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MEDICINE

Comorbidities in Dravet Syndrome and Lennox–Gastaut Syndrome

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Abstract

This study aims to describe the main cognitive and behavioral comorbidities of Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS), their impact on the health-related quality of life (QOL) of patients and their caregivers, and provide a summary of the neuropsychological tools available for the evaluation of these comorbidities. The cognitive and behavioral comorbidities in patients with DS and LGS have a profound effect on the QOL of affected individuals and their caregivers and, as patients grow, tend to surpass the impact of the seizures. DS is a genetic condition associated with loss-of-function mutations in the *SCNA1* sodium channel gene; LGS is an etiologically heterogeneous condition that is often secondary to structural brain abnormalities. The first seizures associated with DS typically present in the first year of life, and developmental delay becomes progressively evident thereafter. LGS usually starts between the ages of 3 and 8 years, with cognitive impairment becoming clinically evident in most patients within 5 years from the onset. In both DS and LGS, cognitive impairment is generally moderate to severe and is often accompanied by behavioral problems such as hyperactivity and inattention. In addition to optimal seizure control, regular assessment and active management of cognitive and behavioral comorbidities are required to meet the complex needs of patients with DS or LGS.

Keywords Behavioral comorbidity · Cognitive comorbidity · Dravet syndrome · Lennox–Gastaut syndrome · Quality of life

Introduction

Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS) are severe developmental and epileptic encephalopathies (DEEs) that begin in childhood and persist throughout adulthood [1–4]. In both conditions, epileptiform activity, seizures, and the underlying genetic, structural, or metabolic defect can result in neurodevelopmental delay or regression [5–7]. DS is a genetic condition that is primarily associated with loss-of-function mutations in the *SCNA1* gene for voltage-gated sodium channels, which result in loss of action firing in gamma-aminobutyric acid (GABA)-ergic interneurons [8, 9]. In contrast, LGS has a relatively heterogeneous etiology [2, 10, 11] with an identifiable (genetic, structural, or metabolic) cause in 65–75% of patients [1, 2, 9–11]. LGS occurs most often as a result of a structural brain abnormality, such as tuberous sclerosis complex, cerebral malformation, or hypoxic-ischemic injury, and very rarely as a result of a progressive metabolic disorder [2, 9–12].

LGS accounts for an estimated 1–10% of childhood epilepsies, and the reported incidence of DS is between 1 in 15,700 and 1 in 40,000 live births, so these are rare diseases [2, 3, 13, 14]. However, the morbidity associated with LGS

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and DS leads to disproportionately large costs to the healthcare system and society in general [7, 13].

Treatment of DS and LGS focuses on alleviation of seizure burden, but some patients may have treatment-resistant seizures. In addition, DS and LGS are associated with multiple comorbidities, which present further management challenges [4, 10, 15–17]. Despite their different etiologies, DS and LGS share several comorbid features, including developmental delays in several domains: social–emotional, cognitive, motor, adaptive, and communicative [18–22]. Thorough and accurate early assessment and diagnosis, including careful assessment of clinical and electroencephalography (EEG) features, are important to ensure that patients receive the most appropriate treatment and support as soon as possible, to optimize long-term neurodevelopmental outcome [4, 19, 23].

In this review, we describe the most common cognitive and behavioral comorbidities of DS and LGS and their impact on the health-related quality of life (HRQOL) of patients and their caregivers. Management implications and neuropsychological tools for the evaluation of cognitive and behavioral aspects of LGS and DS are also discussed.

Cognitive and Behavioral Comorbidities of Dravet Syndrome and Lennox–Gastaut Syndrome

Cognitive Impairment

Moderate-to-severe cognitive impairment is common in DS and LGS and is a diagnostic feature of both disorders [2–4, 15]. Cognitive delay generally occurs earlier in life with DS than with LGS [2, 19], but cognitive impairment is not necessarily apparent at the onset of seizures in either syndrome [1, 21, 24].

Dravet Syndrome

Intellectual disability (ID) is a comorbidity of DS, but it is still unclear if ID results from damage caused by seizures, the abnormal levels of $Na_v1.1$ protein, the use of inappropriate medications, such as sodium channel inhibitors, or a combination of these factors [25]. DS typically presents in the first year of life in children with no pre-existing developmental problems [3, 21, 26, 27]. It was generally thought that DS patients show typical cognitive development until the second year of life, followed by a gradual decline which leads to moderate or severe ID by 6 years of age (Fig. 1) [26–32]. However, recent data indicate variability in cognitive development among DS children tested before 24 months of age, suggesting that cognitive delay may begin before 2 years of age in some patients [33]. A study by Nabbout et al. [31] in 67 children with DS showed that, after 6 years of age, IQ decreased with age, but patients continued acquiring new skills during the first decade. Therefore, the progression of developmental delay seen from 2 years of age [22, 26, 27, 31–35] could reflect an early arrest of cognitive development, followed by an increasing discrepancy between developmental age and chronological age [26], rather than consistent cognitive regression.

