Beyond Seizures:
Comorbid Clinical Features and Multidisciplinary Management of Lennox-Gastaut Syndrome and Dravet Syndrome
ABSTRACT

Lennox-Gastaut syndrome and Dravet syndrome are two examples of rare, childhood-onset epilepsy syndromes with a considerable disease burden. These epilepsy syndromes impact everyday life for patients and families not only due to severe, treatment-resistant seizures, but also from the extent and severity of nonseizure comorbidities and associated symptoms experienced by patients. These symptoms may be disruptive to day-to-day activities, preclude attendance in mainstream school, affect ability to perform activities of daily living, reduce social participation or lead to social isolation, hinder development of interpersonal relationships, and strain spouse, sibling, and other family relationships. Ultimately, these comorbid features create a heavy physical, financial, social, and mental burden on patients and their caregivers, decreasing both patient and caregiver quality of life. Although data on the impact of nonseizure symptoms on patients and caregivers remain limited, this white paper outlines the available evidence and considerations for multidisciplinary approaches to care and individualizing clinical management.

BACKGROUND

Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) are two rare, severe, treatment-resistant epileptic encephalopathies with childhood onset.\(^1,2\) In both syndromes, seizures begin early in childhood and persist into adulthood.\(^1,3\) Despite the availability of several treatment options, seizure control is difficult to achieve and patients are unlikely to become seizure-free even with treatment.\(^2,4\) In addition, LGS and DS are associated with numerous comorbid features, which can further complicate the management of these syndromes.\(^2,4\)

Both LGS and DS are characterized by multiple seizure types and developmental delay, but characteristic features of each condition, variability of symptoms over time, and the many nonseizure comorbid features associated with the syndromes present unique challenges in diagnosis and management of each disease.\(^1,2,4\) LGS is characterized by an abnormal electroencephalogram (EEG) pattern of slow spike-wave complexes (<3 Hz) and generalized paroxysmal fast activity,\(^1\) while there is no signature EEG pattern in DS.\(^3\) In LGS, there are multiple etiologies, which can cause variation in clinical presentation or evolution of symptoms over time.\(^4\) Symptomatic LGS (≈70% to 80% of cases) has an identifiable etiology, most typically caused by injury to the brain.\(^1\) No current biomarker exists for LGS, adding to the diagnostic challenge,\(^1\) but in DS, 70% to 80% of patients have mutations in the voltage-gated sodium channel alpha-1 subunit (SCN1A) gene.\(^2\) While an SCN1A mutation is strongly indicative of DS, a mutation without clinical signs is not sufficient for and its absence does not exclude a diagnosis of DS.\(^2\)

Patients with LGS and DS face a higher mortality risk than both the general population and patients with other forms of epilepsy, notably due to the high rate of sudden unexpected death in epilepsy (SUDEP) and status epilepticus (SE) in these patient populations.\(^5-7\) The mortality rate in children with LGS is estimated to be 5%,\(^1\) although one epidemiologic study reported a rate as high as 14% over 10 years.\(^5\) Compared with the general
population, the risk of death due to all causes is 14 times greater in pediatric patients with LGS; the risk of death due to neurologic causes, such as prolonged seizures and SE, is 179 times greater in patients with LGS. In DS, mortality rates range from 7% to 18% in people under 18 years of age. Sudden Unexpected Death in Epilepsy (SUDEP) and SE are the two leading causes of death, accounting for 80% of all deaths in DS.

In addition to their seizure burden and a high rate of mortality, patients with LGS and DS show a greater frequency and severity of comorbid features (Figure 1) than patients with other forms of epilepsy, which can contribute to substantial physical, mental, emotional, psychosocial, and financial burden for patients and their families. These comorbid features have consequences that tend to affect everyday life, and can disrupt day-to-day activities, preclude attendance in mainstream school, reduce social participation, and hinder personal relationships. They also limit patient independence, with the majority of patients relying upon others—either family members or institutional caregivers—for most activities of daily living (ADLs). In a long-term follow-up of patients with LGS, only 13% were able to function independently, while 58% were completely dependent on others for all ADLs. Almost all (90%) were financially dependent on others. Unsurprisingly, home care and long-term care costs are elevated in this population.

