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Understanding neurodevelopmental trajectories and behavioral profiles in *SCN1A*-related epilepsy syndromes

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ABSTRACT

Background: A pathogenic variant in *SCN1A* can result in a spectrum of phenotypes, including Dravet syndrome (DS) and genetic epilepsy with febrile seizures plus (GEFS +) syndrome. Dravet syndrome (DS) is associated with refractory seizures, developmental delay, intellectual disability (ID), motor impairment, and challenging behavior(1,2). GEFS + is a less severe phenotype in which cognition is often normal and seizures are less severe. Challenging behavior largely affects quality of life of patients and their families. This study describes the profile and course of the behavioral phenotype in patients with *SCN1A*-related epilepsy syndromes, explores correlations between behavioral difficulties and potential risk factors.

Methods: Data were collected from questionnaires, medical records, and semi-structured interviews. Behavior difficulties were measured using the Adult/Child Behavior Checklist (C/ABCL) and Adult self-report (ASR). Other questionnaires included the Pediatric Quality of Life Inventory (PedsQL), the Functional Mobility Scale (FMS) and the Sleep Behavior Questionnaire by Simonds & Parraga (SQ-SP). To determine differences in behavioral difficulties longitudinally, paired T-tests were used. Pearson correlation and Spearman rank test were used in correlation analyses and multivariable regression analyses were employed to identify potential risk factors.

Results: A cohort of 147 participants, including 107 participants with DS and 40 with genetic epilepsy with febrile seizures plus (GEFS +), was evaluated. Forty-six DS participants (43.0 %) and three GEFS + participants (7.5 %) showed behavioral problems in the clinical range on the A/CBCL total problems scale. The behavioral profile in DS exists out of withdrawn behavior, aggressive behavior, and attention problems. In DS patients, sleep disturbances ($\beta = 1.15$, $p < 0.001$) and a lower age ($\beta = -0.21$, $p = 0.001$) were significantly associated with behavioral difficulties. Between 2015 and 2022, behavioral difficulties significantly decreased with age ($t = -2.24$, CI = -6.10 – −0.15, $p = 0.04$) in DS participants aging from adolescence into adulthood. A decrease in intellectual functioning ($\beta = 3.37$, $p = 0.02$) and using less antiseizure medications in 2022 than in 2015, ($\beta = -1.96$, $p = 0.04$), were identified as possible risk factors for developing (more) behavioral difficulties.

Conclusions: These findings suggest that, in addition to epilepsy, behavioral difficulties are a core feature of the DS phenotype. Behavioral problems require personalized management and treatment strategies. Further research is needed to identify effective interventions.

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1. Introduction

A pathogenic variant in *SCN1A* can result in a spectrum of phenotypes, including, Dravet syndrome (DS) and genetic epilepsy with febrile seizures plus (GEFS+) spectrum phenotype (including febrile seizures) [2–3]. Dravet syndrome (DS) is associated with refractory seizures, developmental delay, intellectual disability (ID), motor impairment, and challenging behavior [1–2]. In most DS patients a pathogenic variant in the *SCN1A* gene causes the disease. GEFS + is a less severe phenotype, in which cognition is often normal and seizures are less severe [2,4].

Epilepsy enormously impacts patients with DS and is often the primary focus of treatment [5–7]. However, comorbidities like behavioral difficulties, sleep disturbances and eating difficulties are common in [2,8–12] and have a major impact on quality of life of patients and their families [10–11,13–14,5–7]. The reported prevalence of behavioral difficulties in DS ranges between 37 % and 100 % [2,10–11,15]. Previously described behavioral difficulties include anger management issues, hyperactivity, inattention, conduct problems, problems with peer relationships, withdrawn behavior and dangerous behavior [7,10–11]. In a previous study, we found that 56.5 % of individuals with DS and 25.8 % with GEFS + had behavioral problems in the clinical or borderline range [2,11].

Little is known about risk factors for these behavioral problems and why some patients show behavioral difficulties while others do not. Several risk factors have been suggested in the DS population, including ID, seizure severity, and antiseizure medication (ASM) [2,7,11]. Additionally, parents have suggested that other comorbidities in DS, such as eating difficulties and sleep disturbances, may also be correlated with behavioral difficulties [7]. Previous studies did not comprehensively explore these potential risk factors. Moreover, information on the pattern of behavioral symptoms over the course of DS, is also scarce. Some cross-sectional studies that reported on the relationship between behavioral aspects and age, found contradicting results [1–2,16–17]. Two longitudinal studies among patients with DS on predictors of health-related quality of life (HRQoL) [14] and predictors of developmental outcome and disease burden [12], provided contradicting insights on behavioral difficulties. Makiello et al. [14] found a small, non-significant, decline in behavioral difficulties over 10 years based on a standardized questionnaire. Feng et al. [12] suggested a significant increase in behavioral problems and autistic features over 10 years based on one yes/no question regarding the presence of behavioral difficulties. Detailed information on the course of behavioral difficulties and the association with the course of seizures and other comorbidities is lacking. Gaining a better understanding of developmental and behavioral patterns, as well as identifying risk factors associated with behavioral difficulties, throughout the life course of patients with DS, could provide valuable insights for guiding their treatment and care management. Therefore, this study aims to 1) describe the profiles and course of behavioral difficulties in patients with *SCN1A*-related epilepsy syndromes, and 2) explore correlations between behavioral difficulties and potential risk factors, including comorbidities, seizure frequency, ASM, and age, and between behavior and HRQoL.

2. Materials & Methods

2.1. Study design

The current study is a follow-up study of our cohort of 164 patients with *SCN1A*-related seizure disorders that we studied in 2015 [2,11] and we have included additional patients. As a result, this study has a longitudinal and cross-sectional design: some patients participated at two timepoints (2015 and 2021/2022) and others only participated at the second timepoint (which will be referred to as 2022 henceforth). The same measurements were carried out at both time points, except for questions regarding eating difficulties and sleep disturbances, which were added at the second timepoint. This study is part of a larger project describing the course of *SCN1A*-related seizure disorders and HRQoL [18] and 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.

