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Gastrointestinal and eating problems in *SCN1A*-related seizure disorders

C.A. Minderhoud [a,*,1], A. Postma [b], F.E. Jansen [a,1], J.S. Verhoeven [c], J.J. Schrijver [d], J. Goudswaard [e], G. Andreae [e], W.M. Otte [a,1], K.P.J. Braun [a,1], E.H. Brilstra [f]

[a] Department of Neurology, UMCU Brain Center, University Medical Center Utrecht, Heidelberglaan 100, 3584CX Utrecht, the Netherlands
[b] Department of Psychiatry, UMCU Brain Center, University Medical Center Utrecht, Heidelberglaan 100, 3584CX Utrecht, the Netherlands
[c] Department of Neurology, Academic Centre for Epileptology Kempenhaeghe, Heeze, the Netherlands
[d] Department of Dietetics, University Medical Center Utrecht, Utrecht, the Netherlands
[e] Speech Therapy, Stichting Epilepsie Instellingen Nederland, Postbus 540, 2130 AM Hoofddorp, the Netherlands
[f] Department of Genetics, UMC Utrecht Brain Center, University Medical Center Utrecht, the Netherlands

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ABSTRACT

Objective: Our study aimed to describe the prevalence and characteristics of gastrointestinal and eating problems in Dravet syndrome (DS) and other *SCN1A*-related seizure disorders and to determine the association between the occurrence of gastrointestinal and eating problems and core features of DS.
Methods: Gastrointestinal and eating problems were assessed with a questionnaire in a Dutch cohort of participants with an *SCN1A*-related seizure disorder. Associations between the number of gastrointestinal and eating problems and core features of DS, seizure severity, level of intellectual disability, impaired mobility, behavioral problems, and use of anti-seizure medication, were explored by multivariate ordinal regression analyses. Symptoms were divided into the categories dysphagia-related, behavioral, and gastrointestinal, and were assessed separately.
Results: One hundred sixty-nine participants with an *SCN1A*-related seizure disorder, of whom 118 (69.8%) with DS and 51 (30.2%) with Generalized Epilepsy with Febrile Seizures Plus / Febrile Seizures (GEFS+/FS), the non-DS phenotype, were evaluated. Gastrointestinal and eating problems were highly prevalent in DS participants, 50.8% had more than three symptoms compared to 3.9% of non-DS participants. Of participants with DS, 17.8% were fully or partly fed by a gastric tube. Within the three different symptom categories, the most prevalent dysphagia-related symptom was drooling (60.7%), distraction during mealtimes (61.4%) the most prevalent behavioral symptom, and constipation and loss of appetite (both 50.4%) the most prevalent gastrointestinal symptoms. DS participants who use a wheelchair (odds ratio (OR) 4.9 95%CI (1.9–12.8) compared to walking without aid), who use ≥3 anti-seizure medications (ASM) (OR 5.9 95%CI (1.9–18.2) compared to <3 ASM) and who have behavioral problems (OR 3.0 95%CI (1.1–8.1) compared to no behavioral problems) had more gastrointestinal and eating problems.
Conclusion: Gastrointestinal and eating problems are frequently reported symptoms in DS. Distinguishing between symptom categories will lead to tailored management of patients at risk, will improve early detection, and enable a timely referral to a dietitian, behavioral expert, and/or speech therapist, ultimately aiming to improve the quality of life of both patients and caregivers.

1. Introduction

Patients with pathogenic variants in the *SCN1A* gene can develop a spectrum of seizure disorders of widely varying severity. Disorders on the milder end of the spectrum include non-Dravet syndrome (non-DS) phenotypes mainly referred to as febrile seizures (FS) and genetic epilepsy with febrile seizures plus (GEFS+). The latter is characterized by familial (a) febrile seizures with neurodevelopmental outcomes in the normal range [1]. The most severe end of the spectrum is represented by a diagnosis of Dravet syndrome (DS), an epileptic and developmental encephalopathy, presenting in the first year of life with prolonged generalized or unilateral tonic-clonic or clonic, fever-sensitive seizures, that progress to, often therapy-resistant, epilepsy over the course of the disease [2]. After the first year of life, neurodevelopment slows, resulting in intellectual disability (ID), autistic traits, ADHD-like

* Corresponding author at: G03. 129, Department of Neurology, UMCU Brain Center, University Medical Center Utrecht, Heidelberglaan 100, 3583CX Utrecht, the Netherlands.
E-mail address: c.a.minderhoud-2@umcutrecht.nl (C.A. Minderhoud).
[1] Member of the European Reference Network EpiCare.

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features, and other behavioral problems [2,3]. Additional features, such as sleep disturbances and autonomic dysregulation, have increasingly been reported over the past years and can be highly impactful on the daily functioning of patients and caregivers [4,5]. Gastrointestinal and eating problems have also been described by caregivers of DS patients as frequent, burdensome features of the disease [4,6].