In the literature, many authors have found that seizure frequency and severity, the presence of status epilepticus (SE), or EEG activity may influence the cognitive outcome in patients with DS [28, 29, 31, 32, 36, 37]. However, in other studies, there was no significant correlation between the severity of cognitive delay and seizure activity [31, 38]. Preclinical

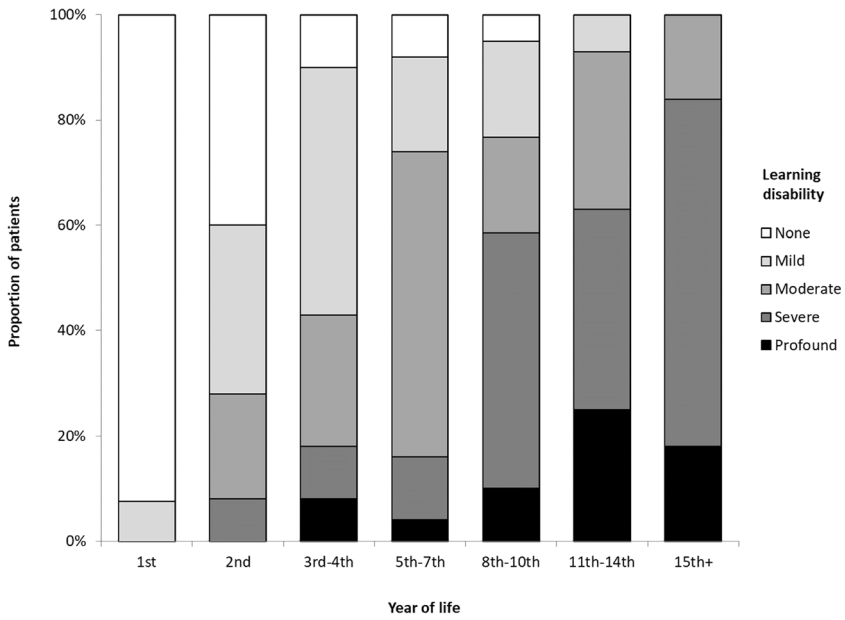

Fig. 1 Cross-sectional analysis of cognitive development over time in 241 patients (aged 6 months to 42 years) with *SCN1A* mutation-positive Dravet syndrome, reproduced with permission [28]

studies suggest that *SCN1A* mutation by itself may play a role in determining the final cognitive outcome [26, 31]. The pattern of cognitive deficits observed in patients with DS is consistent with cerebellar cognitive syndrome, as language comprehension tends to be better preserved than language production and visuospatial functions [22, 31, 34, 35, 37, 39, 40].

Lennox–Gastaut Syndrome

In contrast to DS, 20–60% of LGS patients have cognitive impairment before the onset of seizures, particularly when LGS is a consequence of an identifiable etiology [15, 19, 41]. Children with LGS of unknown origin may seem to develop normally before the appearance of the first seizures [15, 19]. In general, cognitive impairment becomes progressively evident over time [1, 2, 15], and the proportion of patients with serious ID may increase to 75–95% at 5 years after the onset of seizures [42]. The cognitive outcome of patients with LGS is variable [43], and there is no evidence that it correlates only with epilepsy severity. LGS is characterized by alterations in specific thalamocortical networks, which normally support a broad range of cognitive functions [44]. Disruption of normal interactions within and between brain networks that support key cognitive processes has been reported in an EEG-functional magnetic resonance imaging study of 15 adult patients with LGS [45]. It has been proposed that epileptic activity in LGS, which intersects with cognitive networks, may initiate sustained abnormal network behavior, and the persistence of these abnormal cognitive network interactions in the absence of detectable epileptic activity potentially contributes to impaired cognition [45]. The relatively preserved cognitive status observed in late-onset LGS may, in part, be because these patients did not experience epileptic activity during sensitive periods of neurodevelopment when cognitive networks are most vulnerable to disrupted maturation [36, 45–47].

Behavioral Problems

In DS and LGS, cognitive impairment is frequently associated with social–emotional problems, but there is not necessarily a linear relationship between the severity of the cognitive disability and the frequency of behavioral difficulties [4, 20, 48–50]. Attention and hyperactivity problems, as well as autistic traits, are commonly observed in both DEEs [2–4, 15, 16, 51].

