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The severe epilepsy syndromes of infancy: a population-based study

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Summary

Objective: To study the epilepsy syndromes amongst the severe epilepsies of infancy and assess their incidence, etiologies, and outcomes.

Methods: Population-based cohort study of severe epilepsies with onset before age 18 months in Victoria, Australia. Two epileptologists reviewed clinical features, seizure videos and EEGs to diagnose ILAE epilepsy syndromes. Incidence, etiologies, and outcomes at age two years were determined.

Results: 73/114 (64%) infants fulfilled diagnostic criteria for epilepsy syndromes at presentation, and 16 (14%) had 'variants' of epilepsy syndromes in which there was one missing or different feature, or where all classical features had not yet emerged. West syndrome (WS) and 'WS-like' epilepsy (infantile spasms without hypsarrhythmia or modified hypsarrhythmia) were the most common syndromes, with a combined incidence of 32.7/100,000 live births/year. The incidence of epilepsy of infancy with migrating focal seizures (EIMFS) was 4.5/100,000 and of early infantile epileptic encephalopathy (EIEE) was 3.6/100,000. Structural etiologies were common in 'WS-like' epilepsy (100%), unifocal epilepsy (83%) and WS (39%), while single gene disorders predominated in EIMFS, EIEE and Dravet syndrome. Eighteen (16%) infants died before age two years. Development was delayed or borderline in 85/96 (89%) survivors, being severe-profound in 40/96 (42%). All infants with EIEE or EIMFS had severe-profound delay or were deceased but only 19/64 (30%) infants with WS, 'WS-like' or 'unifocal epilepsy' had severe-profound delay and only 2/64 (3%) were deceased.

Significance: Three-quarters of severe epilepsies of infancy could be assigned an epilepsy syndrome or 'variant syndrome' at presentation. In this era of genomic testing and advanced brain imaging, diagnosing epilepsy syndromes at presentation remains clinically useful for guiding etiologic investigation, initial treatment and prognostication.

Key words: epilepsy syndrome, West syndrome, epilepsy of infancy with migrating focal seizures, early infantile epileptic encephalopathy, Dravet syndrome

1 | INTRODUCTION

Severe epilepsies of infancy (SEI), characterized by frequent, drug-resistant epileptic seizures and epileptiform EEG, affect 1:2000 infants.[1] Seizure and developmental outcomes are often devastating and carry a significant health burden.[1, 2] Most SEI are considered developmental and epileptic encephalopathies, although developmental abnormalities may not be evident at presentation.[3]

An epilepsy syndrome is a recognizable cluster of electroclinical features, including specific seizure types, typical age of seizure onset and EEG characteristics.[3] The International League Against Epilepsy (ILAE) epilepsy syndromes such as West syndrome (WS), Dravet syndrome (DS), early infantile epileptic encephalopathy (EIEE, Ohtahara syndrome) and epilepsy of infancy with migrating focal seizures (EIMFS) constitute SEI.[4-7] Apart from WS and DS, their specific incidences are unknown.[8-10] Complex electroclinical phenotypes that do not fit a defined epilepsy syndrome are reported in up to 50% of infants, these being either undiagnosed at the syndrome level or assigned the non-ILAE syndrome label 'early onset epileptic encephalopathy' (EOEE). [2, 11, 12]

With increasing ability to diagnose the underlying etiology of epilepsies with genomic testing and neuroimaging, and with knowledge that etiologic diagnosis may dictate treatment, one might question whether an epilepsy syndrome diagnosis remains clinically relevant.

In this population-based cohort study of SEI, we attempted to determine the epilepsy syndromes at presentation, their incidence, etiologies, and outcomes, and the usefulness of epilepsy syndrome diagnoses.

2 | MATERIALS AND METHODS

2.1 | Cohort

We identified all infants born in the state of Victoria, Australia, during 2011-2013 with SEI. The Victorian population and health system, and the study's design and screening sources, are reported in detail.[1] Briefly, SEI was defined as (i) onset of frequent seizures (≥daily for 1 week or ≥weekly for 1 month) before age 18 months, (ii) epileptiform abnormality on EEG,

and (iii) ongoing seizures despite trials of two appropriate anti-seizure medications (ASMs). The only exception to this definition was the automatic inclusion of infants with epileptic spasms, regardless of treatment response. Status epilepticus was not an automatic inclusion, as EEG was the main ascertainment source and not all infants (particularly those with febrile status epilepticus) would have had an EEG. 114 children were ascertained and studied in detail. Infants with only acute symptomatic seizures or febrile seizures were excluded.

2.2 | Phenotyping

We reviewed clinical features up to age two years. History, examination, and investigation findings were obtained from medical records and clinical assessment. All available EEGs (1-19 per infant) and seizure videos (from families and video-EEG recordings) were reviewed by two pediatric epileptologists (KBH, ASH). One hundred and seven (94%) infants had their first EEG within two weeks of presentation, while seizures were ongoing and before evolution of their epilepsy; six infants had their first EEG after their epilepsy had evolved and one after spontaneous resolution of infantile spasms. Ictal EEG with video was available for 82 (72%) infants. Home video recordings of seizures was available for an additional nine (8%) infants.

