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IAN Reviews in Neurology 2022

Epilepsy–Innovations and Advances

Editor
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JAYPEE

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CHAPTER

2

Infantile Epileptic Spasms Syndrome: From Past to Future

Jithangi Wanigasinghe

ABSTRACT

Infantile Epileptic Spasms Syndrome (IESS) is the new nomenclature proposed by the International League Against Epilepsy, to the most researched childhood epilepsy syndrome. This may soon replace the old terminology of West syndrome, named in honor of its descriptor. Despite the significant advances in basic neurosciences and genetics, we still struggle with this unique childhood epilepsy syndrome due to lack of clear understanding of its pathogenesis, refractoriness to antiseizure medications, and difficulties in managing the multitude associated comorbidities.

Conventionally, the discussions have focused on which medication immediately controls the epileptic spasms. However, we understand the need to reach beyond in order to conquer the effects of diseased neuronal network, which significantly affect life expectancy, freedom from spasms and other epilepsies, and comorbidities due to "epilepsy plus". While it is important to develop new therapeutic options, supported by the expanding understanding of the genetic landscape of IESS, it seems appropriate that we march from the front to prevent development of spasms as much as we attempt to control them. This calls for medical, social, and political commitment so that common antecedents contributory toward development of IESS are minimized.

Keywords: West syndrome, Epileptic spasms, Infantile spasms

HISTORY

It is only 20 more years to celebrate 200 years since Dr William West wrote to the Lancet in 1841 describing infantile spasms, as "a peculiar form of infantile seizures", which he saw in his own son.[1] Even in this initial description, many of the features currently known about this condition, including disease characteristics, refractoriness to treatment, and associated comorbidities were briefly described. Though commonly known as West syndrome, in honor of this initial description, changes to the nomenclature have been proposed from time to time. In 2017, West syndrome was included into a broad group of epilepsies known as developmental and epileptic encephalopathy.[2] Very recently, the International League Against Epilepsy (ILAE) Task Force on nosology and definitions proposed the terminology of infantile epileptic spasms syndrome (IESS).[3] This latest nomenclature highlights the trade mark seizure type and the characteristic age of presentation of epileptic spasms (ES).

From this point onward, in this chapter which discusses etiopathogenesis, disease characteristics, treatment options, and finally the long-term outcome and the future, the terminology of IESS will be preferred to describe this spectrum of disorder and ES to describe the associated seizure type.

ETIOLOGY

Etiology is identified to be the most significant determinant of the long-term outcome of IESS. For many years all the etiologies responsible for causing ES have been divided as those with a *proven etiology* which forms the larger proportion and those *without an identified etiology* comprising of a smaller proportion. With advancement of neuroimaging techniques and better diagnostics for both genetics and inborn errors of metabolism, there has been expansion of understanding on etiologies generating further subclassification. In 2015, the National Infantile Spasms Consortium reported that proven etiology is identified

