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Chapter 20

The future of FS, FSE, and their epileptogenic and cognitive outcomes

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Chapter outline

Epidemiology

Across decades of epidemiological studies, employing widely varying methods of case ascertainment and analysis, the incidence of FS remains fairly constant at 2%–5% of children in the susceptible age range [1] (Penn & Stafstrom chapter in this book). There has been a recent upsurge in interest in geographical, ethnic, racial, and sex-related diversity in FS and FSE that may provide new insights into our understanding of these seizures, aided by new information about genetics.

Some data suggest that the incidence of long, untreated FSE and subsequent mesial temporal sclerosis (MTS), and hence the need for surgery for MTS, has declined, as evidenced by fewer MTS surgeries across multiple centers [2]. Others have suggested that the apparent decline is a result of better MRI and the increased detection of "dual pathology," i.e., lesions additional to MTS [3]. Future work will be required to determine ongoing trends worldwide in the incidence of FSE and MTS (McGrath et al., this book). Epidemiological studies

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will continue to provide critical information about FS and FSE, with the need for meticulous attention to how cases are defined, analyzed, and interpreted.

The genetic revolution and FS

Knowledge about FS genetics has clearly blossomed in recent decades, providing information about FS/FSE risk and phenotype. Specific mutations can lead to epilepsy and to FS, as well as epilepsies that present with FS as a first sign (e.g., genetic epilepsy with febrile seizures, GEFS, and see chapters by Rosch & Goldberg and by Fuerte & Mefford). Major advances in this area come from our increasing understanding, using both human studies and experimental models of the relation of Dravet syndrome and other sodium channel mutations to FS (Rosch & Goldberg; Fuerte & Mefford, Chen et al., chapters) [4,5]. Indeed, there are now numerous genetic mutations associated with FS (Chen et al., Wenzel et al., Fuerte & Mefford chapters) so that the view has been raised that all FS occur in predisposed individuals. However, this is likely not the case, as temperature elevation or fever in children (e.g., hot baths, anticholinergic or sympathetic drugs in infants), and in rodent models (Chen et al. and Juul et al., Ravizza et al. chapters in this book), provokes seizures during sensitive developmental periods regardless of genetic background. In addition, it is likely that the majority of children with FS do not harbor variants or mutations that predispose to FS. Finally, there is a strong correlation between environmental factors (daycare and other exposures, cosleeping with parents) and the prevalence of FS. Thus, the consensus remains that there is both a strong genetic predisposition to FS in some children, whereas in others, little role for a genetic predisposition is present. Future work will undoubtedly add to our understanding of the genetic contribution to FS.

Epileptogenesis: Neurobiological, neuroimmunological, and epigenetic mechanisms

The age window during which FS occur remains a unique and incompletely explained observation in children, and animal models are poised to help address the age-dependence of FS susceptibility and consequences (Juul et al., chapter). Animal models allow some control over variables that are not possible in humans, including temperature rise (rate and range), age, duration, correlative pathophysiology, and novel treatment modalities. In both typical and potentially predisposed developing brain, there is an increasing recognition of a role for neuroimmune mechanisms in FS occurrence and outcomes (Reid, et al., Ravizza et al., Gallentine, Brennan et al., and Chen et al., chapters). This is an arena in which clinical studies complement animal models in arriving at potential mechanisms (chapters by Gallentine, Reid et al., and Ravizza et al.). The emerging role of cytokines and interleukins in seizure susceptibility, especially with FS/FSE, will reveal new insights into the pathophysiology of this disorder.

Importantly, such studies should lead to therapeutic targets. For example, prevention or treatment of FS with agents such as dexamethasone, which dampen neuroimmune responses, is being investigated in both animals and humans [6].

New technologies as well as the development of several types of models for FS and FSE in several species allow for improved experimental study of FS, FSE, and their consequences (Reid et al., Chen et al., Ravizza et al., and Juul et al., chapters). In addition to neuroinflammation, such studies focus on specific molecules such as ion channels (Wenzel et al., Rosch & Goldberg, Fuerte & Mefford, Chen et al. chapters), microRNA (Henshall & Brennan chapter), and epigenomic/transcriptomic approaches (Ravizza et al. chapter). The enhanced ability to detect and interrogate more subtle cognitive impairments (Lewis & Scott and Kloc et al., chapters) also adds significantly to our understanding of FS, FSE, and their outcomes. Many of these approaches rely on animal models, which offer a panoply of opportunities to address issues such as age dependence, temperature sensitivity, potential response to specific types of infection, and the role of seizure duration [7]. Relevant topics that require future work include the temperature sensitivity of ion channel function, network transmission of FS and FSE, enduring effects of gene expression in neurons and microglia, and the relationship between structural and functional changes in brain network properties.

Predictive markers of epileptogenic and cognitive outcomes after FS and FSE

Findings from the comprehensive longitudinal FEBSTAT study of FSE have been pivotal in recent understanding of underlying clinical phenotypes, seizure characteristics, radiological accompaniments, and outcomes (Shinnar, Gallentine Lewis & Scott and Nordli & Moshe chapters). The FEBSTAT study, the largest prospective comprehensive analysis of ~200 infants and children with FSE, has both shattered existing dogmas and identified novel discoveries. The type and duration of FSE, the accompanying EEG and MRI changes, the long-lasting changes on MRI, and the emergence of cognitive issues that impact quality of life are now being recognized. Indeed, this important clinical trove of critical information supports prior and ongoing work in animal models of FS [8].

As validated in both the FEBSTAT and British studies, neuroimaging in the form of high-resolution magnetic resonance imaging (MRI) scans will remain a foundation for future FS studies (Lewis & Scott Chapter). Likewise, EEGs will continue to be valuable. Whereas the only identified EEG biomarker to date, focal slowing, does not appear to be specific for FS (Nordli & Moshe Chapter), animal studies have identified EEG changes that foretell epileptogenesis [6–8].

Management implications: Current and future

From a clinical standpoint, the emerging findings from studies over the past 20 years, as summarized in this volume, add to our ability to explain to families

the phenomenology, management options, and outcomes of FS and FSE (Shinnar, and Seinfeld & Goodkin chapters). Yet, the basic principles of management have not changed fundamentally.

Our ability to provide outcome assessments for FSE should improve as the long-term results from the FEBSTAT study become available. Several challenges face clinicians and families now, and in the coming decades: If a single episode of FSE can increase risk for epilepsy, then can or should we prevent the first occurrence of FSE? In addition, if neuroimmune mechanisms indeed play a critical role in the pathophysiology of FSE and cognitive and epileptogenic outcomes, should we treat FS/FSE with drugs such as dexamethasone [6]? Finally, as only a subset of children with FSE will develop cognitive problems or epilepsy, can we identify those at risk early and target them for intervention? And if so, then what and when are ideal intervention strategies?

These questions remain unanswered at the present time and provide impetus for further clinical and experimental work on FS, FSE, and their outcomes. The editors look forward to these studies and hope that the answers will not require twenty years to emerge.

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