Seizure types were determined from parent and clinician descriptions, videos, and ictal EEG recordings. Epilepsy syndrome diagnoses were based on age of seizure onset, seizure types, EEG findings and developmental history. Acute symptomatic seizures (e.g. neonatal seizures following acute stroke) were not considered part of the epilepsy. SEI was considered controlled at age two years if children had not had seizures in the previous month, given the high seizure frequency in most infants while their epilepsy was active.

Seizure types were classified according to the 2017 ILAE Classification, with two modifications.[13] Epileptic spasms were considered a single category and focal seizures were divided into motor and non-motor groups, without further characterization for awareness.

Interictal EEGs were classified as normal, background abnormality (focal or generalized) without interictal epileptiform discharges (IEDs), or having IEDs (unifocal, multifocal, burst-

suppression, hypsarrhythmia/modified hypsarrhythmia, generalized spike-wave +/- paroxysmal fast activity, or mixed (focal and generalized IEDs)).

Epilepsy syndromes were strictly defined as listed in Table 1. Additional and 'variant' syndrome categories were defined for the purpose of this study. ‘Unifocal epilepsy’ referred to infantile-onset epilepsy with focal seizures from a single, unilateral brain region (e.g. left temporal lobe epilepsy). ‘Variant syndromes’ were used to denote an electroclinical phenotype resembling an epilepsy syndrome with one missing feature, one different feature, or a presentation consistent with the initial features of an epilepsy syndrome before all the typical characteristics had emerged; this was instead of categorizing such patients as 'unknown' or 'EOEE'. Specifically, we used ‘WS-like’ to denote infantile spasms without hypsarrhythmia or modified hypsarrhythmia, most commonly with focal epileptiform abnormalities . We used 'possible DS’ to denote a presentation with recurrent or prolonged seizures which were febrile, vaccine-proximate or afebrile bilateral or hemiclonic seizures, acknowledging that these features are the typical presentation of DS, and that the full diagnostic criteria (e.g. presence of additional seizure types) may become evident in early childhood. If an epilepsy syndrome or ‘variant’ could not be diagnosed, the term ‘other’ (multifocal, generalized or combined focal and generalized) was used.

Development was determined by parental report and clinician assessment of developmental milestones. Development at seizure onset was classified as normal or abnormal, or ‘N/A’ if seizure onset was before age one month given normal or abnormal pre-seizure development may be difficult to determine. Development at age two years was determined using a developmental quotient (DQ, developmental age/chronological age x100) estimated from gross motor and expressive language milestones achieved. Development was classified as severely-profoundly delayed (DQ <35, i.e. developmental level equivalent to <9 month-old at chronological age 2 years), mildly-moderately delayed (DQ 35-69), borderline (DQ 70-85) or normal (DQ>85). For infants deceased before age two years, developmental outcome was taken at the age of death.

Etiologies were classified as structural (acquired or malformative), metabolic, chromosomal, single gene (non-structural, non-metabolic), or unknown. Etiology was previously reported for 76 patients, with etiologic investigations as described.[1] Briefly, MRI brain imaging with research review of images was performed in 113 infants, the remaining infant having a

single gene etiology. Genomic testing (predominantly exome sequencing and/or molecular inversion probe-based epilepsy gene panel) was performed in 44/49 infants whose aetiology was unknown after brain imaging, chromosomal microarray and basic metabolic testing. Genetic testing was not systematically performed in individuals with malformative aetiologies. Nine patients had their etiology determined subsequently following repeat brain imaging or further genetic testing.

2.3 | Incidence and statistical analyses

The incidence of each epilepsy syndrome was calculated using live birth rates from the Australian Bureau of Statistics and the Victorian Births, Deaths, and Marriages Registry (www.abs.gov.au, www.bdm.vic.gov.au). Crude incidences greater than 1:10,000 were corrected for population migration.

Summary statistics for demographic variables, age of seizure onset, seizure types and epilepsy syndromes at onset and evolution, and outcomes at age two years were analyzed. Associations between epilepsy syndromes and the underlying etiologies and outcomes were analyzed using the chi-square statistic, with statistical significance set at $p<0.05$. Analyses were confined to comparison of WS (including 'WS-like' epilepsy) with all other syndromes of SEI (including 'other' syndromes), given WS is the most common syndrome of SEI and structural etiologies are more commonly reported.[2, 14-16] 'Unifocal epilepsies' were excluded from these comparisons given structural etiologies are well-established.[4]

2.4 | Ethics and consent

The study was approved by the Human Research Ethics Committees of the Royal Children's Hospital, Monash Children's Hospital, Austin Health, Geelong Hospital, Mercy Hospital for Women, and the Royal Women's Hospital in Victoria, Australia. Written informed consent was obtained from the parents of all patients who were personally assessed or underwent research genetic testing.