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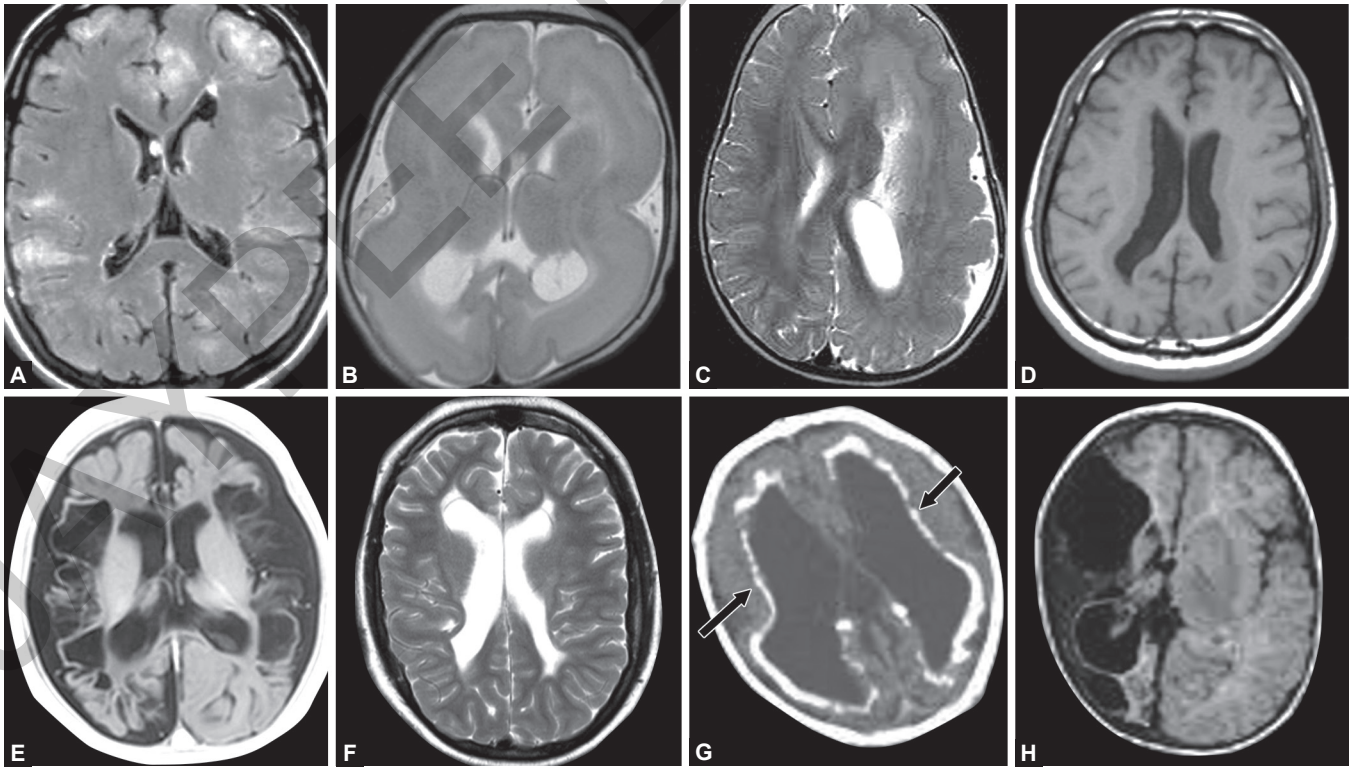
only in 65% after detailed evaluation. This comprised of structural 33.2%; either acquired or congenital, genetic 24.4%; which includes structural genetic, infective (2%), and metabolic (4.8%) categories.[4] These proportions were based on bench marked investigations for each category. This study showed that 35% of children with ES from US did not have an identified etiology. However, in a more recent study from China on 541 children, this proportion increased to 43% despite advanced testing for etiology.[5] It is interesting to note that the fraction with unknown etiology differs significantly in cohorts reported from low-income settings.[6] Further, a clear understanding on the burden related to known etiology is difficult in poorly resourced countries. A large proportion of children in low-income countries (LICs) does not achieve a clear identification of the underlying etiology; thence categorized as *etiology not identified*.[7] Disease-specific differences in presentation, response to treatment, and long-term outcome have been described for a few etiologies such as tuberous sclerosis and Down syndrome. Genetics in the pathogenesis of IESS is being understood at an exponential pace. A specific genetic defect was identified in 26.9% of children with IESS using whole exome sequencing.[5] *STXBP1* followed by *CDKL5* were the most common gene mutations directly associated with its pathogenesis.[5] Despite these advances, disease specifics of more common acquired structural etiologies such as perinatal birth injuries, hypoglycemia-related injury, and prematurity-related injury are hugely lacking **(Figs. 1A to H)**.

PATHOPHYSIOLOGY AND RECENT ADVANCES IN BASIC SCIENCES

In spite of advances in experimental modeling and animal studies, the exact pathogenesis of ES remains elusive. Several models of disease causation have been postulated. The alteration of several specific functions, which independently affect the pathogenic mechanism formulated part of the early understandings. One of these models described altered hypothalamic-pituitary-adrenal axis function, resulting in a stress-related abundance of corticotrophin-releasing hormone (CRH), which triggers epileptogenic changes in brainstem circuits.[8] Other theories on pathogenesis include abnormal cortico–subcortical projections caused by focal or diffuse cortical pathology[9] and spasm generation through dysfunction at brainstem level that causes abnormal activity in ascending tracts projecting to cortical neurons. In another hypothesis, an immune dysfunction in response to insult to the immature brain is suggested to contribute.[10] All these proposed mechanisms indicate a possible single pathogenic process responsible for the causation. This resulted in many deficits in the explanation of the complex processes that encapsulated its presentation in infancy, causation by multiple etiologies, differential response to therapy, and potential autoresolution with increase of age. In 2005, a theory of a developmental desynchronization was proposed as its pathogenic process. Here, two or more developmental processes that fail to synchronize, during early brain maturation, eventually results in altered or disturbed brain



