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Behavior problems and health-related quality of life in Dravet syndrome

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ABSTRACT

Objective: Behavior problems in Dravet syndrome (DS) are common and can impact the lives of patients tremendously. The current study aimed to give more insight into (1) the prevalence of a wide range of specific behavior difficulties and aspects of health-related quality of life (HRQoL) in patients with DS compared with the general population (gp) and patients with epilepsy without DS, (2) the relations between these behavior problems and different aspects of HRQoL, and (3) the associations between seizure frequency, cognitive impairment (CI), behavior problems, and HRQoL, based on a conceptual model.
Methods: One hundred and sixteen patients (aged between 2 and 67 years), affected by *SCN1A*-related seizures, were included in the study. Eighty-five were patients with DS, 31 were patients with epilepsy without DS. Behavior problems were measured using the Child/Adult Behavior Checklist (C/ABCL), HRQoL was measured using the Pediatric Quality of Life Inventory (PedsQL) Measurement Model. Other characteristics were obtained by clinical assessments, medical records, and semi-structured telephone interviews with parents. Comparisons between patients with DS, patients without DS, and the gp were calculated by the exact goodness of fit χ^2 analyses, relations between subscales were analyzed using Pearson's correlations, and the conceptual model was tested in a path analysis.
Results: (1) Patients with DS show significantly more behavior problems compared with the gp and patients with epilepsy without DS. A total of 56.5% of patients with DS scored in the borderline and clinical ranges for total behavior problems. Problems with attention were most prevalent; 62.3% of patients with DS scored in the borderline and clinical ranges. Health-related quality of life was significantly lower for patients with DS compared with the gp and patients without DS. Physical and social functioning scores were especially low and decreased even more in the older age categories. (2) Problems with attention, aggression, and withdrawn behavior were most related to social functioning. Somatic problems and anxiety/depression were most related to emotional functioning. (3) Cognitive impairment and behavior problems were both independent predictors of poorer HRQoL in patients with DS, with behavior problems being the strongest predictor. Seizure frequency was only indirectly related to HRQoL, mediated by cognitive impairment.
Implications: The high prevalence of behavior problems in DS and the significant impact on quality of life (QoL), independent of epilepsy-related factors, emphasize the need for active management and treatment of these problems and should be considered as part of the management plan.

1. Introduction

Dravet syndrome (DS) is a devastating, life-threatening epilepsy syndrome first described by Charlotte Dravet in 1978 [1]. The incidence of the syndrome is estimated at 1/20,000 to 1/40,000 in the general population [2]. The first symptoms of DS typically occur during the first year of life in an otherwise healthy child [3]. The syndrome is characterized by intractable epileptic seizures, developmental delays, speech impairment, and motor/orthopedic issues [4]. It is associated with mutations of the *SCN1A* gene in 75% of cases [5]. Pathogenic variants in the *SCN1A* gene can result in extremely variable disease severities, ranging from severely affected patients with DS on the severe end of the spectrum to milder phenotypes such as genetic epilepsy with febrile seizures plus (GEFS+) syndrome or febrile seizures only (FS or FS+) on the other side of the spectrum [6–8].

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Besides the high seizure burden and the therapy resistance [1], DS also dramatically impacts the development and behavior of the affected children. Comorbidities such as cognitive impairment (CI), psychiatric problems, and social difficulties are common, and children with DS nearly always develop behavior problem [9]. Those comorbidities tend to be less severe in patients with milder *SCN1A* phenotypes [10–12]. While research and treatment often mainly focus on managing seizures, comorbidities such as behavioral problems can play a major role in the lives of children with DS and their parents and are sometimes considered to be even more disabling than the seizures [13].

1.1. Behavior problems in DS

Behavior problems in patients with DS can comprise specific features such as hyperactivity [1,3,13–16], attention-deficit [1,14,17], limited concentration [18], mood instability [15], short temper [17], opposing behavior [1,3], perseveration [16], impulsive actions [18], and autistic-like features [3,16,19]. Studies investigating the incidence of behavior problems typically find that at least one of those problems occur in 95% to 99% of patients, with the highest rates found for autism, Attention Deficit Hyperactivity Disorder (ADHD), oppositional behavior, attention problems, anxiety, and peer relationship problems [13,20,21]. However, most of the studies on behavior in DS did not use standardized methods and compared the results with norm groups of the general population. An exception to this is the study of Brunklaus et al. [13]. The authors screened for behavioral and psychiatric problems in 163 children with DS aged between 2 and 18 years old using the Strengths and Difficulties Questionnaire (SDQ), which compares the results with norm groups. Of the four SDQ subscales (i.e., 'emotional problems', 'conduct problems', 'hyperactivity/inattention', and 'peer relationship problems'), patients with DS scored significantly higher than the norms on three; 35% of patients with DS scored in the abnormal range for 'conduct problems', 66% for 'hyperactivity/inattention', and 76% for having 'peer relationship problems'.

The long-term prognosis of DS is usually unfavorable. In general, seizures persist and are drug-resistant [22], although seizure frequency and severity tend to improve slightly after childhood [22–24]. All patients with DS are reported to be cognitively impaired, often severely, and language remains poor [22].