2.2. Participants

Between October 2021 and December 2022, we included participants with an *SCN1A*-related seizure disorders. We included only participants with heterozygous pathogenic or likely pathogenic variants in the *SCN1A* gene (classes IV and V, according to the American College of Medical Genetics and Genomics criteria) [19]. Eligible patients were invited to participate by the researchers (if they had given prior consent to be recontacted), their physician, or responded to an invitation to participate in the newsletter of the parent/patient organization 'Dravet syndrome Foundation Netherlands/ Flanders' [20]. Many participants were minors or incapacitated and could therefore not provide consent, so their parents or legal caretakers were informed about the study. Informed consent was obtained from participants or their legal representatives, according to the Declaration of Helsinki. Participants were categorized into two clinical subgroups: GEFS + or DS. The treating physician made the syndrome diagnosis which was verified by the researchers (AP, CM, FJ, EB), based on the most recent guidelines [21–22].

2.3. Measures

We collected data from patient medical records, administered questionnaires to participants or their caregivers, and conducted semi-structured telephone interviews with participants or their caregiver. The interviews were conducted after completion of the questionnaires. Measures were selected on basis of information collected in focus groups where parents of individuals with DS shared lived experiences of caring for a child with DS and research preferences on behavioral difficulties [7].

2.4. Behavioral difficulties

During the interview, parents/caretakers were asked about their child's behavioral difficulties and treatment (e.g., medication or therapy) or guidance to address these difficulties. Information on psychiatric diagnoses and the use of behavior modifying medication was collected from questionnaires, medical records, and interviews. Behavioral challenges were evaluated with the Dutch parent report version of the Child Behavior Checklist (CBCL) 1.5–5 years and 6–18 years, the Dutch version of the Adult Behavior Checklist 18–59 years (ABCL) and the Dutch version of the Adult Self-Report (ASR) [23–27], consisting of respectively of 100, 113, 123 and 123 quantitative questions. The reliability and validity of these questionnaires and norm scores have been established in past research [26–28]. The child's behavior was rated during the past 6 months using 3-point scales, where 0 = not true, 1 = somewhat or sometimes true, and 2 = very true or often true. The 'total problems', 'total internalizing problems' and 'total externalizing problems scale' were generated from several subscales. T-scores were calculated according to CBCL, ABCL and ASR manuals and defined as normal, borderline, or clinically abnormal. Only the subscales which were for all three age groups (i.e., anxiety/depression, somatic problems, withdrawn behavior, attention problems, and aggressive behavior) were selected for further analysis.

2.5. Seizure severity

Information on seizure severity was retrieved from medical records and questionnaires. Seizure severity was reported as the frequency of minor seizures, defined as absences, focal motor seizures, or myoclonus, and major seizures defined as generalized tonic-clonic, hemiclonic,

tonic, atonic and focal seizures with impaired awareness. The frequency was defined as daily, weekly, monthly, or yearly seizures or seizure freedom for over 1 year.

2.6. Intellectual functioning

Intellectual functioning was classified based on intelligence quotient (IQ) and developmental level (DQ) and rated on a five-point scale: 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), and severe ID (IQ or DQ < 30). Information on intellectual functioning, based on neuropsychological assessments, was retrieved from medical records and questionnaires. When no recent IQ or DQ was available (n = 39), ID was categorized based on employment status, type of received education or daycare, communication skills and global functioning in a consensus meeting by a child neurologist (FJ), neuropsychologist and clinical geneticist (EB).

2.7. HRQoL

The Dutch version of the PedsQL Measurement Model, was used to measure HRQoL on a 0–100 scale [29]. The generic measure consisted of 23 items making up 4 subscales and a Total HRQoL. Items were answered on a five-point Likert scale (0='never a problem' to 4='almost always a problem'). Scores are reversed and computed from 0 to 100, with higher scores indicating higher HRQoL.

2.8. Eating difficulties

A questionnaire, designed by the researchers, a child nutritionist, and a child speech therapist, was developed to explore gastro-intestinal symptoms (see supplement A). Parents/caretakers answered questions on current eating difficulties, feeding habits and the frequency of gastro-intestinal symptoms.

2.9. Sleep disturbances

To evaluate sleep disturbances, parts two and four of the Dutch translation of the Sleep Behavior Questionnaire by Simonds & Parraga (SQ-SP), modified version for use in individuals with ID were used [30–31]. Information on sleep disturbances was only provided for pediatric GEFS + and DS participants. The questionnaire addresses the child's current sleep behavior and sleep habits, including frequency of these habits, and any treatment and management strategies and was scored on a 7-point Likert scale. We calculated the Composite Sleep Index (CSI) which reflects the severity of sleep problems, and ranges between 0 and 12, with scores of 4 or up indicating severe sleep problems.

2.10. FMS

To explore functional mobility, the Dutch version of the Functional Mobility Scale (FMS) was used [32]. Participants and caregivers were asked to rate walking distance on a scale 1 through 6, where 1 means using a wheelchair, stroller or buggy; 6 means independent on all surfaces on three distances (5 m,50metersand500meters). We reported the outcome for 500 m.