Figs. 1A to H: Structural etiologies of IESS. [A to D (Top row)] Genetic structural etiologies: (A) Tuberous sclerosis complex; (B) Lissencephaly; (C) Hemimegalencephaly; (D) Periventricular gray matter heterotopia. [E to H (Bottom row)] Acquired structural etiologies: (E) Hypoxic ischemic encephalopathy; (F) Periventricular white matter injury; (G) Periventricular calcification in congenital cytomegalovirus CMV infection; (H) Perinatal arterial ischemic stroke in the right middle cerebral artery territory.

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function.[11] In this hypothesis, the causality played by diverse etiological factors occurring at variable time points of early brain maturation, was explained through their effect on the desynchronization.

Over the years, further achievements at the bench and animal sciences paved way for better understanding. This includes success over several animal models developed to understand the pathogenesis as well as genetic models to experiment therapy screening and cross validation. Some of them considering the complexity of deciphering the pathogenic process of IESS, a "team science" approach was employed by the Citizens United for Research in Epilepsy (CURE) to advance our understanding.[12] This was a first-of-its-kind collaborative initiative. The scientific outcomes are likely to enhance the pathophysiological understanding of IESS.

CONCEPT OF DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY

The 2017 ILAE commission on classification and terminology elaborated the position on the newly introduced phenomenology of developmental and epileptic encephalopathy.[2] IESS is a prototype epilepsy syndrome that characterized "epileptic encephalopathy", where the epileptic activity contributes to the encephalopathy over and above the effect caused or imparted by the underlying etiology. This encephalopathy is evident as effect on cognition and/or behavior which in IESS may manifest as developmental regression, cerebral visual impairment, and/or psychiatric and behavioral consequences such as autism or autism-like behavior. The encephalopathy is best appreciated in those with IESS of unknown etiology, who often have a normal development prior to the onset of ES. The early amelioration of the abundant epileptic activity as is desired in treatment of IESS helps to retard or minimize the adverse consequences of the encephalopathy on development and behavior. Hence, early diagnosis and treatment without delay should be the essential goal of treatment. On the other hand, some of the single gene mutations that cause ES such as STXBP1 and KCNQ2 may also result in a developmental encephalopathy, even before the onset of IESS signifying a specific role played by the underlying etiology on the development, over and above the impact caused by the epileptic encephalopathy.[2]

DIAGNOSIS

As intimated earlier, early diagnosis is crucial. Many research papers highlight the delay in diagnosis, evident in both resourceful and resource-limited countries. The subtle and unusual nature of ES as a seizure type is a concern for delay in presentation. Unfamiliarity among first contact persons on the characteristic features of ES and misdiagnosis as nonepileptic phenomena, both by parents and healthcare workers contribute toward the delay in diagnosis. Prolonged lead time to treatment (LTTT), the time from onset of ES to commencement of therapy, results in low long-term cognitive outcome.[13] Establishing strategies to facilitate early suspicion particularly in those at high risk of developing ES is important for early diagnosis. Rapid access to confirmatory electroencephalography (ideally combined with video monitoring) is paramount for initiation of treatment with minimal delay.

TREATMENT OF EPILEPTIC SPASMS

The ongoing debate on the best treatment choice for IESS is unlikely to achieve much consensus imminently. This is related to the variability in the therapeutic options trialed as well as in the outcome measures evaluated. In most instances this judgment as the most efficacious treatment option is passed on based on the clinical and or electroclinical response at the end of 2 weeks (14 days). Based on the evidence available, hormonal therapies; intramuscular adrenocorticotropic hormone (ACTH) and oral prednisolone, have clearly established its role as the recommended first-line treatment option for all etiologies except for tuberous sclerosis, for which the favored choice is high dose vigabatrin. These recommendations are also backed by evidence on duration to achieve spasm control, which for hormonal therapy range between 5 and 6.25 days and for vigabatrin, 3 and 13.5 days.[14-16] A recent meta-analysis of 19 randomized clinical trials concluded that there was no significant difference in the effectiveness of oral corticosteroids and ACTH in electroclinical response [risk ratio (RR) 0.85; 95% confidence interval (CI) 0.41–1.76].[17]

