Dysautonomia and functional impairment in rare developmental and epileptic encephalopathies: the other nervous system

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ABBREVIATIONS

ANS	Autonomic nervous system
DEE	Developmental and epileptic encephalopathy
LGS	Lennox–Gastaut syndrome

AIM To determine whether functional impairments and autonomic symptoms are correlated in young people with developmental and epileptic encephalopathies (DEEs).
METHOD Cross-sectional, online surveys (2018–2020) of parents recruited from family groups obtained information on several aspects of children's conditions including functional abilities (mobility, hand use, eating, and communication), 18 autonomic symptoms in six groups (cardiac, respiratory, sweating, temperature, gastrointestinal, and other), and parental stress. Bivariate and multivariable logistic regression analyses examined associations of dysautonomias with functional impairment, adjusted for type of DEE and age.
RESULTS Of 313 participants with full information on function and dysautonomias, 156 (50%) were females. The median age was 8 years (interquartile range 4–12y); 255 (81%) participants had symptoms in at least one autonomic symptom group; 283 (90%) had impairment in at least one functional domain. The number of functional impairment domains and of autonomic symptom groups varied significantly across DEE groups (both $p<0.001$). The number of functional impairment domains and of autonomic symptom groups were correlated (Spearman's $r=0.35$, $p<0.001$) on bivariate and multivariable analysis adjusted for DEE group and age. Parental stress was also independently correlated with dysautonomias ($p<0.001$).
INTERPRETATION Parent-reported dysautonomias are common in children with DEEs. They correlate with extent of functional impairment and may contribute to caregiver stress.

Developmental and epileptic encephalopathies (DEEs) often entail pharmacoresistant seizures and impaired development. Disruption of other neurological functions, particularly of the autonomic nervous system (ANS), is infrequently considered. ANS dysfunction commonly occurs after acute brain injury and may presage poorer outcomes.[1–3] Abnormal heart rate variability is well documented in patients with epilepsy.[4] Autonomic signs may accompany acute seizures, before, during, and after the ictus,[5–8] and the role of disruption in cardiac and respiratory function is the focus of research into sudden unexpected death in epilepsy.[9–11] Selected disorders, such as Rett syndrome, present with several dysautonomic features.[12,13] For DEEs as a group, however, little is known about the range and frequency of autonomic symptoms or the association between ANS symptoms and severity of a child's condition.

We queried parents about autonomic symptoms they observed and elicited information about basic functional abilities to assess the frequency of autonomic symptoms and their association with functional impairment, a marker of disease severity.

METHOD

Parents from rare disease organizations participated in discussions to identify features of their children's disorders that were most challenging and of greatest concern. This reflected US Food and Drug Administration guidance about the importance of natural history for rare disorders and that trial outcomes should reflect life-altering and life-limiting disease features.[14] The initial survey was designed with the Dravet Syndrome Foundation, the Lennox–Gastaut Syndrome (LGS) Foundation, and the online communities for *KCNB1*-associated disorder and electrographic status epilepticus in sleep. The survey was slightly modified at parents' request for *KCNQ2*-associated disorder with the *KCNQ2* Cure Alliance and Jack Pribaz Foundation. Subsequently the *PACS1* Smiles Foundation and the *CHD2* Facebook groups modified the survey further to include additional items of importance to them. Core items that

formed the basis of this report were preserved or were in forms easily harmonized across the surveys. Web-based, online surveys were open from June 2018 to March 2020. We aimed to recruit at least 400 participants. Surveys were disseminated through the individual family groups' websites and e-mail announcements.