2.11. Statistical analysis

Data on group characteristics including type of mutation, seizure severity, ASM use, ID, eating difficulties, sleep disturbances, living situation, quality of life, psychiatric diagnoses and psychotropic and homeopathic medication use were reported as descriptive statistics for GEFS + participants and DS participants separately. Due to lack of literature suggesting an explanatory relationship between behavioral difficulties and other disease characteristics in the GEFS + group, we decided against conducting multivariable regression analyses. Correlations were calculated between behavioral difficulties and age, gender, minor and major seizure frequency, ASM use, the use of contra-indicated medication (CIM), eating difficulties, sleep disturbances and HRQoL in the GEFS + group and between behavioral difficulties and HRQoL in the DS group. In case of continuous data, these correlations were analyzed with a Pearson correlation or Spearman rank test and, in categorical data, calculated with a Chi-square test or a Fisher's exact test. Based on prior studies that have examined correlations between behavior and epilepsy or other patient characteristics within the DS population [2,7,10–11], we formulated the hypothesis that behavior would be a dependent factor. Therefore, we decided to employ regression analyses instead of correlations in the DS cohort. We used univariable and multivariable regression analyses to determine potential risk and protective factors for behavioral difficulties in DS cross-sectionally and longitudinally. In the cross-sectional analyses, these factors included gender, age, level of ID, frequency of major and minor seizures, ASM use, previous use CIM, SQ-SP CSI, FMS 500 m (dichotomized in wheelchair use or not), eating difficulties and living situation. For the longitudinal analyses, these variables include gender, age at the first timepoint of data collection (2015), differences between 2022 and 2015 in ID scores, in frequencies of minor and major seizures, in ASM use and FMS 500 m scores. To handle missing values, we used multiple imputations ('mice' R package) with Rubin's rule [33]. We created and analyzed 20 imputed datasets and pooled the estimates in our univariable and multivariable regression analyses. The determinants in our final multivariable regression analyses were created using a stepwise model selection. To determine the differences in behavioral difficulties over time, paired T-tests were used. All tests were performed two-tailed with an alpha level of significance of p-value of < 0.05. Statistical analyses were performed with R version 3.2.2.

3. Results

We studied a cohort of 147 participants with an *SCN1A*-related seizure disorder of whom 47 DS participants and 22 GEFS + participants had also been included in our study in 2015. Table 1 shows the characteristics of our study population, which included 107 participants with DS and 40 with GEFS +. The DS cohort's median age at data collection was 16 years (range 2–53 years). Thirty-two individuals (30.8 %) resided in institutional care. Daily major seizures occurred in 11 DS participants (10.4 %) and ID was present in most of them and was severe in 40 participants (37.7 %). The average HRQoL score was 59.7 in the DS participants. The median age in GEFS + participants was 22 years (range 8–73). None of the GEFS + participants had daily major seizures and their average HRQoL score was 86.1, slightly higher than in the general population (mean HRQoL = 83.0, SD = 14.79) [29].

3.1. Descriptive overview of behavioral difficulties

Of the 147 participants, behavioral difficulties were explored during the telephone interview in 139. In 85 (82.5 %) of the DS participants and 8 (22.2 %) of the GEFS + participants, challenging behavior was reported (Table 1) and of those 56 (65.9 %) DS participants and 5 (62.5 %) GEFS + participants received any kind of treatment or parental support to address these difficulties. Psychotropic medication was used by 17.0 % of the DS participants and 10.0 % of the GEFS + participants (see supplement B for more detailed information). The use of complementary medicine, e.g., homeopathic medication, to address behavioral challenges was reported by 26 DS participants (24.5 %) and 4 (10.0 %) GEFS + participants.

3.2. A/CBCL outcomes

Table 2 shows the total- and subscale scores on the CBCL, ABCL and

Table 1
Characteristics of the 2022 cohort.

	GEFS + 2022 cohort	DS 2022 cohort
N	40	107
Gender female, n(%)	26 (65.0)	52 (48.6)
Age, in years median(range)	22 (8–73)	16 (2–53)
Age groups in years, n(%)		
2–10	7 (17.5)	37 (34.6)
11–17	10 (25.0)	24 (22.4)
18+	23 (57.5)	46 (43.0)
Living in institutional care n = 121, n(%)	0 (0.0)	32 (30.8)
Major seizure frequency n = 146, n(%)		
Seizure free	25 (62.5)	8 (7.5)
Yearly seizures	14 (35.0)	23 (21.7)
Monthly seizures	1(2.5)	27 (25.5)
Weekly seizures	0 (0.0)	37 (34.9)
Daily seizures	0 (0.0)	11 (10.4)
Minor seizure frequency n = 146, n(%)		
Seizure free	35 (87.5)	37 (34.9)
Yearly seizures	3 (7.5)	8 (7.5)
Monthly seizures	1 (2.5)	11 (10.4)
Weekly seizures	1 (2.5)	16 (15.1)
Daily seizures	0 (0.0)	34 (32.1)
Level of ID[a] n = 146, n(%)		
No ID	40 (100.0)	3 (2.8)
Borderline ID	0 (0.0)	4 (3.8)
Mild ID	0 (0.0)	35 (33.0)
Moderate ID	0 (0.0)	24 (22.6)
Severe ID	0 (0.0)	40 (37.7)
ASM n = 145, n(%)		
No use of ASM	19 (48.7)	1 (0.9)
Use of one ASM	13 (33.3)	8 (7.5)
Use of two ASM	5 (12.8)	15 (14.2)
Use of three or more ASM	2 (5.1)	82 (77.4)
Ever used CIM n = 145, n(%)	15 (38.5)	66 (62.3)
HRQoL[b] n = 134, mean(SD)	86.1 (10.1)	59.7 (15.4)
FMS score (500 m) n = 137, n(%)		
Uses a wheelchair	0 (0.0)	42 (42.4)
Uses a rollator	1 (2.6)	1 (1.0)
Independent walking on flat surfaces	0 (0.0)	29 (29.3)
Independent walking on all surfaces	37 (97.4)	27 (27.3)
Eating difficulties		
Currently eating/drinking concerns n = 145, n (%)	2 (5.0)	53 (50.5)
Picky eating [c] n = 55	0 (0.0)	37 (69.8)
Distracted during mealtime [c], n = 55	0 (0.0)	43 (82.7)
Anger issues during mealtime [c], n = 53	0 (0.0)	19 (35.8)
Tube feeding n = 146n(%)		
Partly	0 (0.0)	9 (17.0)
Completely	0 (0.0)	10 (18.9)
Sleep difficulties SP-SQ		
Reported sleep difficulties[d] n = 120, n(%)	2 (11.8)	24 (23.3)
SQ-SP CSI [e], n = 121, median (range)	0.0 (0–4)	1.0 (0–12)
Severe sleep disorder[e] (csi ≥ 4) n = 121, n(%)	1 (5.9)	18 (17.3)
Interview outcomes		
Behavior difficulties n = 139, n(%)	8 (22.2)	85 (82.5)
Treatment[F,g] N = 93, n(%)		
No treatment	3 (37.5)	29 (34.1)
Therapeutic intervention[h]	3 (37.5)	38 (44.7)
Psychotropic medication	1 (12.5)	11 (12.9)
Therapeutic and psychotropic medication	1 (12.5)	6 (7.1)
Unknown	0 (0.0)	1 (1.2)
Psychiatric diagnoses[i] n = 146, n(%)		
ASD	2 (5.0)	47 (44.3)
ADHD	5 (12.5)	19 (17.9)
Use of complementary medication to improve behavior n = 146n(%)	4 (10.0)	26 (24.5)