Several survey or interview-based studies of caregivers have also linked nonseizure symptom burden in LGS and DS with decreased patient quality of life (QOL). One study of 584 children with DS surveyed parents about nonseizure symptoms (such as motor, speech, and behavioral complications) and found that overall parent-reported QOL scores, as measured by the EuroQol 5D-5L (EQ-5D) instrument, were much lower for patients with DS compared with both the general population and patients with epilepsy. A higher number of comorbidities was associated with higher seizure frequency and lower QOL. In another study of 163 children with DS, parent-assessed QOL for patients (via the Pediatric Quality of Life Inventory [PedsQL]) was significantly lower than for age-matched healthy controls. Psychosocial health, and physical, emotional, social, and school functioning PedsQL scores were also lower in patients with DS than matched controls.

The following sections will highlight some of the most common comorbid features of LGS and DS for healthcare practitioners to consider when managing patients with LGS and DS and areas of support that might benefit caregivers. A multidisciplinary, individualized approach to care, which addresses the unique treatment needs of the patient and provides support for the caregiver and family, is optimal.

COGNITIVE IMPAIRMENT—A DIAGNOSTIC AND COMORBID FEATURE OF LGS AND DS

Given that several clinical features of LGS and DS are used in diagnosis, it can be difficult to identify which issues are comorbidities versus symptoms inherent to the syndromes. Cognitive impairment is a function of the epileptic encephalopathy and is also an essential diagnostic feature of LGS and DS.
Figure 1. Comorbid Features of LGS and DS That Contribute to Disease Burden

**Prevalence of Comorbid Features (%):**

- **Nonverbal Developmental Delay**
  - 70%

- **Language Delay**
  - 80%

- **Difficulty to Understand Speech**
  - 32%

- **Unable to Read/Write**
  - 60%

- **Autistic Traits**
  - 50%

- **Aggression**
  - 43%

- **Inattention/Hyperactivity**
  - 15%

- **Sleep Disturbances**
  - 50%

- **Insomnia**
  - 43%

- **Premature Awakening**
  - 15%

- **Hypersomnia**
  - 50%

- **Sleep Apnea**
  - 43%

- **Narcolepsy**
  - 15%

*Depending on study.

Numbers in parentheses and arrows within the bars represent range of prevalence and bars represent upper limit of the range reported in the literature.

Figure 1 adapted from multiple publications: 1, 8, 10-13, 16, 18-23.

LGS: Language Dysfunction Widely Reported but No Prevalence Rates Provided

LGS: Sleep Disturbance Widely Mentioned as Comorbid Feature in LGS but No Reported Prevalence

**Developmental Delay**

- **Language**
  - Delayed Language
  - Language Dysfunction
  - Difficulty to Understand Speech
  - Nonverbal
  - Unable to Read/Write

**Behavior**

- **Autistic Traits**
  - Aggression
  - Inattention/Hyperactivity

**Sleep**

- **Sleep Disturbances**
  - Insomnia
  - Premature Awakening
  - Hypersomnia
  - Sleep Apnea
  - Narcolepsy

LGS: Sleep Disturbance Widely Mentioned as Comorbid Feature in LGS but No Reported Prevalence

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Figure 1 (continued). Comorbid Features of LGS and DS That Contribute to Disease Burden

Numbers in parentheses and arrows within the bars represent range of prevalence and bars represent upper limit of the range reported in the literature.

Figure 1 adapted from multiple publications. 1,8,10-13,16,18-23

Gait/Movement

LGS: No Prevalence Reported for Ataxia, Tremor, Hypotonia, Hypertonia, Hypermobile Joints, Foot Deformities, and Scoliosis

Bone/Dental

LGS: No Prevalence Reported for Osteopenia, Bruxism, Delayed Tooth Eruption, Malocclusion, and Missing, Extra, or Malformed Teeth

Numbers in parentheses and arrows within the bars represent range of prevalence and bars represent upper limit of the range reported in the literature.