Parents self-identified with different DEE groups. We accepted parent-reported diagnoses of Dravet syndrome, LGS, and electrographic status epilepticus in sleep. For gene-specific groups, we accepted a parent's assertion that a child had a causative variant. If the parent indicated the child did not have a causative variant, we included the child in the 'other' group.[15]

Functional abilities

The Gross Motor Function Classification System (GMFCS)[16] was used for the first two surveys and the Functional Motor Scales[17] for the *PACS1* and *CHD2* surveys. The GMFCS was specifically created for rating functional mobility in children with cerebral palsy; however, it is used in other populations[18] and is a respected legacy measure. The Communication Function Classification System identifies the level of communication from 'communicates effectively with familiar and unfamiliar people' to 'rarely communicates with familiar people'. Feeding assessed current use of a gastrotomy tube and independence for feeding (from completely self-sufficient to completely dependent on someone else). Hand use was based on having palmer or pincer hand grasp purposefully to manipulate objects to any extent. Because the GMFCS, Functional Motor Scales, and Communication Function Classification System are for children at least 2 years old, we asked parents of younger children to describe their children's motor and communication development as appropriate for age or mildly, moderately, and severely delayed.

We dichotomized the four functions to represent independence (without assistance or device) versus dependence.[15] Dependence for walking was classified as GMFCS levels of III, IV, or V or Functional Motor Scales 5-yard scores of 1, 2, 3, or 4; eating dependence as requiring considerable assistance or completely dependent (including exclusively gastrostomy tube fed); communication dependence as Communication Function Classification System levels of III, IV, or V. For children under 2 years, moderate to severe delay was considered impaired, and age-appropriate or mild delay was considered consistent with being independent.

An index of impairment was created by summing the number of domains (0–4) in which severe impairment or dependence occurred.

Autonomic symptoms

Autonomic symptoms present in the previous month were grouped: (1) cardiac (tachycardia, bradycardia, arrhythmia); (2) respiratory (fast or deep breathing, apnea, air swallowing, cyanosis); (3) diaphoresis (sweaty hands or feet, excessive sweating, lack of sweating); (4) temperature regulation (cold hands or feet, hands or feet becoming reddish or blue, temperature asymmetry, excessively cold, unexplained face/chest flushing); and (5) other (mydriasis/miosis, sialorrhea). Medical words were defined in lay terms.

Parents were advised that 'Many of these symptoms can happen in response to changes in the environment (temperature or lighting) or activity, or during a seizure, but here, only report these symptoms if they occur without any apparent reason, spontaneously'.

A separate question assessed constipation or gut dysmotility. If endorsed, parents were asked for frequency (daily, 1–6d/wk, 1–4d/mo, <1/mo) and whether the symptoms caused pain or discomfort (no, yes on occasion but not a serious concern, and yes common and serious concern). Symptoms that occurred 1 to 4 days per month and more often or that were reported to cause pain and be a serious concern were counted as an additional autonomic symptom and symptom group.

From 18 separate symptoms queried, we constructed (1) total number of symptoms endorsed (0–18) and (2) the total number of groups with one or more symptoms endorsed (0–6): cardiac, pulmonary, diaphoresis, temperature regulation, constipation, and other.

Caregiver stress

We also asked questions about caregiver-felt stress: 'Do you feel your life is like a rollercoaster (in crisis when your child is acutely ill, okay when things are stable)?' and 'Is fatigue a problem for you because of your child's illness?'. Responses were on a 5-point scale from 'not at all' to 'very much'. We used ordinal logistic regression with parent response on the 5-point scale as an ordinal outcome variable to assess the association of the responses with autonomic symptoms after adjustment for number of functional impairments, and DEE type.

Statistical analysis

Non-parametric bivariate (χ^2 test, non-parametric analysis of variance with a Kruskal–Wallis test) and multivariable logistic regression analyses with dichotomous and ordered outcomes were performed in SAS 9.4 (SAS Institute, Cary, NC, USA) to assess the relation between frequency of reported autonomic symptoms and functional impairments. On the basis of the brain-injury literature, we hypothesized that autonomic symptoms would be associated with more functional impairment independent of age and type of epilepsy. We also explored whether there were any intersyndrome/epilepsy differences after adjustment for age and degree of functional disability. We did not adjust *p*-values for multiple comparisons; however, we conservatively

What this paper adds

- Dysautonomic symptoms are common in young people with developmental and epileptic encephalopathies (DEEs).
- Burden of dysautonomias is strongly correlated with burden of functional impairments.
- Aspects of dysautonomic function may provide biomarkers of DEE disease severity.

interpreted p=0.01 to p<0.05 as marginally significant, p=0.001 to p≤0.01 as evidence of moderate significance, and p<0.001 as evidence of strong significance.