The underlying cause of gastrointestinal and eating problems in DS is probably multifactorial. Aspects such as neurodevelopmental deficits including intellectual disability, impaired mobility, behavioral problems, use of anti-seizure medication (ASM), or a ketogenic diet may contribute to the occurrence of symptoms, such as dysphagia, constipation, and a decrease in food tolerance [7–10]. Dysphagia-related symptoms such as impaired chewing and impaired swallowing, and gastrointestinal symptoms such as constipation might play a role, but also behavioral symptoms, such as picky eating, poor appetite, and temper tantrums, that might find their origin in behavioral problems or intellectual disability, need to be addressed. Therefore, a multifaceted evaluation is needed to fully appreciate and understand the extent and impact of gastrointestinal and eating problems. A recent qualitative study on the lived experiences of caregivers of a patient with DS underlined this [6]. In this study, caregivers identified eating problems as a prominent stressor and described mealtimes as an extremely stressful event. Behavioral symptoms such as poor appetite, decreased food tolerance, prolonged mealtimes, and picky eating were emphasized by caregivers as prominent, highly burdensome events [6]. A comprehensive analysis of gastrointestinal and eating problems in *SCN1A*-related disorders and their causes, however, is lacking.

In this study, we aimed to assess the prevalence and characteristics of gastrointestinal and eating problems in *SCN1A*-related seizure disorders. The impact of gastrointestinal and eating problems is relatively unexplored and therefore often overlooked by treating physicians [6]. Consequently, referral to a dietitian or speech therapist may be delayed, which can result in aggravation of the problem. Clarifying the causes of these problems and their association with core features of DS will improve the identification of patients at risk for gastrointestinal and eating problems. Early detection allows for counseling of caregivers at the earliest stage possible and if necessary, a timely referral to a dietitian, behavioral expert, or speech therapist, to ameliorate the burden of care and improve the quality of life of the patient and caregiver.

2. Methods

2.1. Study design

We performed an explorative cross-sectional cohort study in participants with an *SCN1A*-related seizure disorder. The study was carried out at the University Medical Center Utrecht. Data collection took place between October 2021 and December 2022.

2.2. Study population

This study is part of a broader research project. Participants were eligible for inclusion if they carried a symptomatic heterozygous pathogenic, or likely pathogenic variant in *SCN1A* and if they were 2 years of age or older. Children younger than two years of age were excluded because not all questionnaires are validated in this age group. We included a nationwide cohort of patients with an *SCN1A*-related seizure disorder, who had participated in previous research [11,12] and had given their consent to be contacted for participation in further studies, were invited to participate by their physician, or responded to an invitation to participate in the newsletter of the parent/patient organization 'Dravet syndrome Foundation Netherlands/ Flanders' (Stichting Dravetsyndroom Nederland/Vlaanderen). Core features of part of this cohort have been described previously [11,12] in 2015. The cohort has been expanded since. Gastrointestinal and eating problems were, however, not evaluated in 2015.

The total current cohort consisted of participants with DS and those with a non-DS phenotype. The non-DS group consisted of participants with the diagnosis GEFS+ or FS. The diagnostic categorization was made by the treating physician and verified by the researchers (CM, AP, FJ, EB) based on the most recent guidelines [13]. Informed consent was obtained from participants digitally. For minors or incapacitated subjects, informed consent was given by their caregiver or legal guardian. The study does not fall under the Medical Research Involving Human Subjects Act according to the Medical Research Ethics Committee (MREC) Nedmec due to the non-invasive nature of the study, hence no ethical clearance was requested.

2.3. Clinical data

Clinical data were retrieved from medical records and questionnaires filled in by participants or caregivers of participants. Information on genetic diagnosis, seizure frequency, development, and medication use were retrospectively retrieved from medical records. Participants or caregivers completed a set of questionnaires, adjusted for their age group.

Gastrointestinal and eating problems were measured with a questionnaire, developed by the researchers (CM, AP, FJ, EH) in consultation with a specialized dietitian (JS) and two specialized speech therapists (AG, JG) for the purpose of the present study (see supplementary material). The questionnaire is divided into two parts. Part one named nine symptoms, to be responded to by presence and their frequency (never or almost never, monthly, weekly, daily, or clustered) and one symptom, 'picky eating', to be responded to only by presence. The answers to symptom questions were dichotomized into whether or not they were present regardless of frequency (yes or no), and whether or not they were present on a weekly or more frequent basis (yes, weekly, or more versus less than weekly or not present), if applicable. Participants who responded to symptom frequency with 'clustered', were categorized as 'weekly or more frequent'. The primary outcome measure was the number of gastrointestinal and eating symptoms, regardless of frequency, as rated in part one of the questionnaires, with a maximum of 10 symptoms. The ten symptoms were then classified into three symptom categories: dysphagia-related symptoms, behavioral symptoms, and gastrointestinal symptoms. Dysphagia-related symptoms included 'impaired chewing', 'impaired swallowing', 'choking,' and 'drooling'. Behavioral problems included 'picky eater', 'distraction during mealtimes,' and 'temper tantrums during mealtimes'. Gastrointestinal symptoms included 'vomiting', 'constipation,' and 'loss of appetite'. Part two of the questionnaire is composed of four yes or no questions, such as 'does your child/do you have a gastric tube' and 'does your child/do you currently have eating problems', with free text space to elaborate on answers. Answers to these questions in part two of the questionnaire were included to characterize the study population, but were not considered to reflect specific symptoms and were thus excluded from the primary outcome.