Adrenocorticotropic Hormone

Adrenocorticotropic hormone is used in doses with marked variability ranging from low (<25 U/day) to high (up to 150 IU/m^2) as well as with variable durations ranging from 14 days up to 3 months **(Table 1)**. Further, trials across the Atlanta use natural form of ACTH given daily (acts for 12–18 hours) versus the synthetic long-acting form given every other day (acts for 24–48 hours) in Europe. The American Academy of Neurology (AAN) and Child Neurology Society, in its review in 2012, concluded that the low dose of ACTH is probably as effective as the high dose for control of spasms. The high dose was associated with a higher relative risk of adverse effects (RR = 1.71). For example, brain shrinkage is greater in those treated with high dose in comparison to that with lower dose.[17] The AAN concluded that there is insufficient data to recommend an optimal duration of treatment. However, response at 2 weeks being the most frequently assessed in clinical trials is favored as adequate duration of therapy. This period is supported by the median number of days required to achieve spasm control often remaining less than 10 days.

Corticosteroids

Variability in dose as well as type of preparation is also evident in clinical trials investigating role of oral corticosteroids **(Table 1)**. Prednisone and hydrocortisone which

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TABLE 1 **Comparison of different first-line treatment options and their respective doses.**

First-line treatment option	Derivative	Dose	Study
ACTH	Natural ACTH	150 IU/m^2/day 75 IU/m^2/day 20–30 IU/day	Baram et al.[19] Knupp et al.[36] Hrachovy et al.[37]
	Depot ACTH	10 IU/day 8 IU/day	Vigevano and Cilio[16] Yanagaki et al.[38]
	Tetracosactide	0.5 mg every other day	Lux et al.[15]
Cortico-steroids	Prednisolone	40–60 mg/day 2 mg/kg/day 4 mg/kg/day	Lux et al.[15] Chellamutthu et al.[18]
	Prednisone	2 mg/kg/day	Baram et al.[19]
	Hydrocortisone	15 mg/kg/day	Chiron et al.[39]
Vigabatrin		18–36 mg/kg/day 100–148 mg/kg/day	Elterman et al.[40]
		100–150 mg/kg/day	Lux et al.[15]
Combined therapy	Prednisolone and vigabatrin	40–60 mg/kg/day 100–150 mg/kg/day	O'Callaghan et al.[23]

(ACTH: adrenocorticotropic hormone)

were used in trials previously have been replaced by prednisolone in the post millennium trials. A moderate-to-high dose of 40–60 mg/day of oral prednisolone has been preferred in many trials. A single clinical trial described higher efficacy when treated with high dose of prednisolone (4 mg/kg/day) compared to usual dose (2 mg/kg/day).[18] Comparison of the response rates for the two main hormonal therapies at 14 days, indicate intramuscular long-acting ACTH as the preferred first line based on class I evidence describing 86% response rate over that for oral prednisone for electro-clinical resolution.[19] However, this superiority was not shown in subsequent larger scale trials[15] and a single trial from Sri Lanka [The Sri Lanka Infantile Spasms Study (SLISS) trial] described better response rate for oral prednisolone over ACTH.[14] Therefore, oral corticosteroids are recommended as a first-line therapy and should be considered early if ACTH is not available.