Dravet Syndrome

Behavioral difficulties in children with DS usually include attention disorders and hyperactivity, aggressive behavior, and social problems [16, 33]. These problems, which do not appear to be related to the severity or frequency of epilepsy, seem to increase in childhood, peak in adolescence, and then plateau or decrease in adulthood, while autistic traits tend to persist [28, 49, 52–54]. Parents and caregivers often report high levels of attention difficulties in patients affected by DS, which have been confirmed in several studies, but the prevalence of ADHD among children with DS is unknown [16, 50, 53].

DS patients may display autistic traits, such as stereotyped, repetitive and disinhibited behavior, obsessions, and poor peer relationships [38, 50–52, 54, 55], but the prevalence of autism spectrum disorder (ASD) in DS varies significantly across studies. One reason may be that communicative skills are relatively preserved, leading to an underestimation of ASD prevalence among patients with DS [38, 50–52]. When gold-standard ASD assessment tools were used, ASD prevalence ranged from 22 to 39% [16, 51]. Studies in mice show that impairment of sodium channel function and the resulting GABAergic signaling dysfunction likely contribute to behavioral and cognitive impairment in DS [8, 56, 57].

Lennox–Gastaut Syndrome

Hyperactivity/inattention, anxiety, agitation, depression, and aggression are commonly seen in patients with LGS [1, 2, 15, 42, 58, 59]. Autistic behavior has also been reported, but only in a few cases of LGS, and is less common in LGS than DS, despite the similar prevalence and severity of IDs in the two forms of encephalopathy [42]. It has been suggested that factors other than cognitive impairment are involved in the pathogenesis of autistic traits in LGS and DS [42], such as epilepsy itself, abnormal brain neural network characteristics, and the effect of medications [1].

Other Comorbidities of Dravet Syndrome and Lennox–Gastaut Syndrome

Patients with DS often develop disabling motor impairment, involving all motor domains (balance, coordination, visuomotor integration, power, and locomotion) [60]. As a result, walking becomes increasingly ataxic, and gait tends to worsen with age [3, 17, 20, 21, 28, 30, 50, 61–63], such that, from adolescence, many patients require the use of a wheelchair for longer distances [20]. A “crouch gait” (defined as the increased ankle, knee, and hip flexion during the whole gait cycle, plus rotations of the femur and/or tibia, and muscle retraction) is not specific to DS but often appears by 13 years of age [61, 63]. In fact, a study by Di Marco et al. [64] showed that the crouch gait pattern could appear as early as 4 years of age in patients with DS. By adolescence (age > 13 years), some patients have developed a flexed gait pattern with passive knee extension deficit and bony malalignment. In adulthood, extrapyramidal signs and Parkinsonian gait become evident [17, 18, 61–63].

Gitiaux et al. proposed that to understand gait disturbance, we should consider DS as a sodium channel interneuronopathy causing complex clinical presentations of varying nature [17]. So depending on the site or structure where the voltage-gated sodium channel type 1 ($Na_V1.1$) is expressed, different movement disorders are induced. In particular, motor neuron dysfunction could partially explain the gait features observed at first as mild distal motor deficits, followed by proximal (crouch-like) deficits. In a genetic mouse model of DS, ataxia was caused by deficits in the cerebellar Purkinje neurons conveying output information on movement, coordination, and balance from the cerebellar cortex [65]. In contrast, mobility problems in LGS are often a direct result of seizures, particularly drop attacks, which are physically demanding and often result in injury [10, 48].

Sleep disturbances, which are common in DS and LGS, may contribute to cognitive, behavioral, and psychological issues [10, 48, 50, 55, 66–68]. Tonic seizures occurring during sleep, with the potential to disrupt the sleep cycle, are characteristic of LGS [48]. DS children and adults have more nighttime awakenings, reflective of poor quality of sleep [25]. *SCNA1* mutations dysregulate neurological sleep networks [8, 66], as demonstrated in a mouse model, in which $Na_V1.1$ channels encoded by *SCN1A* are expressed in the GABAergic neurons in the hypothalamus, thalamic reticular nucleus, and cortex [69]. In both DS [66] and LGS [70], nocturnal seizures, polypharmacy, developmental delay, and environmental factors (such as co-sleeping) may also contribute to a high frequency of sleep disturbances.

Epilepsy patients have a 24- to 28-fold higher rate of sudden death compared with the general population [71]. It has been proposed that channelopathy common to both epilepsy and cardiac disease may contribute to the increased risk of death via a lethal cardiac arrhythmia [72, 73]. Patients with DS have a genetic predisposition to cardiac autonomic dysfunction, heart rate abnormalities, and arrhythmias, reflecting *SCN1A* expression in the heart and contributing to a high risk of sudden unexpected death in epilepsy [74–76].