3 | RESULTS

The cohort comprised 114 patients, 61 (54%) being male.[1] Detailed individual data is available on request.

Seizure onset occurred from age 1 day to 17.3 months (median 4.6 months, IQR 5.4 months). Maximum seizure frequency was multiple daily in 109 infants, daily in one and multiple weekly in four. The emergence of a new seizure type between the initial presentation and age two years was observed in 44 patients. The most common seizure type at presentation or evolution was infantile spasms (74, 65%), followed by focal seizures (61, 54%) and generalized seizures, typically tonic (15, 13%) or myoclonic (16, 14%).

The most common interictal EEG abnormalities at presentation were hypsarrhythmia/modified hypsarrhythmia (39), multifocal IEDs (33), unifocal IEDs (15), and burst-suppression (9). The interictal EEG evolved to a new specific pattern (e.g. to hypsarrhythmia or slow spike-wave) in 41 infants with ongoing seizures, most commonly to hypsarrhythmia or modified hypsarrhythmia (15/41).

Ictal EEG abnormalities were epileptic spasms (44), focal seizures (40, 10/40 with intra-ictal activation of a contralateral focus), and generalized seizures (23). More than one type of seizure was recorded in 44/82 (54%) infants.

3.1 | Epilepsy syndromes

At presentation, 73 (64%) infants were diagnosed with an epilepsy syndrome, 16 (14%) with a ‘variant syndrome’, and 25 (22%) with 'other' epilepsies (18 other-multifocal, 5 other-generalized, 2 other-combined) (Table 2). WS and ‘WS-like’ epilepsy occurred in 52 (46%) infants (WS 41 (36%), ‘WS-like’ 11 (10%)). Twelve (11%) infants had ‘unifocal epilepsy’, 10 (9%) EIMFS and 8 (7%) EIEE.

The epilepsy syndrome at presentation evolved to a different syndrome in 45 (39%) infants by age two years (Table 3). Three infants developed new seizure types without a change in the epilepsy syndrome. The most common syndromes at evolution were WS and ‘WS-like’ epilepsies (25). One infant's epilepsy evolved to Lennox-Gastaut syndrome (LGS) and 11 to LGS-like epilepsies (8 with tonic seizures but no slow spike-wave, 3 with slow spike-wave but no tonic seizures). Only one infant evolved to a focal epilepsy. All four infants with ‘possible DS’ evolved to DS. Other syndromes with high rates of evolution to another syndrome were ‘unifocal epilepsy’ (10/12 (83%), most commonly to WS), WS (14/41 (34%), most commonly

to LGS-like (7) and 'WS-like' (5)), and other-multifocal (9/18 (50%), most commonly to WS (6)). There was no second evolution to another syndrome before age two years.

3.2 | Incidences

The incidence of WS at presentation or evolution was 26.5/100,000 live births/year (confidence interval (CI) =20.5-34.2). The combined incidence of WS and 'WS-like' epilepsies was 32.7/100,000 live births/year (CI = 26-41). The incidences of EIMFS, EIEE and EME were 4.5/100,000 live births/year (CI =2.4-8.4), 3.6/100,000 live births/year (CI =1.8-7.2) and 0.9/100,000 live births/year (CI =0.23-3.6) respectively.

3.3 | Development

Prior to seizure onset, development was normal in 44 (39%) and delayed in 53 (46%) infants. For the 17 (15%) infants who had seizure onset during the first month of life, it was not possible to determine whether development was ever normal. Development prior to seizure onset was normal in 22/52 (42%) of infants with WS or 'WS-like' epilepsy. Normal early development was present in the 4 infants with 'possible DS' and 8/12 (67%) infants with 'unifocal epilepsy'. Developmental plateau or regression occurred in 96 infants, commonly coinciding with seizure onset or evolution to infantile spasms. Five infants died during the neonatal period and the developmental trajectory was not documented in five infants.

3.4 | Etiology

The underlying etiology was identified in 85 (75%) infants. Structural etiologies were the most common, being malformative in 32 (28%) and acquired in 14 (12%). Single gene disorders were identified in 23 infants (20%), chromosomal disorders in 9 (8%) and metabolic conditions in 7 (6%). Genetic testing in 5/7 (71%) infants with metabolic conditions and 9/21 (42%) of infants with structural etiologies revealed pathogenic variants. Therefore, a genetic basis was identified in 46% (46/100) infants with non-acquired etiologies.

The most common individual etiology was FCD.[1] Eleven of the 15 infants with FCD underwent epilepsy surgery, 4 before age two years. Histopathology was FCD IIA in 6, FCD IIB in 3, FCD I in 1, and normal in one infant who was seizure free following a temporo-parieto-occipital disconnection.

Etiology was identified in the majority of infants with each epilepsy syndrome (Table 4). Structural etiologies were identified in 10/12 (83%) infants with 'unifocal epilepsy', all 11 infants with 'WS-like' epilepsy and 16/41 (39%) with WS. The proportion of infants with structural etiologies was significantly greater in infants with WS and 'WS-like' epilepsy (27/52 (52%) than in the other syndromes (9/50 (18%), ($p < 0.01$).