ID = intellectual disability; ASM = antiseizure medication; CIM = contra-indicated medication; HRQoL = Health-related quality of life; FMS = functional mobility scale; SQ-SP CSI = Sleep Behavior Questionnaire by Simonds & Parraga composite sleep index; ASD = autism spectrum disorder; ADHD = attention deficit hyperactivity disorder.

[a] 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 ID = IQ or DQ < 30.

[b] HRQoL: health-related quality of life, based on PedsQL Measurement Model questionnaire results. Scaled 0–100; a higher score indicates a higher health-related quality of life.

[c] These results are only exhibited for the participant who answered positively on the previous question: 'Are there eating/drinking concerns?'.

[d] Caregivers answered 'yes' on the question 'Do you think your child currently has a sleep problem'?

[e] The CSI ranges between 0 and 12 and reflects the severity of sleep problems, with scores of 4 or up indicating severe sleep problems.

[f] The information is exclusively shown for participants who answered positively regarding the presence of challenging behavior.

[g] Treatment refers to parental guidance, therapeutic or medication treatment for behavior difficulties.

[h] Therapeutic interventions are for example play therapy or social skills interventions.

[i] Psychiatric diagnoses were reported by parents/participants and/or in medical records.

Table 2
C/ABCL and ASR outcomes of the 2022 cohort (n = 147). Distribution of behavior problem subscales and total scales (in percentages) for the DS (n = 107) and GEFS+ (n = 40) groups.

	Normal range n (%)		Borderline n(%)		Clinical range n (%)	
	DS	GEFS+	DS	GEFS+	DS	GEFS+
Syndrome scales						
Anxiety/ depression	99 (92.5)	37 (92.5)	6 (5.6)	3 (7.5)	2 (1.9)	0 (0.0)
Somatic problems	78 (72.9)	36 (90.0)	17 (15.9)	3 (7.5)	12 (11.2)	1 (2.5)
Withdrawn behavior	72 (67.3)	36 (90.0)	2 (19.6)	3 (7.5)	14 (13.1)	1 (2.5)
Attention problems	48 (44.9)	34 (85.0)	19 (17.8)	4 (10.0)	40 (37.4)	2 (5.0)
Aggressive behavior	73 (68.2)	36 (90.0)	18 (16.8)	4 (10.0)	16 (15.0)	0 (0.0)
Total scales						
Internalizing problems	67 (62.6)	33 (82.5)	17 (15.9)	4 (10.0)	23 (21.5)	3 (7.5)
Externalizing problems	56 (52.3)	32 (80.0)	20 (18.7)	4 (10.0)	31 (29.0)	4 (10.0)
Total problems	38 (35.5)	30 (75.0)	23 (21.5)	7 (17.5)	46 (43.0)	3 (7.5)

For all syndrome subscales: borderline range T 65–69, clinical range T ≥ 70. For all: internal problems, external problems, and total problem scales: borderline range T 60–63, clinical range T ≥ 64.

ASR questionnaires. On the total problems scale 23 DS participants (21.5 %) scored in the borderline range and 46 (43.0 %) in the clinical range. Seven GEFS + participants (17.5 %) scored in the borderline range and 3 (7.5 %) in de clinical range. On the syndrome scales, 40 (37.4 %) of DS patients had a score in the clinical range on the attention problems scale, 16 (15.0 %) on the aggressive behavior scale and 14 (13.1 %) on the withdrawn behavior scale. A small number of participants with GEFS had a score in the clinical range on the syndrome scales, one participant (2.5 %) on the somatic problems scale, one participant (2.5 %) on the withdrawn behavior scale, and two participants (5.0 %) on the attention problems scales.

3.3. Correlations between behavioral difficulties and clinical characteristics

There were no significant correlations between the total CBCL or ASR score and age, gender, minor or major seizure frequencies, ASM use, usage of CIM, eating difficulties or sleep disturbances in GEFS + participants. However, a statistically significant correlation existed between behavioral difficulties and HRQoL for both the GEFS + and the DS group. Among GEFS + participants, who scored in the normal range on

the CBCL or ASR, mean HRQoL was 88.7, whereas for those with a score in the borderline/clinical range, the mean HRQoL was 78.7 (rho = -0.51, CI = -0.71 – −0.23, p = <0.001). For the DS participants these mean HRQoL scores were 70.6, and 53.3, respectively (r = -0.59, CI = -0.70 – −0.44, p < 0.001). The results of the univariable and multivariable regression analyses in the DS cohort, with the score on the total problems A/CBCL scale as dependent variable, are depicted in Table 3. A higher SQ-SP CSI score and a lower age were significantly associated with a higher total problems score on the A/CBCL, which indicates that more severe sleep difficulties and a lower age were associated with more behavioral difficulties. The end model explained 18.6 % of the variation (adjusted $R^2 = 0.1863$).