Impact of Comorbidities on Patients and Caregivers

Comorbidities of DS and LGS increase the complexity of the patient's care needs and can disrupt daily activities, limit educational and social progress, and have a profound impact on the HRQOL of patients with DS or LGS and their families (Fig. 2) [20, 48–50, 54, 77–80]. Cognitive impairment and behavioral problems both independently predict reduced HRQOL, but behavioral problems can be particularly burdensome [20, 49, 53, 54, 81]. With their impact on mobility, motor impairments further detract from HRQOL [20, 78, 81].

Whereas the nature of seizures can change and seizure burden can decrease, the burden of comorbidities in DS and LGS does not improve and increases with age [25, 29, 48, 50, 59]. Although seizures remain a prominent problem, cognitive, behavioral, and physical comorbidities can eclipse seizures as a higher management priority in adolescent and adult patients with LGS, reflecting the importance of education, independence, and the ability to work, interact with peers, and form relationships [15, 48, 59].

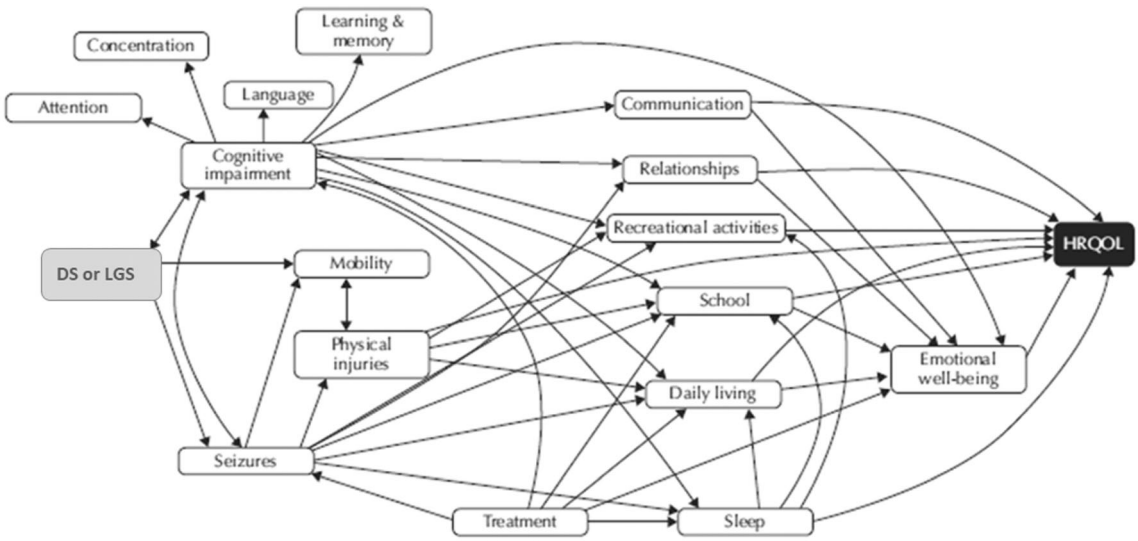

Fig. 2 Conceptual model of ways in which DS and LGS affect the HRQOL of patients, reproduced with permission [77]. DS, Dravet syndrome; HRQOL, health-related quality of life; LGS, Lennox–Gastaut syndrome

General Management Implications

Although seizures must be controlled, management of DS and LGS should focus not only on pharmacologic seizure control but should also address comorbidities [2, 4, 10, 20, 21, 48, 50, 79, 82]. Seizures may aggravate the cognitive and behavioral comorbidities of DS and LGS, and therefore, pharmacologic treatment should be tailored to each patient based on the type of seizure, age, and clinical history [83]. Moreover, currently used antiepileptic drugs (AEDs) may also contribute to cognitive impairment and behavioral disorders in these patients, and few data are available on the most appropriate antiepileptic therapy for patients with LGS or DS. Comorbidities and the risk of AED-related adverse events (AEs) can also influence the therapeutic choice [4, 10, 20, 41, 53, 79, 83, 84].