Single gene disorders were uncommon in WS and 'WS-like epilepsy' (4/41 (10%) and 0/11 (0%)). In contrast, single gene or metabolic disorders were found in at least half the cases with EIMFS, EIEE, EME and 'possible DS', most commonly channelopathies. Overall, the proportion of infants with WS and 'WS-like' epilepsy who had single gene, chromosomal or metabolic etiologies (11/52 (21%)) was lower than in the other syndromes (27/50 (54%) ($p<0.01$).

3.5 | Outcomes at age 2 years

Eighteen (16%) infants were deceased by age two years, due to lower respiratory tract infection (7), cardiorespiratory failure (7), necrotizing enterocolitis (2) and unknown cause (2). At least 50% of infants with EIEE (4/8), EME (1/2) and EIMFS (6/10) were deceased. In contrast, only 1/12 (8%) infants with 'unifocal epilepsy' was deceased. Mortality was significantly lower in infants with WS or 'WS-like' epilepsy (1/52 (2%)) than in the other syndromes (16/50 (34%) ($p<0.01$) (Table 5).

At age two years, 46/96 (48%) surviving infants had ongoing seizures, on ASM. The remaining 50 infants had controlled seizures (i.e. none during the previous month), 25 being on ASM. 17/18 (94%) deceased infants had seizures until death. The proportion of infants with EIEE, EME, EIMFS or 'possible DS' with ongoing seizures until death or age two years was 21/24 (88%); all three seizure-free infants had *KCNQ2* pathogenic variants, associated with severe-profound developmental delay. Seizures were ongoing in 8/12 (67%) infants with 'unifocal epilepsy'. The proportion of infants with ongoing seizures was significantly lower for those with WS or 'WS-like' epilepsy (18/52 (35%) compared to the other syndromes (37/50 (74%)), ($p<0.01$). However, if the epilepsy syndrome evolved from WS, typically to LGS-like epilepsy, there was a high likelihood of ongoing seizures (12/14 (86%)). Of the 11 individuals who had epilepsy surgery, five are seizure free after surgery and two

had only infrequent seizures post-operatively (one of whom later had an idiopathic generalized epilepsy phenotype, with seizures presumed unrelated to dysplasia).

Development at age two years in 96 surviving infants was normal in 11 (11%), borderline in 15 (16%), mildly-moderately delayed in 30 (31%) and severely-profoundly delayed in 40 (42%). 17/18 deceased infants had severe-profound global developmental delay at the time of death or died during the neonatal period. All infants with EIEE, EME and EIMFS had severe-profound developmental delay, and all infants with 'possible DS' had mild-moderate developmental delay. A broader range of developmental impairments was present in infants with 'unifocal epilepsy'; 5/12 (42%) had normal development, 2/12 (17%) borderline development, 3/12 (25%) mild-moderate delay, and 2/12 (17%) had severe-profound delay or had died. Among infants with WS and 'WS-like' epilepsies, 5/52 (10%) infants had normal development, 12/52 (23%) borderline development, 16/52 (31%) had mild-moderate delay and 19/52 (37%) had severe-profound delay or had died, the relative proportions being similar in each of these two syndromes (p=0.47). Overall, developmental outcomes were less severe in WS and 'WS-like' epilepsy than in the other syndromes (normal development 1/50 (2%), borderline development 1/50 (2%), mild-moderate delay 11/50 (22%), severe-profound delay 37/50 (74%) (p<0.01). Infants with WS and WS-like epilepsies at onset, with normal or borderline developmental outcome (n=17) had malformative (n=9, FCD 7, PMG 1, TSC 1) or unknown etiologies (n=8). Given that only four individuals had epilepsy surgery before age two years, we are not able to comment on whether early surgery was associated with better developmental outcomes.

4 | DISCUSSION

We previously reported the incidence of SEI in a population-based cohort and showed that genetic testing for etiology was a cost-effective diagnostic approach.[1] Here we report the range of severe epilepsy syndromes of infancy, their incidences and etiologies, and their outcomes at age 2 years. We showed that diagnosis of an epilepsy syndrome, with allowance for minor variations, is feasible in most infants and remains clinically useful, potentially helping to guide investigation and prognostication given important differences in etiology and outcome between syndromes.