All procedures were approved by the Ann & Robert H Lurie Children's Hospital of Chicago Institutional Review Board. Informed consent and General Data Protection Regulation consent, when applicable, were obtained electronically through CLIRINX (Dublin, Ireland).

RESULTS

From the four surveys, 454 parents registered and provided some information about their children. Of these, 313 (69%) completed survey sections on autonomic symptoms and the four functional domains (mobility, hand use, communication, and feeding). Half of the participants were female (n=156, 50%); the median age at enrolment was 8 years (interquartile range [IQR] 4–12y, maximum 37y). Twenty-six participants were younger than 2 years, and 29 (9%) were at least 20 years old. Parents belonged to groups representing *CHD2* (n=42, 13%), Dravet syndrome (n=65, 21%), electrographic status epilepticus in sleep (n=15, 5%), *KCNB1* (n=28, 9%), *KCNQ2* (n=66, 21%), LGS (n=23, 7%), *PACS1* (n=29, 9%), and other DEEs (n=45, 14%).

Severe impairment or dependency was reported in 78 (25%) children for mobility, 42 (13%) for hand grasp, 204 (65%) for communication, and 100 (32%) for feeding. Ninety-two (29%) children were considered independent in all four domains; 112 (36%) were dependent in one, 45 (14%) in two, 34 (11%) in three, and 30 (10%) in all four domains.

A median of two (IQR 1–4, maximum 16) autonomic symptoms was endorsed. Reported symptoms involved temperature dysregulation (n=140, 45%), diaphoresis (n=103, 33%), respiration (n=63, 20%), cardiac function (n=31, 10%), and other symptoms largely reflecting sialorrhea and mydriasis/miosis (n=131, 42%). Any dysmotility or constipation was reported by 156 (50%), with frequent or pain-causing constipation endorsed for 114 (36%). The number of different affected autonomic symptom groups was zero (n=58, 19%), one (n=88, 28%), two (n=55, 18%), three (n=54, 17%), four (n=37, 12%), five (n=10, 3%), and six (n=11, 4%).

Comparisons across DEE groups

The distribution of sex across DEE groups was not substantially different (p=0.23). There were, however, substantial age differences across DEE groups (Table 1). Participants in the LGS group had the oldest median age (16 years, IQR 10–20y) and *KCNQ2* the youngest median age (4y, IQR 2–8y; p<0.001).

The median number of autonomic symptoms varied across the groups from one to four (p<0.001, Table 2). By symptom group, there was substantial variation across DEE groups for cardiac (p=0.001), respiration (p=0.002), temperature (p<0.001), diaphoresis (p=0.002), constipation (p<0.001), and other symptoms (p<0.001). The number of affected autonomic symptom groups also varied across DEE groups (Fig. 1a; p<0.001).

Table 1: Age at enrolment and sex across the developmental and epileptic encephalopathy (DEE) groups studied

DEE group	Age at enrolment, y:mo (IQR; maximum)	Sex, *n* (% female)
Total cohort (n=313)		
CHD2 (n=42)	10:11 (7:7–15:7; 28:11)	15 (36)
Dravet syndrome (n=65)	7:6 (4:8–16:4; 37:2)	34 (52)
ESES (n=15)	8:6 (6:1–9:7; 12:11)	4 (27)
KCNB1 (n=28)	8:5 (4:10–12:6; 22:11)	17 (61)
KCNQ2 (n=66)	4:6 (2:0–8:5; 20:4)	35 (53)
LGS (n=23)	16:10 (10:5–20:7; 37:10)	11 (48)
PACS1 (n=29)	8:5 (4:7–13:4; 26:5)	17 (59)
Other (n=45)	9:1 (5:4–12:10; 23:8)	23 (51)
p (7 df)	<0.001	0.23

The p-values are based on the non-parametric Kruskall–Wallis test for age and on a χ^2 test for sex. IQR, interquartile range; ESES, electrographic status epilepticus in sleep; LGS, Lennox–Gastaut syndrome; df, degrees of freedom.

