.0 – 240.0), thus our result was in between the averages of studies where accepted minimum length of seizure was either 5 or 30 minutes.

Majority of our patients demographically were from the site of our hospital – Edmonton city, Alberta province, and it seems to be logical that patients mostly refer to the hospitals located closer to their neighborhood. Clinically, the majority of our patients had either focal or focal with secondary generalization types of seizures (48,15% counting together), and lateralizing features were not always possible to determine based on the medical chart records. While some studies

report to have subjects only with generalized seizures (secondary or not), some state to have majority of patients with partial onset seizures [33, 36]. Thus, until focal versus generalized type of seizure proven to be the leading risk factor for developing future epilepsy, any clinical differentiation of patients seems to be acceptable. Also, even in the prospectively designed FEBSTAT study with the largest number of recruited subjects only 30% of patients were identifiable as having lateralization signs [36]. EEG data in our study in the majority of cases was not specific for pathology and did not contribute to the differentiation of the type or lateralization of the seizures.

The majority of previous studies tried to either perform MRI within 3 days (72 hours) of FSE episode or retrospectively recruit only those subjects whose MRI was within first 3 days [31, 32, 36, 40]. However, even prospectively designed studies still include cases with MRI done more than 1 week after FSE [5, 36]. We had to broaden our inclusion criteria for imaging data up to 30 days after FSE to be able to recruit more patients for statistical analyses purposes and also to overcome recruitment bias, because of the absence of imaging guidelines for FSE only patients with severe forms might have got MRI shortly after FSE leading to later imaging of patients with milder forms of the disease. The majority of our subjects were imaged within 7 days (76%) and it is comparable to the results of other studies (86%) [36].

The scoring system of hippocampal signal intensity on coronal T2 images was taken from previous studies and adopted to the conditions of existing MR images [5, 32]. For example, to have T2Score=2, we needed mildly abnormal T2 signal on ≥1 slices, however due to the thickness of slices sometimes the hippocampus was visible or available for visual signal assessment only on 1 slice. Our result of 26% of patients with abnormal T2 signal was higher than the result of the FEBSTAT study (11.5%) [36], less than the result of other smaller prospective study (40%) [32], and almost the same to the study with DWI assessment (27%) [40]. So far, it seems that the greater the number of recruited subjects the smaller the number of the patients with initial hippocampal signal hyperintensity, however, this notion needs to be tested scrupulously and proven to be true.

Also, according to the Okujava et al T2 assessments are an objective way to detect temporal lobe anatomical changes [49], and T2-relaxometry is even more useful for assessing bilateral hippocampal changes, can be effectively and easily estimated, and therefore can contribute in predicting outcomes [49]. However, we could not estimate T2 relaxation times in this study, but

Okujaya's results suggest this may be a promising MRI technique, and should be considered as part of routine scanning in future prospective studies.

Our result of hippocampal asymmetry (41%) is higher than the result of the study where 14% of patients with prolonged FS had hippocampal asymmetry [61]. The possible explanation for this dissimilarity may be the difference in the diagnosis of recruited patients, prolonged FS versus FSE. However, in the previous study hippocampal volumetry was performed on the MPRAGE and FLASH images, while we used T2 coronal images, in that study hippocampal volume was measured from the 3D contour after reformatting the images to make them perpendicular to the long axis of the hippocampus, while we did not reformat original images and used available scans. Also, the authors did not describe what features were considered as symmetry versus asymmetry of hippocampal volumes, however, it is obvious that even paired organs in humans are not absolutely symmetrical and some small degree of asymmetry might be present in "normal" scans. Other studies mostly reported hippocampal malrotation and different volumetric measurement results such as the distance of the hippocampus from the midline, hippocampal height:width ratio, hippocampal angle, collateral sulcus angle, and width of the temporal horn, thus the comparison of our results is impossible [37, 39].

In our sample, 42.6% of patients developed an epileptic syndrome following FSE (our study outcome). This percentage is higher than that seen in population-based studies with short-term follow-up, which found that 2–3% of children develop epilepsy by the age of seven [62, 63] ; this result is higher than the majority of other hospital-based studies as well (6–27%) [40, 56, 62]. Although, a study with small number of patients (n=11), where 54.6% of subjects had further seizures demonstrated the results is closer to ours, the authors of that study did not specify if all seizures were epilepsies [33].

Moreover, our retrospective study is based on our university hospital data, which is a regionally centralized and specialized tertiary pediatric hospital, so unintentionally patients with more severe forms of FSE may be included in the study. The higher epilepsy incidence rates we saw may also be due to the longer follow-up period (14-19 years) of our study.