There is no conclusive evidence about whether and how behavioral problems develop with age in patients with DS, although some studies have found that in general, behavior problems seem to increase in childhood, peek in adolescence, and then plateau or slightly decrease in adulthood [13,21]. Because most research on behavior in DS has focused on children and adolescents, unfortunately, there is not much information about behavior problems in adults with DS yet. However, a few small studies found that in general, behavior problems such as hyperactivity seem to become less prevalent while symptoms of autism, cognitive impairment, and language impairment persist [19,22]. There is a need for additional research on behavioral problems in DS in adulthood and what the effects are on quality of life.

1.2. Quality of life

Many studies have focused on quality of life (QoL) of children with DS because QoL assessments are important in the clinical management of any disease, and QoL improvement is one of the most important goals for clinicians. Quality of life or health-related quality of life (HRQoL) is typically shown to be much lower in patients with DS compared with the general population [13]. Factors affecting QoL, such as seizures, antiepileptic drugs, cognitive impairment, and psychological, social, and behavioral factors, have been explored without conclusive evidence about which (constellation of) factors contribute most to QoL at varying points in life [25,26].

There is some evidence that patients with a higher seizure frequency have more (severe) comorbidities and lower QoL scores [21]. Brunklaus et al. [13] examined the relations between QoL and behavioral and psychiatric problems in patients with DS and found that young age at seizure onset, presence of myoclonic seizures, motor disorder, learning difficulties, seizure frequency, and behavioral difficulties each independently predicted a poorer HRQoL, with behavioral problems as the strongest predictor.

Studies investigating other epilepsy syndromes and epilepsy in general show the importance of psychosocial factors over seizure-specific factors in determining the QoL as well [26,27]. Bilgic et al. [28], for example, found that epilepsy is associated with a poor psychiatric status and HRQoL in childhood and that the impact of epilepsy on the HRQoL occurs mainly through child-related psychiatric factors. In addition, Fayed et al. [29] focused on the children's own perspectives on their QoL by using child self-reports instead of parental reports. From the perspective of 8- to 14-year-old children, QoL was not related to seizure frequency but instead was associated with mental health and peer and parental support. This finding is in line with literature reviews showing that repeated positive daily experiences (such as in the family or at school) are more important to children's perceived life satisfaction than 1 or 2 major life stressors (such as the diagnosis of a chronic disease) [30,31]. Even though the children that participated in the study had sufficiently high intelligence quotient (IQ) to be able to respond to a self-report questionnaire (and so most probably have significantly higher IQs than patients with DS), it seems plausible that these child-related psychiatric factors are important for children with DS as well.

1.3. Current study

Given the severity of DS, with life-threatening seizures and developmental and behavioral issues, patients with DS seem to experience unique problems, and the issues are likely to continue in adulthood. The current study aimed to look more closely at a wide range of specific behavior difficulties in patients with DS between the ages of 2 and 44 years by using the Child Behavior Checklist (CBCL) that compares the results with norm groups of the general population. We also compare these results to patients with other types of *SCN1A*-related epilepsy (patients without DS). In patients with DS, we explore the effects of specific behavior problems on specific aspects of QoL functioning. This will provide a better insight into the nature and possible effects of behavior problems in DS. Finally, we aimed to investigate the direct and indirect relationships between seizure frequency (frequency of major seizures), cognitive impairment, behavior problems, and HRQoL. We graphed these relationships in a conceptual model.

2. Methods

2.1. Participants

One hundred and sixteen patients, aged between 2 and 67 years, that are part of a previously described cohort [12,32,33] affected by *SCN1A*-related seizures were included in this study. They consisted of 85 patients with DS, which was our main study population, and 31 patients without DS (patients with GEFS +, FS +, or FS). Only symptomatic participants with heterozygous pathogenic or likely pathogenic variants (classes IV and V, according to the American College of Medical Genetics and Genomics criteria [34]) in *SCN1A* were included. All eligible individuals of at least 1.5 years of age known to the University Medical Center Utrecht were approached for study inclusion. Informed consent was obtained from participants or their legal caretakers, according to the Declaration of Helsinki. The study was approved by the Ethical Committee of the University Medical Centre Utrecht.

2.2. Clinical data

All participants were categorized into two clinical subgroups: DS ($n = 85$) or non-DS ($n = 31$). Dravet syndrome was diagnosed based on previously published criteria [35]. The diagnoses were in

line with recently published recommendations [36]. The non-DS group consisted of patients with either GEFS + or FS.

2.2.1. Mutation type and psychiatric diagnoses

Mutation type is classified as either protein-truncating variants or missense mutation. Protein-truncating variants include nonsense variants, small frameshift deletions and/or insertions, splice-site variants, gross deletions or duplications, and complex chromosomal rearrangements disrupting *SCN1A*. Both mutation type and diagnoses of ADHD and autism were collected from medical records and semi-structured telephone interviews with parents/caretakers.

2.2.2. Seizure frequency

Seizure frequency at the time of inclusion was classified based on the frequency of major seizures (defined as seizure types with loss of consciousness and prolonged seizures, excluding short absences, short focal seizures or myoclonias), at the time of inclusion (score 4 = daily seizures, score 3 = weekly seizures, score 2 = monthly seizures, score 1 = yearly seizures, score 0 = seizure-free). This information was obtained from parents/caretakers by semi-structured telephone interviews.