3.4. Behavioral problems in DS patients at two time points

Because the CBCL and ASR scores in the GEFS + cohort do not deviate from other epilepsy cohorts or the general population, behavioral challenges within the GEFS + cohort will not be discussed further [23,25,34–38].

Table 4 shows the characteristics of DS patients in 2015 and 2022, for the patients who participated at both time points. The minor and major seizure frequencies somewhat decreased over time. Slightly more patients used three or more ASM in 2022. The severity of the ID had increased over time; in 2015, 12 participants (25.5 %) had a severe ID and in 2022 this number was 22 (46.8 %). Likewise, the mobility deteriorated; the number of participants who used a wheelchair to traverse 500 m increased from 7 DS participants (20.6 %) in 2015 to 16 participants (35.6 %) in 2022. However, the mean HRQoL score in the DS cohort improved: in 2015 the mean score was 54.5 and in 2022 it was 63.3.

3.5. Comparing A/CBCL scores over two time points

The mean total problems A/CBCL score of DS patients in 2022 was slightly lower than in 2015 (63.4 in 2015 to 61.9 in 2022), but this difference was not significant (t = -1.491, p = 0.143). For the distribution of the total problems A/CBCL over two time points in the DS cohort, see Fig. 1. Seven years after the first assessment, 30 participants (64 %) remained in their initial category.

3.6. Differences at two time points in A/CBCL scores per age group

The course of A/CBCL scores in different age groups is depicted in Fig. 2. In 2015, there were 21 participants (44.7 %) in the DS cohort aged between 2 and 10 years (group A), 16 participants (34.0 %) aged between 11 and 17 years (group B), and 10 participants (21.3 %) who were 18 years or older (group C). As shown in Fig. 2, the mean A/CBCL score of the total problems scale improved at the second timepoint (2022) for all age groups but was only significant for group B (t = -2.24, CI = -6.10 – −0.15, p = 0.04). Means of the other subscales are also displayed in Fig. 2. Although, some increased and some declined, none of these changes were statistically significant.

3.7. Multiple regression analyses longitudinal DS cohort

The results of the univariable and multivariable regression analyses, with the difference between the 2022 and the 2015 total problems A/CBCL score as dependent variable, are depicted in Table 5. The multiple regression model implicates that developing a more severe ID and using less ASMs in 2022 is associated with an increase in behavioral difficulties over time, with developing a more severe ID as the strongest predictor. This end model explained 14.6 % of the variation (adjusted $R^2 = 0.1457$).

Table 3
Univariable and multivariable regression analyses of cross-sectional DS cohort with total problems A/CBCL as dependent variable.

Predictor variables	Univariable regression			Multivariable regression end model		
	β	CI 95 %	p-value	β	CI 95 %	p-value
Gender (male) n(%)	−1.171	−4.20 – 1.86	0.445			
Age	−0.232	−0.36 – −0.10	**0.001**	−0.208	−0.33 – −0.09	**0.001**
Level ID[a] n(%)						
Severe ID	Ref	…	…			
Moderate ID	2.458	−1.54 – 6.45	0.225			
Mild ID	4.400	0.82 – 7.98	**0.017**			
No ID or borderline ID	2.143	−4.19 – 8.48	0.504			
Minor seizures n(%)						
Seizure free	Ref	…	…			
Yearly	−5.084	−11.10 – 0.93	0.097			
Monthly	−0.550	−5.85 – 4.75	0.837			
Weekly	1.603	−3.01 – 6.22	0.492			
Daily	2.776	−0.89 – 6.44	0.136			
Major seizures n(%)						
Seizure free	Ref	…	…			
Yearly	4.527	−1.89 – 10.95	−0.165			
Monthly	2.468	−3.83 – 8.76	0.439			
Weekly	0.361	−5.74 – 6.46	0.907			
Daily	2.784	−4.48 – 10.05	0.449			
ASM use	−1.206	−2.68 – 0.26	0.106			
Ever used CIM used n(%)	−2.769	−5.88 – 0.34	0.081			
SQ-SP CSI[b] n(%)	1.261	0.57 – 1.95	**0.000**	1.153	0.49 – 1.82	**<0.001**
FMS 500 m (wheelchair) n(%)	−1.489	−4.53 – 1.55	0.334			
Eating difficulties n(%)	0.224	−2.84 – 3.29	0.885			
Currently living in institutional care n(%)						
	−4.461	−7.69 – −1.24	**0.007**			

β = standardized beta regression coefficient; CI = confidence interval; ID = intellectual disability; ASM = antiseizure medication; CIM = contra-indicated medication; SQ-SP CSI = Sleep Behavior Questionnaire by Simonds & Parraga composite sleep index; FMS = functional mobility scale.

[a] No intellectual disability or borderline ID = IQ or DQ > 70; Mild ID = IQ or DQ = 50–70; Moderate ID = IQ or DQ = 30–50; Severe ID = IQ or DQ < 30.

[b] The SQ-SP CSI ranges between 0 and 12 and reflects the severity of sleep problems, with scores of 4 or up indicating severe sleep problems.

Table 4
Characteristics of the longitudinal 2022 cohort.