4.1 | Epilepsy syndrome diagnoses

Analysis of electroclinical features in each infant, including ictal video in 80% and ictal EEG recordings in over 70% led to diagnosis of an ILAE epilepsy syndrome or 'variant syndrome' in over three-quarters of infants at presentation, a higher proportion than previously reported.[2, 11, 17] As expected, WS was the most common syndrome; EIEE and EIMFS were more common than previously reported.[18]

For infants who did not present with all the hallmarks of an ILAE epilepsy syndrome of infancy, we chose to diagnose a 'variant syndrome' rather than considering them unclassified or diagnosing EOEE. Infantile spasms with a focal epileptiform EEG, which we termed 'WS-like' epilepsy, is sometimes considered with classically-defined WS under an infantile spasms umbrella.[19-21] Evidence would support combining WS and 'WS-like' epilepsies given that outcomes at age two years were similar in this study, and that a previous study showed similar response to treatment.[22] Further, several children had syndrome evolution from WS to 'WS-like' epilepsy in our study, supporting that these two entities are related. However, we showed that infantile spasms without hypsarrhythmia confers an increased likelihood of an underlying structural etiology.[15, 16, 23, 24] Although the full diagnostic criteria for DS are not typically met at presentation, the initial features of DS are characteristic, albeit not specific.[25] Recognition of 'possible DS' at presentation with status epilepticus during infancy can enable early genetic diagnosis that informs ASM choice and may improve developmental outcomes.[26, 27] These two examples demonstrate that there is clinical utility in making a syndromic diagnosis even when strict criteria for an epileptic syndrome are not all met. This could be done either by allowing broader diagnostic criteria for epilepsy syndromes, or by maintaining strict criteria for epilepsy syndromes but recognizing 'variants' of these, as was done in this study.

The incidence of infantile spasms in this study, with and without hypsarrhythmia, is congruent with earlier estimates.[8] The incidence of EIMFS in this study (4.5/100,000) is considerably higher than the previously-estimated prevalence of 0.11/100,000 children[18], likely due to our high number of ictal EEG recordings. Our incidences of EIEE (3.6/100,000) and EIMFS are not dissimilar to the reported incidence of DS, in contrast to the perception that EIEE and EIMFS are considerably rarer. [9, 10]

4.2 | Etiologies

We identified the etiology in 75% of infants and showed differences between epilepsy syndromes, with structural etiologies predominating in WS, 'WS-like' and 'unifocal epilepsies', and single gene disorders in the other syndromes.

Structural etiologies, predominantly malformative, were identified in most infants with 'WS-like' and 'unifocal epilepsies', and 39% with WS. FCD was the most common cause in these syndromes, identified on imaging in 23%, and confirmed on histology in 10/11 children who underwent epilepsy surgery. Identifying FCD has major treatment implications, as epilepsy surgery may cure the epilepsy and improve developmental outcomes.[24] Our finding of FCD in 18% of infants with infantile spasms at presentation or evolution is in contrast with the United Kingdom Infantile Spasms Study, the International Collaborative Infantile Spasms Study and a recent large US study of IS, which identified FCD in only 0.5-2.3% of infants.[14, 28, 29] Just three infants in our study had their FCD diagnosed on their initial MRI; the remaining FCDs were identified on research review of MR imaging or follow-up high resolution imaging during or after infancy.[1] This highlights the important role of expert review of high-resolution MRI for identifying subtle lesions.

Single gene and chromosomal etiologies were identified in 28% of the cohort. The syndromes with the largest yield were 'possible DS' (75%), EIEE (50%) and EIMFS (50%), being most commonly channelopathies as expected for DS and as previously reported in non-population-based studies of EIEE and EIMFS.[25, 30, 31] In contrast, just 10% of infants with WS (16% of infants with non-structural WS) in our cohort had a single gene disorder (and 15% a chromosomal abnormality), confirming findings in a Scottish population-based study and several case series.[32-34]

4.3 | Outcomes

Outcomes were poor overall, adding to the recent literature calling for better therapies.[12] One in six infants were deceased before age two years. Of those who died after the neonatal period, all had severe-profound developmental delay and all but one had ongoing seizures. Just 11% of survivors had normal development.

Poor outcomes were universal in EIEE, EME and EIMFS, with approximately half of infants in our cohort deceased by age two years and severe-profound developmental delay in the surviving infants. Nevertheless, there are rare reports of children with milder, or even normal, outcomes.[35] In contrast, in our study, the mortality rate of epilepsies with infantile spasms (WS and 'WS-like') or unifocal seizures was lower and developmental impairments milder; normal development was seen in 14% of children, comparable to the 6-33% reported in previous cohorts.[36]

Infants with WS at presentation also had relatively favorable seizure outcomes compared with those with EIEE, EME and EIMFS, similar to a recent report showing 10% lower risk of drug-resistant epilepsy in infants with IS than infants with other epilepsies.[12] However, where there was clear evolution from WS to another syndrome during infancy, such as LGS or LGS-like epilepsies, the likelihood of seizure remission by age two years was low. This highlights the prognostic value of epilepsy syndrome diagnosis at evolution as well as at presentation.

4.4 | Limitations

The etiologic spectrum of SEI will vary around the world depending on the frequency of acquired causes such as hypoxic-ischemic encephalopathy, neonatal meningitis, and other causes of perinatal and infantile morbidity. Acquired causes of SEI present most commonly with WS, thus, etiologic differences are likely to be most marked in that syndrome. [37]

Infants in this series were followed only to age two years and their developmental outcomes were classified according to milestones achieved. Thus, mild deficits may have been missed, and small differences in outcomes between groups not detected.