Valproic acid (VPA) is used in both syndromes; it is a broad-spectrum AED and is highly unlikely to aggravate seizures [10, 83]. In the pediatric LGS population, VPA has been associated with cognitive AEs (such as confused state or attention disturbances) or behavioral AEs (such as aggression or agitation); it is rarely associated with AEs such as abnormal behavior or hyperactivity [10]. However, VPA is known to be associated with two types of hepatotoxicity: dose dependent and reversible elevation of serum liver enzymes (type I), and rare but often fatal, idiosyncratic hepatotoxicity (type II) [85]. The risk of VPA-related hepatotoxicity is increased in children below 2 years of age and in patients receiving other anticonvulsants [86–89]. Also, VPA has been reported to cause some coagulopathies (von Willebrand's disease, factor XIII deficiency, thrombocytopenia); however, their clinical relevance remains uncertain [85]. Clobazam (CLB) is a benzodiazepine with antiepileptic properties and is also used in both syndromes. It has been associated with cognitive and behavioral AEs, including slowed reaction time, confusion, irritability, and numbed emotions [10]. Stiripentol (STP) is an orally active unique AED, indicated for use with CLB and VPA as adjunctive therapy for refractory seizures in DS [90, 91]. AEs associated with STP treatment include somnolence and motor impairment such as ataxia or tremor. Felbamate (FLB), which is licensed in some European countries as adjunctive therapy in patients with LGS, showed adverse effects on cognition (abnormal thinking) in 6.5% of pediatric patients; behavioral AEs associated with FLB include agitation, aggression, or psychological disturbance [10]. Lamotrigine (LTG) was approved by the US Food and Drug Administration (FDA) in 1998 as an adjunctive treatment for patients with LGS aged > 2 years [83, 92]. It is considered a second-line AED after the failure of VPA. Common AEs associated with LTG include ataxia, rash, headache, anorexia, and drowsiness [83], or very rarely, confusion or hallucinations [10]. Behavioral AEs, such as aggression, irritability, and agitation, may also occur [10]. Rufinamide (RUF) was approved by the European Medicines Agency (in 2007) and by the US FDA (in 2008) as adjunctive seizure therapy in patients with LGS older than 4 years of age [93]. Anxiety is a common behavioral AE associated with RUF [10, 94, 95]. Topiramate (TPM) was approved by the US FDA in 2001 as adjunctive therapy for the treatment of seizures in patients with LGS aged ≥ 2 years [83]. Its tolerability profile in the pediatric population is characterized by AEs occurring early in the treatment course, and most are CNS related, including somnolence and psychomotor impairment [83]; depression has also been commonly observed [10].

In addition to optimal seizure control, long-term treatment goals should focus on maximizing developmental potential and HRQOL [4, 11, 19, 96].

Given the various comorbidities of DS and LGS, comprehensive multidisciplinary management involving different healthcare professionals is required to ensure that individual patients' medical, educational, psychological, and social needs are met throughout their lives (Fig. 3) [4, 10, 11, 48, 50, 54, 77, 97]. Transitioning from pediatric to adult care can be particularly challenging as the provision of care becomes more dispersed and there are generally fewer resources available for adults compared with pediatric patients [10, 48, 50, 77, 96]. To ensure as smooth a transition as possible, patients and their families should receive appropriate educational and psychosocial support [19, 48].

Cannabidiol (CBD), a nonpsychoactive compound derived from *Cannabis* plants, is a recent addition to the treatment options for patients with DS and LGS [98]. In the USA, CBD (Epidiolex®, Greenwich Biosciences, Inc., Carlsbad, CA, USA) has been approved for the treatment of seizures associated with LGS or DS in patients aged ≥ 2 years [99]. In the EU, CBD (Epidyolex®, GW Pharmaceuticals, Cambridge, UK) has been approved for the adjunctive treatment (in combination with CLB) of seizures associated with LGS or DS in patients aged ≥ 2 years [100] and for seizures associated with tuberous sclerosis complex in patients aged ≥ 1 year [101]. There is some evidence that, in addition to reducing the frequency and severity of seizures, CBD improves mood and quality of life in patients with treatment-resistant epilepsy [87, 102]. In this population, long-term use of CBD does not appear to be associated with negative effects on cognitive functioning [103].

Neuropsychological Assessment in the Management of Cognitive and Behavioral Problems

Comprehensive care of patients with DS or LGS must involve a careful assessment of comorbidities, routine monitoring of