Figure 1 adapted from multiple publications. 1,8,10-13,16,18-23
Figure 1 (continued). Comorbid Features of LGS and DS That Contribute to Disease Burden

**Cardiac**
- Tachycardia: (14%-31%)
- Bradycardia: (5%-15%)
- Arrhythmia: (9%-15%)
- Structural Abnormalities: (2%-5%)  

**Gastrointestinal**
- GERD: 7%
- Slow Digestion/Poor Bowel Motility: (10%-32%)
- Constipation: (29%-54%)

**Dysautonomia/Growth/Endocrine**
- Body Temperature Dysregulation: (57%-85%)
- Lack of Sweating: 67%
- Failure to Thrive/Slow Growth/Underweight/Small Stature: (26%-39%)
- Delayed or Precocious Puberty: 9%

**Figures**
- GERD, gastroesophageal reflux disease.
- Numbers in parentheses and arrows within the bars represent range of prevalence and bars represent upper limit of the range reported in the literature.
- Figure 1 adapted from multiple publications 1, 8, 10-13, 16, 18-23.

LGS: Tachycardia Reported in a Small Number of Patients With LGS but No Overall Prevalence Reported; No Prevalence Reported for Bradycardia, Arrhythmia, and Structural Abnormalities

LGS: No Prevalence Reported for GERD, Slow Digestion/Poor Bowel Motility, and Constipation

LGS: No Prevalence Reported for Body Temperature Dysregulation, Lack of Sweating, Failure to Thrive/Slow Growth/Underweight/Small Stature, and Delayed or Precocious Puberty

GERD: gastroesophageal reflux disease.

Numbers in parentheses and arrows within the bars represent range of prevalence and bars represent upper limit of the range reported in the literature.
Figure 1 (continued). Comorbid Features of LGS and DS That Contribute to Disease Burden

- ADD, attention deficit disorder; ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder.

- † Not specified.

- ‡ Depending on type of infection. Numbers in parentheses and arrows within the bars represent range of prevalence and bars represent upper limit of the range reported in the literature.

- Figure 1 adapted from multiple publications: 1,8,10-13,16,18-23

Problems With Peer Relationships

<table>
<thead>
<tr>
<th>Comorbid Diagnoses</th>
<th>LGS: No Prevalence Reported for Sensory Disorder, Movement Disorder, and Infections</th>
<th>DS: No Prevalence Reported for Cerebral Palsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>ADD/ADHD</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Mood Disorder</td>
<td>25% (21%-31%)</td>
<td></td>
</tr>
<tr>
<td>Anxiety Disorder</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Sensory Disorder</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Movement Disorder†</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>Infections†</td>
<td>(13%-40%)</td>
<td></td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>32%</td>
<td></td>
</tr>
</tbody>
</table>

Described as Relevant in LGS but Specific Prevalence Not Reported

ADD, attention deficit disorder; ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder.

1Not specified. 2Depending on type of infection. Numbers in parentheses and arrows within the bars represent range of prevalence and bars represent upper limit of the range reported in the literature.
Studies have demonstrated that the majority of patients with LGS and DS have significant cognitive impairment, with almost one-third of patients with LGS exhibiting cognitive delay at onset and almost all (up to 99%) becoming cognitively impaired within 5 years of onset. Children with DS are typically developmentally normal in the first year of life, but ≈70% become developmentally delayed with delay beginning in the second year and usually evident by age 5 years. In both syndromes, higher rates of intellectual disability (ID) are reported in older versus younger children.

Several independent risk factors for more severe forms of cognitive impairment (intelligence quotient [IQ] <35) have been identified from retrospective and prospective studies in LGS and DS. For patients with LGS, these include (in descending order of risk) a history of nonconvulsive status epilepticus (NCSE), a previous diagnosis of West syndrome, a symptomatic etiology, and age at onset of epilepsy <3 years. In patients with DS, presence of motor disorder, abnormal EEG in the first year, SE, and early onset of myoclonic, absence, and focal seizures have all been demonstrated to be associated with worse cognitive outcome (differential general quotient >20 points).

While several studies in LGS and DS have shown a decrease in IQ and an increase in percentage of patients meeting criteria for ID over time, this disparity in cognitive ability compared with peers more likely reflects a plateau in cognitive development due to the syndromes and severity of the seizures rather than a progression in cognitive impairment. In contrast, there is no evidence to support true deterioration or progressive loss of function akin to a neurodegenerative condition.

