LENNOX-GASTAUT SYNDROME & DRAVET SYNDROME

The Evolving Nature of Lennox-Gastaut Syndrome and Dravet Syndrome

THE IMPLICATIONS FOR TRANSITION TO ADULT HEALTHCARE

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ABSTRACT

Severe epileptic syndromes of childhood are among the most challenging conditions for patients, families, and clinicians. They can strike otherwise normal infants, toddlers, and children, and are often extremely challenging to diagnosis accurately, control seizures, and prevent progressive cognitive disability. These epileptic encephalopathies are often devastating and the consequences long-lasting with adverse consequences on learning, behavior, and socialization. Inevitably, as these children mature into young adults, there are significant and often unmet needs around transition of care to an adult-focused provider. This brief white paper outlines some issues for consideration when assessing the long-term management of patients with epilepsy syndromes with emphasis on two model disorders—Lennox-Gastaut syndrome and Dravet syndrome.

BACKGROUND

Many of the most severe and complex epilepsy syndromes begin in early childhood.[1,2] The literature focuses predominantly on younger cohorts, and there is extensive description of seizure semiology, diagnostic evaluation with emerging insights in neurogenetics, and treatment combinations to control seizures. Although less well-described, the long-term care of these patients presents considerable challenges and risks given the chronic nature of the disorders with evolving symptoms and syndrome presentation often adversely impacting intellectual, physical, social, and emotional maturation.[3] This white paper highlights two early onset epileptic encephalopathies—Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS).[1,4] Although both are unusual, they highlight the challenges of many severe, often drug-resistant epileptic disorders presenting in early childhood. LGS is rare, but it is thought to constitute approximately 4% of all cases of pediatric epilepsy.[5] Prevalence of LGS at age 10 has been reported as 0.26 per 1,000 children and annual incidence as 2 per 100,000 children 0 to 14 years.[5,6] Even less common, the incidence of DS is estimated to be between 1 in 15,700 and 1 in 30,000 live births.[7,8] Still, the prevalence accounts for 1.4% of all epilepsies in children <15 years.[9]

There is significant burden from distinctive severe seizures and associated comorbidities in these severe epilepsy syndromes.[10-12] In LGS, drop seizures are common, occurring in more than 50% of patients who have slow spike-wave activity.[13] These seizures significantly increase risks for injury and fatality, and it is common for patients to wear protective helmets or to remain confined to a wheelchair.[1,2,14] Patients with DS often present with hemiclonic seizures associated with febrile illness or even with increases in body temperature during baths or warm weather.[15,16] They have a particular risk early in life for prolonged seizures or status epilepticus.[15,16] Patients with DS often have significant gait impairments that may require the use of adaptive medical equipment or wheelchairs, and may also suffer from growth and nutritional issues, sleep disturbances, chronic upper respiratory infections, sensory integration disorders, dysregulation of the autonomic nervous system, and cardiac abnormalities.[11,16] Patients with LGS and DS also experience significant intellectual disabilities (ID), including verbal, visual-spatial, and fine motor dysfunction, as

well as general intellectual impairment.[15,17] These physical and cognitive impairments have implications for healthcare transition (HCT) as they limit independence in both children and adults. The majority of patients with LGS and DS rely on others for most activities of daily living (ADL) and cannot live independently.[2,15,18-20] In long-term studies, most adults reside at home with a family member as caregiver or in an institutional setting.[19,20] These cognitive and physical impairments also have a significant negative impact on both patient and caregiver quality of life.[10-12]

In addition, patients with LGS and DS suffer from increased risk of mortality relative to their peers, due, in part, to the considerable challenges with controlling seizures. The mortality rate for LGS is generally estimated to be between 3% and 7%, over mean follow-up periods of 8.5 and 9.7 years, respectively.[21] For DS, the estimated mortality rate is 7% to 18% by age 18 years and an estimated 16% of patients with DS die within 11 years of diagnosis.[11,22] The majority of deaths in LGS and DS are epilepsy related, with sudden unexpected death in epilepsy (SUDEP) and status epilepticus being the most common causes of mortality.[11,23]

The majority of children with severe epileptic encephalopathies now survive into adulthood,[1,4] but their challenges are far from over. Transitioning from special education usually means the termination of comprehensive programs that have often provided specific therapies, individual aides, and daily activities that relieve over-burdened parents. These young adults are almost never capable of independent medical decision-making, and require support for ADL from adherence to the prescribed medical regimen to personal hygiene. The process of transition, ideally begun in early adolescence, remains a major challenge as transfer from pediatric to adult healthcare occurs at the same time as the completion of schooling with the need to accept a new culture, new insurance, and fewer resources.

CLINICAL PRESENTATION FROM ONSET TO ADULTHOOD

Evolving Signs and Symptoms of Lennox-Gastaut Syndrome

LGS is typically defined by a clinical triad of features, including the presence of multiple seizure types; EEG pattern with slow spike-wave complexes (SSW) <3 Hz and generalized paroxysmal fast activity (GPFA); and developmental delay.[1] However, there is considerable heterogeneity in clinical presentation, and not all children with LGS present with the characteristic triad of symptoms at onset or at any one time (Figure 1).[1,21] This may make identification of the syndrome a challenge (Figure 2).[21] Retrospective studies have indicated that only one-third to one-half of patients diagnosed with LGS present with characteristic features of the syndrome at any one time.[6,24,25] Onset generally occurs between 1 and 8 years of age, with a peak between 3 and 5 years; however, it is not unusual for the diagnosis to be missed until later in life, including adulthood.[1,21] Either in cases of late onset or late recognition, clinical features typically differ in seizure type and EEG patterns from younger patients, and clinical and caregiver-reported history may be critical to provide clues to an accurate diagnosis.[26]