In our study, status epilepticus was not an automatic inclusion criterion, despite it being a potentially severe manifestation of epilepsy in some infants. The reason for this was in part methodological, EEG being the main ascertainment source and not all infants with status epilepticus undergoing EEG. As a consequence, children whose later severe epilepsy manifest during infancy as recurrent status epilepticus, such as some children with DS or

Sturge-Weber syndrome, would not be ascertained. However, status epilepticus in infants is often febrile, acute symptomatic or solitary, and not always associated with severe outcomes, such that it was not necessarily part of the disease spectrum under investigation.[38]

Similarly, we chose not to make DS an automatic inclusion criterion, despite it being a severe epilepsy and sometimes considered an infantile epileptic encephalopathy. We conceptualized SEI as epilepsies with high seizure frequency, epileptiform EEG and drug resistance during infancy, these 'severe' features often not being present in DS until early childhood.

4.5 | Conclusions

Determining etiology provides complementary information to the epilepsy syndrome, in terms of prognostication and treatment. For example, in *KCNQ2* encephalopathy it is recognized that seizures may respond to sodium channel blocking ASMs and that, in contrast to many other severe infant epilepsies, spontaneous seizure remission may occur in late infancy or early childhood. [39, 40] However, an epilepsy syndrome diagnosis is still important even in the setting of a known etiology, as many epilepsy genes are associated with a spectrum of epilepsy syndromes that require different interventions. This can include genes that can cause both milder and severe epilepsies, such as the spectrum of *SCN1A* pathogenic variants, which ranges from DS to febrile seizures. [26, 41] Even within the severe epilepsies due to a single gene, different epilepsy syndromes may show the opposite response to an ASM, such as sodium channel blockers in *SCN2A*, reflecting the underlying mechanism. [42, 43] Understanding both epilepsy syndrome and etiology is thus essential as knowledge of individual etiologies increases and novel etiology-specific and syndrome-specific treatments become available.

Key points

- An epilepsy syndrome, allowing for minor variations, can be diagnosed at presentation in three-quarters of infants with severe epilepsies
- The incidence of early infantile epileptic encephalopathy is 3.6/100,000 and epilepsy of infancy with migrating focal seizures is 4.5/100,000

- Etiologies and outcomes of West syndrome and 'unifocal epilepsies' differ significantly from other severe epilepsies of infancy
- The proportion of infants with West syndrome due to focal cortical dysplasia is much higher than previously appreciated
- Epilepsy syndrome diagnoses remain clinically useful to guide investigation and initial treatment

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a patent for *SCN1A* testing held by Bionomics Inc and licensed to various diagnostic companies; has a patent molecular diagnostic/theranostic target for benign familial infantile epilepsy (BFIE) [PRRT2] 2011904493 & 2012900190 and PCT/AU2012/001321 (TECH ID:2012-009) with royalties paid. She has received research support from the National Health and Medical Research Council of Australia, Medical Research Future Fund, Health Research Council of New Zealand, CURE, Australian Epilepsy Research Fund, March of Dimes and NIH/NINDS. The remaining authors have no conflicts of interest.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Table 1: Epilepsy syndrome definitions for this study

Epilepsy syndrome	Age of onset	Seizure types	Interictal EEG	Ictal EEG (where recorded)	Other
EIEE (Ohtahara syndrome)	<3m	Tonic +/- other	Burst-suppression or markedly discontinuous	Generalized or focal	
EME	<3m	Myoclonic +/- other	Burst-suppression or markedly discontinuous	Generalized	
EIMFS	<6m	Focal (multiple different types) +/- other	Typically multifocal IEDs	Focal (multiple locations of seizure onset, in both hemispheres independently)	Seizures 'migrating' between hemispheres and occurring frequently enough to constitute status epilepticus
West syndrome	<18m	Epileptic spasms +/- other	Hypsarrhythmia/ modified hypsarrhythmia	Spasm complexes/ decrements	With or without developmental plateau/regression

Epilepsy syndrome	**Age of onset**	**Seizure types**	**Interictal EEG**	**Ictal EEG (where recorded)**	**Other**
'West Syndrome-like'	<18m	Epileptic spasms +/- other	**Other (not hypsarrhythmia/modified hypsarrhythmia)**	Spasm complexes/ decrements	
Dravet syndrome	4-15m	Febrile and/or afebrile generalized and/or unilateral clonic or tonic-clonic seizures, and afebrile seizures including myoclonus, atypical absences and focal seizures	Normal or generalized spike-wave	Generalized spike-wave, focal	Normal development before seizure onset Resistant to antiseizure treatment
'Possible Dravet syndrome'	4-15m	**Multiple febrile and/or afebrile generalized and/or unilateral clonic or tonic-clonic seizures (without other seizure types), or single prolonged febrile seizure and afebrile seizures**	Normal or generalized spike-wave	Generalized spike-wave, focal	Normal development before seizure onset **Knowledge of treatment response not required as may be too early to determine if resistant or responsive**
Myoclonic encephalopathy in a non-progressive disorder	Any	Myoclonic (episodes of myoclonic status), +/- other	Not burst-suppression	Variable (mainly spike-wave)	Absence of a progressive neurologic disorder
Lennox-Gastaut syndrome	>1 year	Multiple seizure types including generalized tonic	Generalized slow spike-wave +/- paroxysmal fast activity		Must have both generalized tonic seizures and generalized slow spike-wave activity
'Lennox-	**Any**	**Generalized +/-**	**Generalized or**		**Must have at**