Overall, cognitive impairment in children with LGS and DS has been reported to have broad impact on everyday life, including peer relationships, social and family interactions, recreational activities, self-care, and independent living. In patients with LGS, the most impaired cognitive functions are reaction time and information processing, which may subsequently affect other behaviors, including socialization and communication. This, in turn, can result in difficulty forming and maintaining peer relationships. ID also affects language ability, and impaired language or communication is frequently reported in caregiver surveys about children with LGS and DS. Two surveys of parents of children with DS reported ≈80% of patients with delayed language, up to 70% with language dysfunction, and 60% with inability to read or write. In a third survey using PedsQL, the speech and communication domain was the third most affected area in children with DS. The language and speech impairments may result in frustration over an inability to communicate their needs (such as vocalizing pain) and result in other behavioral reactions. However, there is evidence that early treatment and better seizure control may help to produce better cognitive outcomes for patients with epilepsy, thus, highlighting the relationship between seizure burden and cognitive impairment.

As LGS and DS are lifelong syndromes, patients will eventually require healthcare transition but the complexity of the syndromes along with the presence of ID require unique considerations for healthcare practitioners. Because patients with LGS and DS may outlive their parents, determining guardianship is an important decision and is critical in ensuring that the patient continues to receive necessary resources (such as health insurance coverage) and that medical history is not lost after healthcare transition.
self-management goals should be set for patients depending on the severity of ID. Understanding the complexity of seizure and noneizure features of LGS and DS by adult providers is essential to a successful transition; however, many adult neurologists (85%) expressed low confidence in the ability to treat patients with ID or features of autism spectrum disorder (ASD), according to a survey of adult practitioners assessing their confidence level in managing epilepsies. Almost all (90%) stated they would need additional support to manage the care of these young adults, including support from psychiatrists, psychologists, and physical, speech, and occupational therapists. Therefore, for healthcare transition to be effective, it is essential that pediatric and adult providers develop a collaborative working relationship and involve integral members of the multidisciplinary care team, such as dieticians, geneticists, emergency medicine specialists, neuropsychologists, and speech, occupational, and physical therapists, in order to provide an individualized treatment plan.

ADDITIONAL COMORBID FEATURES AND IMPLICATIONS FOR CLINICAL MANAGEMENT

Neurobehavioral Associations

Behavioral problems have been noted in several studies to be linked with cognitive impairment in LGS and DS. One observational study of 573 children with treatment-resistant epilepsy included 27 patients with LGS, all of whom demonstrated cognitive impairment and behavioral problems (behaviors not specified). A semi-structured interview study of parents of children with DS found that 88% of patients displayed some level of cognitive delay and behavioral problems (behaviors not specified). Aggression (37%) and hyperactivity (15%) were the two most common behavioral issues identified in a retrospective study of LGS, while in DS, hyperactivity (34% to 66%), impulsivity (53%), irritability (49%), repetitive behavior (20% to 46%), and aggression (43%) were also frequently noted behaviors in caregiver surveys. These behaviors may be a contributing factor to the frequency of neuropsychiatric diagnoses that have been reported to co-occur in patients with LGS and DS, such as pervasive developmental disorder, sensory disorders, attention deficit/hyperactivity disorder (ADHD), and ASD. The behavioral comorbidities may also limit the ability of people with LGS or DS to engage in functional social interactions and may lead to anxiety, depression, or mood disorders. Furthermore, these behaviors may be a contributing factor that can interfere with patients from attending mainstream school and patients with LGS and DS may require special education services or additional support. Patients may also benefit from referral to a psychologist or psychiatrist to specifically address these comorbid features.

Orthopedic and Movement Considerations

Gait disturbances, fine and gross motor issues, and orthopedic disorders are common comorbid features in LGS and DS. In a long-term observational study, gait disturbances developed in one-third of patients with LGS. Caregiver surveys have reported a variety of gait disturbances in patients with DS, including crouched gait (47% to 75%), ataxia (58% to 65%), hypotonia (35% to 56%), foot deformities (12% to 29%), and hypermobile joints (21% to 35%), with the prevalence of gait disturbances increasing in adolescents and adults with DS. These motor symptoms
may contribute to the increased rates of scoliosis in patients with DS compared with the general pediatric population. Many children with LGS were noted to be unable to walk and have balance issues, placing them at risk for falls. The presence and severity of these motor symptoms may limit mobility, can lead to frequent falls and subsequent injuries, and may also interfere with the ability to perform ADLs. A majority (70%) of patients rely on wheelchairs or adaptive strollers for ambulation at least part of the time, with 13% using them as their primary means of mobility. Due to the frequency of gait disturbances found in patients with LGS and DS, children should be regularly screened and referral to physiotherapy may be required.