The multiple seizure types most commonly experienced by patients with LGS at onset are generalized tonic, atonic, and atypical absence seizures, but other types may also occur (Figure 1).[13,21] Patients who present at the usual

age (between 2 and 5 years) often have prominent myoclonic or myoclonic-astatic seizures, which makes the distinction from myoclonic-astatic epilepsy (Doose syndrome) a particular challenge.[13] Tonic seizures during sleep are particularly characteristic of LGS, but not all patients display this feature at onset.[13,21] Estimates of tonic seizures at onset vary widely, ranging from 17% to 95% of cases of LGS, which may reflect ascertainment bias due to variable parental awareness of nocturnal seizures and limited use of overnight video EEG.[27-29] Over time, the types and frequency of seizures experienced by patients with LGS change as they enter adolescence and adulthood, such as a tendency to experience fewer tonic, atonic, and atypical absence seizures during wakefulness (Figure 1).[20,26,30-32]

The EEG characteristics of LGS can be very helpful in making the diagnosis. The signature EEG pattern of SSW complexes <3 Hz is present during wakefulness or non-rapid eye movement (REM) sleep at onset for most patients (Figure 1).[13] These complexes consist of a spike or sharp wave, followed sequentially by a positive deep "trough," and a negative wave.[1] Paroxysmal fast rhythms (10-20 Hz), known as GPFA, during non-REM sleep is considered near pathognomonic for LGS.[1] However, only 50% of patients who have whole-night EEGs display these abnormalities.[21] Further heterogeneity in EEG presentation occurs as patients mature and patterns change over time or disappear entirely (Figure 1).[1,21] In studies of adults with LGS, the typical SSWs observed in childhood decreased or disappeared in 33% to 74% of patients, and 44% displayed normal EEG during wakefulness with abnormal fast rhythms persisting during sleep.[20,33] Loss of the classic EEG signature in adults with LGS may reclassify them as having non-specific, symptomatic generalized epilepsy, severe epilepsy with multiple independent spike foci, or focal epilepsy.[33,34] Because of the evolving nature of seizure types and EEG patterns, it is important for clinicians to continuously re-evaluate awake and asleep EEGs and clinical symptoms in adults with LGS.[32] When an older child or adult presents with symptoms consistent with LGS, it is incumbent on the clinician to revisit and review earlier childhood descriptions of seizure semiology and EEG reports.

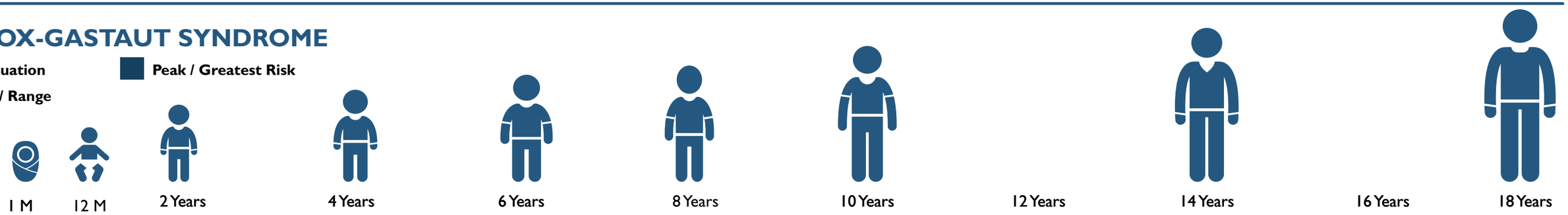
Cognitive impairment is a near universal outcome for individuals with LGS.[21] Approximately two-thirds of patients display pre-morbid cognitive and developmental impairment, but over time >90% have cognitive impairment with significantly low intelligence quotient (IQ) (Figure 1).[1,13,33,35] Even the small minority of children who fall within accepted ranges for normal cognitive function still display slow mental processing and difficulty performing day-to-day activities.[1] Cognitive impairment is often accompanied by behavioral problems like hyperactivity, aggression, and features falling within the autism spectrum in up to 50% of patients with LGS.[32] Especially in drug-resistant cases of LGS, cognitive development plateaus and the gap between patients with LGS and their peers widens over time.[21] This is likely due to a lack of expected skill progression rather than regression.[36] Virtually all patients with LGS display some level of cognitive impairment in adulthood but in cases diagnosed during adulthood, the impairment may be less pronounced (Figure 2).[32]

Figure 1.

Evolution of Lennox-Gastaut Syndrome and Dravet Syndrome

LENNOX-GASTAUT SYNDROME

Continuation **Peak / Greatest Risk** **Onset / Range**



Seizure Types

- Most commonly generalized tonic, atonic, and atypical absences
- Tonic seizures during sleep
- Myoclonic, generalized tonic-clonic, focal seizures may also occur
- Change in seizure types, including tonic, generalized tonic-clonic, absence, atypical absence, myoclonic, atonic, and partial seizures
- Tonic seizures decrease during wakefulness but remain present during sleep

Seizure Frequency

- Seizures several times per week with most patients experiencing daily seizures
- Change in seizure frequency
- Decrease in daytime seizures (some pts) & increase in violent drop attacks

SUDEP

- High risk of SUDEP
- Increased risk as young adult

SE

- Average onset of NCSE at age 4 years

EEG

- Diffuse SSW <3 Hz
- Polyspikes/paroxysmal fast rhythms (≥10 Hz) during sleep
- Decrease in or disappearance of SSW
- Multiple independent spike foci
- Background slowing
- EEGs may be normal during wakefulness
- Persistence of fast rhythms during sleep