	DS 2015 cohort	DS 2022 cohort
N	47	47
Gender female, n(%)	22 (46.8)	22 (46.8)
Age, in years median(range)	11.0 (2-44)	18.0 (8-51)
Age groups in years, n(%)		
2–10	21 (44.7)	7 (14.9)
11–17	16 (34.0)	16 (34.0)
18+	10 (21.3)	24 (51.1)
Major seizure frequency n = 47/47, n(%)		
Seizure free	4 (8.5)	4 (8.5)
Yearly seizures	8 (17.0)	9 (19.1)
Monthly seizures	10 (21.3)	14 (29.8)
Weekly seizures	19 (40.4)	14 (29.8)
Daily seizures	6 (12.8)	6 (12.8)
Minor seizure frequency n = 47/47, n(%)		
Seizure free	14 (29.8)	15 (31.9)
Yearly seizures	3 (6.4)	5 (10.6)
Monthly seizures	3 (6.4)	10 (21.3)
Weekly seizures	6 (12.8)	4 (8.5)
Daily seizures	21 (44.7)	13 (27.7)
Level ID[a] n = 47/47, n(%)		
No ID	1 (2.1)	0 (0.0)
Borderline ID	6 (12.8)	1 (2.1)
Mild ID	15 (31.9)	12 (25.5)
Moderate ID	13 (27.7)	12 (25.5)
Severe ID	12 (25.5)	22 (46.8)
ASM n = 46 / 47, n(%)		
No use of anticonvulsant	0 (0.0)	1 (2.1)
Use of 1 anticonvulsant	2 (4.3)	3 (6.4)
Use of 2 anticonvulsants	13 (28.3)	9 (19.1)
Use of 3 or more anticonvulsants	31 (67.4)	34 (72.3)
HRQoL[b] n = 43/ 46, mean(SD)	54.4 (14.7)	63.6 (13.0)
FMS score (500 m) n = 34/45, n(%)		
Uses a wheelchair	7 (20.6)	16 (35.6)
Uses a rollator	0 (0.0)	0 (0.0)
Independent walking on flat surfaces	14 (41.2)	14 (31.1)
Independent walking on all surfaces	13 (38.2)	15 (33.3)

ID = intellectual disability; ASM = antiseizure medication; HRQoL = Health-related quality of life; FMS = functional mobility scale.
[a] 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 ID = IQ or DQ < 30.
[b] HRQoL: health-related quality of life, based on PedsQL Measurement Model questionnaire results. Scaled 0–100; a higher score indicates a higher health-related quality of life.

4. Discussion

4.1. Main results

This study explored behavioral phenotypes in a large cohort of GEFS + and DS patients. The results showed that the prevalence of behavioral difficulties in the GEFS + group is comparable to scores in the general population [23,25,34] and slightly lower than in other cohorts of patients with epilepsy [35–38]. In the DS group, the A/CBCL questionnaire scores revealed high percentages of participants with deviant behavior (borderline range 21.5 %; clinical range 43.0 %). These scores are higher than in the general population and in other epilepsy cohorts [23–25,35–38]. This indicates that behavioral problems are common in DS, and are part of the DS phenotype. The behavioral profile in DS exists out of withdrawn behavior, aggressive behavior, and attention problems and is consistent across age groups.

4.2. Behavioral difficulties

The high prevalence and type of behavioral difficulties in our DS cohort aligns with existing literature [2,10–11,15]. Brunklaus et al. [10] described conduct problems and difficulties with peer relationships among DS patients. Although the current study did not examine these behavior specifications, the presence of withdrawn behavior and high number of ASD diagnoses implies the presence of similar difficulties. Additionally, the true prevalence of behavioral difficulties may be even higher than revealed by the A/CBCL questionnaire. The A/CBCL questionnaire results indicate a prevalence of deviant behavior in 64.5 % of DS patients, while during the interviews of 84.0 % DS participants such behavior was reported. This disparity might be due to challenges associated with completing the A/CBCL questionnaire. Parents of participants with ID may perceive certain questions as unrelated to their child's situation and alternatively, might miss questions about behaviors they consider significant. Additionally, parents may interpret certain behaviors as deviant, while clinicians may not, or vice versa. Importantly, 34.1 % of parents caring for DS patients with behavioral difficulties reported that they never received any form of guidance to address challenging behavior, nor did their child receive treatment. This suggests that behavioral difficulties may be underrecognized. In our study, 18 participants (17.0 %) used psychotropic medication, with some possibly prescribed aiming to control for both seizure frequency and behavioral difficulties (e.g., cannabidiol and topiramate) [39]. Therefore, the exact number of patients solely using medications for behavioral difficulties may be lower. In a prior study, examining the experiences of parents of children with DS, we found that behavioral difficulties in children with DS lead to distress in parents, and that parents sometimes seek solutions outside mainstream medicine to address challenging behavior [7], for example homeopathic medication. This might explain the high number of DS participants (24.5 %) using homeopathic medication. Furthermore, our findings confirm the previously established significant correlation between behavioral difficulties and lower HRQoL [10–11,14]. These findings emphasize again the need for recognition and individualized treatment and management of behavioral difficulties in patients with DS.

4.3. Behavioral profile and course of behavioral difficulties

Among GEFS + patients, only a small number of patients (n = 4) had scores in the clinical range on some of the syndrome scales. Therefore, no specific behavioral profile can be recognized for this group. Among DS patients, a behavioral profile was observed, existing out of withdrawn behavior, aggressive behavior, and attention problems, with an exceptional high score on the subscale 'attention problems'. This is line with previous literature on DS patients [7,10–11]. Brunklaus et al., employing a different questionnaire to assess behavioral difficulties, also reported abnormal scores on 'conduct problems' and 'peer relationships', which have characteristics that align with the definition of withdrawn behavior. Behavioral difficulties were most common among DS patients within the age group 2–10 years. Overall, aging resulted in decreased behavioral difficulties, specifically, aging from adolescence to adulthood. However, the profile of behavioral difficulties remained the same over time. Previous studies reported contradicting findings on the relationship between age and behavioral difficulties, with some studies finding an increase of behavioral difficulties with an increasing age [1,16] and another found no differences across ages at all [10]. These variations may result from differences in measuring tools or data collection [1–2,10,14,16]. Our findings are consistent with the findings of Makiello et al. [14] who also described a small non-significant decline in behavioral difficulties over time based on a standardized questionnaire. In contrast, Feng et al. [12] described a significant increase in behavioral problems and autistic features over 10 years based on one yes/no question regarding the presence of behavioral difficulties. Further longitudinal studies, employing standardized questionnaires regarding behavior, should be performed.