The developmental level was rated on a five-point Likert scale based on intelligence quotient (IQ) and developmental level reported in medical records and questionnaires (no intellectual disability (ID) (IQ or DQ > 85), borderline ID (IQ or DQ 70–85), mild ID (IQ or DQ 50–70), moderate ID (IQ or DQ 30–50) or severe to profound ID (IQ or DQ < 30)). When no recent IQ or DQ was available, the developmental level was estimated based on the type of

received education or daycare, employment status, communication skills, and general functioning. Participants for whom the rating was not evident (due to lack of recent information) were discussed and their developmental level was categorized in a consensus meeting by a child neurologist (FJ), neuropsychologist, and clinical geneticist (EB).

Total seizure frequency was rated with information from medical records and questionnaires at the time of data collection and was classified as no seizures for >1 year, yearly seizures, monthly seizures, weekly seizures, or daily seizures. All seizure types were included. To reduce the risk of over- or underestimation of seizure frequency, a secondary analysis with only motor seizures was performed, since motor seizures are considered better countable than, for example, (a)typical absences. Generalized tonic-clonic, hemiclonic, tonic, atonic, focal motor seizures, and myoclonus were included as motor seizures.

Mobility was measured with the Dutch version of the Functional Mobility Scale (FMS) questionnaire to rate a child's functional mobility on three distances (5 m, 50 m and 500 m) in six categories [14]. We reported the outcome for 500 m. The Functional Mobility Scale is validated in participants over four years old.

Behavioral problems were quantified and characterized with the Dutch parent-report version of the Child Behavior Checklist 1.5–5 years (CBCL), Child Behavior Checklist 6–18 years, the Adult Behavior Checklist 18–59 years (ABCL) or the Adult Self-Report 18–59 (ASR). T-scores that compare the scores to norm groups from the general population were calculated as instructed by the CBCL/ABCL manual. Based on T-scores of the total problems scale, participants were divided into normal, borderline, and clinical range behavioral problems [15,16].

2.4. Statistical analyses

Baseline characteristics and outcomes are reported for DS and non-DS separately. No statistical test was used to test differences because the diagnostic categorization inherently depended on these disease characteristics. In our association analyses, the outcome measure 'number of gastrointestinal and eating problems, regardless of frequency' was categorized as: '0–1 symptoms', '2–3 symptoms', '4–6 symptoms' or '7–10 symptoms'. The FMS score was simplified to 'uses a walking device' or 'independent on 500 meters distance'. For the level of disability scale the 'no intellectual disability' and 'borderline intellectual disability' were merged into one group 'no to borderline intellectual disability', because of the small sample size of the two groups. The other subgroups remained unchanged. The current use of ASM was dichotomized into 'use of 0–2 ASM' or 'use of $\geq$3 ASM'.

First, univariate ordinal regression analyses were performed between the primary outcome measure and each of the core features of DS separately: level of intellectual disability, seizure frequency, motor disability, behavioral problems, and use of ASM, to explore separate associations.

Because of the expected interaction between the different core features, a multivariate ordinal regression analysis was performed to explore associations in a model. All core features of DS were included. We hypothesized that the prevalence and severity of gastrointestinal and eating problems differ per age group. Therefore, age was also added to the model as an independent variable to correct for a possible effect.

We performed two sensitivity analyses. First, we performed a multivariate ordinal regression analysis with total motor seizure frequency as a measure for epilepsy severity, instead of total seizure frequency, to reduce the risk of over- or underestimation of seizure frequency. Secondly, because the FMS is not validated in the age group 2–4 years old, we performed a separate ordinal regression analysis excluding this age group.

We then assessed the association of dysphagia-related, behavioral, and gastrointestinal symptoms with core features separately using ordinal regression analyses. For all analyses, missing questionnaire data were imputed with multiple imputations (n = 20) and pooled into single estimates with Rubin's rule [17]. All tests were performed two-tailed with an alpha level of significance of $p < 0.05$. Statistical analyses were performed using R-studio (version 1.4.1106).

3. Results

3.1. Demographic and clinical characteristics of the study population

One hundred eighty-five participants were found eligible for inclusion in this study. The gastrointestinal and eating problems questionnaire was completed by 169 participants, of whom 118 (69.8%) had DS and 51 (30.2%) non-DS. Table 1 provides an overview of the demographic and clinical characteristics of the study population. The frequency of 'motor seizures only' in DS participants is depicted separately in the supplementary material. Compared to the non-DS group, the DS group was markedly younger (median age 16 years versus median 23 years) and had a more severe manifestation of all characteristics, in line with diagnostic criteria.

3.2. Gastrointestinal and eating problems

Table 2 depicts the prevalence of gastrointestinal and eating problems as reported in the questionnaire. Of the participants with DS, 87.2% of parents reported two or more symptoms. Within the three different symptom categories, drooling (60.7%) was the most prevalent dysphagia-related symptom, distraction during mealtimes (61.4%) was the most prevalent behavioral symptom, and constipation and loss of appetite (50.4%) were the most prevalent gastrointestinal symptoms. Drooling and distraction during mealtimes were reported to occur on a weekly basis or more frequently in the largest number of participants. The majority of participants with DS experienced more than three symptoms. In the supplementary material illustrative quotes on picky eating are displayed.