The possible outcomes of CSE were recently reviewed by Chin [64], who described recurrence; short-term mortality; subsequent epilepsy; neurological, cognitive, and behavioral impairments outside of epilepsy; long-term mortality; association with hippocampal injury and MTS; and white

matter changes. The reported incidence of epilepsy 9 years after CSE was 25% (95% CI: 16-36), with 89% of cases occurring within 18 months of CSE. Previous reports of the incidence of post-CSE epilepsy have ranged from 13% to 74% [65]. In addition, this study reported that children with a neurologically healthy premorbid baseline have a lower incidence of subsequent epilepsy compared to those with initial neurological impairments (14% versus 46%, respectively) [64]. In the FEBSTAT study, children with FSE had an elevated risk of later FSE compared to controls, meaning that patients who had experienced an initial sustained seizure were more likely to have a prolonged recurrence [66]. When FSE was compared to simple FS, or when FSE was analyzed alone, any baseline MRI abnormality was found to be associated with an increased chance of recurrence [66].

A retrospective analysis of clinical parameters in FS patients suggested that certain clinical characteristics of FSs may be predictive of a particular type of subsequent epilepsy and revealed an association between development of TLE-MTS and younger age of FSs onset, and a high incidence of episodes of febrile status and of complex FSs [67]. In the same study, there was established an association between development of partial epilepsies and clinical features of FSs at a younger age at onset, presence of focal features and of febrile status, longer interval between the first FS and the first afebrile seizure, and a family history of a high incidence of FSs. For generalized epilepsies these characteristics included a shorter interval between the first FS and the first afebrile seizure, a high incidence of single FS and of a family history of epilepsy [67].

MTS displaying as hippocampal atrophy on MRI and clinically manifesting as TLE, is believed to be the most common consequence of FSE [4, 68]. Also, an alternative body of thought postulates that generalized epilepsies may develop in children with generalized febrile seizures, and focal epilepsies may develop in patients with focal febrile seizures [15]. However, the evaluation of the association of the early hippocampal MRI changes with any specific type of epilepsy was not prioritized in our study, so we did not take into account types of epilepsies developed in our cohort.

Univariate logistic regression analysis was performed to evaluate the predictive value of demographic, clinical characteristics, and imaging findings independently from each other. None of these factors, including age, gender, seizure length, body temperature, hippocampal T2Score ≥ 2, and hippocampal asymmetry, predicted the further development of epilepsy better than chance. Even though, there was not detected statistical significance, the odds ratio of approximately 2 of

patients with T2Score ≥2 developing epilepsy, seems to have clinical significance and the T2Score may have the potential to predict epilepsy in larger cohorts.

T-test was performed to compare demographic, clinical, and MRI findings between the groups of patients who developed and did not develop epilepsy. All characteristics were similar and there was not a statistically significant difference detected between the groups. However, borderline significance was found in the mean number of days between the admission and MRI examination, where shorter interval was found in the no-epilepsy group. It might be thought that those patients who had earlier MRI exams were managed better to prevent the development of epilepsy, however, most MRI scans were reported as normal and hippocampal areas were not evaluated more specifically, moreover, it is impossible to make inference about causal relation. Another study also reported a significant difference in the duration between seizure end and MRI examination between groups of patients with and without restricted diffusion, however this interval was calculated in hours while we calculated in number of days, and thus they have a better temporal resolution [41]. The same study also found male sex to be significant difference between those two groups, however our study did not reveal particular dominance in gender [41]. In the FEBSTAT study the presence of any MRI abnormality, including abnormal T2 signal was significantly different between the FSE and simple FS groups [36].

Multivariate logistic regressions were performed to evaluate the association of both hippocampal signal hyperintensity and volume asymmetry with subsequent development of epilepsy after adjusting for age, gender, body temperature, and the day of imaging. Though they also did not reveal any statistically significant associations, adjusted OR equal to approximately 4 of patients with T2Score ≥2 developing epilepsy again seems to have clinical significance and might be promising as predictive factor. However, bigger prospective studies with detailed focus on hippocampal imaging are necessary to prove this idea.

The majority of previous studies reported clinical and imaging differences between groups of patients divided according to the clinical diagnoses or presence/absence of specific imaging findings, and never subsequent development of epilepsy (as we did). Crude or adjusted ORs were not calculated for patients neither with hippocampal T2 signal hyperintensity nor hippocampal volume asymmetry in previous studies. However, OR is the statistical observation, capable of showing the probability of the development of future epilepsy in one group versus another.

Although, the crude and adjusted ORs were calculated for other various hippocampal volumetric findings to associate them with FSE, and lateral ventricle width was found to have approximately 2 to 4.5 an OR on both right and left sides [39].

Limitations

Retrospective hospital-based enrollment of patients of this study was one of its limitations, and because we recruited patients from a university hospital PICU database there might be unintended potential bias towards including more severe cases of FSE. However, due to the inclusion of patients with shorter seizure length (>5 minutes vs ≥30 minutes) and the regionalization of pediatric care to our hospital, this criterion could get balanced autonomously.

Systematically accurate coding of diagnoses, recording of exact length of seizure and body temperature immediately after the seizure are crucial. Diagnoses were primarily indicated as seizures in the PICU database, with no diagnoses reported as FS or FSE. Patients with the same clinical pattern had different not always specific diagnoses upon being discharged. This created difficulties in the patient search, inclusion/exclusion criteria, and evaluating processes, and thus we had to look more carefully in medical charts to make sure that patients fit a diagnosis of FSE.