2.2.3. Cognitive impairment

Cognitive impairment at the time of inclusion was classified in a consensus meeting by a child neurologist, neuropsychologist, and clinical geneticist, and rated on a five-point scale based on available data on IQ and developmental level, (1 = no CI (IQ or developmental quotient (DQ) >85), 2 = borderline CI (IQ or DQ 70–85), 3 = mild CI (IQ or DQ 50–70), 4 = moderate CI (IQ or DQ 30–50), 5 = severe or profound CI (IQ or DQ <30)). When no (recent) IQ or DQ was available, the assessment was made based on school functioning, communication, and/or adaptive behavior.

2.2.4. Behavior problems

To evaluate behavior problems, we used the Dutch parent report version of the CBCL 1.5–5 years (CBCL 1.5–5), 6–18 years (CBCL 6–18), or the Dutch version of the Adult Behavior Checklist 18–59 years (ABCL) [37–39]. These screening questionnaires consist of 99, 123, and 123 quantitative questions respectively, and caregivers are asked to rate the child's behavior 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. A total score is generated from 8 subscales, and several subscales together make up for 'total internal problems' and 'total external problems'. *T*-scores were calculated according to the C/ABCL manual that compares the results with norm groups of the general population. Based on that, scores could be defined as normal, borderline, or clinically abnormal. The subscales that were similar for all three age groups (i.e., anxiety/depression, somatic problems, withdrawn behavior, attention problems, and aggressive behavior) were selected to investigate further. The reliability and validity of the C/ABCL as well as norms based on age and gender, have been established in past research [37,38,40].

Parents/caretakers also responded to two open questions of the C/ABCL. The first question was: 'What are your main worries about your

Table 1
Characteristics of the sample — patients with DS.

	Complete DS cohort	1.5–5 years	6–17 years	18 + years
N	85	*16*	*47*	*22*
Gender	48 males (56.5%)	8 males (50%)	27 males (57.4%)	13 males (59.1%)
	37 females (43.5%)	8 females (50%)	20 females (42.6%)	9 females (40.9%)
Age: range	2–44 years	2–5 years	6–17 years	18–44 years
M (SD)[a]	13.74 (9.09)	3.81 (1.17)	11.11 (3.10)	26.59 (6.71)
Mutation type[b]	Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)
Protein-truncating variants	43 (50.6%)	7 (43.8%)	24 (51.1%)	12 (54.5%)
Missense	42 (49.4%)	9 (56.3%)	23 (48.9%)	10 (45.5%)
Major seizure severity[c]	Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)
Seizure-free (0)	6 (7.1%)	0 (0%)	4 (8.5%)	2 (9.1%)
Yearly seizures (1)	13 (15.3%)	0 (0%)	10 (21.3%)	3 (13.6%)
Monthly seizures (2)	22 (25.9%)	9 (56.3%)	8 (17.0%)	5 (22.7%)
Weekly seizures (3)	32 (37.6%)	6 (37.5%)	17 (36.2%)	9 (40.9%)
Daily seizures (4)	12 (14.1%)	1 (6.3%)	8 (17.0%)	3 (13.6%)
Major seizure severity (0–4)	Median = 3	Median = 2	Median = 3	Median = 3
Cognitive impairment[d]	Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)
No CI (1)	5 (5.9%)	2 (12.5%)	0 (0%)	3 (13.6%)
Borderline CI (2)	9 (10.6%)	3 (18.8%)	5 (10.6%)	1 (4.5%)
Mild CI (3)	19 (22.4%)	4 (25.0%)	13 (27.7%)	2 (9.1%)
Moderate CI (4)	27 (31.8%)	5 (31.3%)	18 (38.3%)	4 (18.2%)
Severe/profound CI (5)	25 (29.4%)	2 (12.5%)	11 (23.4%)	12 (54.5%)
Cognitive impairment (1–5)	Median = 4	Median = 3	Median = 4	Median = 5
HRQoL (range: 0–100)[e]	M (SD) completed	M (SD) completed	M (SD) completed	M (SD) completed
HRQoL: physical funct.	45.7 (27.0) *86%*	61.9 (27.3) *94%*	43.6 (26.1) *96%*	34.4 (22.6) *59%*
HRQoL: emotional funct.	70.5 (15.7) *85%*	61.9 (14.6) *94%*	72.2 (15.5) *98%*	75.0 (14.8) *50%*
HRQoL: social funct.	54.7 (24.4) *80%*	66.5 (22.3) *94%*	54.0 (23.2) *89%*	41.4 (26.1) *50%*
HRQoL: school/work funct.	55.3 (22.3) *75%*	61.5 (22.9) *75%*	54.5 (21.5) *89%*	51.4 (25.9) *45%*
HRQoL: psychosocial funct.	60.1 (14.9) *82%*	62.8 (13.7) *94%*	60.0 (15.5) *94%*	57.0 (14.4) *50%*
HRQoL: total score	54.7 (16.5) *84%*	62.2 (17.4) *94%*	54.3 (15.7) *94%*	46.6 (15.1) *55%*
ADHD, frequency (%)	16 (18.8%)	0 (0%)	9 (19.1%)	7 (31.8%)
Autism, frequency (%)[f]	33 (38.8%)	1 (6.3%)	19 (40.4%)	11 (50%)

