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Prospects for imaging-related biomarkers of human epileptogenesis: a critical review

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Abstract

To facilitate the study of epileptogenesis in humans, noninvasive biomarkers of epileptogenesis are required. No validated biomarker is currently available, but brain imaging techniques provide many attractive candidates. In this article we examine the imaging features of temporal lobe epilepsy, focusing on those that may precede the onset of epilepsy and correlate with epileptogenesis. Hippocampal volumetry and T₂ relaxometry are proposed as candidate biomarkers of epileptogenesis in temporal lobe epilepsy following febrile status epilepticus. Preliminary data suggest that these have promise, and the ongoing Consequences of Prolonged Febrile Seizures in Childhood (FEBSTAT) study will provide more conclusive evidence as to their validity. At this time there are no other clear candidates for imaging-related biomarkers of epileptogenesis in human studies.

Keywords

biomarker; epilepsy; epileptogenesis; febrile status epilepticus; MRI

Epileptogenesis is the process by which a brain acquires the propensity for spontaneous seizures. This process has been extensively studied in animal model systems, and a variety of molecular and cellular events critical to epileptogenesis have been described [1]. It is now clear that by the time epilepsy occurs following an insult, such as head trauma or status epilepticus, a long process of epileptogenesis has already taken place [2]. Once clinical epilepsy has occurred, the epileptogenic process may be well established and less amenable to intervention.

Therefore, the period of epileptogenesis that precedes epilepsy represents an important opportunity to intervene. Accordingly, it is a primary goal of contemporary epilepsy research to inhibit epileptogenesis in humans, prior to the onset of epilepsy [3]. To

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accomplish this goal, it will be necessary to identify biomarkers that can be both surrogate markers for the progression of epileptogenesis and targets for intervention in patients at high risk, prior to the onset of epilepsy [4]. The availability of a reliable biomarker would greatly facilitate targeted trials of novel epileptogenic therapies. In particular, the efficacy of a putative antiepileptogenic treatment could be assessed in the short term, rather than waiting (potentially for years) for the onset of epilepsy.

A practical biomarker would ideally possess several additional features. First, it would be widely available and relatively easy to implement, to ensure broad availability. It would also be reproducible, such that its utility is not influenced by minor variations in technique. It would be quantitative, to facilitate objective analysis and standardization across sites. Finally, it would be capable of demonstrating the progression of epileptogenesis, not just its presence, in order to measure the longitudinal effects of antiepileptogenic therapy.

Brain imaging techniques, including MRI and PET, have become routine in the evaluation of patients with epilepsy. Given the ubiquity of brain imaging and the frequent association of imaging abnormalities with epilepsy, imaging techniques are attractive candidates for biomarkers of epileptogenesis. A host of abnormalities have been defined in patients with epilepsy using brain imaging, in particular, using morphometric analysis, magnetic resonance (MR) relaxometry, diffusion-weighted imaging, MR spectroscopy and PET imaging [5,6]. Many of these abnormalities could, in theory, serve as biomarkers of epilepsy [7]. However, in most cases, there is little evidence to support a specific connection between these epilepsy-related abnormalities and epileptogenesis.

Temporal lobe epilepsy (TLE) is a common form of partial epilepsy and is frequently medically refractory [8,9]. Due to its clinical importance, TLE is and has been extensively studied in humans and animal model systems. The best available data are for mesial TLE (MTLE). It is proposed that certain common MRI findings in patients with MTLE could be used as biomarkers of epileptogenesis [7,10]. In this article, we examine the prospective biomarkers of epileptogenesis in TLE, particularly with respect to TLE that occurs following febrile status epilepticus (FSE).

Pertinent imaging & clinical features of TLE

Several pertinent clinical features are observed in many patients with TLE. First, there is frequently an antecedent event, most commonly febrile seizures in early childhood. This event is followed by a latent (or silent) period, lasting on average 8–11 years [11,12], in which seizures are infrequent or entirely absent. Eventually, the latent period ends with the onset of unprovoked seizures. It is unclear to what extent early febrile seizures initiate or contribute to epileptogenesis. However, it is known that particularly prolonged febrile seizures (those that meet the definition for FSE of 30 min or longer) lead to brain injury, with the hippocampus being the most susceptible target. It is hypothesized that this injury plays a causal role in the pathogenesis of clinical TLE. While the relationship is clearly plausible, the long latency period has been a major impediment to prospectively ascertaining the relationship and demonstrating causality. Conversely, the long latency period offers an excellent opportunity to study the epileptogenic process in real time. This opportunity is pursued in the current Consequences of Prolonged Febrile Seizures in Childhood (FEBSTAT) study, which will be discussed later in this article [13].

