Disruptive Impacts of Developmental and Epileptic Encephalopathies on Patient and Family Life: A Quality-of-Life Survey

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Background

- Developmental and epileptic encephalopathies (DEEs) have a profound impact on the quality of life (QoL) of patients, their primary caregivers, and their siblings[1]
- Some individual DEE studies have examined the affected areas of daily living in Lennox-Gastaut syndrome (LGS),[2] *SCN2A*-related DEEs,[3] and *STXBP1*-related DEEs[4]
  - However, caregiver definitions of "normal" and "disruptive" symptoms in individuals with any DEE, and their impact on QoL, have not been extensively explored
- DEEs are characterized by high seizure burden and developmental disability[5] and can cause sleep problems[6] and behavioral difficulties,[7] which in turn can affect QoL of patients, their caregivers, and their siblings[1]
- Activities of daily living (ADLs) are fundamental skills required for independent living and personal care, including feeding, dressing, personal hygiene/bathing, and toileting[8]
  - Communication, while not included as an ADL, is an important ability for the QoL of patients and their families
- As genetic variants associated with DEEs are discovered and the diagnostic tools become more widespread, diagnosis of DEEs can occur at earlier stages
  - A study on genetic testing for diagnosis of epilepsy found that a genetically verified diagnosis improved patient outcomes[9]
  - Further, informing patients with neurological disorders improved QoL[10]
  - Older, undiagnosed, and treatment-resistant patients can now be diagnosed due to improved understanding of DEE etiologies

Objective

- To characterize normal and disruptive symptoms of each individual with DEE and their caregiver, and to understand the effects on daily life

Methods

An internet-based anonymous survey (63 questions, English), codeveloped in consultation with Dravet syndrome (DS) and LGS communities, was distributed for 7 weeks beginning in March 2024 via patient advocacy websites, social media, and patient community events

- Topics included: demographics; defining normal seizure and sleep patterns; frequency of disruptive seizure, sleep, and behavior; defining typical ability to communicate and perform ADLs; and assessing the effects of disruption on communication and ADLs
- Actively distributed by the CACNA1A Foundation, Dravet Syndrome Foundation, Dup15q Alliance, International Foundation for CDKL5 Research, KCNT1 Epilepsy Foundation, Lennox-Gastaut Syndrome Foundation, PCDH19 Alliance, SLC6A1 Connect, STXBP1 Foundation, Syngap Research Fund, and Tuberous Sclerosis Complex (TSC) Alliance
- Criteria: primary caregiver to, or helps care for, a person diagnosed with DEE

Definitions of experiences for individuals with DEE included in the survey:

Normal: the typical daily experience during the current phase of the DEE journey

Disruptive: a deviation from the normal daily experience

Always disruptive: no pattern or distinguishable "typical" experience

Table 1. Descriptions of the Five Key Domains in the Survey

Domain	Description
Seizures	Frequency, clustering, and average length of seizure; duration of seizure freedom; rescue medication/device use
Sleep	Number of >30 min awakenings, amount of total sleep per night; number of awakenings with inability to return to sleep per week
Behavior, disruptive	Any of the following – hitting, biting, kicking, shouting, hair pulling, swearing, harsh language, throwing objects, refusal to cooperate, destruction of property, threatening physical harm, invading a person's personal space, anger
ADLs	Feeding; toileting; bathing/personal hygiene; dressing
Communication	Basic methods, tools, or devices used to exchange information

ADL, activity of daily living.

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Overview

QUESTIONS : How do caregivers to a person diagnosed with developmental and epileptic encephalopathy (DEE) define "normal" and "disruptive" symptoms?
: How do disruptive symptoms affect other domains involved in quality of life?

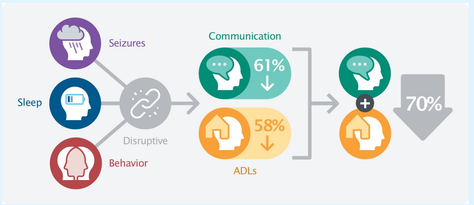
INVESTIGATION

ADLs include feeding, toileting, dressing, and bathing/hygiene.
ADLs, activities of daily living.