[a] M = mean, SD = standard deviation.
[b] Mutation type: two types of mutations*: protein-truncating variants*: this group comprises patients with nonsense variants, small frameshift deletions and/or insertions, splice-site variants, gross deletions or duplications, and complex chromosomal rearrangements disrupting *SCN1A*; *Missense variants*: this group comprises patients with nonsynonymous point mutations.
[c] Major seizures: seizure types with loss of consciousness and prolonged seizures, excluding short absences, short focal seizures, or myoclonias.
[d] CI = cognitive impairment: based on available data on intelligence quotient (IQ) and developmental level/quotient (DQ), adjusted for age at assessment (1 = unaffected [IQ or DQ > 85], 2 = very mild [IQ or DQ = 70–85], 3 = mild [IQ or DQ = 50–70], 4 = severe [IQ or DQ = 30–50], 5 = profound [IQ or DQ < 30]). When no (recent) IQ or DQ was available, the assessment was made based on function in school, communication, and adaptive behavior.
[e] HRQoL: health-related quality of life, based on results of PedsQL Measurement Model questionnaire. Scaled 0–100; a higher score indicates a higher health-related quality of life. Health-related quality of life scores were only collected from patients <25 years.
[f] Autism diagnoses and ADHD were asked for during telephone interviews with parents and/or found in patients' medical files.

child?' The second question was: 'What are you most proud of in your child?' Parents/caretakers were free to write their answers in the open space.

2.2.5. HRQoL

The Dutch version of the PedsQL Measurement Model was used to measure HRQoL on a 0–100 scale for participants aged 0–25 years [41]. The generic measure consists of 23 items making up 4 subscales, which evaluate physical functioning, emotional functioning, social functioning, and school functioning separately. The last 3 subscales together make up the scale for psychosocial functioning, and all 4 make up for Total HRQoL. Items are answered by parents/caretakers on a five-point Likert scale (0 =' never a problem' to 4 =' almost always a problem'). Scores are reversed and computed to a range from 0 to 100, with higher scores indicating higher HRQoL. We did not measure HRQoL in patients older than 25, because the PedsQL is only validated for patients up to the age of 25 years. At the time of inclusion, the majority (91.8%) of our participants was under the age of 25 years (8 patients were older than 25), so we decided that it was sufficient to use these data.

2.3. Statistical analysis

Data on major disease outcomes and variables (mutation type, seizure frequency, cognitive impairment, HRQoL, and psychological diagnoses) are reported as total counts, percentages, and/or mean/median scores for all patients. Because we used three different versions of the C/ABCL, we also reported these outcomes per age group for all our patients with DS. One sample *T*-tests were carried out to compare HRQoL scores of patients with DS with patients without DS (from our cohort), the general population (gp) and other chronically ill patients (data from a study of Varni, Seid, & Kurtin [41]) and general epilepsy patients (data from Modi et al. [42]). One-way Analyses of Variance (ANOVA)s were performed to test the differences between the different age categories of patients with DS regarding both HRQoL and behavior problems.

For behavior problems, the C/ABCL scores were classified as normal, borderline, or clinically abnormal, based on the normative data of the C/ABCL. These normative data indicate that 95% of the general population score in the normal range, 3% in the borderline range, and 2% in the clinically abnormal range for each subscale, and 82, 8, and 10% score in the normal, borderline, and clinically abnormal ranges for the total problem scales [39,40]. Exact goodness of fit chi-square tests were performed to determine whether the C/ABCL distribution for patients with DS was different from the normative distribution and distribution of the patients without DS.

For patients with DS, we identified relations between the behavior problem subscales of the C/ABCL (i.e., anxiety/depression, somatic problems, withdrawn behavior, attention problems, and aggressive behavior) and the HRQoL subscales of the PedsQL (i.e., physical functioning, emotional functioning, social functioning, psychosocial functioning, and school/work functioning). We performed a partial Pearson correlation analysis, controlling for the other variables (mutation type, cognition, seizure frequency, age, and sex).

To test the conceptual model, we performed a path analysis based on the data of 85 patients with DS on cognitive impairment, seizure frequency, total behavior problems, and total HRQoL. To adjust for the influence of age, age was added to the model in every path. Robust weighted least squares estimator was used to estimate the effect sizes for the estimation. Missing data were dropped pairwise. We hypothesized that seizure frequency will affect cognitive impairment, behavior problems, and HRQoL of patients with DS. In addition, we hypothesized that cognitive impairment and behavior problems will also both independently affect HRQoL. Thirdly, we hypothesized that cognitive impairment affects behavior problems. Finally, we hypothesize that the effect of seizure frequency on HRQoL is (partly) mediated by cognitive impairment as well as behavior problems, and that the effect of cognitive impairment on HRQoL is (partly) mediated by behavior problems.

All statistical analyses were performed using SPSS statistics software (IBM SPSS Statistics for Windows V21, Armonk, NY: IBM Corp.), except for the path analysis which was performed in MPlus6.