Twenty-one (17.8%) of responding DS participants were fully or partly fed via a gastric tube. Of the 26 DS participants who had used a ketogenic diet, three (11.5%) developed gastrointestinal and eating problems during the diet. Of the DS participants who reported having a gastrointestinal or eating problem, 49.2% indicated the problem as highly impactful on daily life. The majority of DS participants were under the care of a speech therapist at the time of the study or in the past. For most participants, the indication for treatment by a speech therapist was speech (55.1%) or language (39.8%) deficits, and therapy was not focused on impaired swallowing or chewing. A dietitian was involved in the care of one-third of DS participants.

For the non-DS population, the most prevalent symptoms were loss of appetite (21.6%), constipation (18%), and being distracted during mealtimes (20%). The latter occurred most frequently, namely on a weekly basis in 14% of non-DS participants, 25.5% indicated that they are or had been treated by a speech therapist, mainly for problems with speech and language. Of the three participants that reported that there were gastrointestinal or eating problems, one participant reported that these problems were highly impactful on daily life.

3.3. Associations between gastrointestinal and eating problems and core features of DS

Univariate and multivariate ordinal regression analyses were performed for the DS group only, since the prevalence of gastroin-

Table 1
Characteristics of the study population.

	Complete cohort	Dravet	Non-Dravet
N (%)	169	118 (69.8)	51 (30.2)
Age, years (median, range)	17 (2-73)	16 (2-53)	23 (5-73)
Sex: female (%)	91 (53.8)	58 (49.2)	33 (64.7)
Developmental level n (%)*	168		
- 1: no ID	54 (32.1)	3 (2.6)	51 (100.0)
- 2: borderline ID	4 (2.4)	4 (3.4)	0
- 3: mild ID	37 (22.0)	37 (31.6)	0
- 4: moderate ID	28 (16.7)	28 (23.9)	0
- 5: severe ID	45 (26.8)	45 (38.5)	0
Total seizure frequency n (%)	169		
- No seizures	33 (19.5)	5 (4.2)	28 (54.9)
- Yearly seizures	35 (20.7)	16 (13.6)	19 (37.3)
- Monthly seizures	20 (11.8)	17 (14.4)	3 (5.9)
- Weekly seizures	39 (23.1)	38 (32.2)	1 (2.0)
- Daily seizures	42 (24.9)	42 (35.6)	0
Current use of anti-seizure medication n (%)	166		
- No ASM	26 (15.7)	1 (0.9)	25 (50.0)
- 1–2 ASM	50 (30.1)	27 (23.3)	23 (46.0)
- ≥3 ASM	90 (54.2)	88 (75.9)	2 (4.0)
Use of ketogenic diet n (%)	166		
- In the past	25 (15.1)	24 (20.7)	1 (2.0)
- Currently	2 (1.2)	2 (1.7)	0
Gastric tube use			
- Partly	11 (6.5)	11 (9.3)	0
- Completely	10 (5.9)	10 (8.5)	0
Functional mobility score 500 m n (%)**	157		
- Uses a wheelchair	49 (31.2)	49 (44.5)	0
- Uses a rollator	2 (1.3)	1 (0.9)	1 (2.1)
- Independent walking on flat surfaces	31 (19.7)	31 (28.2)	0
- Independent walking on all surfaces	75 (47.8)	29 (26.4)	46 (97.9)
ABCL/CBCL/ASR behavioral problems total score n (%)***	145		
- Normal range	67 (46.2)	37 (35.2)	30 (75.0)
- Borderline range	30 (20.7)	23 (21.9)	7 (17.5)
- Clinical range	48 (33.1)	45 (42.9)	3 (7.5)
Speech therapy n (%)	115 (68.5)	(87.2)	(25.5)
Indication:****			
- Speech	72 (42.6)	65 (55.1)	7 (13.7)
- Language	51 (30.2)	47 (39.8)	4 (7.8)
- Impaired swallowing	21 (12.4)	18 (15.3)	3 (5.9)
- Impaired chewing	11 (6.5)	11 (9.3)	0
- Other	9 (5.3)	9 (7.6)	0
Involvement of a dietitian n (%)	31 (24.2)	31 (32.6)	0

ID = intellectual disability, ASM = anti-seizure medication, ABCL/CBCL/ASR = Adult Behavior Checklist / Child Behavior Checklist / Adult Self-Report.
* No intellectual disability IQ or DQ > 85, borderline ID (IQ or DQ 70–85), mild ID (IQ or DQ 50–70), moderate ID (IQ or DQ 30–50), severe or profound ID (IQ or DQ < 30).
** The outcome for 500 m distance on the Dutch version of the Functional Mobility Scale (FMS).
***Based on the Dutch parent report version of the Child Behavior Checklist 1.5–5 years (CBCL), Child Behavior Checklist 6–18 years, the Adult Behavior Checklist 18–59 years (ABCL) or the Adult Self-Report 18–59 (ASR).
**** Participants could fill in more than one indication for therapy.

testinal or eating problems in the non-DS group was observed to be low.