MRI

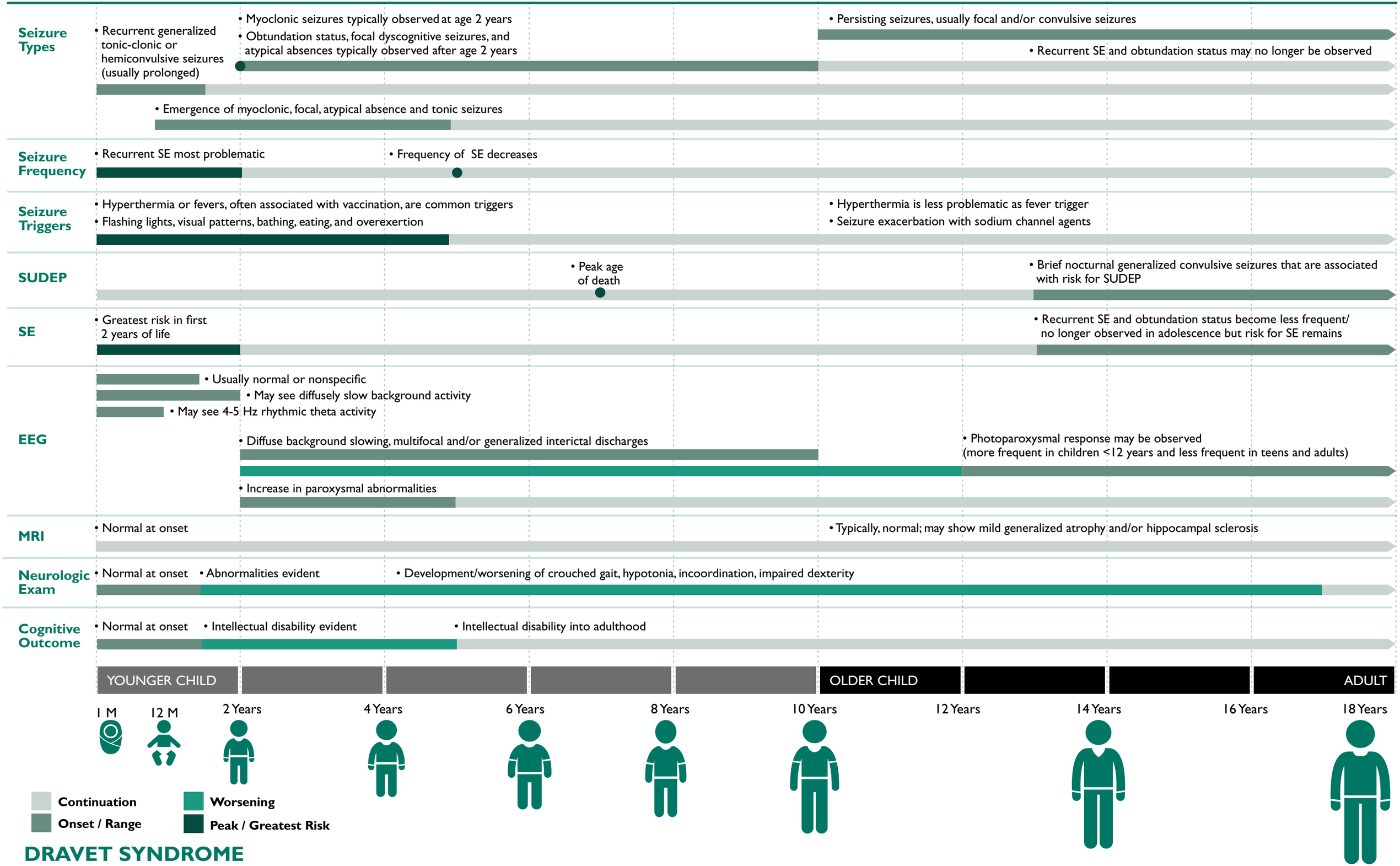
- Variable; normal in some, abnormalities in others
- More common abnormalities include leukoaraiosis with or without parieto-occipital infarct and cerebral hemisphere hemiatrophy
- Variable; normal in some, abnormalities in others
- Abnormalities include cortical, diffuse cortical, cerebellar, left hemisphere, and moderate diffuse atrophy, occipital polymicrogyria, frontal lesions, and cranial fossa cyst

Neurologic Exam

- Nonspecific
- Neurologic deficits, such as spastic paraparesis and quadriparesis, hemiparesis, generalized hypotonia, and extrapyramidal features, become apparent
- Gait deterioration over time
- Progressive dysphagia

Cognitive Outcome

- Cognitive delay or impairment at onset but may be normal in 30% of cryptogenic cases
- Behavior disorders, mostly hyperactivity and aggressiveness
- Significant decrease in IQ over time: 75%-95% have cognitive impairments 5 years from onset



DRAVET SYNDROME

EEG, electroencephalogram; IQ, intelligence quotient; MRI, magnetic resonance imaging; N/A, not applicable; NCSE, non-convulsive status epilepticus; pts, patients; SE, status epilepticus; SSW, slow spike-wave; SUDEP, sudden unexpected death in epilepsy.
Figure 1 adapted from multiple publications.[1,13,16,20,21,26,30,31,33,34,37-42]

As no single genetic test or biomarker exists for LGS, differential diagnosis remains challenging, especially in light of the evolving nature of the disease and variability in clinical presentation (Figure 2).[1] Because of all these factors, distinguishing LGS from other pediatric-onset epilepsy syndromes is difficult.[1] One of the main distinctions in early childhood is myoclonic-astatic epilepsy. In distinction to LGS, these children are developmentally normal and typically have normal waking EEG background prior to their epileptic encephalopathy.[2] There is an overlap between LGS and Dravet syndrome, but the latter typically starts much earlier (within the first 18 months of life) with atypical, prolonged febrile seizures followed by more focal seizures.[2,16] Atypical benign partial epilepsy, which is frequently termed "pseudo-Lennox syndrome," can be distinguished by the persistently normal background, sleep activation of central-temporal spikes, and lack of tonic seizures.[43]

Careful examination of clinical and EEG features, exclusion of other underlying causes of disease, detailed review of medical and caregiver-reported histories, and understanding the defining aspects of the syndrome usually help to differentiate LGS from other epileptic disorders.[1,21]

Evolving Signs and Symptoms of Dravet Syndrome

Although DS shares some overlapping signs and symptoms with LGS, there are distinct features that differentiate DS from LGS and other pediatric-onset epilepsy syndromes, including myoclonic astatic epilepsy. Compared with LGS, DS typically presents earlier (within the first 18 months of life) and usually in a developmentally normal infant without a history of significant central nervous system (CNS) trauma or prior significant medical history.[4,16] Seizures triggered by hyperthermia and/or exacerbated by sodium channel agents are characteristic.[16] DS is also unique in that it is usually possible to make a firm genetic diagnosis; the presence of sodium voltage-gated channel alpha-1 subunit (***SCN1A***) mutation is found in 70%-85% of (90% are de novo) patients.[4,44] It is important for a confirmatory genetic diagnosis to be made early since there are both treatment and long-term prognostic implications. However, presence of ***SCN1A*** or other Dravet-related mutations without clinical signs is not sufficient for diagnosis and absence of mutation does not exclude a diagnosis of DS.[4]