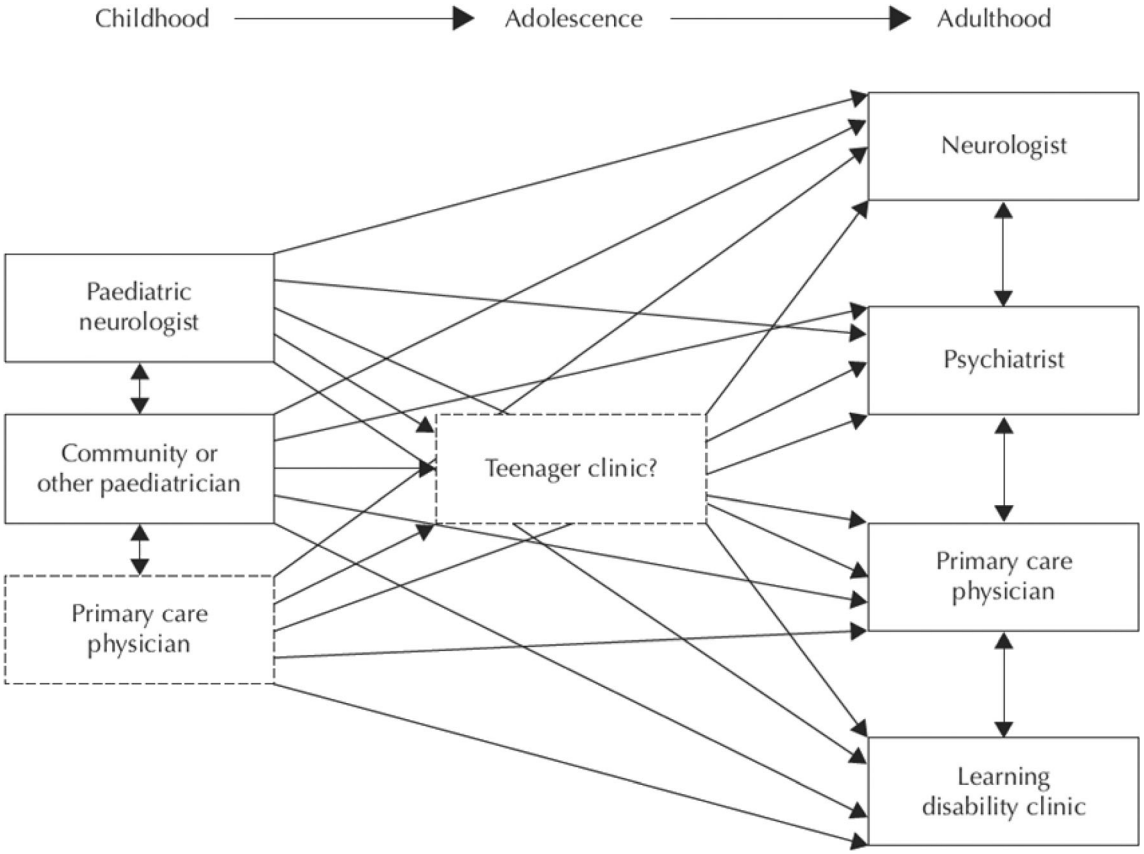

Fig. 3 Multidisciplinary division of care as patients with LGS transition from pediatric to adult services, reproduced with permission [48]. LGS, Lennox–Gastaut syndrome

development and behavior at clinic visits, a formal developmental or cognitive assessment before starting school or earlier if there are clinical concerns about development, regular school assessments, and reassessment when transitioning from pediatric to adult care [4, 48]. Table 1 summarizes the timepoints for conducting neuropsychological testing in pediatric patients with DS or LGS.

Active management of cognitive and behavioral problems is a high priority, but there are no neuropsychological assessment tools specifically for the evaluation of DS or LGS patients, and characterization of cognitive performance and behavior in these patients is challenging [15, 51]. General standardized assessment tools should be chosen according to the patient's age and neurodevelopmental level, and the neuropsychological components that are typically compromised in children with DS or LGS (i.e., speech, attention, spatial, sensory-motor, and executive function). Many of the same tests are appropriate for use in both DS and LGS (Table 2).

The Wechsler Intelligence Scale for Children (WISC) and the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) are useful for an initial general

Table 1 Suggested time points for assessment of cognition and behavior

Age/stage	Dravet syndrome	Lennox–Gastaut syndrome
Age range	1–7 years	4–10 years[a]
Onset/diagnosis	✓	✓
Preschool	✓	✓
24 months	✓	✓
36 months	✓	✓
4–5 years	✓	✓
School age	Yearly ↓ to 2nd year of elementary school	Yearly ↓ to 12–13 years

[a] Age of onset in LGS does not necessarily coincide with age of diagnosis

Table 2 Tools for the assessment of cognitive and behavioral comorbidities in patients with Dravet syndrome or Lennox–Gastaut syndrome