Sleep Disturbances

Both patients with LGS and DS experience sleep cycle disruptions, which may be a partial function of frequent nocturnal seizures. According to caregiver surveys, ≈60% to 85% of patients with DS experience some form of sleep disturbance. Other specific sleep issues noted in caregiver surveys are insomnia (20% to 71%), sleep apnea (3.5% to 34%), premature awakening (28% to 62%), hypersomnia (14% to 48%), and narcolepsy (6% to 15%). Sleep disruption may be a seizure trigger and could further exacerbate patients’ behavioral and psychological problems, such as hyperactivity, anxiety, and depression. Due to the frequency of sleep disorders in LGS and DS, physicians should routinely inquire about sleep issues at clinic visits and referral to a sleep medicine specialist may be required if sleep concerns are identified.

Dysautonomia, Growth, and Metabolism

Dysautonomia, or abnormal autonomic regulation, is observed in individuals with DS, most likely due to the genetic etiology of the disease and the effect of sodium or chloride ion channelopathies on the central nervous system. In one survey of 139 parents, signs of dysautonomia, such as the tendency to overheat, decreased sweating, facial/chest flushing, and slowed gastric emptying, were three to nine times elevated in patients with DS when compared with children with other neurologic diagnoses. These patients with DS displayed a mean 2.71 dysautonomic signs weekly versus 0.93 signs in the comparison group of children with other neurologic diagnoses. Perhaps for these reasons, it has been reported in an additional parental survey that children with DS experience chronic constipation (>50%), become either easily overheated or chilled (≈80%), and show signs of failure to thrive or slow growth (≈40%). Both delayed and precocious puberty (9% each) has also been reported in a caregiver survey of patients with DS. Although the numbers in the study were too small to determine statistical significance, none of the SCN1A mutation-negative patients experienced precocious puberty but were more likely to experience delayed puberty than patients who were SCN1A mutation-positive. While there is no consensus on the clinical management of dysautonomia, some symptoms may pose a high risk for patients, given that elevated body temperature is a common seizure trigger for patients with DS.
Cardiac Irregularities

DS is associated with arrhythmias and cardiac structural abnormalities with potential implications for treatment management. Caregiver studies have reported tachycardia, bradycardia, other arrhythmias, and structural defects at higher rates in patients with DS than in healthy children. A prospective study found patients with DS had depressed heart rate variability (HRV) parameters when compared with both age- and sex-matched healthy controls and patients with other forms of epilepsy. Tachycardia has also been reported in a small number of patients with LGS from a prospective study of 19 patients with treatment-resistant focal or generalized epilepsy.

Cardiac arrhythmias have been proposed as a mechanism for some cases of SUDEP, and while the definitive causes are unknown, a sodium channel mutation (SCN5A) has been previously reported to be associated with an elevated risk of cardiac arrhythmias and sudden cardiac death in several studies. Postictal arrhythmias appear to be a risk factor for SUDEP. Patients with SCN mutations were found in one recent study of 80 patients with epilepsy to have higher rates of SUDEP if they had reduced awake HRV when compared with their non-SCN drug-resistant epilepsy counterparts, indicating that HRV could potentially be used as a biomarker of SUDEP risk. Therefore, management of patients with DS (and LGS) may require monitoring of arrhythmias by electrocardiogram (ECG) and treatment should be optimized to reduce effect on arrhythmias.

Immune-Related Associations

Upper respiratory, gastric, and urinary tract infections are also commonly reported in patients with DS, which may be due to syndrome-related dysfunction in patients’ immune systems. Two surveys of caregivers have found that ≈10% of patients with DS have been diagnosed with an immune system abnormality but the specific abnormalities were not noted in either study. Since hyperthermia is a common seizure trigger, prophylactic use of antipyretics with vaccinations and illnesses are important considerations in the management of patients with DS.