Vigabatrin and Combined Therapy

Vigabatrin is the choice for control of spasms in tuberous sclerosis. Variable doses ranging between 30 mg/kg/day to higher doses of 100–150 mg/kg/day have been used, but majority of trials favor use of higher dose. There is limited evidence for control of spasms beyond 6 and 12 weeks in head-to-head trials using vigabatrin.[15] However, there is evidence for the two main rival forms of hormonal therapy with regard to efficacy on control of spasms and development of other types of epilepsies over short-term, i.e., during first 12 months[20,21] to medium term follow-up spanning into preschool age group.[13,22] These trials do not seem to show a significantly different outcome between ACTH or the oral steroids on control of spasms at 12 months or during medium term follow-up. The International Collaborative Infantile Spasm Study (ICISS) described significantly better spasms cessation and a shorter duration for spasm control with combined therapy (high dose oral prednisolone and high dose vigabatrin).[23] This was more clearly seen in those infants considered to be at a less risk of developmental impairment. Although the immediate outcome was promising, the same superiority was not evident for spasm control at 18 months and it did not show an advantage of combined therapy over developmental outcome.[24] Replication is needed to confer a frank benefit of combined therapy, particularly in relation to potential for more rapid control of ES. However, the risk of cumulative adverse effects of both medications, administered in high doses needs extra caution. High dose vigabatrin has been reported to associate with irreversible retinal damage as well as reversible nonspecific white matter changes. Several other clinical trials have investigated short-term spasm control with other antiseizure medications. These include sodium valproate, clonazepam, zonisamide, nitrazepam, topiramate, etc., and intravenous and oral methylprednisolone as an alternative corticosteroid derivative. Pyridoxine and pyridoxal phosphate are used in Japan as the first meditation. There are no randomized clinical trials looking at control of spasms and epilepsy beyond this age group.

Nonpharmacological Treatment Strategies

Two important nonpharmacological treatment strategies have been successfully deployed to achieve better control of ES. Ketogenic diet and modified Atkins diet have been shown to cease spasms as well as reduce the spasm load and even normalize the electroencephalogram (EEG) **(Fig. 2)** when used as an adjunctive therapy. However, the reported response rates remain variable. Further, variable research methodologies and outcome measures and absence of any placebo-controlled trial evidence, blurs the specific contribution of ketogenic diet for spasm control. A median 65% of improvement of spasm load to more than 50% of pretreatment burden and a median 35% of spasm cessation is reported in a meta-analysis of 341 patients.[25] Ketogenic diet is particularly important in treating spasms in those with glucose transporter 1 (GLUT1) deficiency as the etiology. The second strategy, which reports the single modality with the highest success rates is epilepsy surgery for selected patients which structural etiologies.[26] Despite its high success rates in carefully selected patients, this option of management is often sorted as last resort resulting in a significant loss of time without spasm freedom. Highest seizure freedom is reported in those operated before 3 years (with 88% achieving spasm control) and with focal and or hemispheric lesions.[27]

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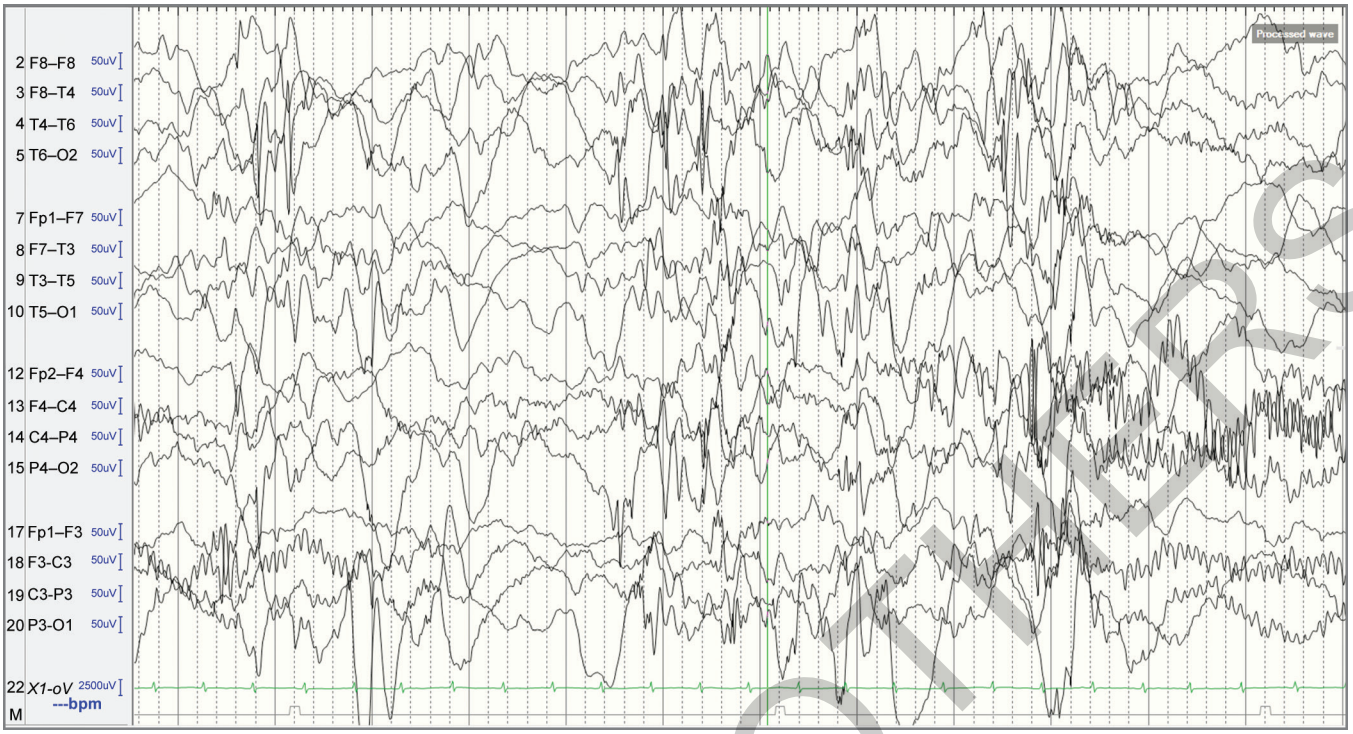