All reported tests were performed 2-tailed with a significance level of 0.05. Missing data were dropped pairwise.

To organize and analyze the open questions of the C/ABCL (i.e., parents'/caretakers' main worries and prides), we used NVivo, a software program designed for computer-assisted qualitative data, text, and multimedia analysis. The answers were imported in the program, after which they were analyzed by designing codes. The coding scheme was driven by the data collected from these two open questions. This analysis resulted in a top 6 of parents'/caretakers' most mentioned worries and prides.

3. Results

3.1. Characteristics of the participants

The characteristics of the participants are shown in Tables 1 and 2. A total of 116 patients affected by *SCN1A* pathogenic variants participated in the study, consisting of 85 patients with DS (Table 1) and 31 patients with GEFS+, FS+, or FS (non-DS; Table 2). Among the 85 patients in

Table 2
Characteristics of the sample — patients without DS.

N	31
Gender	17 males (54.8%) 14 females (45.2%)
Age: range	2–67 years
M (SD)[a]	34.55 (19.18)
Mutation type[b]	
Protein-truncating variants	3 (9.7%)
Missense	28 (90.3%)
Major seizure severity[c]	Frequency (%)
Seizure-free (0)	24 (77.4%)
Yearly seizures (1)	6 (19.4%)
Monthly seizures (2)	1 (3.2%)
Weekly seizures (3)	0 (0%)
Daily seizures (4)	0 (0%)
Major seizure severity (range: 0–4)	Median = 0
Cognitive impairment[d]	Frequency (%)
No CI (1)	28 (90.3%)
Borderline CI (2)	3 (9.7%)
Mild CI (3)	0 (0%)
Moderate CI (4)	0 (0%)
Severe/profound CI (5)	0 (0%)
Cognitive impairment (range: 1–5)	Median = 1
HRQo5 (range: 0–100)[e]	M (SD) completed
HRQoL: physical funct.	99.6 (1.1) *26%*
HRQoL: emotional funct.	85.6 (18.2) *26%*
HRQoL: social funct.	95.0 (7.6) *23%*
HRQoL: school/work funct.	92.4 (10.7) *23%*
HRQoL: psychosocial funct.	90.1 (7.4) *23%*
HRQoL: total score	93.5 (4.8) *23%*
ADHD, frequency (%)	3 (9.7%)
Autism, frequency (%)[f]	1 (3.2%)

[a] M = mean, SD = standard deviation.
[b] Mutation type: two types of mutations*: protein-truncating variants*: this group comprises patients with nonsense variants, small frameshift deletions and/or insertions, splice-site variants, gross deletions or duplications, and complex chromosomal rearrangements disrupting *SCN1A*; *Missense variants*: this group comprises patients with nonsynonymous point mutations.
[c] Major seizures: seizure types with loss of consciousness and prolonged seizures, excluding short absences, short focal seizures, or myoclonias.
[d] CI = cognitive impairment: based on available data on intelligence quotient (IQ) and developmental level/quotient (DQ), adjusted for age at assessment (1 = unaffected [IQ or DQ > 85], 2 = very mild [IQ or DQ = 70–85], 3 = mild [IQ or DQ = 50–70], 4 = severe [IQ or DQ = 30–50], 5 = profound [IQ or DQ < 30]). When no (recent) IQ or DQ was available, the assessment was made based on function in school, communication, and adaptive behavior.
[e] HRQoL: health-related quality of life, based on results of PedsQL Measurement Model questionnaire. Scaled 0–100; a higher score indicates a higher health related quality of life. Health-related quality of life scores were only collected from patients <25 years.
[f] ADHD- and autism diagnoses were asked for during telephone interviews with parents and/or found in patients' medical files.

Table 3
C/ABCL all participants. Distribution of behavior problem subscales and total scales (in percentages) for the DS (n = 85) and non-DS (n = 31) groups.

	Normal Range in %		Borderline Range in %		Clinical Range in %	
	DS	Non-DS	DS	Non-DS	DS	Non-DS
	(gp: 95)		(gp: 3)		(gp: 2)	
Anxiety/depression	92.9	83.9	4.7	9.7	2.4	6.5
Somatic problems*,+	77.6	90.3	12.9	6.5	9.4	3.2
Withdrawn behavior*	77.6	83.9	5.9	3.2	16.5	12.9
Attention problems*,+	37.6	90.3	34.1	9.7	28.2	0
Aggressive behavior*,+	75.3	90.3	16.5	6.5	8.2	3.2
	(gp: 82)		(gp: 8)		(gp: 10)	
Internal problems*	71.8	74.2	9.4	6.5	18.8	19.4
External problems*,+	56.5	87.1	16.5	3.2	27.1	9.7
Total problems*,+	43.5	74.2	16.5	16.1	40.0	9.7

gp = general population.
To determine normal, borderline, and clinical ranges, *T* scores are used according to C/ABCL manual:
For 1.5–5 years & 18 + years: problem subscales: borderline range *T* 65–69, clinical range *T* > 70.
For 6–18 years: problem subscales: borderline range *T* 67–70, clinical range *T* > 71.
For all: internal problems, external problems, and total problem scales: borderline range *T* 60–63, clinical range *T* > 64.
* Patients with DS significantly different from the general population, calculated by exact chi-square goodness-of-fit analysis, significant at $p < .05 (df = 2)$.
+ Patients with DS significantly different from the patients without DS, calculated by exact chi-square goodness-of-fit analysis, significant at $p < .05 (df = 2)$.