The number of autonomic symptoms increased with child's age from a median of one for children 0 to 4 years and 5 to 9 years old, to two for 10- to 14-year-olds, and three for those 15 years and older (p=0.03 for trend). For individual symptom groups, only temperature (p=0.001) and diaphoresis (p=0.01) were significantly associated with age.

Domains with functional impairments varied across DEE groups (p<0.001; Fig. 1b). These findings were previously reported in detail for the first two surveys[15] although not for the *PACS1* and *CHD2* groups.

Autonomic symptoms

Presence versus absence of impairment in each of the four functional domains was strongly associated with a higher median number of autonomic symptoms with a median of one symptom in those without each specific impairment and a median of about three symptoms in those with the impairment (all p<0.001). Each autonomic symptom group, with the exception of diaphoresis, was associated with functional impairments (Table 2).

We used multiple logistic regression to adjust for age and DEE group and to test the associations of the number of functional impairment domains with number of affected autonomic symptoms groups (as an ordinal outcome variable) and with each of the individual autonomic symptom types (cardiac, respiratory, etc.) as binary outcome variables (Table 3). Adjusted for age and DEE group, increasing number of functional impairment domains (from 0 to 4) was associated with more affected autonomic symptom groups (0–6; p<0.001). The number of functional impairment domains was associated with each of the symptom groups reflecting cardiac, respiratory, temperature, and other autonomic systems (all p<0.001). Functional impairments were only marginally or not clearly associated with constipation (p=0.02) and diaphoresis (p=0.19).

Table 2: Total number of endorsed types of autonomic symptom and presence of symptoms for each system by type of developmental and epileptic encephalopathy (DEE), age group, and functional impairment[a]

DEE group	Individual reported symptoms, median (IQR)	Cardiac, *n* (%)	Respiration, *n* (%)	Temperature, *n* (%)	Diaphoresis, *n* (%)	Constipation, *n* (%)	Other, *n* (%)
Total cohort (*n*=313)	2 (1–4)	31 (10)	63 (20)	140 (45)	103 (33)	114 (36)	131 (42)
DEE group							
CHD2 (*n*=42)	1 (0–1)	2 (5)	5 (12)	10 (24)	4 (10)	11 (26)	12 (29)
Dravet (*n*=65)	2 (1–4)	9 (14)	15 (23)	36 (55)	35 (54)	18 (28)	26 (40)
ESES (*n*=15)	1 (0–2)	0	0	7 (47)	6 (40)	1 (7)	1 (7)
KCNB1 (*n*=28)	3 (1–5.5)	6 (21)	8 (29)	17 (61)	10 (36)	8 (29)	18 (64)
KCNQ2 (*n*=66)	2 (1–4)	5 (8)	18 (27)	28 (42)	17 (26)	40 (61)	38 (58)
LGS (*n*=23)	4 (3–6)	7 (30)	10 (43)	19 (83)	11 (48)	12 (52)	14 (61)
PACS1 (*n*=29)	1 (1–2)	0	1 (3)	10 (34)	8 (28)	10 (34)	6 (21)
Other (*n*=45)	1 (0–3)	2 (4)	6 (13)	13 (29)	12 (27)	14 (31)	16 (36)
p (7 df)	<0.001	0.001	0.002	<0.001	<0.001	<0.001	<0.001
Age group (y)							
0–4 (*n*=94)	1 (0–3)	6 (9)	24 (26)	33 (35)	24 (26)	35 (37)	40 (43)
5–9 (*n*=95)	1 (0–3)	8 (9)	15 (16)	39 (41)	27 (28)	28 (29)	36 (38)
10–14 (*n*=59)	2 (1–5)	3 (5)	6 (10)	29 (49)	25 (42)	20 (34)	27 (46)
15 and older (*n*=65)	3 (1–5)	12 (18)	18 (28)	39 (60)	27 (42)	31 (48)	28 (43)
p for trend (1 df)	0.03	0.10	0.89	0.001	0.01	0.19	0.74
Functional impairments							
Mobility							
Independent (*n*=235)	1 (0–3)	16 (7)	27 (11)	97 (41)	77 (33)	75 (32)	80 (34)
Dependent (*n*=78)	3 (2–5)	15 (19)	36 (46)	43 (55)	26 (33)	39 (50)	51 (65)
p	<0.001	0.003	<0.001	0.03	0.92	0.005	<0.001
Hand use							
Independent (*n*=271)	1 (1–3)	25 (9)	42 (16)	113 (42)	88 (32)	91 (34)	105 (39)
Dependent (*n*=42)	3.5 (2–6)	6 (14)	21 (50)	27 (64)	15 (36)	23 (55)	26 (62)
p	<0.001	0.33	<0.001	0.006	0.68	0.009	0.005
Communication							
Independent (*n*=109)	1 (0–2)	1 (1)	11 (10)	36 (33)	31 (28)	30 (28)	26 (24)
Dependent (*n*=204)	2 (1–5)	30 (15)	52 (25)	104 (51)	72 (35)	84 (41)	105 (51)
p	<0.001	<0.001	<0.001	0.002	0.22	0.02	<0.001
Eating							
Independent (*n*=213)	1 (0–3)	11 (5)	27 (13)	78 (37)	64 (30)	61 (29)	65 (31)
Dependent (*n*=100)	3 (1–5)	20 (20)	36 (36)	62 (62)	39 (39)	53 (53)	66 (66)
p	<0.001	<0.001	<0.001	<0.001	0.12	<0.001	<0.001