The initial presentation of DS usually includes prolonged, recurrent convulsive seizures that are generalized tonic-clonic or hemiclonic in nature.[16] Patients with DS are typically highly sensitive to increased body temperature; initial seizures may be triggered by fever or infection and misdiagnosed as more benign febrile seizures in an otherwise normal infant with a normal EEG and MRI.[4,16] However, not all patients with DS present with febrile seizures; several studies have shown that between 28% and 48% of initial convulsive seizures were afebrile.[45-47] Over the years, elevated body temperature becomes less of a seizure trigger for older patients with DS.[16] Also, as children age, additional seizure types develop (Figure 1). These include myoclonic seizures by age 2 years and obtundation status, focal dyscognitive, atypical absence, and tonic seizures after age 2 years.[16] Adolescents and adults with DS experience persisting focal and/or generalized convulsive, myoclonic, focal, atypical absence, and tonic seizures, while recurring status epilepticus and obtundation status become less frequent.[16]

Unlike LGS, there is no signature EEG pattern in DS. Children with DS typically have normal or nonspecific EEG and normal MRI findings at onset (Figure 1).[16] In some patients, interictal EEG may show 4-5 Hz rhythmic theta activity by the end of the first year.[41,48] Between ages 2-5 years, there is an increase in paroxysmal abnormalities on EEG and background slowing including photoparoxysmal discharges.[16,41] Interictal discharges in adolescents and adults are more common than earlier in childhood, while photoparoxysmal responses often resolve.[16] MRI findings also exhibit changes as patients mature and may show generalized atrophy or hippocampal sclerosis.

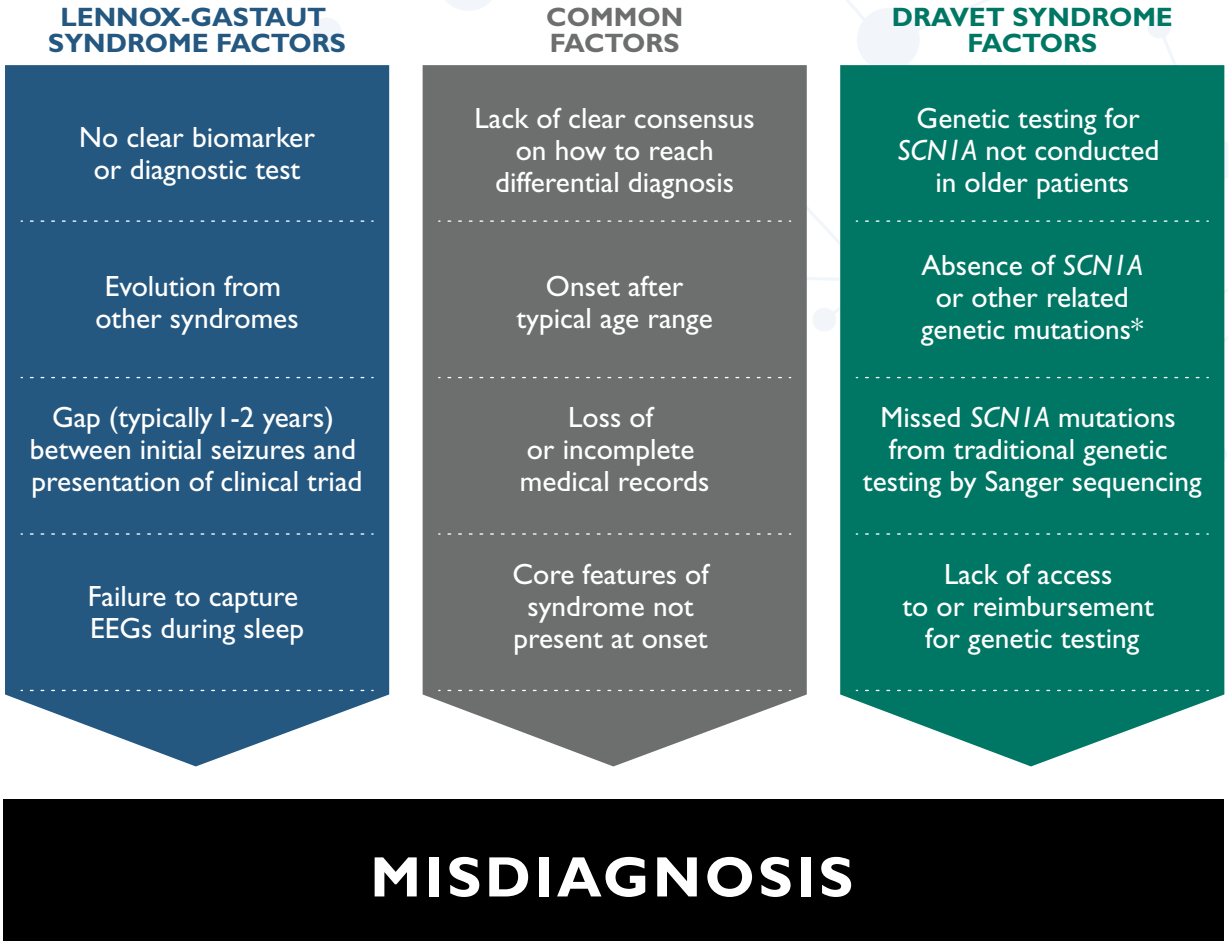
DS is an epileptic encephalopathy, which means that cognitive impairment is a characteristic feature even though, as previously mentioned, most infants display normal cognitive, language and motor development at seizure onset.[2,16] Global developmental delay usually becomes apparent between 18 and 60 months (Figure 1), and almost all patients show ID later in life.[4,16] Motor dysfunction, such as impaired dexterity, crouched gait, and hypotonia is evident by age 3-4 years and may worsen after puberty.[4,16,49] Behavioral issues, such as lack of attention, hyperactivity, and traits fulfilling the diagnosis of autism spectrum disorder, often accompany the cognitive impairment of DS into adulthood.[11,12] Although cognitive delay is characteristic of DS, there is no universal pattern or level of severity.[4]

Diagnosis of DS may be relatively straightforward in infants who present with all the typical semiology of the syndrome; however, there is heterogeneity in clinical presentation and clinical and EEG features evolve from childhood to adulthood, which may lead to challenges in differential diagnosis and potential for misdiagnosis.[4] Diagnosis of DS is often delayed, as one study has found that the median time from seizure onset to definitive diagnosis of DS was 4.8 years.[16,50] Many factors may contribute to delayed diagnosis (Figure 2). Adults with DS may not have had access to genetic testing earlier in childhood. Furthermore, healthcare providers may be unaware of a need for testing in adults or unfamiliar with newly available epilepsy gene panel tests.