Fig. 2: Electroencephalogram showing characteristic abnormalities of hypsarrhythmia.

OUTCOME AND PROGNOSIS

Both these important determinants of disease impact are rather complex for IESS and include treatment response, myriad of comorbidities, and mortality. These contribute independent of the underlying etiology toward poor quality of life in affected children.[28] Descriptors underpinning short-term and long-term outcome are described in literature, but the time factor determining each category is arbitrary. Outcome during the first year of diagnosis which spans infancy is considered under short-term outcome in this review. The spasm control, relapsing disease, and developmental outcome are commonly cited descriptors of outcome within this period. Majority of trials or prospective studies limit their observations to outcome at 14 days of therapy though parameters such as sustained control of spasms and reduced relapse rates are definitely better determinants. The response rates vary between the three recommended first-line medications. The electroclinical resolution at 2 weeks range from 40 to 86% for intramuscular ACTH, 29 to 60% for oral prednisone and prednisolone, and 33 to 54% for high dose vigabatrin.[29] The control of spasms over a longer period, i.e., 3–12 months is reported in 48–75% and relapse is reported in 30%.[20,21] These are indicative of a moderate response to most treatment options.

Reports of developmental outcome indicate no significant difference over the choice of initial therapy; however, the major determinant of better outcome relates to the underlying etiology. In the group with absence of a known etiology, previously identified as "cryptogenic ES", a clear association with a better developmental outcome is described, than in those with an identified etiology.[30] Though not clearly established, unknown etiology has also been suggested to be associated with better spasm control. Shorter treatment lag is also important to achieve optimal long-term cognitive development in those with a known etiology as well as those with no identifiable etiology.

Although short-term prognosis and outcome attracts attention, the true effect of disease burden is signified by the spectrum of comorbidities seen in affected children. The magnitude of these problems is heavily influenced by the standard of healthcare system and disability care in a country. Improved living standards, better life expectancy, and living without dependence are described in patient series from high income countries.[31] The mortality rates are highest during early years of life and reach one-third by 30 years[17] and approximately half by 50 years.[32] Respiratory tract infections is the leading killer in all age groups and sudden unexpected death in epilepsy (SUDEP) is responsible in the older age group. Those with a known etiology are more likely to succumb than those without an etiology.