[a]The *p*-values were obtained with a Kruskal–Wallis test for the association of number of autonomic symptoms and DEE group and each of the individual types of functional impairment. A Spearman's rank order correlation was used for age group and number of autonomic symptoms. A χ^2 test was used to test the associations of DEE group, age group, and individual functional impairment types with individual autonomic symptom groups. ESES, electrographic status epilepticus in sleep; LGS, Lennox–Gastaut syndrome; df, degrees of freedom.

Increasing age was moderately to strongly associated with the number of autonomic symptom groups ($p<0.001$) and temperature ($p=0.002$). Age was marginally associated with diaphoresis ($p=0.01$), cardiac symptoms ($p=0.05$), and constipation ($p=0.01$), and not associated with respiratory ($p=0.79$) or other autonomic symptoms ($p=0.25$). Finally, the associations of autonomic symptoms with type of epilepsy were complex. There were statistically significant differences among the eight DEE groups for number of autonomic symptom groups ($p<0.001$), temperature ($p=0.001$), diaphoresis ($p<0.001$), and constipation ($p=0.004$). This, by itself, does not explain where those differences arose. The *CHD2* and *PACS1* groups had lower and LGS higher autonomic symptom levels than the other groups. The LGS group had higher levels of temperature dysregulation, the group with Dravet syndrome had higher levels of symptoms related to diaphoresis, and the *KCNQ2* group stood out for higher levels of constipation/dysmotility. As there were no specific hypotheses for group differences, these are considered descriptive analyses only.

The number of seizure medications being taken at the time of the survey was zero (*n*=58, 19%), one (*n*=82, 26%), two (*n*=69, 22%), and three or more (*n*=104, 33%). Neither the number of medications nor any of the most common medications (cannabidiol, *n*=36; clobazam, *n*=86; lamotrigine, *n*=34; levetiracetam, *n*=70; topiramate, *n*=34; valproic acid, *n*=97) contributed to autonomic symptoms after multivariable logistic regression adjustment for age, DEE type, and functional impairments.