4.4. Risk and predictive factors

In both our models, only a small part of the variation in behavioral difficulties could be explained (cross-sectional 18.6 %; longitudinal 14.6 %), which implies that most factors contributing to behavioral

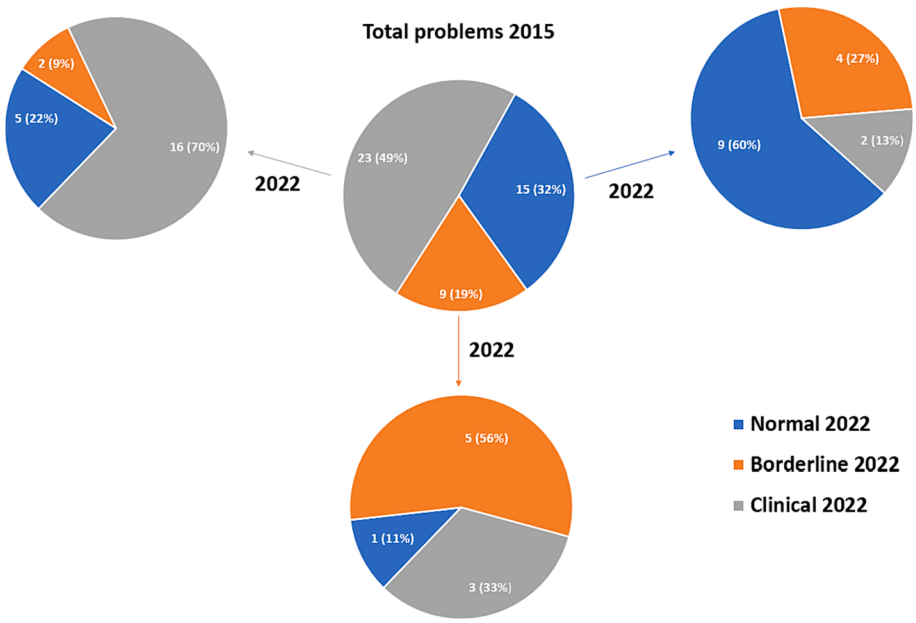

Fig. 1. Distribution of total problems A/CBCL of the DS cohort between 2015 and 2022 in normal, borderline, and clinical range (n = 47).

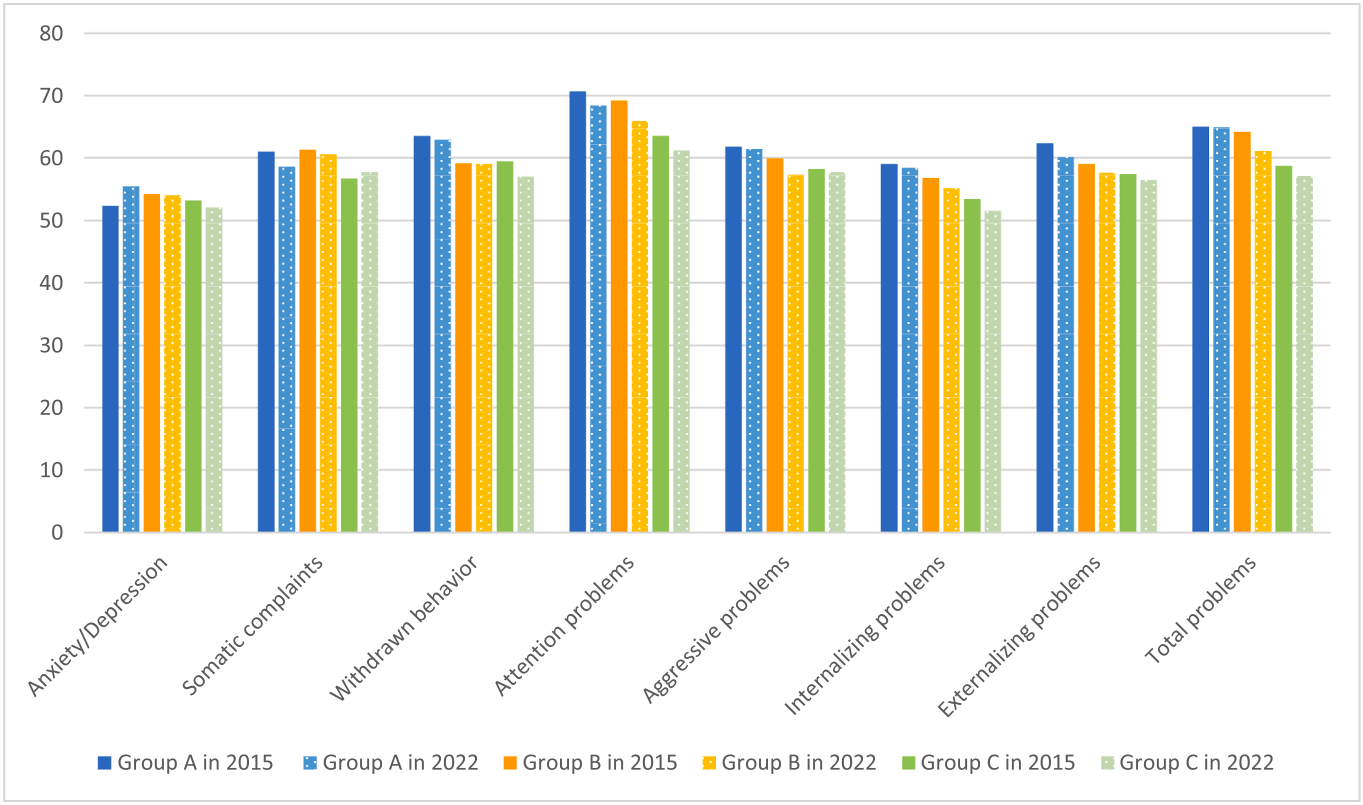

Fig. 2. Mean scores in A/CBCL subscales in 2015 and 2022.