- An internet-based anonymous survey was distributed via patient advocacy websites, social media, and patient community events
  - Respondents were primary caregivers to a person diagnosed with DEE
- Survey questions were designed to:
  - Define, for each individual, normal and disruptive seizures, sleep, and behavior
  - Normal seizures and sleep were defined as the typical daily experience during the current phase of DEE
  - Disruptive symptoms were defined as those that deviate from the typical daily experience
  - Determine, for each individual, how often disruptive symptoms affect communication and activities of daily living (ADLs)

RESULTS

- Of 524 total respondents, 489 caregivers consented, completed the study, and were included in the analysis
- Lennox-Gastaut syndrome (n=67, 13.7%), *SLC6A1* (n=67, 13.7%), and *STXBP1* (n=64, 13.1%) were the most common primary diagnoses reported
- The median patient age at diagnosis and at the time of the survey was 3 y (0-64 y) and 8 y (0.2-67y), respectively



ADLs, activities of daily living; DEE, developmental and epileptic encephalopathy.

7.6% of individuals with DEE reportedly experienced a temporary loss of all 4 ADLs due to at least one disruption.

CONCLUSIONS

Disruptive seizures, disruptive behavior, and disruptive sleep patterns are defined individually by families of an individual with DEE – no two individuals or caregivers experience the same disruptions, or their effects on daily life

- These disruptive symptoms affect communication or at least one of the aspects of daily living in over 70% of the individuals with DEE according to their caregivers

Understanding the individual definitions of normal and disruptive symptoms would allow tailored treatments and experiences for families based on their needs

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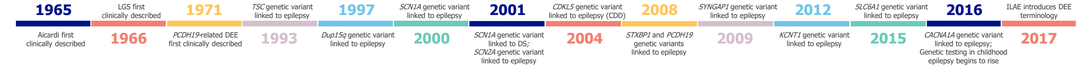


DEEs reported as the primary diagnosis for >1 individual in this survey are included in this figure.
References by timeline order: Acardi clinically described[11]; LGS clinically described[12]; Clinically described PCDH19[13]; TSC[14]; Dup15q[15]; SCN1A[16,17]; SCN2A[18]; CDKL5[19]; STXBP1[20]; PCDH19 gene[21]; SYNGAP1[22]; KCNT1[23]; SLC6A1[24]; Genetic testing w/ NGS[25]; CACNA1A[26]; ILAE classification.[27]
CDD, *CDKL5* deficiency disorder; DEE, developmental and epileptic encephalopathy; DS, Dravet syndrome; ILAE, International League Against Epilepsy; LGS, Lennox-Gastaut syndrome; TSC, tuberous sclerosis complex.

Results

In total, 524 responses were collected; 489 were included in the analysis

- Reasons for exclusion: responder did not consent (n=3), was not a caregiver to a patient with rare epilepsy or DEE (n=26), or reported a non-qualifying disorder (n=5); or was a replicate (n=1)
- 323 (66.1%) individuals with DEE reportedly lived with at least one sibling
- Median age at DEE diagnosis and at the time of the survey was 3 y and 8 y, respectively
  - Diagnoses at the youngest ages were observed in individuals with primary diagnosis of TSC (0 y), *STXBP1*, DS, *CACNA1A*, *KCNT1*, and *Dup15q* (0.1 y each); diagnoses at the oldest ages were observed in individuals with primary diagnosis of *SYNGAP1*-related DEE (64 y), DS (36 y), LGS, and *SLC6A1* (35 y each; **Table 2**)

Table 2. Age at Diagnosis of Primary DEE

DEE	Mean Age of Diagnosis, y	Median (min, max) Age of Diagnosis, y
TSC, n=13	0.9	0.5 (0, 3)
DS, n=54	3.9	1.5 (0.1, 36)
KCNT1, n=43	4.3	0.8 (0.1, 20)
STXBP1, n=64	4.4	1.4 (0.1, 25)
CACNA1A, n=54	4.7	2 (0.1, 31)
SLC6A1, n=67	5.1	3 (0.9, 35)
SYNGAP1, n=48	6.2	4 (1, 64)
Dup15q, n=21	6.7	5 (0.1, 20)
LGS, n=67	7.3	4 (0.3, 35)

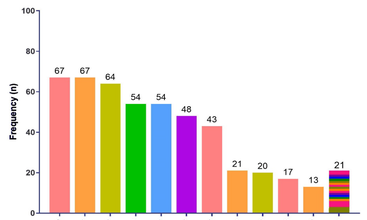
DEE diagnoses included in the table include those with the lowest and highest age at diagnosis of the primary DEE, within DEEs reported in >1 individual in the survey.
Within the table, the following are gene variants associated with DEE: *STXBP1, CACNA1A, KCNT1, Dup15q, SLC6A1, SYNGAP1.*
CDD, *CDKL5* deficiency disorder; DEE, developmental and epileptic encephalopathy; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; TSC, tuberous sclerosis complex.