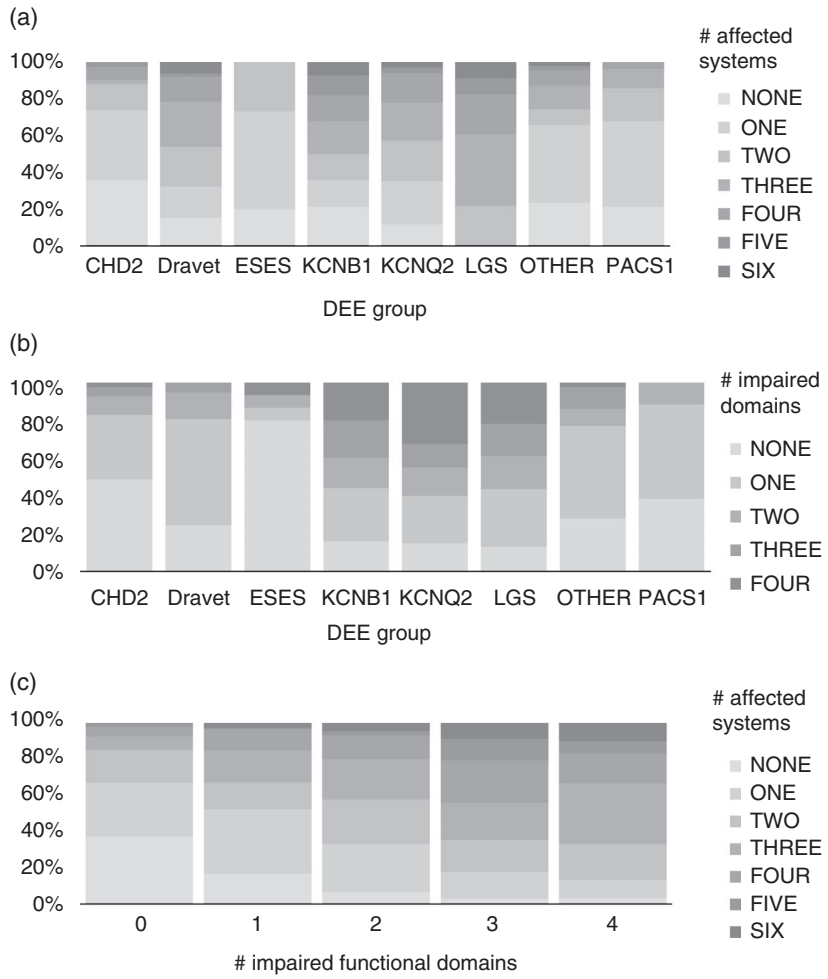

Figure 1: Associations between (a) developmental and epileptic encephalopathy (DEE) types and number of systems with dysautonomias (p<0.001, Kruskal–Wallis test, 7 degrees of freedom [df]), (b) DEE types and number of impaired functions (p<0.001, Kruskal–Wallis test, 7 df), and (c) number of systems affected by dysautonomias and number of impaired functions (Spearman's r=0.35, p<0.001).

Parental stress

The median response on parent-stress questions (n=293 respondents) was four (IQR 3–5), corresponding to a response of 'moderately'. The number of autonomic symptom groups was correlated with fatigue (Spearman's r=0.33, p<0.001) and 'life-like-a-rollercoaster' (Spearman's r=0.22, p<0.001). Both findings persisted after adjustment for number of domains with functional impairment, age, DEE group, and an indicator for seizure recency (<6 vs ≥6mo).

DISCUSSION

For children with rare and severe DEEs, concern must focus first on seizures, the life-interrupting and often dangerous symptom that initially brings most children to attention. Development, cognition, and behavior – disruptions in which often contribute to impairment in basic functional abilities (mobility, communication, etc.) – are next priorities. A large proportion of parents, however, report a range of autonomic symptoms that typically do not come under the standard rubric of epilepsy care yet are frequently reported by parents of patients with DEEs.