difficulties are not included in this study. In the cross-sectional analyses, aging from adolescence to adulthood appears to be associated with declining behavioral difficulties. However, this finding could not be confirmed in the longitudinal data, probably due to the small number of participants who had reached adulthood in the longitudinal cohort (n = 14 (29.8 %)). A specific factor associated with more behavioral problems was sleep disturbance. Previous literature recognized the association between sleep disturbances and behavioral disorders for a range of neurodevelopmental disorders with supporting evidence for a bidirectional relationship [40–41]. The question remains whether sleep disturbances are part of the behavioral phenotype, or are the underlying reason for behavioral disturbances, or both? Future research should explore strategies to improve these comorbidities [2,8–11]. Another factor associated with behavioral problems in the longitudinal analyses, was a decrease of intellectual functioning. However, in the cross-sectional analysis, a more severe ID alone did not show this

Table 5
Multiple regression analyses of longitudinal DS cohort with the difference between the 2022 and the 2015 total problems A/CBCL score as dependent variable.

Predictor variables	Univariate regression			Multivariate regression end model		
	β	CI 95 %	p-value	β	CI 95 %	p-value
Gender (male) n(%)	1.897	−6.42 – 1.32	0.179			
Age at 2015 data collection[a]	−0.065	−0.30 – 0.17	0.327			
Difference ID[a]	3.027	0.16 – 5.90	**0.039**	3.371	0.56 – 6.18	**0.020**
Difference frequency minor seizures[a]	0.227	−0.885 – 1.340	0.683			
Difference frequency major seizures[a]	−0.335	−1.962 – 1.291	0.680			
Difference in ASM use[a]	−1.791	−3.74 – 0.16	0.071	−1.964	−3.82 – −0.11	**0.039**
Difference of FMS score (500 m)[a]	−2.516	− 8.625 – 3.592	0.406			

β = standardized beta regression coefficient; CI = confidence interval.
[a] *These 'difference' variables were established by calculating the disparity between the outcomes in 2022 and that of 2015 (e.g. ID in 2022 – ID in 2015).*

association. Previous research concerning adolescents with intellectual disabilities indicated a positive correlation between ID and challenging behavior [42–43]. This linear relationship was not consistently observed in studies on DS participants, including our current findings [2,11]. Nonetheless, we believe that ID contributes to the extent of behavioral difficulties, although not following a linear pattern. One explanation for this disparity in literature could be that patients with more severe ID are less capable to express deviant behavior and, secondly, that literature might not always include patients with more severe ID. Moreover, we found no correlation between behavioral difficulties and seizure frequency, suggesting that these difficulties cannot be solely attributed to epilepsy [2,16]. Consequently, a treatment strategy entirely focused on seizure control is unlikely to result in sufficient improvements in challenging behavior. A somewhat surprising finding was that using more ASMs in 2022 than 2015 was associated with less behavioral difficulties. Parents have previously reported that ASMs negatively affected behavior rather than vice versa [7]. An explanation could be that behavioral difficulties are not related to the number of ASMs used, but only to specific types and dosages of ASMs. Use of newly approved ASMs may result in less adverse effects on behavior, or even improvement of behavioral difficulties [44]. Also, the number of ASMs used was not defined as a risk factor for behavioral difficulties in the cross-sectional analyses.

5. Strengths and limitations

This study has several strengths. First, we used a participative research approach. Before the start of the study, we organized focus groups with parents caring for children with DS and asked them about their wishes regarding research on behavioral difficulties. This information was taken into account when designing this study. Second, this study included a longitudinal assessment of the behavioral phenotype in patients with DS, thereby confirming the correlation between age groups and behavioral difficulties. And third, we managed to include a substantial cohort of DS participants, providing a good representation of the Dutch DS population.

A limitation of this study is that we used the A/CBCL questionnaires which are not validated for behavioral evaluation in patients with intellectual disabilities, even though they are often used in this population. Moreover, the level of intellectual functioning is for some participants determined without the use of standardized scales due to lack of information. Furthermore, we did not explore the correlation between behavioral difficulties and the specific types and dosages of ASMs. A more comprehensive examination of this relationship could provide valuable treatment insights for patients with DS. An additional limitation is that parents completed most questionnaires and therefore reflect the parent's perspective, which could be different from the participants' perspective. We recommend that future studies also use objective measures to ascertain the behavioral phenotype in patients with DS, in addition to the parental perspective.

6. Conclusion

Behavioral difficulties are prevalent in DS and persist throughout an individual's lifespan. Many patients with DS show challenging behavior which significantly affects HRQoL. These findings demonstrate the need for recognition and personalized management of behavioral difficulties in DS. We recommend a comprehensive approach including care of patients with DS by a multidisciplinary team, encompassing treatment strategies for behavioral difficulties. This team should have knowledge on strategies for handling and treating behavior like, aggression, attention problems and withdrawn behavior. Adopting a multidisciplinary care approach, enhances early recognition of behavioral difficulties and results in more specialized treatment and guidance for the patient and the parents. Previous studies on behavioral difficulties in DS, have primarily relied on the use of questionnaire based or qualitative research involving parents. Therefore, future research should prioritize the definition of behavioral phenotypes assessed by trained clinicians who can interpret behavior in terms of psychiatric symptoms and diagnoses. By assessing this phenotype, a better understanding of underlying causes of behavioral manifestations and interpretations can be achieved, and suitable treatment strategies applied.

CRediT authorship contribution statement

Amber Postma: Writing – review & editing, Writing – original draft, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Crista A. Minderhoud:** Writing – review & editing, Visualization, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Wim . M. Otte:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Floor .E. Jansen:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Conceptualization. **W.B. Gunning:** Writing – review & editing. **Judith S. Verhoeven:** Writing – review & editing, Data curation. **Marian J. Jongmans:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Janneke R. Zinkstok:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Eva H. Brilstra:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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

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