The results from the univariate ordinal regression analyses are depicted in the supplementary material. A higher odds of more gastrointestinal and eating problems were seen in participants who depended on a wheelchair or walker to traverse a distance of 500 m (OR 4.3 (95%CI 2.1–9.0)) as well as in participants who used more than three ASM (OR 6.3 (95%CI 2.6–15.1)).

A lower odds of gastrointestinal and eating problems were seen in participants who had either yearly seizures (OR 0.1 (95%CI 0.0–0.2)) or monthly seizures (OR 0.3 (95%CI 0.1–0.9)) compared to daily seizures as well as in participants with either mild intellectual disability (OR 0.4 (95%CI 0.2–1.0)) or moderate intellectual disability (OR 0.4 (95%CI 0.2–0.9)) compared to severe intellectual disability. In the univariate analysis, behavioral problems measured with the ABCL/CBCL were not associated with gastrointestinal and eating problems.

Table 3 shows the results of the multivariate ordinal regression analysis. Use of a wheelchair or a walker at 500 m distance, use of three or more ASM, and behavioral problems in the clinical range were significantly associated with an increase in total number of gastrointestinal and eating problems. A yearly seizure frequency, compared to a daily seizure frequency, was associated with less gastrointestinal and eating problems. To minimize the risk of an overestimation of seizure frequency and its influence on association analyses, we performed additional ordinal regression analyses with only motor seizures, which can be more objectively recognized and counted. This analysis yielded similar results (see supplementary material). Excluding participants aged 2–4 years old from the regression analysis did not significantly alter the results.

Next, multivariate regression analyses were performed for the three categories: dysphagia-related, behavioral, and gastrointestinal symptoms separately (Table 3). Fig. 1 provides an overview of prevalence per symptom type with the associated core features. The use of a wheelchair or walker at 500 m distance was significantly associated with an increase in all symptom categories compared to walking 500 m without aid. The use of three or more ASM was associated with an increase in the number of dysphagia-related and behavioral symptoms, but not with gastrointestinal problems. Behavioral difficulties in the clinical range were only

Table 2
Gastrointestinal and eating problems.

Symptom	All patients	Dravet	Non-Dravet
mean BMI (range)	21.2 (12.4–42.9)	20.1 (12.4–37.5)	23.8 (12.8–42.9)
Presence of symptoms n (%)			
Impaired chewing	44 (26.3)	43 (37.1)	1 (2.0)
- Weekly or more frequent	28 (16.8)	27 (23.3)	1 (2.0)
Impaired swallowing	39 (23.5)	39 (33.9)	0
- Weekly or more frequent	20 (12.0)	20 (17.4)	0
Choking	50 (29.9(	45 (38.8)	5 (9.8)
- Weekly or more frequent	20 (12.0)	20 (17.2)	0
Drooling	73 (43.5)	71 (60.7)	2 (3.9)
- Weekly or more frequent	47 (28.0)	47 (40.2)	0
Vomiting	20 (12.0)	19 (16.5)	1 (2.0)
- Weekly or more frequent	5 (3.0)	5 (4.2)	0
Loss of appetite	68 (41.5)	57 (50.4)	11 (21.6)
- Weekly or more frequent	31 (18.9)	26 (23.0)	5 (9.8)
Constipation	67 (40.6)	58 (50.4)	9 (18.0)
- Weekly or more frequent	33 (20.0)	31 (27.0)	2 (4.0)
Distracted during mealtime	80 (48.8)	70 (61.4)	10 (20.0)
- Weekly or more frequent	65 (39.6)	58 (50.9)	7 (14.0)
Temper tantrums during mealtime	28 (16.6)	27 (23.5)	1 (5.0)
- Weekly or more frequent	10 (7.4)	10 (8.7)	0
Picky eater*	61 (36.1)	53 (44.9)	8 (15.7)
Total no. symptoms			
- 0–1 symptoms	31 (18.3)	15 (12.7)	38 (74.5)
- 2–3 symptoms	62 (36.7)	43 (36.4)	11 (21.6)
- 4–6 symptoms	50 (29.6)	36 (30.5)	2 (3.9)
- ≥7 symptoms	26 (15.4)	24 (20.3)	0
Start of problems during ketogenic diet n (%)	3 (11.1)	3 (11.5)	0
Current gastrointestinal or eating problems n (%) **	61 (36.1)	58 (49.2)	3 (5.9)
Impact of eating problems on daily life? n (%)***	31 (50.8)	30 (51.7)	1 (33.3)

BMI = Body mass index.
* Frequency of picky eating was not asked.
** Participants were asked a yes or no question about whether there were currently eating problems. This question was asked regardless of how many symptoms they had.
***Percentage of participants who indicated that there were eating problems in the previous yes or no question.

associated with an increase in the number of behavioral symptoms. Both a monthly and a yearly seizure frequency, compared to daily, was associated with a decrease in gastrointestinal symptoms. Only a yearly seizure frequency was associated with a decrease in dysphagia-related symptoms. Behavioral symptoms were not associated with seizure frequency.