HEALTHCARE TRANSITION FOR PATIENTS WITH LENNOX-GASTAUT SYNDROME AND DRAVET SYNDROME

Transition of care is defined as "the planned, coordinated movement of adolescents from the child-oriented, family-centered environment of pediatrics to the adult-oriented care setting."[51] Achievement of full independence and acceptance of the adult responsibilities for self-management of one's medical condition is challenging for all youth. However, this becomes even more difficult in adolescents and young adults with intellectual disability. Optimal HCT addresses both the medical and psychosocial needs of young people with special healthcare needs, such as epilepsy, as they move into the adult healthcare system.[3] HCT is dynamic and involves a skilled multidisciplinary team, which may include social workers, psychologists, physiotherapists, dieticians, occupational therapists, psychiatrists, genetic counselors, and pharmacists in order to provide holistic care to patients with significant comorbidities.[3,52-54] The addition of ID makes the process more complicated as the family needs to consider issues of competency and the importance of guardianship or power of attorney, as well as the combined impact of changes in primary care, insurance, and the loss of services with the end of special education.[51] On the positive side, transition also affords an opportunity for a fresh look at the medical condition. There is the opportunity to reassess the etiology of disease and re-evaluate MRIs, EEGs, and other signs and symptoms (Figure 3),[32,49,51] which is especially important given the evolving nature of LGS and DS and the potential for earlier misdiagnosis.

Figure 2. Factors that Contribute to Misdiagnosis



*Mutations in chromodomain helicase DNA binding protein-2 *(CHD2)*; gamma-aminobutyric acid type A alpha-1 *(GABRA1)*, gamma-2 (*GABRG2*), and gamma-3 *(GABRG3)* subunits; protocadherin-19 *(PCDH19)*; syntaxin binding protein 1 *(STXB1)*; and voltage-gated sodium channel beta-1 subunit *(SCN1B)* genes have also been implicated in DS.[55-61] EEG, electroencephalogram; *SCN1A*, voltage-gated sodium channel alpha-1 subunit.

HCT models emphasize the need for preparation as early as ages 12-14 years and the involvement of the patient and caregiver in understanding the medical diagnosis, gradually increasing self-management skills, expectations for eventual care transition, understanding the impact of puberty and importance of making good choices, as well as considerations for reproductive health and plans beyond high school or special education.[51] Physicians, parents, and patients confront considerable complexity around these issues when dealing with a severe epilepsy syndrome that is associated with significant morbidity and both physical and intellectual disability. Given the significant cognitive impairments in patients with LGS and DS, self-management goals may differ substantially for patients with severe ID versus those with average or normal functioning (Figure 3).[51,62] Determining guardianship and who has the right to make legal decisions regarding the patient's health is also critical.[43,52,53] Expectations around long-term care needs and settings will also differ based on level of disability. Ideally, a group home setting can provide the training and support needed to promote self-sufficiency.[43] However, for many patients, moving from the familiar home setting to a foreign environment such as an assisted living facility, or moving from home-based care by a family member or nurse caregiver to a group facility can be distressing. Furthermore, an institutional setting may not always provide adequate access to specialized care and staff turnover can lead to caretaker unfamiliarity with patients' medical histories and functional abilities.[52] For adults with significant ID, it is critical to ensure that the patient does not get

lost when they graduate to a community living arrangement or when their aging parents become unable to care for them, and become "known well by no one."[43,52,53]

As outlined earlier, both patients with LGS and DS experience changes in seizure types and frequency and EEG signatures in adolescence (Figure 1). These changes are confounded by the physical, emotional, and behavioral changes associated with puberty. Expertise managing these complex syndromes during adolescence is important, as AEDs may aggravate seizures or behavioral problems, medications may reduce the effectiveness of oral contraceptives, and polypharmacy increases the risk of adverse effects (Figure 3).[32,37,54] Recognition and understanding of the features of LGS and DS by adult providers is essential to maintaining optimal care; however, half of adult general neurologists surveyed felt uncomfortable treating epileptic encephalopathies and only 15% felt confident in treating patients with ID or features of autism spectrum disorder.[63] These adult neurologists also felt that they had insufficient training to care for adolescents with chronic epilepsy, especially those with cognitive and behavioral issues.[54] Therefore, for transition to be effective, it is essential that the pediatric neurologist develop a good working relationship with adult providers who have a strong understanding of the patient's condition, especially where complex needs are high and familiarity is low. This is particularly true for rare conditions such as LGS and DS.

Transition is not only challenging for health care providers; it can also introduce significant stress for patients and their families.[43,49,62] Caregivers may delay transition and continue to be followed by the pediatric neurologist due to a sense of familiarity and security.[43,53,64] One solution may be an epilepsy transition clinic which can help families to adjust to the adult healthcare system and alleviate concerns. In one such model program, over 95% of adolescents with epilepsy and their caregivers reported reduced fears in transition to adult care.[65] It is optimal for the youth with special needs to have a medical home with a pediatrician who has provided continuity of care—he or she can alleviate families' concerns about transition to adult healthcare providers.[53,62,66] In a survey of patients with DS and their families, satisfaction with transition was correlated with longer duration of follow-up, good availability of pediatric staff, age >18 years at transition, and good health condition at transfer.[67] A final pediatric visit after age 18 years also favored better transition. Several epilepsy centers have reported better patient/caregiver satisfaction with transition when there is adequate amount of prior preparation.[3] While HCT is particularly challenging for patients with LGS and DS, who have significant comorbidity and ID, transition clinics provide one way to ease the transition for patients and their families.