Area of assessment	Assessment tool	DS	LGS	Authors' comments
Development and intelligence	Bayley Scales of Infant and Toddler Development III	✓		Used ideally at the onset of DS Used up to age 2.5–3 years
	Griffiths Mental Development Scales	✓		Useful for baseline assessment at the onset of DS
	Raven's Matrices	✓	✓	May be used in place of WPPSI and WISC
	Leiter-R Scale	✓	✓	Useful for initial screening Leiter's cancellation test can be used in non-verbal patients
	Wechsler Scale and subtests	✓	✓	Used no more than once yearly Useful for an initial general assessment Use WISC and WPPSI specifically at onset of LGS In DS, switch to WPPSI at age of 2.5–3 years if cognitive delay is not significant
Sensorimotor integration	Test of Visual Perception	✓		Useful considering visual impairment in DS patients Used in DS patients aged 4–11 years
	Visual–Motor Integration Test	✓		Used at age of 36 months (may be used in patients aged up to 18 years) Useful considering visual-spatial and motor coordination impairment in DS patients
Language	**TVL**	✓	✓	Test recommended for assessing language
	TROG	✓	✓	A sensitive test for assessing speech in children aged ≥ 4 years Useful test since it also has a working memory component
	Boston Naming Test	✓	✓	Useful for assessing the expressive component of language use
	Peabody Picture Vocabulary Test	✓	✓	Useful for assessing the receptive component of language use
	MacArthur-Bates Communicative Development Inventories	✓	✓	Assessment completed by the parent/caregiver Widely used internationally
Executive function	Tower of London	✓	✓	Optional test for assessing executive function
	Porteus	✓	✓	
	Trail Making Test	✓	✓	
	Wisconsin Card Sorting Task	✓	✓	May not be suitable in a hospital setting given its complexity and time taken to administer
	NEPSY-II subtests	✓	✓	Costly test Useful for assessing onset LGS, and up to 3 years of age
Attention	**Bell's Cancellation Test-Revised**	✓	✓	To be used in children aged ≥ 4 years
	Trail Making Test	✓	✓	
Verbal and visuospatial memory	**Digit Span** (Wechsler subtest)	✓	✓	Recommended for testing working memory Rapid Widely used
	Rey–Osterrieth complex figure copy and recalling	✓	✓	Informative test but more complex than Digit Span
	Benton Visual Retention Test	✓	✓	
	Corsi Test	✓	✓	Rapid Widely used
Behavior	**Child Behavior Checklist**			Important to use this test as it provides the parent/caregivers' perspective Recommended over Conners scale
	Ages 1–5	✓	✓	
	Ages 6–18	✓	✓	
	K-SADS	✓	✓	
	Vineland Adaptive Behavioral Scales	✓	✓	Recommended for assessing autonomy Useful when it is not possible to test the child directly
	Conners Scale	✓	✓	Optional test of behavior
	ABAS-III			Useful test of everyday life (eating, getting dressed, etc.) Completed by a parent/caregiver Recommended for assessing autonomy at the level of adaptive behavior

Table 2 (continued)

Area of assessment	Assessment tool	DS	LGS	Authors' comments
	Aberrant Behavior Checklist	✓	✓	

Items in bold are recommended tests to be conducted as a minimum assessment of each aspect

ABAS-III, Adaptive Behaviour Assessment System 3rd edition; *DS*, Dravet syndrome; *BVN*, Batteria di valutazione neuropsicologica; *ID*, intellectual disability; *K-SADS*, Kiddie Schedule for Affective Disorders and Schizophrenia; *LGS*, Lennox–Gastaut syndrome; *MASC*, Multidimensional Anxiety Scale for Children; *NEPSY*, developmental neuropsychological assessment; *TROG*, *Test for Reception of Grammar*; *TVL*, Test di Valutazione del Linguaggio; *WISC IV*, Wechsler Intelligence Scale for Children; *WPPSI III*, Wechsler Preschool and Primary Scale of Intelligence

assessment of cognitive abilities in children with DS or LGS [40, 84]. The Leiter-R test is a nonverbal assessment of intellectual functioning, comprising visualization and reasoning, and attention and memory components [104], and is also recommended as an initial test at diagnosis/onset. The Griffiths or Bayley Scales can be used for very young DS children up to 3 years of age [40, 84]. From 3 years, the Visual–Motor Integration Test can be used to assess visual function, which is particularly compromised in DS and precedes detectable cognitive decline [22, 35, 40]. Other tests that can be used to assess specific skills in patients with DS or LGS include the Corsi Test for visuo-spatial memory, Bell's Cancellation Test for attention, the Boston Naming Test for language, the Tower of London procedure for executive function [40] in patients with minimal cognitive impairment, and the *MacArthur-Bates Communicative Development Inventories* for assessment of language [105].

Behavior assessment may be performed using tools such as the Child Behavior Checklist (CBCL) for children aged 1–5 years (CBCL/1–5) or older children and adolescents (CBCL/6–18) [40]. The CBCL questionnaire is completed by parents/caregivers, thereby acknowledging the importance of the role of the caregiver in evaluating the patient. Another generalized behavior assessment tool that is suitable for use in patients with DS or LGS [38, 51] is the Vineland Adaptive Behavioral Scales (Vineland-3), which focus on age-dependent adaptive behavior, including communication, daily living, and socialization skills [106].

Conclusions

DS and LGS are multifaceted diseases with a range of clinical comorbidities that are not purely the result of poorly controlled seizures. Moderate-to-severe cognitive impairment and general behavioral problems are characteristic comorbidities in both DS and LGS. The profound impact of cognitive and behavioral comorbidities on the lives of patients with DS or LGS and their caregivers and families highlights the importance of active multidisciplinary management, careful treatment choice, and appropriate educational and psychosocial support systems. In particular, psychoeducation (e.g., cognitive behavioral therapy or mood management) and community support may help patients and their family/caregivers in coping and adapting to the distress of pervasive and severe behavioral comorbidities of DS and LGS. Therefore, in addition to the medical management of seizures, comprehensive assessment and careful management of comorbidities should be a core aspect of care (Table 3).