Length of seizures were frequently recorded in approximate numbers, or measured accurately not at the presenting seizure but at later in hospital seizures, or merely stated as recurrent or prolonged. Parents often do not recall the exact time of seizure onset during the first seizure at home because of the initial desire to access medical help as well as the anxiety from these first episode seizure events. Almost all patients' body temperatures were recorded every day during their stay at hospital, but the exact temperature and the way of measurement either during or after the first episode of FSE or upon admission were not always recorded, rather simply stated as "febrile". However, in evaluating febrile seizure versus other types, body temperature measured immediately after the episode plays a crucial role [2]. Missing data in the variables of seizure length and body temperature led to the case-wise exclusion of some subjects from particular statistical analyses and led to the exclusion of seizure length variable from multivariate analyses.

MRI done within first 3-7 days would be preferred for more accurate detection and interpretation of imaging findings as compared to other imaging modalities such as CT. However, due to the

absence of imaging guidelines indicating specific timeframes required to evaluate the hippocampal area prior to the imaging of patients, MRI was done in varying period of time after the first episode of FSE; and as we included the first performed MRI in all study subjects, there were patients whose MRI was done up to 30 days after their admission.

Substantial variety in imaging protocols leading to the differences in thickness and number of slices visualizing the hippocampus was a limitation. We had to adapt T2score evaluation accordingly, because some MRI slices had a ≥5mm thickness and due to the small age and hence the head size of patients, hippocampi were visualized on only 1 slice. Dedicated thin section coronal T2 imaging of the hippocampus, which would improve visualization, may increase MRI detection of hippocampus abnormalities in these patients.

Also, it was difficult to determine when the patients subsequently developed epilepsy due to the retrospective design of this study, to evaluate survival analysis and calculate the average time necessary for follow-up to observe the maximum number of patients who developed epilepsies. Six (11%) patients were deceased by the time of follow-up, and due to the lack of the access to the files of deceased patients through electronic systems we were not able to evaluate the causes of death and its association with FSE. However, with the exception of developing countries, there were no documented cases of febrile seizure-related deaths on record [17]. Also, we were unable to evaluate the presence of HHV6 or HHV7 viremia, which was assessed in some other studies, and sometimes believed to have prognostic value as well. Some of our patients had laboratory data available in their medical charts, but because we did not prioritize the assessment of the association of these causes with further development of epilepsy, we did not collect such information. Moreover, again due to the retrospective character of study, viral lab tests were not available for all of our subjects.

Conclusion

Our study shows that FSE patients with early T2 signal hyperintensities may have increased odds of developing future epilepsy, and it is even greater after adjusting for demographic (age, gender) and clinical (body temperature, interval between FSE and MRI) features of the patients. Even though the results were not statistically significant, the two to four times the odds ratio of developing subsequent epilepsy may be of great clinical significance. Hippocampal asymmetry, on the other hand, was found to have a minimally increased OR, without statistical significance.

According to the results of our literature review in children acutely after FSE following MRI findings may be seen:

- increased T2 signal intensity in the hippocampus by MRI,
- an increase in hippocampal size due to cytotoxic edema,
- hippocampal malrotation.

While acute brain edema seems to be transient and harmless, the significance of the association between increased T2 signal intensity and hippocampal malrotation and seizure activity remains unclear.

On follow-up MR imaging the following imaging findings may be seen:

- persistent increase in T2 signal, which may be a sign of gliosis or HS;
- hippocampal atrophy or a decrease in hippocampus size;
- delay in hippocampal growth compared to controls.

Patients with increased T2 signal intensity will also have increased signal in hyperacute DWI. MRS seems to be a promising modality for the early detection of seizure-related metabolic changes, but larger studies with prolonged follow-up are necessary to evaluate the prognostic value of these findings. Animal studies have demonstrated the predictive value of asymmetry in T2 relaxation times in various brain areas and changes in the reduction in T2 relaxation times over time, but these findings need to be replicated clinically.

Detailed attention to the hippocampus, in larger studies, may prove helpful in finding MRI changes that predict long term outcomes in children with FSE.

Future directions

Unified standardized neuroimaging guidelines are necessary for the evaluation of patients with FSE. These guidelines should include criteria defining the patients who need to be imaged, the optimal imaging modality, imaging protocols, timing, and the specific brain areas and structures to be evaluated and reported, along with their characteristics.

Due to the changes in the definitions of SE and FSE, seizures lasting between 5 and 30 minutes should be accounted for in SE and FSE. Studies reporting imaging findings in FSE and those comparing complex versus simple FS employed different inclusion/exclusion criteria, so comparing these results may not be appropriate. Larger prospective studies with detailed attention to the hippocampus are necessary to establish exactly which features in early MRI are associated with long-term outcomes in children with FSE. These studies should also include DWI, ADC, FLAIR sequences, with proper angulation of images to better evaluate both early signal changes and quantitative volumetric findings, and their association between further development of epilepsy.

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