4. Discussion

This explorative cohort study provided the prevalence and characteristics of gastrointestinal and eating problems in *SCN1A*-related seizure disorders. Four or more gastrointestinal and eating problems were reported in 50.5% of DS and 3.9% of non-DS participants. Caregivers of participants with DS reported gastrointestinal and eating problems as highly impactful on daily life. Participants with decreased functional mobility, who used more than 3 ASM, and with severe behavioral problems experience significantly more total gastrointestinal and eating problems. When dividing symptoms into dysphagia-related, behavioral, and gastrointestinal symptoms, the associations differ to some extent. Most notably, behavioral problems in the clinical range are only associated with an increase in behavioral symptoms and not with other symptom categories. Moreover, a decrease in seizure frequency, monthly or yearly seizure frequency compared to daily, is associated with a decrease in gastrointestinal symptoms, but not with behavioral symptoms. Our findings can help physicians, treating DS patients, to identify those at risk of gastrointestinal and eating problems and subsequently adequately monitor patients to enable a timely referral to a dietitian, behavioral expert, or speech therapist.

Prior studies have described gastrointestinal and eating problems in children and adults with intellectual disability with and without epilepsy. In cohorts of developmental and epileptic encephalopathies, gastrointestinal problems were reported in 35 to 92% and eating problems in 33 to 81% of participants [8,18,20], with 11 to 50% requiring a feeding tube [8,18,19]. Stiripentol use was found to be associated with an increase in gastrointestinal symptoms in DS [8]. Our findings confirm these previously published high occurrences of problems in similar developmental and epileptic encephalopathies. The findings may be generalizable to children and adults with intellectual and motor disability without epilepsy, as well. In cohorts of children with intellectual disability, including children with Down syndrome, cerebral palsy, and other etiologies, the frequency ranges between 11% and 99% depending on the etiologies included [7,21]. Children and adults with intellectual or motor disability seem more likely to develop

Table 3
Multivariate analyses: association between the number of gastrointestinal and eating problems (either dysphagia-related, behavioral, or gastrointestinal) and core features in DS patients.

Symptom	Total OR (95% CI)	Dysphagia-related OR (95%CI)	Behavioral OR (95%CI)	Gastrointestinal OR (95%CI)
Age	1.0 (0.9–1.1)	1.0 (1.0–1.1)	1.0 (0.9–1.0)	1.0 (0.9–1.0)
FMS 500 m–use of a wheelchair or another supportive device*	**4.9 (1.9–12.8)**	**3.2 (1.3–8.2)**	**3.9 (1.6–9.7)**	**3.4 (1.3–9.1)**
Total seizure frequency**				
- no seizures	4.1 (0.5–32.8)	3.5 (0.5–25.5)	2.0 (0.3–13.8)	2.3 (0.3–18.5)
- yearly seizures	**0.1 (0.0–0.7)**	**0.1 (0.0–0.7)**	1.6 (0.4–6.4)	**0.2 (0.0–0.9)**
- monthly seizures	0.4 (0.1–1.3)	0.6 (0.2–1.9)	1.7 (0.5–5.9)	**0.3 (0.1–1.0)**
- weekly seizures	1.1 (0.4–2.9)	0.9 (0.3–2.5)	2.5 (0.9–6.9)	0.7 (0.3–2.0)
Use of ASM–3 or more***	**5.9 (1.9–18.2)**	**3.5 (1.2–10.1)**	**3.5 (1.2–10.4)**	1.8 (0.6–5.7)
Level of disability±				
- No to borderline ID	1.5 (0.2–12.8)	1.5 (0.2–12.7)	1.4 (0.2–10.9)	2.7 (0.3–23.6)
- Mild ID	0.8 (0.2–2.3)	0.7 (0.2–2.4)	1.9 (0.6–6.7)	1.3 (0.4–5.0)
- Moderate ID	0.7 (0.2–1.9)	0.5 (0.2–1.8)	1.0 (0.3–3.0)	1.7 (0.5–6.1)
Behavioral problems±±				
- Borderline range	0.7 (0.2–1.9)	0.8 (0.3–2.2)	0.9 (0.3–2.4)	0.7 (0.3–2.2)
- Clinical range	**3.0 (1.1–8.1)**	1.5 (0.6–4.1)	**3.5 (1.3–9.3)**	2.1 (0.8–5.6)

FMS = Functional Mobility Scale, ASM = anti-seizure medication, ID = intellectual disability.
*Independent on 500 m was set as reference.
**Daily seizures was set as reference.
***Use of < 3 ASM was set as reference.
±Severe ID was set as reference.
±± normal range CBCL/ABCL/ASR (Adult Behavior Checklist / Child Behavior Checklist / Adult Self-Report) was set as reference.