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Data Availability Not applicable.

Declarations

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Consent to Participate Not applicable.

Consent for Publication Not applicable.

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Table 3 Antiepileptic drugs used in the treatment of Dravet syndrome and/or Lennox–Gastaut syndrome

Drug	Approved indication	Dose	Adverse drug reactions
Valproic acid [107]	Treatment of generalized epileptic seizures (including absence, myoclonic, tonic–clonic, atonic, or mixed seizures) Treatment of focal epileptic seizures (simple or complex, secondary generalized) Treatment of specific syndromes (West, LGS)	300 mg and 500 mg prolonged-release tablets	Anemia, thrombocytopenia, hyponatremia, dose-dependent weight gain or weight loss, increased or decreased appetite, confusion, hallucinations, aggression, agitation, attention disturbances, tremor, dose-dependent paresthesia, extrapyramidal disorders, stupor, postural tremor, drowsiness, seizures, memory disorders, headache, dizziness, nystagmus, deafness, tinnitus, hemorrhage, nausea, vomiting, gum disease, stomatitis, upper abdominal pain, diarrhea, severe or fatal liver dysfunction, hypersensitivity, alopecia, nail and nail bed disorders, and dysmenorrhea[a]
Clobazam [108]	Adjunctive therapy for epilepsy in adults and children over the age of 2 years, when standard treatment with one or more anticonvulsants has not been effective	1 mg/mL and 2 mg/mL oral suspension	Orthostatic hypotension[a]
Stiripentol [109]	Adjunctive therapy (in addition to clobazam and valproate) of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (DS) whose seizures are not adequately controlled with clobazam and valproate	250 mg hard capsules	Neutropenia, anorexia, loss of appetite, weight loss, insomnia, aggressiveness, irritability, behavior disorders, opposing behavior, hyperexcitability, sleep disorders, drowsiness, ataxia, hypotonia, dystonia, hyperkinesias, nausea, vomiting, and raised γ-GT
Felbamate [110]	Adjunctive therapy for the treatment of adults and children aged over 4 years with LGS who are refractory to all other AEDs	400 mg and 600 mg tablets	Weight loss, anorexia, insomnia, somnolence, ataxia, dizziness, headache, diplopia, vision abnormalities, nausea, vomiting, dyspepsia, abdominal pain, diarrhea, and fatigue[a]
Lamotrigine [111]	Adjunctive or monotherapy (adjunctive therapy only in children aged 2 to 12 years) in the treatment of epilepsy, for partial seizures and generalized seizures, including tonic-clonic seizures and the seizures associated with LGS	25 mg, 50 mg, 100 mg and200 mg tablets 2 mg, 5 mg, 25 mg, 50 mg, 100 mg, and 200 mg dispersible/chewable tablets	Aggression, irritability, headache, somnolence, dizziness, tremor, insomnia, ataxia, dizziness, headache, nystagmus, tremor, diplopia, blurred vision, nausea, vomiting, diarrhea, skin rash, and tiredness[a]
Rufinamide [112]	Adjunctive therapy in the treatment of seizures associated with LGS in patients 1 year of age and older	100 mg, 200 mg, and 400 mg film-coated tablets	Headache, dizziness, fatigue, and somnolence
Topiramate [113]	Adjunctive therapy in children aged 2 years and above, adolescents and adults with partial-onset seizures with or without secondary generalization or primary generalized tonic-clonic seizures and for the treatment of seizures associated with LGS	25 mg, 50 mg, 100 mg, and 200 mg film-coated tablets 15 mg, 25 mg, and 50 mg hard capsules	Anorexia, decreased appetite, bradyphrenia, depression, expressive language disorder, insomnia, coordination abnormal, disturbance in attention, dizziness, dysarthria, dysgeusia, hypoesthesia, lethargy, memory impairment, nystagmus, paresthesia, somnolence, tremor, diplopia, vision blurred, diarrhea, nausea, fatigue, irritability, and weight decreased
Cannabidiol [100]	Adjunctive therapy of seizures associated with LGS or DS, in conjunction with clobazam, for patients 2 years of age and older	100 mg/mL oral solution	Somnolence, decreased appetite, diarrhea, pyrexia, fatigue, and vomiting

[a] Common or very common adverse events

AEDs, antiepileptic drugs; *DS*, Dravet syndrome; *γ-GT*, γ-glutamyl transferase; *LGS*, Lennox–Gastaut syndrome

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