Mesial TLE is commonly (albeit not exclusively) associated with mesial temporal sclerosis (MTS), characterized by hippocampal atrophy, neuronal loss and gliosis [14]. Radiologically, MTS is indicated by the combination of increased hippocampal signal on T₂-weighted images and decreased hippocampal volume (Figure 1B) [15]. These features therefore serve as the primary criteria for diagnosing MTS on MRI. The connection of MTS

to MTLE is complicated by the identification of patients with MTLE, who lack overt MTS, and may in fact represent a distinct epilepsy syndrome [16]. Nevertheless, most consider MTS to be a critical element of MTLE and, probably, closely related to epileptogenesis.

Mesial temporal sclerosis is, in most cases, readily demonstrable on anatomic MRI [15]. Hippocampal atrophy can be perceived subjectively and can be quantitated using widely available volumetric techniques [17]. Prolonged T_2 relaxation time is also typically present, which may be quantitated by T_2 relaxometry or identified qualitatively through visual analysis of T_2 -weighted images [18]. The histopathological substrate of prolonged T_2 relaxation time in MTS is not entirely clear, although it may be related to gliosis [19]. Note that the pathological substrate of T_2 signal abnormality observed in MTS, which is accompanied by atrophy, likely differs from that of T_2 abnormality observed following an initial episode of FSE, when the hippocampus is enlarged. Data from animal models of FSE provide important clues as to the underlying substrate [1,20].

The sclerotic hippocampus is reliably abnormal on MR spectroscopy, reflecting neuronal loss, metabolic deficiency of the remaining neurons and gliosis [21]. Abnormality on 18-fluorodeoxyglucose PET imaging also reflects hippocampal metabolic deficit, in the form of decreased glucose utilization [22]. Numerous ancillary signs are described (e.g., atrophy of the hippocampal fornix, obscuration of the internal hippocampal architecture) that assist in the radiologic identification of hippocampal sclerosis [23].

It is clear that in patients with clinical TLE, MTS is a progressive process with continuing hippocampal volume loss [24,25]. Furthermore, progressive hippocampal volume loss correlates with progressive memory impairment [26]. It is less clear whether MTS progresses during the preclinical stage of epileptogenesis (i.e., during the latent period). In theory, MTS could represent a pre-existing abnormality that predisposes to febrile seizures, an acquired condition that develops during the latent period or a combination of both [27]. For MTS to be a useful biomarker of epileptogenesis, rather than just a risk factor, one would need to observe progression in the latent period. This is also necessary if volume loss is to be a therapeutic target. While the matter is not settled, there is increasing evidence that hippocampal volume loss is common and progressive following FSE (Figure 1) [27,28]. Thus, MTS may represent a progressive anatomic and functional defect that evolves during the latent period, concomitant with and mechanistically linked to epileptogenesis. The imaging features of MTS therefore provide attractive candidates for noninvasive biomarkers of epileptogenesis.

Many other abnormalities on brain imaging are described in patients with TLE. These include anomalies of white matter architecture, of functional connectivity and of extrahippocampal metabolism on MR spectroscopy and PET imaging [6,29–31]. Many of these findings could ultimately provide useful biomarkers of epileptogenesis [7]. However, it should be born in mind that none of these abnormalities is as strongly associated with TLE as MTS. Furthermore, these techniques are frequently challenging to implement in a systematic fashion and, therefore difficult to standardize. It seems likely that clinically useful biomarkers of epileptogenesis will be found in techniques that draw on the well-documented features of MTS, at least in the short term.

Imaging biomarkers in TLE: where do we stand?

A biomarker of epileptogenesis in TLE must, by definition, be present during the latent period. As TLE is relatively rare, prospective population-based studies of potential biomarkers for epileptogenesis are not feasible but we must instead focus on populations known to be at increased risk of developing TLE, such as those with a clear predisposing insult. However, 30% of patients with medically refractory MTLE give a prior history of

febrile seizures, often prolonged [11,12,32,33]. Furthermore, such a history is a favorable prognostic factor for a good outcome following temporal lobectomy in patients with medically refractory TLE and MTS [11,12]. Conversely, children who present with very prolonged febrile seizures are known to be at high risk for subsequent epilepsy [33,34]. This is a population that can be studied prospectively, to determine whether the imaging findings of MTLE are useful biomarkers.