Autonomic function is often disrupted after an acute brain insult such as stroke or trauma,[2,19] and autonomic dysfunction presages poorer course of recovery in children[1] and adults.[19] In Alzheimer or Parkinson disease, autonomic impairment is recognized as a complication requiring additional therapy and management and may be a marker of disease severity.[20,21] Thus, our findings of a high level of autonomic symptoms and correlation between burden of autonomic symptoms and functional impairment are consistent with findings of autonomic dysfunction seen in other brain conditions.

Management of autonomic symptoms requires specialized knowledge beyond seizure care per se, as ANS dysfunction affects numerous organ systems other than the brain. Recording symptoms and performing tests of autonomic function can identify what the dysfunction is.

Table 3: Multivariable logistic regression analyses of the associations of number and types of autonomic symptom with number of domains of functional impairment, age, and developmental and epileptic encephalopathy (DEE) group

Outcome	Number of functional domains with impairment, odds ratio[b] (95% CI), *p*	Age group, odds ratio[b] (95% CI), *p*	DEE group: summary of results for eight disease/epilepsy groups
Number of autonomic symptom groups (0–6)	1.88 (1.56–2.27), <0.001	1.42 (1.16–1.73), <0.001	*CHD2* and *PACS1* much less likely and Dravet syndrome and LGS much more likely to have autonomic symptoms overall *p*<0.001 (7 df)
Cardiac[a]	1.83 (1.38–2.42), <0.001	1.39 (1.00–1.93), 0.05	Could not be included in the multivariable model owing to no cells and collinearity with domains and age
Respiration[a]	2.00 (1.53–2.62), <0.001	0.96 (0.72–1.28), 0.79	No disease group stood out as substantially different from the others *p*=0.28 (7 df)
Temperature[a]	1.51 (1.20–1.88), <0.001	1.49 (1.16–1.90), 0.002	*CHD2* was much less likely and LGS somewhat more likely to have symptoms related to abnormal temperature regulation *p*=0.001 (7 df)
Diaphoresis[a]	1.16 (0.93–1.45), 0.19	1.39 (1.08–1.78), 0.01	*CHD2* was much less likely and Dravet syndrome much more likely to have symptoms related to abnormal sweating *p*<0.001 (7 df)
Constipation[a]	1.29 (1.04–1.60), 0.02	1.37 (1.07–1.75), 0.01	*KCNQ2* stood out from the rest as having a much higher risk of constipation/dysmotility *p*=0.004 (7 df)
Other[a]	1.66 (1.33–2.08), <0.001	1.16 (0.91–1.47), 0.25	*KCNB1* stood out as being more likely to have 'other' autonomic symptoms *p*=0.08 (7 df)

[a]Coded as any one or more reported individual symptoms in the group being present or versus all being absent. [b]For an ordinal outcome such as number of affected autonomic symptom groups, the odds ratio represents the odds of an increase of one increment (e.g. from one to two or four to five affected autonomic symptom groups) associated with an increment in the predictor variable (from one to two or three to four functional domains with dependence or from one age group to the next), after adjustment for other independent variables in the model (i.e. DEE type and age). CI, confidence interval; LGS, Lennox–Gastaut syndrome; df, degrees of freedom.

Currently, though, the management of dysautonomias is symptomatic, usually with cholinergic, anticholinergic, and sympathomimetic drugs to treat individual conditions such as hypertension, hyperhidrosis, and gastrointestinal dysmotility. We recommend that clinicians who treat these patients incorporate questions into their standard clinical interviews, evaluate parent-reported symptoms, and, as needed, refer for further evaluation and management.

Autonomic symptoms can also be distressing and negatively affect other aspects of a child's daily function and quality of life.[12] Our secondary analysis demonstrated that autonomic symptoms were associated with greater parental fatigue and life-unpredictability. As parental stress and parent well-being affect the care of the child,[22] clinicians should be familiar with ANS symptoms and acknowledge their existence and importance to parents. For parents and providers, understanding the frequency and reasons for autonomic symptoms in children with DEEs could help demystify what may seem like odd, random, and inexplicable phenomena.