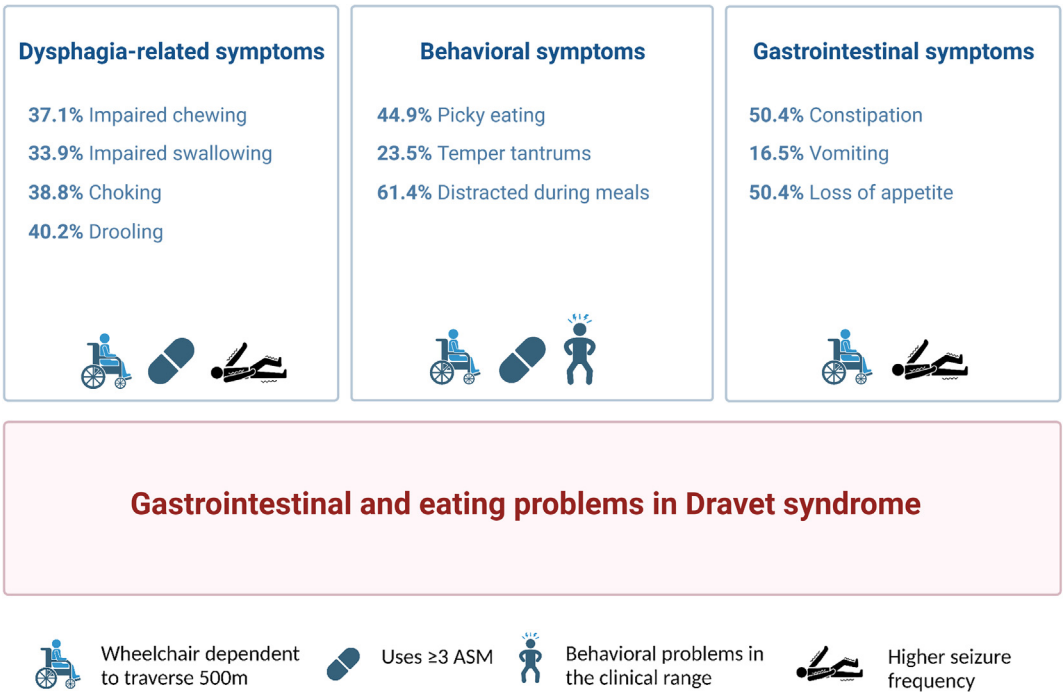

Fig. 1. Overview of gastrointestinal and eating problems per symptom category in DS, with associated comorbidities. Prevalence is displayed per symptom. The icons represent the associated core features of DS per symptom type.

gastrointestinal and eating problems than the general population, regardless of underlying etiology.

The etiology of gastrointestinal and eating problems is multifactorial. In the current study, mobility, behavioral problems, and ASM use were independently associated with more problems. Because of the expected causal differences, we performed additional separate analyses for dysphagia-related, behavioral, and gastrointestinal symptoms separately. A decrease in mobility was associated with an increase in all three symptom categories. The association between a decrease in mobility and dysphagia-related symptoms may be explained by the possible higher prevalence of dysphagia, caused by orofacial dyspraxia, in patients with an overall decreased functional mobility. With regard to gastrointestinal symptoms, decreased mobility is a risk factor for constipation for all ages in the general population [22–24]. Patients with physical disability are therefore more likely to develop constipation [24]. Constipation may result in a decrease in appetite. A decrease in mobility may therefore increase gastrointestinal and eating problems via different mechanisms.

Participants with behavioral problems in the clinical range on the ABCL/CBCL had more gastrointestinal and eating problems than participants without. In line with our expectation, behavioral difficulties in the clinical range on the ABCL/CBCL were associated with an increase in the number of behavioral symptoms. These results concur with previous studies on atypical eating behavior in children with for instance autism spectrum disorder (ASD), where mainly behavioral symptoms are evident. Up to 88% of children with ASD are marked by their caregivers as picky eaters [25,26]. The association between behavioral symptoms and behavioral difficulties in the clinical range may in part be due to the high prevalence of autistic traits in DS [3]. Other studies have suggested a relationship between ASD and gastrointestinal symptoms as well [26,27], however, we did not find an association between behavioral problems measured by the ABCL/CBCL and gastrointestinal symptoms.

Participants who used three or more ASM had more gastrointestinal and eating problems. In the additional analyses, only an increase in dysphagia-related and behavioral symptoms was associated with ASM use. Surprisingly, gastrointestinal symptoms were not associated with ASM use. ASM can have many different side effects, including vomiting, nausea, dysphagia, constipation, and an effect on appetite [10,28]. Polytherapy increases this risk [29]. Topiramate is notorious for leading to poor appetite, which not rarely results in cessation of the drug [30]. Perhaps additional analyses on the relationship between the use of specific ASM, such as topiramate, with gastrointestinal symptoms, would detect an association. However, due to extensive polytherapy and small sample sizes, these analyses could not be carried out reliably. In accordance with findings from the present study, ASM are considered to be associated with behavioral side effects [31,32]. Especially GABA potentiating drugs, such as benzodiazepines, can aggravate behavioral problems [32], which are also the class of ASM that is most effective in seizure reduction, and therefore most prescribed in *SCN1A*-related seizure disorders.