Though ES generally disappear gradually as the child grows older, persistence of spasms is reported in up to 18%.[13] Other types of epilepsies become the most frequent disability in surviving patients. The frequency is variable depending on the years of follow-up; the proportion increasing with the duration of follow-up. Overall, one-third of surviving adults are reported to suffer from infrequent seizures while one-third experience daily seizures.[29] Lennox–Gastaut syndrome is reported in an average of 17% (0–54);[29] however, focal epilepsies was the most frequent epilepsy type reported in 59% of children followed up at 4 years. Contrary to the common association with refractory epilepsy, self-limiting epilepsies have also been reported.[29]

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Some of the less frequently highlighted long-term disabilities include cognitive, behavioral, emotional, and functional outcomes. Etiology is the most important determinant of normal intellect, academic achievements, employment, and marriage.[33] Reports of detailed follow-up are rather limited; however, a cohort of patients followed up in a resourceful country, had 25% of patients achieving some form of employment and 6% entering marriage.[31] The LTTT of less than 4 weeks has been shown to be associated with better neurodevelopmental outcome in a meta-analysis of 2,979 patients.[33] The contrary is experienced in those with a recognizable etiology and living in resource-limited settings.[34] Autism spectrum disorder (20–57%), behavioral comorbidities such as hyperactivity, attention deficit hyperactivity disorder (11%), and sleep disturbances (82%) are also frequent but often overlooked in these children with other demanding comorbidities.

FUTURE

Attention on future developments is heavily attracted toward advancements in the understanding of genetic background of IESS as well as the role of precision medicine and/or disease modifying approach to achieve spasm freedom in affected children. Facilitated collaborations have created a new frontier to understand the complexities of IESS. Some of these areas explored include exploring disease mechanism and consequences as therapeutic targets, identification of biomarkers, and developing and testing new therapies. These advancements are crucial; however, the number benefited from personalized medicine is limited. The author strongly feels that the primacy should be directed to enforcing measures that prevent etiologies that are directly contributory to development of ES. Some of these etiologies include preventable causes such as birth asphyxia, central nervous system (CNS) infections, hypoglycemia-related brain injury, and congenital infections. These are more frequent in LICs and are strongly linked to the provision of improved healthcare such as better maternal nutrition, regular healthcare during pregnancy, safe delivery, and expanded vaccination programs. Apart from these more frequent contributers, improved health education and policies to prevent consanguineous marriages and screening programs for inborn errors of metabolism will help to curtail incidence of specific disorders more frequent in specific regions. Prevention in the broader sense includes use of medication in the pre-epileptic stage in those identified early using appropriate biomarkers as with use of vigabatrin in presymptomatic tuberous sclerosis patients in the EPISTOP trial.[35] Potential interventions that will prevent, minimize the insults, and improve the outcome in large numbers particularly in resource-limited countries are listed in **Table 2**.

TABLE 2 **Strategies for prevention of development of spasms, early detection in at risk children, and optimizing treatment in those affected.**

Level of intervention	Specific strategies
Prevention	• Rubella vaccination to all • Improved nutrition in young females • Prepregnancy counseling • Maternal nutritional supplementation • Group B streptococcal carriage detection and treatment • Improved maternal care including toxemia during pregnancy and peripartum • Provision of safe hospital delivery for all • Prevention of neonatal hypoglycemia and sepsis • Effective child vaccination programs • Early treatment with VGB in prehypsarrhythmic TSC*
Early detection	• Parental education on spasm detection for at risk babies • Health education to midwives and first contacts on spasm detection • Facilitate diagnosis by use of home videos
Early confirmation	• Early clinical suspicion • Priority EEG (ideally within 72 hours) • Rapid EEG interpretation
Commencement of therapy	• Treatment commencement without delay (within 1 week of diagnosis) • Use recommended first-line medication • Target electroclinical resolution; obtain follow up EEG • Avoid treatment failure by detection and management of adverse effects early • Early commencement on alterative first line for treatment failures • Appropriate escalation of therapy for poor responders
Treatment of relapses	• Early management with appropriate first-line medication • Early introduction to ketogenic diet • Early consideration of candidacy for epilepsy surgery

*This requires further studies to introduce as routine practice.

(EEG: electroencephalogram; TSC: tuberous sclerosis complex; VGB: vigabatrin)

CONCLUSION

The near 200-year history of this complex disease has witnessed significant advancements in many aspects. These include better understanding of etiologies, particularly the expanding spectrum of causative genes, development of

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a systematic approach to its diagnosis and treatment and improvement of recognition of multitude of comorbidities which intricately contribute to the long-term outcome of the affected children. However, IESS still remains an enigma with many intricacies undeciphered. Focus on treatment with minimal delay, prompt control of relapses, and intensified care of concomitant comorbidities such as developmental retardation, autism spectrum disorder, and behavioral abnormalities will help improve the long-term prognosis of the affected children.

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