Figure 3. Considerations for Healthcare Transition in Lennox-Gastaut Syndrome and Dravet Syndrome

Diagnosis	• **Etiology** • **Genetic testing (new technologies and epilepsy-linked mutations may have been identified since initial diagnosis)** • **EEG and MRI re-evaluation**
Treatment and Management	• Prior AED and other treatment history, including surgery • **Long-term AED use** • Treatment side effects • History of and protocol for management of status epilepticus • Emergency seizure plan, including rescue medications • Integration of all HCPs, including adult neurologist, and designated point of care coordinator ("medical home") • Other medications for comorbidities or health maintenance • Involvement of PCP for health maintenance, physiotherapy, occupational therapy, speech and language therapy, recreational therapy, and other allied health providers • Involvement of school personnel and other community services providers
Mental and Physical Health	• **Level of cognitive ability (particularly relating to independent living and ADLs)** • Cognitive and behavioral issues • Evaluation of psychiatric comorbidities during and after transition • **Level of physical function (particularly relating to independent living and ADLs)**
Comorbidities	• Sleep disturbances • Need for specialty equipment (eg, wheelchairs, gastric feeding tube) • Mobility issues • Other concomitant neurologic problems, such as visual and hearing defects, difficulty swallowing • Bone health
Timing	• HCT initiated as early as feasible and recommended by age 12 years • Annual assessment of patient's level of assessment and ability to perform ADLs* • Annual planning sessions and updates to HCT plan regarding medical condition, treatment, side effects, etc
Financial Issues	• **Financial support (trust fund, family will, estate planning, government assistance [may require objective assessment of intellectual disability])** • **Changes to health insurance coverage when age of majority is reached or loss of coverage under parents' plan**
Caregiving Setting	• Primary caregiver: family member or non-family member, such as nurse • Availability of respite care for the parent (and for siblings) • Living arrangements: home with family or institutional setting, such as group home or assisted living facility
Legal Issues	• **Legal competency and guardianship (who has the right to make legal decisions, especially after parents are no longer available) to be established before young adult reaches age of majority†**
Psychosocial Needs and Quality of Life	• **Genetic counseling** • **Mental and emotional health support (for both patients and family members)** • Contraception and reproductive healthcare needs • Career opportunities and financial support for family members • Quality of life for siblings • Social integration (for both patients and family members) • **Social service support (may require objective assessment of intellectual disability)**

Factors listed in bold indicate considerations of particular relevance to LGS and DS. *Young adults with mild intellectual disabilities (ID) should not be excluded as they may be able to demonstrate some self-management skills. For young adults with severe ID, assessment of ability to perform ADLs may not be necessary but assessment of parental/caregiver ability to manage evolving healthcare demands is advised. †For young adults with ID, it is recommended that a conversation with caregivers about legal guardianship should take place by age 16 as the process to establish guardianship is lengthy and may take up to 2 years. ADLs, activities of daily living; AED, antiepileptic drug; EEG, electroencephalogram; HCP, healthcare provider; HCT, healthcare transition; MRI, magnetic resonance imaging; PCP, primary care physician. Figure 3 adapted from multiple publications.[32,43,51-53,62,66]

CONCLUSION

Although both are relatively rare, LGS and DS are prototypes of severe, lifelong epilepsy syndromes with poor prognoses, which place a significant burden on patients and their caregivers. In these model syndromes, there are life-threatening seizures and significant unmet medical, educational, social, and environmental needs. Early and effective seizure management is critical to a patient's neurological development and long-term overall risk for disability and even mortality. However, proper diagnosis of childhood epilepsy syndromes such as LGS and DS remains challenging, in part due to the varying clinical and EEG presentation of the syndromes, and their evolving nature as patients mature. In the age of increasingly sophisticated epilepsy genetics, it is critical to define the diagnosis, especially in light of the evolving presentation throughout childhood and young adulthood. Only with a clear understanding of the proper diagnosis is it possible to provide optimal care and guide patients to maximal independence. It is increasingly likely that patients with severe neurological and intellectual challenges will graduate from the pediatric to the adult healthcare system. Introduction of an HCT plan as part of routine care may help all involved, from patients and caregivers to healthcare providers, opening the dialogue to uncover new potential approaches to the challenge of transition and revisiting of patients' individual needs.