A lower seizure frequency was associated with a decrease in total gastrointestinal and eating problems and in the separate analyses with less dysphagia-related and gastrointestinal symptoms, but only when the seizure frequency was considerably lower, i.e. monthly or yearly versus daily seizures. Several factors may explain this finding. A daily seizure frequency means that peri- and postictal phases occur on a daily basis, in which there is loss of consciousness, decreased awareness or drowsiness, which may aggravate symptoms such as dysphagia. or loss of appetite. Moreover, a higher seizure frequency might lead to more acute drug administration, i.e., benzodiazepines, which have a direct effect on gastrointestinal and eating problems [28]. A previous study on gastrointestinal symptoms in DEE did not find an association with seizure frequency [8]. However, different gastrointestinal symptoms, i.e. constipation, gut dysmotility, and/or diarrhea, were evaluated in that study, which are likely to be less dependent on seizure frequency.

In the general population, the prevalence of gastrointestinal and eating symptoms, such as dyspepsia and symptoms of irritable bowel syndrome (IBS), is difficult to ascertain. For IBS the world-

wide pooled prevalence is estimated at 8.8% of the population [33], for dyspepsia this was estimated at 21% [34], but with varying diagnostic criteria. In our study sample, 51.0% of non-DS participants reported any symptom, regardless of frequency, and 23.5% had any symptoms on a weekly basis. Taken together, non-DS patients will probably have a slightly higher frequency of gastrointestinal and eating problems than the general population. The use of anti-seizure medication might play a role in this subtle difference. The association between gastrointestinal and eating problems and the use of ASM in non-DS participants could not be explored due to small sample sizes.

In this cohort, most DS participants were treated by a speech therapist for impaired speech or language, not for dysphagia. However, 71% of DS participants reported problems with chewing or swallowing, around 40% even on a weekly basis. Problems with chewing or swallowing seem to be overlooked as an indication for treatment. Dysarthria due to facial or oral motor impairment and severe language problems are common in DS [35] and therefore speech therapy is often included in the multidisciplinary care of patients. Broadening this standard therapy to incorporate eating problems can result in earlier and better management of these problems.

The three different symptom categories that were highlighted in this study need to be addressed differently. Dysphagia-related symptoms are related to orofacial dysfunction. Patients with these symptoms could therefore likely benefit from referral to a speech therapist. Behavioral symptoms find their origin in behavior difficulties, possibly in part aggravated by ASM use. Counseling by a behavioral expert or if necessary referral to a psychiatrist may improve symptoms, provide coping tools for caregivers and ameliorate the burden of care. In the management of gastrointestinal symptoms, treatment of a dietitian may be beneficial, to assess whether alterations in the diet can help a patient's food tolerance. For both dysphagia-related and behavioral symptoms, a strict evaluation of the need for every ASM used may have a positive effect on symptom prevalence. Therefore, screening for the different symptom categories will help the treating physician to devise a more tailored treatment response.

Several limitations to this study need to be acknowledged. First, the questionnaires for the participants with DS were completed by the caregivers of the participants. Therefore, measures are influenced by the perception of the parent. For instance, some behaviors may be regarded as 'normal' by some parents, but 'abnormal' by others. Similarly, nonepileptic moments of staring can be interpreted as both an absence seizure as well as a focal non-motor seizure with impaired awareness, thereby falsely increasing the reported seizure frequency. However, regression analyses with the frequency of motor seizures only yielded similar results. Secondly, seizure frequency captures only one aspect of the severity and burden of an epilepsy syndrome. Many measures for epilepsy severity incorporate factors such as the use of ASM or the duration of seizures. We chose to consider ASM use as a separate variable due to the presumed direct effect of ASM use on gastrointestinal and eating problems. In addition, we expected that duration of seizures could not be measured reliably through digital questionnaires and medical records, since this is often not recorded by caregivers and treating physicians. Seizure frequency was therefore the most accurate and reliable measure for our study design. Furthermore, we reported that a minority of participants under the care of a speech therapist were treated for dysphagia. These percentages were based on medical records and on questionnaires filled in by caregivers. However, we do not know the treatment indication from the perspective of the speech therapist. Possibly, chewing and swallowing are assessed or even treated by the speech therapist simultaneously, without the caregivers' awareness, leading to an underestimation. Lastly, children under two years of age were excluded from this cohort. However, treating physicians of patients in this age group should remain vigilant, as gastrointestinal and eating problems might be frequent and impactful in these patients as well. The Functional Mobility Scale is not validated under 4 years old. We included this age group due to the expected high prevalence of gastrointestinal and eating problems. To determine the possible influence of this age group on the regression analysis, we performed a separate regression analysis without this age group, which generated a similar outcome.

In conclusion, gastrointestinal and eating problems are common in patients with DS and can pose a heavy burden on patients and caregivers. Establishing which core disease features are associated with gastrointestinal and eating problems helps to treat physicians in the identification of patients at risk. Subsequently, distinguishing which type of symptoms are related to which core features can lead to a treatment plan tailored to the needs of the patient. Frequent assessment of symptoms by treating physicians can promote early detection of gastrointestinal and eating problems and enable a timely referral to a speech therapist, behavioral expert, or dietitian, if necessary, with the ultimate aim to decrease the impact on quality of life.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2023.109361.

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