The considerations about disease management and family impact highlight the importance of multidisciplinary team approaches to children with medically complex neurodevelopmental disorders.[23] Addition of medications for a child already taking one or several seizure medications may require careful planning to avoid harmful interactions. Seizure medications themselves may contribute to dysautonomic symptoms.

Molecular biology has provided much information about the expression of individual genes throughout all tissues in the body, and it is likely that some of the genes associated with DEE are expressed in effector organs of the ANS. For example, genes coding for voltage-gated sodium channels are frequently associated with DEEs such as Dravet syndrome, largely secondary to *SCN1A* variants. *SCN1A* is expressed in the heart to a modest extent;[24] reduced heart rate variability occurs in patients with *SCN1A* variants and may be a biomarker of sudden death in affected individuals.[25,26] Whether decreased heart rate variability is due to abnormal channel function in heart tissue itself, the sinoatrial node, or more central mechanisms is unknown.

Syndromes and genes alone, however, do not explain the finding that autonomic symptoms increase with greater functional impairment. Our findings suggest widespread abnormalities, involving sympathetic, parasympathetic, and enteric divisions of the ANS.[27]

The direction of causality among the underlying etiology, seizures themselves, and dysautonomia is not fully delineated by our results; however, the association of the many underlying etiologies of DEEs with impaired function, independent of seizures, is well established. Our results demonstrate a similar association with autonomic function. The strong correlation between reported autonomic symptoms and impaired functions raises the possibility that markers of autonomic function could serve as biomarkers of disease severity for randomized trials of

precision therapies in which seizures may not be the only or even a primary outcome. Wearable devices are increasingly used to detect seizures through a combination of actigraphy and autonomic markers, thus providing objective measures over time of the frequency and severity of autonomic system symptoms.[5,7,28]

Limitations of our study include our sample being drawn from parent volunteers recruited through online communities. Given the extremely rare nature of these disorders, this is an efficient means of engaging large numbers of caregivers, yet generalizability to the populations represented by participants cannot be assured.

Our autonomic symptoms were parent-reported. Presumably, some parent-reported symptoms (particularly cardiac) were diagnosed by a physician; however, we did not ascertain this. Our symptom groups do not distinguish between symptoms due to brainstem mechanisms and symptoms of increased sympathetic tone (catecholamine) or parasympathetic (cholinergic) effects. Eliciting autonomic symptoms from parents is also not a well-developed area. Questionnaires exist in other settings, for example Parkinson disease,[29] and for children with familial dysautonomic syndromes or autism;[30] it is unknown whether these are appropriate in severely impaired populations. Our findings from parent reports, however, should motivate studies that use more precise and objective measures (specific tests, wearable devices).

Children with DEEs often take multiple antiseizure medications, which may cause some autonomic (especially gastrointestinal) symptoms. For antiseizure medications reported in at least 30 children, we examined the associations with the number of affected autonomic groups and adjusted for each medication in our multivariable logistic models. None contributed significantly to any model or altered the associations we report here.

The associations between autonomic symptoms and parental stress highlight the importance of dysautonomic symptoms to caregivers. Our data do not provide insight into how or why these symptoms are associated with parental stress: are they a direct cause of stress or are they surrogate measures for other sources of stress? Whether specific symptoms, the frequency and severity of symptoms, or combinations of symptoms lead to parental stress is not addressed in this initial survey. Better understanding of these factors could alleviate some of the burden associated with these difficult disorders.

Given the well-known phenomenon of autonomic dysfunction after brain injury and in disease of the central nervous system, it is not surprising that, in children with various developmental brain disorders associated with epilepsy, autonomic dysfunction is common and is associated with severity and pervasiveness of disability in functions of the somatic nervous system. Our parent survey highlights the importance of the ANS in children with DEEs and should engender greater interest in autonomic dysfunction in those with neurodevelopmental disorders.

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DATA AVAILABILITY STATEMENT

A fully de-identified and limited data set may be made available to interested individuals with establishment of an appropriate Data Use Agreement between the author's and requestor's institutions.

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