IATROGENIC FEATURES AND COMPLICATIONS

Most patients with LGS and DS have been exposed to multiple antiepileptic drugs (AEDs) over the course of their life, which can contribute to the development or exacerbation of comorbid features. These features may be inherent to the syndromes themselves, may be related to long-term treatment, or may be the result of a combination of elements.
Dental and bone concerns have been reported in multiple studies of LGS and DS but it is unclear if these dental and bone abnormalities are comorbid features, or the result of long-term treatment with AEDs, or potentially the cumulative effect of a combination of factors (such as medication use, vitamin D deficiency, and long-term immobility). In DS, delayed tooth eruption (20% to 31%), malocclusions (13% to 19%), missing, extra, or malformed teeth (5% to 15%), and bruxism (21% to 42%) are commonly reported dental problems in parental surveys. Dental abnormalities, such as facial deformities, periodontitis, and gingival swellings, have also been noted in case reports of adults with LGS. A retrospective claims-based study found that bone fracture (cause not specified) was more commonly reported in patients with LGS than patients with epilepsy. In a caregiver survey, bone fractures (cause not specified) and osteopenia were reported with increasing frequency as patients with DS age. AEDs have been associated with altered bone metabolism and decreased bone density through induction of the cytochrome P450 enzyme system and other mechanisms of action. Therefore, regular screening and an individualized treatment approach may be required for patients who are at high risk for bone disease.

Long-term polypharmacy can exacerbate adverse effects as many commonly used AEDs can aggravate behavioral and psychiatric symptoms in patients with LGS and DS, such as aggression, agitation, irritability, anxiety, and depression. In one survey of caregivers of children with LGS, parents noted that treatment side effects had negative consequences on their children, including increased sedation and aggression. However, these parents also noted that treatment improved their child’s QOL due to reducing the severity or frequency of seizures, which led to fewer injuries, less disruption from school, and less interference on social or familial relationships. Therefore, treatment selection should consider the side effects and how these may exacerbate comorbid features. Increased seizure control may also reduce the risks associated with these comorbid conditions.

CAREGIVER AND FAMILY IMPACT

Current studies indicate that the comorbid features of LGS and DS place a heavy physical, mental, emotional, psychosocial, and financial burden on caregivers and decrease caregiver QOL as well. In one study of 40 parents of children with LGS, Short Form 36 Health Survey Version 2 (SF-36v2) scores in general health, vitality, social functioning, emotional, and mental health categories were all lower than the US population norms, suggesting that QOL is negatively affected. In another study of 30 caregivers of patients with DS, EQ-5D index score was lower than population norms, again indicating that overall QOL is impacted. Therefore, it is important for practitioners to consider the caregiver in management of LGS and DS (Figure 2), as parents may sacrifice emotional, professional, and financial needs that can then impact their overall health.

Physical Impact

Managing broad and complex care requirements for patients with LGS and DS can pose a significant physical stress for parents according to multiple studies. As many children with LGS and DS have limited mobility, care becomes increasingly physical and more demanding for the parent as their children grow in size, weight, and strength.
Transitions between seats, wheelchairs, baths, and beds become increasingly difficult, and, in surveys, caregivers have revealed they suffer back and shoulder pain due to lifting and maneuvering their children with LGS, reporting greater pain than the general population (as assessed by the SF-36v2 bodily pain score). In surveys and qualitative interviews, caregivers have also reported physical exhaustion from their caregiving duties and sleep disruption, not only from their children’s nocturnal seizures, but also from fears over SUDEP. Due to these concerns, a majority of caregivers disclosed that they use baby or sleep monitors (85%) or sleep with the patient at night (82%), which may then further contribute to their physical exhaustion.