the DS group, which was our main study population, 48 were male, and the average age was 13.74 years (standard deviation (SD) = 9.09), ranging from 2 to 44 years. We made a distinction between the three age categories, based on the C/ABCL that patients completed. The average age of the group of patients without DS (see Table 2) was higher than patients with DS, with an average of 34.55 years (SD = 19.18), ranging from 2 to 67 years. Patients without DS were less often diagnosed with ADHD or autism (9.7% and 3.2% against 18.8% and 38.8% among patients with DS).

3.2. Behavior problems

Table 3 and Fig. 1 show the results of the C/ABCL questionnaires, which provide an overview of the occurrence of behavior problems. We compared our sample of patients with DS with the patients without DS as well as with the gp. The subscales that were similar for all three age groups (i.e., anxiety/depression, somatic problems, withdrawn behavior, attention problems, and aggressive behavior) as well as the total scores for internal problems, external problems, and the overall total scores are depicted in Table 3. There were significantly more patients with DS who scored in the clinical and borderline ranges compared with the gp on all scales ($p < .05$) except for anxiety/depression. Patients with DS also scored significantly more often in the clinical and borderline ranges compared with the patients without DS on somatic problems, attention problems, aggressive behavior, external problems, and total behavior problems ($p < .001$). On total behavior problems, 16.5% and 40% of patients with DS scored in the borderline and clinical ranges, respectively, which is significantly more than observed in the gp ($p < .001$) and in patients without DS ($p < .001$). Furthermore, patients with DS seem to struggle most with attention problems; 34.1% and 28.2% scored in the borderline and clinical ranges respectively. In contrast, patients without DS seem to struggle most with withdrawn behavior and anxiety/depression. In addition, patients without DS scored significantly higher on all the behavior sub- and total scales compared with the gp ($p < .05$).

Furthermore, when comparing the average *T*-scores of patients with DS on behavior problems in the three age categories (see Table 4), we found a difference in total behavior problems between the three different age categories ($p = .024$). Subsequent Gabriel's post hoc tests showed that the second age group (6–17 year-olds) scored significantly higher than the third (adults) category ($p = .022$). For most behavior subscales, there were no statistically significant differences between the age categories. Only for attention problems we found a significant difference ($p = .009$), in which Gabriel's post hoc test revealed that the second age group (6–17 year-olds) scored significantly higher than the third (adults) category ($p = .006$). More detailed information about the C/ABCL scores for the three different age categories can be found in the appendixes, including tables with the normal, borderline, and clinical distribution of behavior problems per age category, and with the additional particular subscales.

3.3. HRQoL in DS

Table 1 shows that patients with DS score an average of 54.7 (SD = 16.5) on HRQoL total score. According to previously reported data of

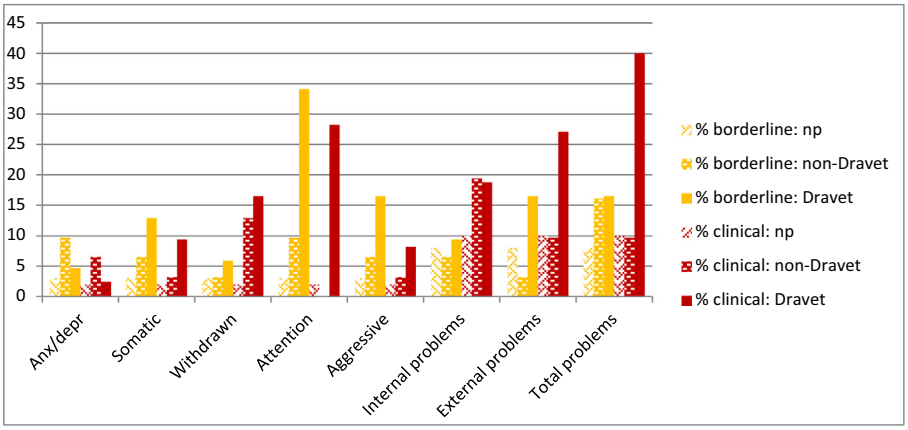

Fig. 1. C/ABCL all participants. Borderline and clinical scores of patients with DS compared with general population (gp) and patients without DS. N = 85 (DS), N = 31 (non-DS).

Table 4
C/ABCL scores — patients with DS. Average *T*-scores of patients with DS on behavior problems, per age category (SD).

N = 85 (DS)	1.5–5 years	6–17 years	18 + years
Anxiety/depression	52.2 (3.7)	52.3 (5.8)	55.8 (10.5)
Somatic problems	60.8 (7.8)	60.5 (7.8)	56.0 (6.7)
Withdrawn behavior	63.6 (10.1)	59.1 (6.9)	59.1 (8.8)
Attention problems*	66.5 (10.5)	69.8 (9.5)	62.5 (6.4)
Aggressive behavior	57.8 (9.5)	60.3 (7.4)	59.7 (10.2)
Internal problems	58.5 (10.2)	55.4 (7.9)	54.0 (13.0)
External problems	58.6 (11.9)	58.9 (8.0)	57.6 (10.4)
Total problems*	59.9 (11.2)	63.5 (6.5)	57.5 (10.2)

T scores were calculated from the patients' raw scores on the C/ABCL according to the C/ABCL manual, compared with norm groups of the general population based on age and gender.