REFERENCES

1. Bourgeois BF, Douglass LM, Sankar R. Lennox-Gastaut syndrome: a consensus approach to differential diagnosis. ***Epilepsia.*** 2014;55(suppl 4):4-9.
2. Camfield PR. Definition and natural history of Lennox-Gastaut syndrome. ***Epilepsia.*** 2011;52:3-9.
3. Rajendran S, Iyer A. Epilepsy: addressing the transition from pediatric to adult care. ***Adolesc Health Med Ther.*** 2016;7:77-87.
4. Dravet C. The core Dravet syndrome phenotype. ***Epilepsia.*** 2011;52(suppl 2):3-9.
5. Trevathan E, Murphy CC, Yeargin-Allsopp M. Prevalence and descriptive epidemiology of Lennox-Gastaut syndrome among Atlanta children. ***Epilepsia.*** 1997;38:1283-1288.
6. Heiskala H. Community-based study of Lennox-Gastaut syndrome. ***Epilepsia.*** 1997;38:526-531.
7. Yakoub M, Dulac O, Jambaque I, Chiron C, Plouin P. Early diagnosis of severe myoclonic epilepsy in infancy. ***Brain Dev.*** 1992;14:299-303.
8. Wu YW, Sullivan J, McDaniel SS, et al. Incidence of Dravet syndrome in a US population. ***Pediatrics.*** 2015;136:e1310-1315.
9. Dura-Trave T, Yoldi-Petri ME, Gallinas-Victoriano F. Epilepsy in children in Navarre, Spain: epileptic seizure types and epileptic syndromes. ***J Child Neurol.*** 2007;22:823-828.
10. Gibson PA. Lennox-Gastaut syndrome: impact on the caregivers and families of patients. ***J Multidiscip Healthc.*** 2014;7:441-448.
11. Skluzacek JV, Watts KP, Parsy O, Wical B, Camfield P. Dravet syndrome and parent associations: the IDEA League experience with comorbid conditions, mortality, management, adaptation, and grief. ***Epilepsia.*** 2011;52(suppl 2):95-101.
12. Brunklaus A, Dorris L, Zuberi SM. Comorbidities and predictors of health-related quality of life in Dravet syndrome. ***Epilepsia.*** 2011;52:1476-1482.
13. Arzimanoglou A, French J, Blume WT, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. ***Lancet Neurol.*** 2009;8:82-93.
14. Gallop K, Wild D, Nixon A, Verdian L, Cramer JA. Impact of Lennox-Gastaut Syndrome (LGS) on health-related quality of life (HRQL) of patients and caregivers: literature review. ***Seizure.*** 2009;18:554-558.
15. Van Dam V, Korff CM. Dravet syndrome: an update. ***Schweiz Arch Neurol Psychiatr.*** 2013;164:153-157.
16. Wirrell EC, Laux L, Donner E, et al. Optimizing the diagnosis and management of Dravet syndrome: Recommendations from a North American consensus panel. ***Pediatr Neurol.*** 2017;68:18-34.e13.
17. Cassé-Perrot C, Wolff M, Dravet C. Neuropsychological aspects of severe myoclonic epilepsy in infancy. In: Jambaqué I, Lassonde M, Dulac O, eds. ***Neuropsychology of Childhood Epilepsy***. Boston, MA: Springer US; 2001:131-140.
18. Ferrie CD, Patel A. Treatment of Lennox-Gastaut syndrome (LGS). ***Eur J Paediatr Neurol.*** 2009;13:493-504.
19. Camfield C, Camfield P. Twenty years after childhood-onset symptomatic generalized epilepsy the social outcome is usually dependency or death: a population-based study. ***Dev Med Child Neurol.*** 2008;50:859-863.
20. Ferlazzo E, Nikaronova M, Italiano D, et al. Lennox–Gastaut syndrome in adulthood: Clinical and EEG features. ***Epilepsy Res.*** 2010;89:271-277.
21. Arzimanoglou A, Resnick T. All children who experience epileptic falls do not necessarily have Lennox-Gastaut syndrome... but many do. ***Epileptic Disord.*** 2011;13(suppl 1):S3-13.
22. Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O. Severe myoclonic epilepsy in infancy: Dravet syndrome. In: Delgado-Escueta AV, Guerrini R, Medina MT, Genton P, Bureau M, Dravet C, eds. ***Advances in Neurology. Myoclonic Epilepsies.*** Vol 95. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.

23. Autry AR, Trevathan E, Van Naarden Braun K, Yeargin-Allsopp M. Increased risk of death among children with Lennox-Gastaut syndrome and infantile spasms. ***J Child Neurol.*** 2010;25:441-447.

24. Beaumanoir A. The Lennox-Gastaut syndrome: a personal study. ***Electroencephalogr Clin Neurophysiol Suppl.*** 1982:85-99.

25. Beaumanoir A, Dravet C. The Lennox-Gastaut syndrome. In: Roger J, Bureau M, Dravet C, Dreifuss F, Perrot A, Wolf P, eds. ***Epileptic Syndromes in Infancy, Childhood and Adolescence***. London, UK: John Libbey; 1992:115-132.

26. Pina-Garza JE, Chung S, Montouris GD, Radtke RA, Resnick T, Wechsler RT. Challenges in identifying Lennox-Gastaut syndrome in adults: A case series illustrating its changing nature. ***Epilepsy Behav Case Rep.*** 2016;5:38-43.

27. Arzimanoglou A, Guerrini R, Aicardi J. Lennox-Gastaut syndrome. ***Aicardi's Epilepsy in Children, 3rd edition***. Philadelphia, PA: Lippincott Williams & Wilkins; 2004:38–50.

28. Niedermeyer E. The Lennox-Gastaut syndrome: a severe type of childhood epilepsy. ***Dtsch Z Nervenheilkd***. 1969;195:263-282.

29. Gastaut H, Dravet C, Loubier D, et al. Evolution clinique et prognostic du syndrome de Lennox-Gastaut. In: Lugaresi E, Pazzaglia P, Tassinar CA, eds. ***Evolution and prognosis of epilepsies***. Bologna: Aulo Gaggi; 1973:133-154.

30. Ogawa K, Kanemoto K, Ishii Y, et al. Long-term follow-up study of Lennox-Gastaut syndrome in patients with severe motor and intellectual disabilities: with special reference to the problem of dysphagia. ***Seizure.*** 2001;10: 197-202.

31. Yagi K. Evolution of Lennox-Gastaut syndrome: A long-term longitudinal study. ***Epilepsia.*** 1996;37:48-51.

32. Kerr M, Kluger G, Philip S. Evolution and management of Lennox-Gastaut syndrome through adolescence and into adulthood: are seizures always the primary issue? ***Epileptic Disord.*** 2011;13(suppl 1):S15-26.

33. Oguni H, Hayashi K, Osawa M. Long-term prognosis of Lennox-Gastaut syndrome. ***Epilepsia.*** 1996;37(suppl 3):44-47.

34. Yamatogi Y, Ohtahara S. Multiple independent spike foci and epilepsy, with special reference to a new epileptic syndrome of "severe epilepsy with multiple independent spike foci." ***Epilepsy Res.*** 2006;70:96-104.

35. Glauser TA. Following catastrophic epilepsy patients from childhood to adulthood. ***Epilepsia.*** 2004;45(suppl 5):23-26.

36. Kim E-H, Ko T-S. Cognitive impairment in childhood onset epilepsy: up-to-date information about its causes. ***Korean J Pediatr.*** 2016;59:155-164.

37. Resnick T, Sheth RD. Early diagnosis and treatment of Lennox-Gastaut syndrome. ***J Child Neurol.*** 2017:883073817714394.