Financial Burden

Various studies have found that the complex care required for patients with LGS and DS can be a financial burden for families attributed to direct costs (such as in-home care, doctor, and emergency department visits, hospitalizations, both conventional and complementary/alternative treatments, and use of durable medical equipment) and indirect costs (loss of productivity, leisure time, and income). One claims-based study calculated that direct healthcare resource utilization by patients with LGS was $25,000 to $37,000, higher than the $7000 to $25,000 estimate for patients with other epilepsies. Home-based care and long-term care were the major cost drivers in this study, respectively, for children and adults with LGS. Purchase of medical equipment, such as helmets or splints, and house renovations may also be needed to manage older, immobile, cognitively impaired children, but these financial needs may not be covered by insurance.

Total cost of DS amounted to $100,000 per patient per year (PPPY), with a direct healthcare resource utilization cost of $27,000 PPPY and an indirect cost three times higher at $81,000 PPPY according to a survey of DS caregivers administered at Children’s Hospital Colorado. In this economic analysis, hospitalizations and in-home medical care were the major direct cost drivers, and indirect costs comprised lost productivity (due to absenteeism and presenteeism), lost income (due to quitting, switching, or losing a job), and lost leisure time. This analysis found that parents spent the equivalent of 380 workdays per year caring for their child with DS. Thus, caregiving may represent a significant time commitment and may contribute to the financial burden for parents. Finances have been listed as one of the top caregiver concerns aside from seizure control in several surveys, potentially contributing to parental stress and anxiety.

Family Relationships

Several caregiver studies have indicated that managing LGS and DS can have both negative and positive influences on family relationships. Qualitative interviews have recorded that marital relationships can become strained as the disease progresses. However, caring for a child with LGS can also have a positive effect as one survey found that 74% of parents reported that having a child with LGS brought them and their partners closer together. LGS and DS may also influence sibling relationships as 17% of parents with a child with LGS noted having no time for their other children as a major concern in one survey. In semi-structured interviews or surveys of caregivers, 74% listed
emotional ramifications of siblings as a top concern, while 86% reported DS as having a negative impact on family members. Caregiver studies have also noted that siblings of patients with LGS or DS may receive less parental attention and, therefore, may act out due to resentment. However, LGS and DS can also have a positive impact on siblings as parents have reported in several surveys or interviews that siblings develop a caring nature and interest in helping others.

Social Burden

Numerous studies have suggested that the seizures, cognitive impairment, and other comorbid features of LGS and DS may be disruptive to families' social relationships and availability for leisure and social activities. Parents of children with LGS described difficulty planning or attending social activities in one semi-structured interview study, while 11% of parents in another study reported social isolation. In one survey of parents of children with DS, 100% (33/33) disclosed they experienced loss of leisure time; caregivers spent over 2000 hours of their leisure time on caregiving duties. Furthermore, due to the stigma surrounding epilepsy and cognitive impairment, parents have noted in multiple qualitative semi-structured interview studies that it is difficult to find respite care for their child. In one such study of 24 parents of children with DS, 15 reported lack of respite care, 12 lack of family support, and 9 lack of support from friends as key areas of need for families. This lack of social support may contribute to the decreased parental QOL identified in caregiver surveys or interview studies.

Mental Health

Having a child with severe epilepsy may affect caregiver mental health as several studies on caregiver QOL have shown increased feelings of anxiety or depression in caregivers. In qualitative interview studies, some parents reported a sense of unfulfilled expectations or loss of hope when it comes to their child with LGS or DS, which may contribute to or be signs of depression. In one semi-structured interview study of 40 parents of children with LGS, half reported borderline to severe depression according to the Hospital Anxiety and Depression Scale (HADS). In a survey of 159 parents of children with DS, 66% reported depression via open-ended response, while another survey of 30 parents found that 70% reported a score of at least 1 or higher in the depression/anxiety domain from EQ-5D, indicating that a majority of these caregivers suffered from slight to extreme anxiety/depression. In one interview study of 40 parents of children with LGS, the mental health component score assessed by the SF-36v2 was below average, with each of the domains (vitality, social functioning, and mental health) below the US population norm. The same study found that 85% of parents reported some level of anxiety according to HADS, with more than half reporting moderate to severe anxiety. Another study found 30% of parents experienced constant stress or worry due to their child's LGS diagnosis. In two semi-structured interviews, parents of children with DS have described that they experience severe anxiety, fear, or worry about their child's diagnosis, which may evolve into extreme stress over the severity, frequency, and treatment-resistance of the seizures. However, only a third of caregivers have reported receiving therapy for their depression.
the demands associated with severe epilepsy, cognitive impairment, and other comorbid features, families have developed personal/internal coping mechanisms to alleviate their caregiving burden, such as turning to religious faith, participating in activities outside the home without the child, and educating themselves about their child’s syndrome (Figure 2). Additionally, families rely on external coping strategies, by turning to friends, family, and other support groups, such as advocacy organizations active in LGS and DS communities, to find much-needed social support. 