* The three age categories are significantly different, calculated by one-way ANOVA, significant at $p < .05 (df = 2)$.

Varni, Seid, & Kurtin [41], this score is significantly lower ($p < .001$) compared with that of the general population, who score an average of 83.0 (SD = 14.79), and compared with that of other chronically ill patients ($p < .001$), who score an average of 77.36 (SD = 20.36). In addition, it is also significantly lower ($p < .001$) compared with that of patients with epilepsy in general, who score an average of 61.38 according to recent data of Modi et al. [42]. Table 2 shows that the patients with epilepsy without DS in our sample scored an average of 93.5 (SD = 4.8) on HRQoL, which is significantly higher than the gp score of 83.0 ($p = .001$). However, this relatively high score could be due to the small sample size.

Furthermore, the HRQoL total score of patients with DS was lower for the higher age categories. There was a significant main effect of age ($p = .045$). However, subsequent Gabriel's post hoc test showed only a statistically significant difference between category 1 (2–5 year-olds) and category 3 (adults) ($p = .039$). Looking at the subscales of HRQoL more specifically, the largest differences between age groups are seen in physical functioning and social functioning, which both seem to decrease with age. Regarding physical functioning, there was a significant difference ($p = .017$) between category 1 (2–5 year-olds) and category 2 (6–17 year-olds) ($p = .048$) and between category 1 (2–5 year-olds) and category 3 (adults) ($p = .019$). Social functioning was also significantly lower for older patients ($p = .031$) but only between category 1 (2–5 year-olds) and 3 (adults) ($p = .026$). In contrast, emotional functioning was relatively high in patients with DS and also seems to stay that way, with even higher scores among older patients. The adults score an average of 75.0 (SD = 14.8) against 61.9 (SD = 14.6) for the 2–5 year-olds. These differences were also statistically significant ($p = .049$).

3.4. Relations between behavior problem subscales and HRQoL subscales in patients with DS

Table 5 shows the results of the partial correlation analysis between the behavior problem subscales and the HRQoL subscales, controlled for the other variables (age, sex, mutation type, cognition, seizure frequency). We also analyzed the total scores.

The most problematic behavior problems and HRQoL aspects of patients with DS that we found in Section 3.3, such as attention problems and social functioning, also show the highest correlations. Health-related quality of life total score was most related to attention problems, and behavior problem total score was most related to social functioning.

Furthermore, both anxiety/depression and somatic problems showed the strongest correlations with emotional functioning. Withdrawn behavior, attention problems, and aggression, on the other hand, all showed the strongest correlations with social functioning. Finally, regarding both physical functioning and school/work functioning, attention problems were most related.

3.5. Path analysis for patients with DS

Our hypothesized model is described graphically in Fig. 2. We performed a path analysis based on the data from 85 patients with DS. Significant relationships are indicated with green arrows and nonsignificant relationships with red arrows. See also Table 6 for the direct and indirect relationships. The hypothesized model appears to be a good fit of the data. The Comparative Fit Index (CFI) is 1.00; Non-Normed Fit Index is 1.00; chi-square is 64.03; and the Weighted Root Mean Square Residual (WMR) is 0.00. We did not conduct post hoc modifications because of the good fit of the data to the model.

3.5.1. Direct effects

The direct effects are depicted in Fig. 2 (direct effects) and Table 6 (direct and indirect effects). Seizure frequency was related positively to cognitive impairment, which means the more severe the epilepsy, the more severe the cognitive impairment (standardized coefficient = 0.37, $p < .001$). Seizure frequency was not significantly related to HRQoL (standardized coefficient = −0.21, $p = .059$) and not significantly related to behavior problems either (standardized coefficient = 0.01, $p = .998$).

Cognitive impairment was related negatively to HRQoL (standardized coefficient = −0.31, $p = .01$); patients with more severe cognitive impairment scored lower on HRQoL. The relation between cognitive impairment and behavior problems was not significant (standardized coefficient = −0.06, $p = .566$). Behavior problems were negatively related to HRQoL; patients with more behavior problems scored lower on HRQoL (standardized coefficient = −0.54, $p < .001$).

To adjust for the influence of age, age was added to the model in every path. Age had significant relationships with HRQoL (standardized coefficient = −0.37, $p = .011$), total behavior problems (standardized coefficient = −0.20, $p = .020$), and cognition (standardized coefficient = 0.25, $p = .009$), which indicates that both HRQoL and behavior problems decrease with age and cognitive impairment increases with age.

3.5.2. Indirect effects

Illustrated by the conceptual model (see Fig. 2), we hypothesized three mediation effects. Firstly, we hypothesized that the relationship

Table 5
Correlations between behavior problem subscales and HRQoL subscales — patients with DS.