The top reported primary diagnoses were LGS (n=67, 13.7%), *SLC6A1* (n=67, 13.7%), and *STXBP1* (n=64, 13.1%; **Figure 1**)

In total, 84 (17.2%) caregivers reported a secondary DEE diagnosis

- LGS (n=58, 69.0%) and DS (n=2, 2.4%) were the most common secondary DEE diagnoses reported
- Caregivers also reported non-DEE secondary diagnoses, including autism (n=3, 3.6%)

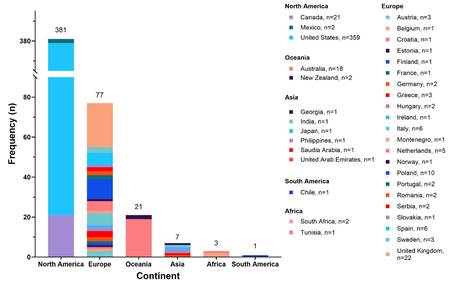
Figure 1. Primary DEE Diagnosis as Reported by Caregiver



Within the primary diagnoses, the following are gene variants associated with DEE: *SLC6A1, STXBP1, CACNA1A, SYNGAP1, KCNT1, Dup15q, PCDH19, SCN2A, SCN1A, 22Q, CHD2, CRELD1, HNRNPU, SETD1B.*
CDD, *CDKL5* deficiency disorder; DEE, developmental and epileptic encephalopathy; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; TSC, tuberous sclerosis complex.

Respondent locations included 36 countries across 6 continents (**Figure 2**), with a majority living in the United States (n=359, 73.4%)

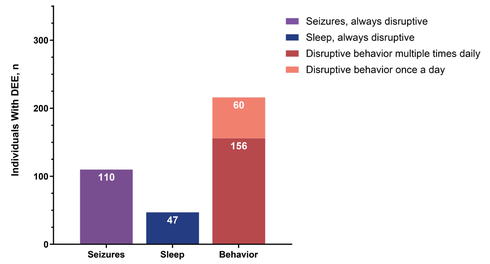
Figure 2. Geographical Spread of Respondents



Normal and Disruptive Symptoms

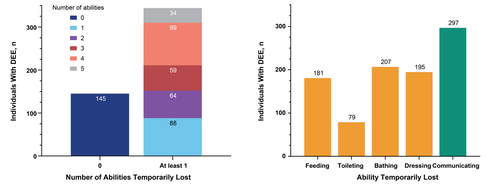
- Unpredictable seizure activity and sleep without a typical pattern was considered "always disruptive" in 110 (22.5%) and 47 (9.6%) individuals, respectively (**Figure 3**)
- Disruptive behavior was observed in 216 (44.2%) individuals at least once per day
  - Disruptive behavior was observed multiple times a day in 156 (31.9%) individuals
- Disruptive seizures, sleep, or behavior reportedly led to temporary loss of communication in 297 (60.7%) individuals, and in any ADL in 282 (57.7%) individuals (**Figure 4**)
  - In 344 (70.3%) individuals, a combined temporary loss in communication and/or an ADL was reported
- In 37 (7.6%) individuals, disruptive seizures, sleep, or behavior reportedly led to temporary loss of all 4 ADLs included in the survey

Figure 3. Symptoms Described as Always Disruptive by Caregivers



DEE, developmental and epileptic encephalopathy.

Figure 4. Temporary Loss of ADLs or Communication Due to Disruptive Symptoms



ADLs, activities of daily living; DEE, developmental and epileptic encephalopathy.

Conclusions

- Each individual with DEE and their family's experience is unique
- A holistic approach has been suggested in improving outcomes for individuals with DEE[28]
- Better understanding of caregiver definitions of normal and disruptive experiences can help researchers and providers prioritize areas of focus to improve outcomes
  - The effect of disruptive experiences on domains important to QoL in individuals with DEE and their families also informs prioritization
  - Prioritizing areas of focus to improve outcomes may result in changes or additions to endpoints in clinical research
- The landscape of DEE research and diagnostic tools is ever evolving[29]
  - Reports of the average age of DEE diagnosis is likely skewed
  - Aging individuals with undiagnosed DEEs are often not genetically tested even as the importance of diagnostic genetic testing is recognized[30]
- Further analyses of the data from this survey will focus on specific domains and their effects on communication and ADLs
  - The upcoming results from this study may be useful in creating clinical assessments and support tools to improve QoL, with a focus on the symptoms that matter most to each individual and their family across DEEs

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