Several prior studies have examined MRI findings in patients following prolonged febrile seizures. These studies are all limited by small patient cohorts and limited duration of follow-up. No one study conclusively demonstrates a correlation between specific imaging findings and later progression to epilepsy. Therefore, they cannot be taken as conclusive validation of a particular candidate biomarker. Nevertheless, they provide important pilot data that are currently being validated in a larger prospective study [13].

Vanlandingham *et al.* reported MRI findings in 27 infants shortly after complex febrile seizures [35]. Of these, four children had evidence of acute unilateral or bilateral hippocampal abnormality, including increased hippocampal volume and elevated T₂-weighted signal, probably reflecting acute hippocampal edema. Delayed follow-up scans in two patients demonstrated hippocampal atrophy with persistent elevation in T₂-weighted signal, consistent with MTS (Figure 1). This study demonstrated the acute effects of febrile seizures on the hippocampus, and tentatively suggested an association between acute hippocampal abnormalities and eventual MTS.

MRI findings were also reported in 21 children within 5 days of a prolonged febrile seizure, with delayed imaging obtained after 4–8 months in 14 children [36,37]. In patients imaged less than 48 h following a febrile seizure, hippocampal volume was increased and T₂ relaxation time was prolonged. On delayed follow-up, hippocampal T₂ properties normalized. Group average hippocampal volume also normalized, although an abnormal asymmetry of hippocampal size was observed in the patients, relative to controls. This asymmetry may reflect the initial stages of hippocampal atrophy.

Provenzale *et al.* subsequently described longitudinal MRI findings in 11 children following FSE [28]. Acute findings were similar to the previous studies, with increased hippocampal volume and elevated T₂-weighted signal (qualitatively reflecting prolonged T₂ relaxation time) present in seven children. Of these, five children progressed to MTS by MRI criteria on delayed imaging. Furthermore, the degree of signal abnormality on initial imaging correlated with degree of volume loss on delayed imaging. Of the five children with MTS, four developed epilepsy within the period of observation. These children continue to be followed as the pilot cohort of the FEBSTAT study [13].

Several additional reports have demonstrated a similar progression of hippocampal edema to MTS, following febrile seizures in smaller cohorts [38–40]. Taken together, the evidence is clear that MTS may be acquired following prolonged febrile seizures in some patients. There is some controversy concerning hippocampal T₂ imaging properties following FSE. Scott *et al.* have reported that the initial T₂ abnormality resolves [36,37], whereas Provenzale *et al.* reported diminished but persistent T₂ abnormality accompanied by progressive volume loss [28]. The temporal changes observed in these studies may reflect progression from acute hippocampal edema, through an interim period in which edema has resolved, to late MTS.

The evidence also suggests that hippocampal atrophy may be acquired following FSE. This interpretation is complicated, however, by several factors. There may well be some degree of increased hippocampal volume in the acute setting, due to edema. In addition, FSE occurs in young children (median age 15 months), in whom the hippocampus is still growing [13].

Furthermore, in the small series that have included serial imaging, there is evidence of partial recovery of hippocampal volume loss [27,28]. Therefore, one must time serial imaging carefully to observe the initial volume loss. For these reasons, absolute hippocampal volume at a single time point is unlikely to provide a useful biomarker for epileptogenesis. However, progressive deviation of hippocampal volume from the mean on longitudinal follow-up may be a more useful indicator. It will also be necessary to define normative values for hippocampal growth in children and reference patient values to this norm.

Thus, there is evidence that the MRI findings relating to MTS can progress following complex febrile seizures. Abnormalities of the hippocampus may therefore provide useful biomarkers of epileptogenesis following FSE. T_2 relaxation time and volume of the hippocampus are promising measures in this context. Both can be measured using relatively straight forward techniques on standard MRI equipment. These are also quantitative measures that could be standardized across differing equipment and institutions. Both could provide longitudinal assessment, with the caveat that evaluation in the acute period will likely be confounded by the effects of acute hippocampal edema and that developmental changes in children must be taken into account.

Imaging biomarkers in TLE: where do we go from here?