Epilepsy syndrome	Age of onset	Seizure types	Interictal EEG	Ictal EEG (where recorded)	Other
Gastaut syndrome-like'		**focal seizure types**	**multifocal**		**least one of generalized tonic seizures or generalized slow spike-wave activity**
'Unifocal'	Any	Focal (single location of seizure onset)	Normal or unifocal	Focal (single location of seizure onset)	
Other-multifocal	Any	Focal (one or more locations of seizure onset)	Multifocal or unifocal (must be multifocal if only a single seizure type)	Focal	Not meeting definition of unifocal, EIMFS or EIEE
Other-generalized	Any	Generalized seizure types	Generalized spike-wave	Generalized	Not meeting criteria for DS, EME or MENPD
Other-mixed	Any	Generalized and focal seizure types	Generalized and/or focal	Generalized and focal	Not meeting criteria for one of the other epilepsy syndromes of infancy

Bolded text in the 'variant syndrome' rows notes the features that may be different to those of the related epilepsy syndrome. A 'variant syndrome' was assigned if there was only one missing/different feature to a named epilepsy syndrome or if the presentation was similar to that of an epilepsy syndrome prior to development of the full hand of classical features. Electroclinical phenotypes with more than one missing/different feature to an epilepsy syndrome were assigned to the 'other' groups.

Table 2: Epilepsy syndromes at presentation

Syndrome at onset	Number	Percent	Notes
Epilepsy syndromes	**73**	**(64%)**	
Early infantile epileptic encephalopathy	8	7	N/A
Early myoclonic encephalopathy	2	2	N/A
Epilepsy of infancy with migrating focal seizures	10	9	N/A

Syndrome at onset	Number	Percent	Notes
West syndrome	41	36	N/A
Unifocal	12	11	N/A
'Variant syndromes'	**16**	**14**	
'West syndrome-like'	11	10	EEG not hypsarrhythmic in 11
'Possible Dravet syndrome'	4	3	Later seizure types not present in 4
'Lennox-Gastaut-like'	1	1	No slow spike-wave in 1
Unclassifiable epilepsies	**25**	**22**	
Other-multifocal	18	16	Multiple types of focal seizures in 8, single type of focal seizures with multifocal interictal EEG in 10
Other-generalized	5	4	MAE-like (abnormal development pre-onset) in 2, CAE-like (early onset) in 1, BMEI-like (pharmacoresistant, bicentral rather than generalized spike-wave) in 1, LGS-like (but >1missing/different feature) in 1
Other-combined focal and generalized	2	2	Possible DS but >1 missing/different feature in 1, LGS-like but >1 missing/different feature in 1
Total	**114**	**100**	

BMEI = benign myoclonic epilepsy of infancy, CAE = childhood absence epilepsy, DS = Dravet syndrome, LGS = Lennox Gastaut syndrome, MAE = epilepsy with myoclonic-atonic seizures, N/A = not applicable

Table 3: Evolution of the presenting epilepsy syndrome before age two years

	Syndrome evolution	Syndromes at evolution
Epilepsy syndromes	**30/73 (41%)**	
EIEE	2/8 (25%)	'WS-like' in 1, LGS-like in 1
EME	1/2 (50%)	'LGS-like in 1
EIMFS	3/10 (30%)	'WS-like' in 2, WS in 1
West syndrome	14/41 (34%)	'LGS-like' in 7, 'WS-like' in 5, LGS in 1, other – generalized in 1
'Unifocal'	10/12 (83%)	WS in 7, 'WS-like' in 2, other – generalized in 1
'Variant syndromes'	**6/16 (38%)**	

	Syndrome evolution	Syndromes at evolution
'West syndrome-like'^	2/11 (22%)	'Unifocal' in 1, 'LGS-like' in 1
'Possible Dravet' syndrome	4/4 (100%)	DS in 4
'Lennox-Gastaut-like'	0/1 (0%)	
Unclassifiable epilepsies	**9/25 (36%)**	
Other-multifocal	9/18 (50%)	WS in 6, 'WS-like' in 1, LGS-like in 1, other – combined focal and generalized in 1
Other–generalized*	0/5 (0%)	
Other–combined focal and generalised~	0/2 (%)	
Total	**45/114 (39%)**	