38. Wirrell EC. Treatment of Dravet Syndrome. ***Can J Neurol Sci.*** 2016;43(suppl 3):S13-18.

39. Cooper MS, McIntosh A, Crompton DE, et al. Mortality in Dravet syndrome. ***Epilepsy Res.*** 2016;128:43-47.

40. Kumar A, Paliwal VK, Agarwal V, Neyaz Z, Lal H, Goel G. Relationship of Lennox–Gastaut syndrome with perinatal event: A cross-sectional study. ***J Pediatr Neurosci.*** 2015;10:98-102.

41. Bureau M, Bernardina BD. Electroencephalographic characteristics of Dravet syndrome. ***Epilepsia.*** 2011;52:13-23.

42. Hoffmann-Riem M, Diener W, Benninger C, et al. Nonconvulsive status epilepticus—a possible cause of mental retardation in patients with Lennox-Gastaut syndrome. ***Neuropediatrics.*** 2000;31:169-174.

43. Camfield PR, Gibson PA, Douglass LM. Strategies for transitioning to adult care for youth with Lennox-Gastaut syndrome and related disorders. ***Epilepsia.*** 2011;52:21-27.

44. Akiyama M, Kobayashi K, Ohtsuka Y. Dravet syndrome: a genetic epileptic disorder. ***Acta Med Okayama.*** 2012;66:369-376.

45. Ohki T, Watanabe K, Negoro T, et al. Severe myoclonic epilepsy in infancy: evolution of seizures. ***Seizure.*** 1997;6:219-224.

46. Ragona F, Brazzo D, De Giorgi I, et al. Dravet syndrome: early clinical manifestations and cognitive outcome in 37 Italian patients. ***Brain Dev.*** 2010;32:71-77.

47. Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O. Severe myoclonic epilepsy in infancy (Dravet Syndrome). In: Roger J, Bureau M, Dravet C, Genton P, Tassinari C, Wolf P, eds. ***Epileptic Syndromes in Infancy, Childhood and Adolescence, 4th edition***. London, UK: John Libbey Eurotext Ltd; 2005:89–113.

48. Dalla Bernardina B, Capovilla G, Gattoni MB, Colamaria V, Bondavalli S, Bureau M. [Severe infant myoclonic epilepsy (author's transl)]. ***Rev Electroencephalogr Neurophysiol Clin.*** 1982;12:21-25.

49. Scheffer IE, Dravet C. Transition to adult life in the monogenic epilepsies. ***Epilepsia.*** 2014;55(suppl 3):12-15.

50. Wirrell EC, Laux L, Franz DN, et al. Stiripentol in Dravet syndrome: Results of a retrospective U.S. study. ***Epilepsia.*** 2013;54:1595-1604.

51. Andrade DM, Bassett AS, Bercovici E, et al. Epilepsy: Transition from pediatric to adult care. Recommendations of the Ontario epilepsy implementation task force. ***Epilepsia.*** 2017;58:1502-1517.

52. Camfield PR, Bahi-Buisson N, Trinka E. Transition issues for children with diffuse cortical malformations, multifocal postnatal lesions (infectious and traumatic), and Lennox-Gastaut and similar syndromes. ***Epilepsia.*** 2014;55(suppl 3):24-28.

53. Camfield P, Camfield C, Nolan K. Helping families cope with the severe stress of Dravet syndrome. ***Can J Neurol Sci.*** 2016;43 Suppl 3:S9-s12.

54. Geerlings RPJ, Aldenkamp AP, de With PHN, Zinger S, Gottmer-Welschen LMC, de Louw AJA. Transition to adult medical care for adolescents with epilepsy. ***Epilepsy Behav.*** 2015;44:127-135.

55. Scheffer IE. Diagnosis and long-term course of Dravet syndrome. ***Eur J Paediatr Neurol.*** 2012;16(suppl 1):S5-8.

56. Carvill GL, Weckhuysen S, McMahon JM, et al. GABRA1 and STXBP1: novel genetic causes of Dravet syndrome. ***Neurology.*** 2014;82:1245-1253.

57. Depienne C, Bouteiller D, Keren B, et al. Sporadic infantile epileptic encephalopathy caused by mutations in PCDH19 resembles Dravet syndrome but mainly affects females. ***PLoS Genet.*** 2009;5:e1000381.

58. Le SV, Le PHT, Le TKV, Kieu Huynh TT, Hang Do TT. A mutation in GABRB3 associated with Dravet syndrome. ***Am J Med Genet A.*** 2017;173:2126-2131.

59. Harkin LA, Bowser DN, Dibbens LM, et al. Truncation of the GABA(A)-receptor gamma2 subunit in a family with generalized epilepsy with febrile seizures plus. ***Am J Hum Genet.*** 2002;70:530-536.

60. Patino GA, Claes LR, Lopez-Santiago LF, et al. A functional null mutation of SCN1B in a patient with Dravet syndrome. ***J Neurosci.*** 2009;29:10764-10778.

61. Suls A, Jaehn JA, Kecskés A, et al. De novo loss-of-function mutations in CHD2 cause a fever-sensitive myoclonic epileptic encephalopathy sharing features with Dravet syndrome. ***Am J Hum Genet.*** 2013;93:967-975.

62. Brown LW, Camfield P, Capers M, et al. The neurologist's role in supporting transition to adult health care: A consensus statement. ***Neurology.*** 2016;87:835-840.

63. Borlot F, Tellez-Zenteno JF, Allen A, Ali A, Snead OC, 3rd, Andrade DM. Epilepsy transition: challenges of caring for adults with childhood-onset seizures. ***Epilepsia.*** 2014;55:1659-1666.

64. Nolan K, Camfield CS, Camfield PR. Coping with a child with Dravet syndrome: insights from families. ***J Child Neurol.*** 2008;23:690-694.

65. Jurasek L, Ray L, Quigley D. Development and implementation of an adolescent epilepsy transition clinic. ***J Neurosci Nurs.*** 2010;42:181-189.

66. Devinsky O, Asato M, Camfield P, et al. Delivery of epilepsy care to adults with intellectual and developmental disabilities. ***Neurology.*** 2015;85:1512-1521.

67. Kuchenbuch M, Chemaly N, Chiron C, Dulac O, Nabbout R. Transition and transfer from pediatric to adult health care in epilepsy: a families' survey on Dravet syndrome. ***Epilepsy Behav.*** 2013;29:161-165.

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