It is clear that prolonged febrile seizures can cause hippocampal damage in some patients, leading to the MRI appearance of MTS. However, several crucial questions remain to be addressed. Specifically, does the presence of hippocampal signal abnormality and/or volume loss, whether at acute or chronic time points, reliably predict the ultimate onset of TLE? Can TLE develop without hippocampal abnormality on MRI? Does progression of hippocampal abnormality on MRI accurately reflect progression of epileptogenesis? Finally, if a candidate antiepileptogenic drug prevents progression of the hippocampal imaging abnormalities, will it prevent the development of epilepsy, or at least the development of memory deficits? If this were to be demonstrated, one could then design therapeutic trials that do not require an 8–11-year observation period. This approach has been successful in the case of multiple sclerosis, for which MRI end points are accepted as valid end points in clinical trials [41].

The FEBSTAT project is a large, prospective, National Institute of Neurological Disorders and Stroke (NINDS)-funded, longitudinal study of FSE and its relationship to TLE that was designed to address these issues. The study population consists of 200 children, aged 1–5 years, who presented with FSE to one of five participating centers between 2003 and 2009. The study design includes serial evaluation of clinical, MRI, electroencephalographic and neuropsychological data. These assessments were performed within 72 h of the initial episode of FSE and are repeated at 1, 5 and 10 years. They are also repeated if the child develops epilepsy and 1 and 5 years after that. Samples were also obtained for virological analysis (human herpes viruses 6 and 7) [42,43]. Genetic specimens are banked for future analysis.

In addition, we are currently monitoring a group of 23 children who were part of the pilot study at Duke University, which ultimately led to FEBSTAT [28]. These children are beginning to develop epilepsy. Long-term follow-up is currently underway, which will be of sufficient duration to characterize the progression to epilepsy in the FEBSTAT and Duke cohorts. Clinical features of the FEBSTAT study population on initial presentation have been described [13].

In FEBSTAT subjects, an MRI examination is performed at presentation and during periodic follow-up visits. A defined MRI research protocol is used, including high-resolution

anatomic imaging, T₂ relaxometry and diffusion-weighted imaging. Initial data analysis will include measurement of hippocampal volumes and T₂ relaxation times, in comparison to age-matched patients with brief febrile seizures, who are unlikely to develop TLE. Imaging features will be sought that distinguish patients who eventually develop epilepsy from those who do not. The longitudinal nature of the study, with repeated MRI examinations in each patient, will allow the evolution of MRI findings to be assessed. It is hoped that this approach will allow the identification of MRI measures that both progress during the latent period following FSE and predict the onset of epilepsy.

Previous findings in the Duke cohort demonstrate a significant proportion with increased T₂ signal on acute imaging [44,45]. Concurrent clinical, EEG and neuropsychological testing is also providing data on the correlation of these imaging findings with EEG and cognitive findings, prior to the development of clinical epilepsy [13]. In animal models, the presence of increased T₂ on initial imaging correlates with impairment of cognitive function [10,46]. These findings are not yet confirmed in humans, but the FEBSTAT study is adequately powered to ultimately address these issues. If they are verified, then imaging measures of increased T₂ and hippocampal volume could be used as biomarkers of epileptogenesis for future observational and therapeutic studies.

Several additional imaging measures will also be evaluated in the FEBSTAT cohort, beyond the hippocampal measures described in this article. A voxel-based morphometry analysis of the structural data is currently underway, which attempts to identify subtle morphological abnormalities that may not be apparent on visual inspection of the MRI data. Abnormalities of extrahippocampal structures, including neo-cortex and basal ganglia, are known to exist in patients with established TLE and these extrahippocampal abnormalities may contribute to epileptogenesis [47]. In addition, diffusion tensor imaging (DTI) has been collected in a subset of the FEBSTAT cohort. Numerous abnormalities of white matter structure on DTI are known to exist in patients with TLE, although the time course and significance of these abnormalities are at present unclear [29]. Analysis of the voxel-based morphometry and DTI data obtained in the FEBSTAT cohort will address the important questions of whether extrahippocampal white matter abnormalities precede the onset of epilepsy and, if so, whether they predict the ultimate onset of epilepsy.