^1 had a new seizure type emerge without evolution of the epilepsy syndrome

*1 had a new seizure type emerge without evolution of the epilepsy syndrome

~1 had a new seizure type emerge without evolution of the epilepsy syndrome

WS = West syndrome, DS = Dravet syndrome

Table 4: Etiologies by epilepsy syndrome at presentation

Epilepsy syndrome at onset	N	Etiology known?	Etiology					
			Acquired	Brain malform-ation	Metabolic	Chromo-somal	Single gene disorders	Diagnoses
EIEE	8	6 (75%)	0	0	2	0	4	Molybdenum cofactor deficiency in 1, mitochondrial* in 1, *KCNQ2* in 2, *SCN2A* in 2
EME	2	2 (100%)	0	0	1	1	0	PNPO deficiency in 1, Wolf-Hirschhorn syndrome in 1
EIMFS	10	7 (70%)	0	1	1	0	5	PMG in 1, mitochondrial* in 1, *KCNT1* in 1, *SCN8A* in 1, *TBC1D24* in 1, *KCNQ2* in 1, *QARS* in 1
West syndrome	41	27 (66%)	8	8	1	6	4	HIE in 3, PVL in 2, perinatal stroke in 1, complicated meningitis in 1, ischemic injury (mechanism unknown) in 1, FCD in 5, TS in 1, malformation of cortical development (other) in 1, lissencephaly in 1, mitochondrial (*PNPT1*) in 1, T21 in 5, chr15 CNV in 1, ALG13 (mosaic) in 1, NSD1 in 1, *NTRK2* in 1, *SMC1A* in 1
'West syndrome-like'	11	11 (100%)	2	9	0	0	0	HIE in 1, perinatal stroke in 1, FCD in 4, PMG in 2 (1 focal PMG), TS in 1, Aicardi syndrome in 1, malformation of cortical development (other) in 1
'Possible Dravet syndrome'	4	3 (75%)	0	0	0	0	3	*SCN1A* in 3, not tested in 1
'Lennox-Gastaut syndrome-like'	1	1 (100%)	0	0	1	0	0	Tay-Sachs disease in 1

Unifocal	12	11 (92%)	1	9	1	0	0	Complicated meningitis in 1, FCD in 6, TS in 2, Sturge Weber in 1, mitochondrial (NDUFAF6) in 1
Other-multifocal	18	12 (67%)	1	5	0	1	5	HIE and hypoglycemia in 1, Lissencephaly in 1, TS in 1, malformation of cortical development (other) in 1, pontocerebellar hypoplasia in 1, achondroplasia in 1, Aicardi-Goutières syndrome in 1, chr 2q24.3 del (incl *SCN1A* and SCN2A) in 1, NRROS in 2, SCN8A in 1, GRIN2B (mosaic) and *NSD1* in 1 (dual diagnoses)
Other–generalized	5	3 (60%)	1	0	0	1	1	Prematurity and PVL in 1, chr 15q21.3q22.2 deletion in 1, *SYNGAP1* in 1
Other–combined focal and generalized	2	2 (100%)	1	0	0	0	1	HIE in 1, *WWOX* in 1
Total	114	85 (75%)	14	32	7	9	23	

Not found = no cause identified on clinical testing or on research genomic testing (usually WES-based gene panel)

Not tested = no research genomic testing done (but routine clinical investigations (imaging, chromosomal testing, basic metabolic testing) were done and did not identify a cause)

*Mitochondrial etiology in infant with EIEE diagnosed on basis of familial complex IV deficiency (gene unknown), and consistent clinical and biochemical features in this infant. Mitochondrial etiology in infant with EIMFS diagnosed on basis of consistent clinical and biochemical features (respiratory chain enzyme analysis not performed); homozygous variants of uncertain significance were identified in the *FARS2* gene but functional testing was not undertaken.

Table 5: Outcomes at age two years by epilepsy syndrome at presentation

Epilepsy syndrome at onset	n	Deceased before two years	Living at two years					
			n	Ongoing seizures	Development			
					Normal	Borderline	Mild-moderate DD	Severe-profound DD
EIEE	8	4 (50%)	4	2 (50%)	0	0	0	4 (100%)
EME	2	1 (50%)	1	1 (100%)	0	0	0	1 (100%)
EIMFS	10	6 (60%)	4	3 (75%)	0	0	0	4 (100%)
'West syndrome'	41	0	41	15 (37%)	3 (7%)	10 (24%)	12 (29%)	16 (39%)
'West syndrome – like'	11	1 (9%)	10	3 (30%)	2 (20%)	2 (20%)	4 (40%)	2 (20%)
'Possible Dravet syndrome'	4	0	4	4 (100%)	0	0	4 (100%)	0
'Lennox-Gastaut syndrome-like'	1	0	1	1 (100%)	0	0	0	1 (100%)
Unifocal	12	1 (8%)	11	7 (64%)	5 (45%)	2 (18%)	3 (27%)	1 (9%)
Other-multifocal	18	4 (22%)	14	7 (50%)	1 (8%)	1 (8%)	5 (36%)	7 (54%)
Other–generalized	5	1 (10%)	4	2 (50%)	0	0	2 (50%)	2 (50%)
Other-combined focal and generalized	2	0	2	2 (100%)	0	0	0	2 (100%)
Total	114	18 (16%)	96	46 (48%)	11 (11%)	15 (16%)	30 (31%)	40 (42%)