**Figure 2. Considerations for Supportive and Multidisciplinary Care**

| Cognitive Impairment/Intellectual Disability/Behavioral Concerns | • Special education support\(^\text{13}\)  
| | • Consultation with social worker\(^\text{3}\)  
| | • Occupational therapist, speech therapist\(^\text{3}\)  
| | • Psychologist/psychiatrist\(^\text{3}\)  
| Cardiac | • Referral to cardiology\(^\text{3}\)  
| | • ECG testing\(^\text{12}\)  
| | • Education on risk of SUDEP\(^\text{12}\)  
| Gait Disturbances and Orthopedic Concerns | • Referral to physiotherapy\(^\text{3}\)  
| | • Use of wheelchairs or adaptive medical equipment\(^\text{12,13}\)  
| Dysautonomia | • No consensus on how to manage\(^\text{3}\)  
| Neurologic Disabilities and Behavioral Concerns | • Consultation with social worker\(^\text{3}\)  
| | • Occupational therapist, speech therapist\(^\text{3}\)  
| | • Psychologist/psychiatrist\(^\text{3}\)  
| Sleep Disturbances | • Sleep medicine specialist\(^\text{3}\)  
| | • Use of baby or sleep activity monitors\(^\text{12}\)  
| Overall Caregiver Support | • Home care services\(^\text{3}\)  
| | • Respite care\(^\text{41}\)  
| | • Internal coping strategies, such as turning to religious faith, participating in activities outside the home without the child, and personal education about the child’s syndrome\(^\text{38}\)  
| | • External coping strategies, such as family support groups, organizations, and websites\(^\text{1,38}\)  
| | • Psychologist/psychiatrist\(^\text{3}\)  

\(^{1}\text{Adapted from Elbedweih A, Asaad ME. Challenges and coping strategies in families of children with Lennox-Gastaut syndrome. J Pediatr Neurosci 2014; 9(3):105-113.}

\(^{2}\text{Adapted from Hutto AR et al. The Lennox-Gastaut syndrome: a review of diagnostic criteria and clinical manifestations. Epilepsy Behav 2006; 8(3):398-405.}

\(^{3}\text{Adapted from Nott et al. The Lennox-Gastaut Syndrome: a comprehensive account of current knowledge. Epilepsy Behav 2006; 8(3):398-405.}

\(^{4}\text{Adapted from Elbedweih A, Asaad ME. Challenges and coping strategies in families of children with Lennox-Gastaut syndrome. J Pediatr Neurosci 2014; 9(3):105-113.}

\(^{5}\text{Adapted from Hutto AR et al. The Lennox-Gastaut syndrome: a review of diagnostic criteria and clinical manifestations. Epilepsy Behav 2006; 8(3):398-405.}

\(^{6}\text{Adapted from Nott et al. The Lennox-Gastaut Syndrome: a comprehensive account of current knowledge. Epilepsy Behav 2006; 8(3):398-405.}
CONCLUSION

LGS and DS are complex and severe syndromes that impact the day-to-day functioning and life of patients and caregivers beyond seizures alone. The breadth and severity of comorbid features and impairments can contribute significantly to stress, patient and caregiver burden, and overall reduced QOL. Ultimately, the physical, emotional, psychological, social, and financial strains of caring for children with LGS and DS represent a significant, but under-studied impact on caregivers. While effective treatment approaches to managing many of the nonseizure features of LGS and DS are still being investigated, patients and families can benefit from established coping strategies (Figure 2) and in particular, social support through active advocacy foundations. Overall, it is evident that the care of patients with LGS and DS requires a comprehensive, multidisciplinary management approach to address the nonseizure comorbid features of the syndromes and to meet the needs of patients and caregivers.

REFERENCES


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