Other forms of epilepsy

Unfortunately, there is a paucity of data that would allow the use of imaging as a biomarker for epileptogenesis in other settings. Many of the findings associated with epilepsy syndromes may be better regarded as risk factors for future epilepsy, and not indicators of epileptogenesis. For example, the degree and nature of imaging abnormalities following severe head trauma predict the risk of future epilepsy, but there is little evidence that they can be used to measure epileptogenesis [48]. In tuberous sclerosis, both the specific mutation (*TSC1* vs *TSC2*) and the number and location of the hamartomas influence the risk of epilepsy, but there is little evidence that they can be used as a marker of epileptogenesis [49,50]. Furthermore, many forms of epilepsy lack specific findings on standard neuroimaging.

Standard neuroimaging may, therefore, be unable to provide useful biomarkers of epileptogenesis in some epilepsy syndromes. It is hoped that other methods, including functional MRI techniques and novel PET agents, may provide useful candidates. For example, resting state functional MRI, which aims to demonstrate functional connectivity between brain regions, may allow direct demonstration of epileptogenic circuits as they develop [51]. DTI, which demonstrates white matter structure, is also promising in this respect [29]. MR spectroscopy techniques allow noninvasive quantitation of certain brain

metabolites and may permit the identification of metabolic abnormalities related to epileptogenesis [52]. These possibilities, while promising, remain somewhat speculative. To evaluate novel imaging techniques as potential biomarkers of epileptogenesis, longitudinal analysis in humans during the period of epileptogenesis will be required.

Future perspective

The potential for noninvasive biomarkers of epileptogenesis to revolutionize epilepsy research and treatment is enormous. This field is in its infancy, however, and no validated biomarker of epileptogenesis is presently available. In the case of TLE, attractive candidate biomarkers have been identified through the analysis of children following FSE. The ongoing FEBSTAT study is designed and powered to assess these candidates in a rigorous fashion.

The clinical model of prolonged febrile seizures causing acute hippocampal injury and ultimately leading to the onset of TLE appears the most promising setting in which to study imaging biomarkers of epileptogenesis. The prolonged latent period of TLE presents challenges from the perspective of conducting a clinical study, but also offers opportunities to intervene at several points (e.g., acute injury, early development of radiologic progression) and, possibly, to prevent the onset of clinical TLE.

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Executive summary

The need for biomarkers of epileptogenesis

- To prevent epilepsy, we must stop epileptogenesis.
- At present, we cannot directly identify or measure the progress of epileptogenesis in humans.
- Noninvasive biomarkers are needed to facilitate trials of antiepileptogenic therapy.

Clinical features of temporal lobe epilepsy

- The initial event is often febrile status epilepticus.
- This is followed by a seizure-free latent period lasting 8–11 years (delayed onset of clinical epilepsy).

Candidate biomarkers in temporal lobe epilepsy

- Temporal lobe epilepsy is associated with mesial temporal sclerosis.
- Mesial temporal sclerosis likely develops during the latent period.
- MRI findings of mesial temporal sclerosis may serve as biomarkers of epileptogenesis.
- Hippocampal atrophy and T₂ signal abnormality are the best candidate biomarkers.

Consequences of Prolonged Febrile Seizures in Childhood study

- Prolonged Febrile Seizures in Childhood (FEBSTAT) is a large, ongoing, prospective, longitudinal, National Institute of Neurological Disorders and Stroke (NINDS)-funded clinical study.
- A total of 200 children, age 1–5 years were recruited after febrile status epilepticus.
- Clinical, MRI, EEG and neuropsychological evaluations were performed on presentation and after 1, 5 and 10 years.
- This study is designed to evaluate hippocampal MRI findings as biomarkers of epileptogenesis after febrile status epilepticus.
- Initial results are promising.

Conclusion

- Biomarkers of epileptogenesis are required for future clinical trials.
- No validated imaging biomarker of epileptogenesis exists.
- Hippocampal volume and T₂ measurements may serve as biomarkers in temporal lobe epilepsy.
- FEBSTAT is currently assessing these candidate biomarkers.

Figure 1. Hippocampal atrophy following febrile status epilepticus

Coronal T₂-weighted magnetic resonance images obtained (A) 2 days and (B) 9 months after febrile status epilepticus in a 2-year-old girl. Initial imaging demonstrates asymmetric enlargement of the right hippocampus with abnormal T₂-weighted signal intensity (A). On delayed imaging, the right hippocampus, which continues to demonstrate abnormal T₂-weighted signal intensity, has decreased in size and is asymmetrically small (B). This patient subsequently developed temporal lobe epilepsy. Adapted with permission from [35].