	HRQoL Physical	HRQoL Emotional	HRQoL Social	HRQoL School/work	HRQoL total Psychosocial	HRQoL Total
Anxiety/depression	−0.186	−0.471***	−0.389**	−0.172	−0.443***	−0.484***
Somatic	−0.229	−0.310*	−0.154	−0.100	−0.271*	−0.358**
Withdrawn	−0.216	−0.384***	−0.425***	−0.189	−0.430***	−0.413***
Attention	−0.356**	−0.181	−0.474***	−0.394**	−0.470***	−0.504***
Aggressive	−0.079	−0.371**	−0.509***	−0.228	−0.495***	−0.428***
Total behavior problems	−0.341**	−0.402***	−0.575***	−0.384**	−0.604***	−0.636***

* $p < .05$.
** $p < .01$.
*** $p < .001$.

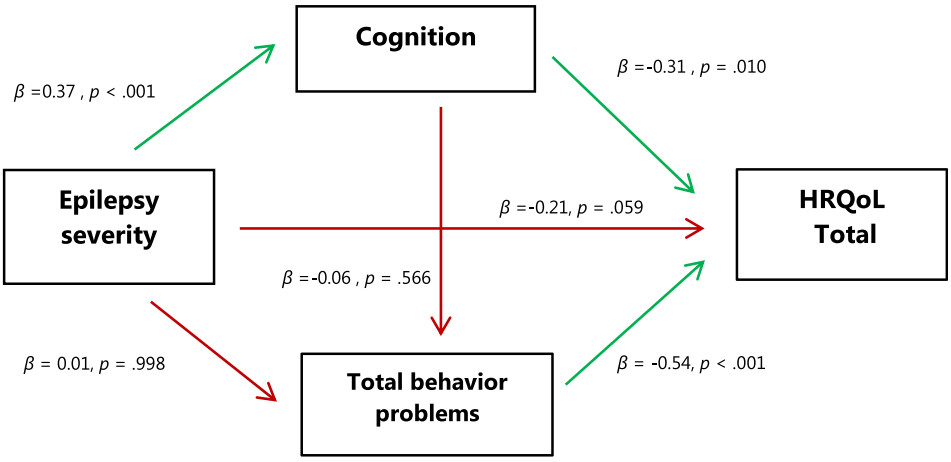

Fig. 2. Path analysis of the conceptual model — patients with DS. Results for the path analysis for patients with DS. Significant relationships are in green, nonsignificant relationships are in red. Non-normed fit index = 1.00; comparative fit index = 1.00; weighted root mean square residual = 0.00; chi-square = 64.03; degrees of freedom = 10.

between seizure frequency and HRQoL was mediated by cognitive impairment (1) and behavior problems (2). In addition, we hypothesized that the relationship between cognitive impairment and HRQoL was mediated by behavior problems (3). The result of the first hypothesized relationship (standardized indirect coefficient = −0.12) was statistically significant ($p = .049$), which means seizure frequency has an indirect effect on HRQoL, mediated by cognitive impairment. As described above in Section 3.5.1, seizure frequency did not have a significant direct effect on HRQoL. This means that the relation between seizure frequency and HRQoL is completely mediated by cognitive impairment. The other two mediation relationships were not significant.

3.6. Qualitative results — patients with DS

Table 7 shows the results of the open questions parents/caretakers of patients with DS responded to in the C/ABCL. They include parents'/caretakers' main worries, as well as the things they are (most) proud of. Number one worry was the future and self-reliance of their child. One parent describes: 'I worry about how things will turn out in the future, where he can live for example, what kind of home. He needs constant checking because of his epilepsy, he is not independent enough to live on his own'. And, as another parent said: 'I worry about the day she has to leave home, will she be cared for lovingly and carefully?' Physical health, cognitive development, and psychological and behavioral problems share a second place. As one parent described it: 'The increasing degree of discontent with his own body manifests itself in melancholy.' Another parent describes her daughter: 'Her vulnerability and stress sensitivity. She is sad very often. She feels alone. She needs friendships but does not get it.' Many parents/caretakers said they worry about behavior problems, mostly with attention and stubbornness/disobedience, as one parent mentioned: 'She "listens" badly and has a strong mind of her own.'

Things that parents/caretakers were proud of included mostly the aspects of their child's character. Being sweet and caring for other people and being cheerful were mentioned most. As one parent describes: 'He is sweet and cheerful, a sunshine for everyone around him'. And, as another one said: 'She enjoys in her own way'.

4. Discussion

4.1. Behavior problems

We found that patients with DS have significantly more behavior problems compared with the gp and patients with epilepsy without DS. On the total score for behavior problems, 16.5% and 40% of patients with DS scored in the borderline and clinical ranges, respectively. This adds up to a total of 56.5% of patients with DS who score in the deviant/abnormal range for total behavior problems. Furthermore, patients with DS seem to struggle most with attention problems: 34.1% score in the borderline range and 28.2% in the clinical range, which adds up

Table 6
Results path analysis, direct and indirect effects — patients with DS.

Model	B			β			S.E			R^2
	Epilepsy severity	Cognitive impairm.	Total behavior problems	Epilepsy severity	Cognitive impairm.	Total behavior problems	Epil. sev.	Cog imp	Beh. prob	
Direct										
Cognition	0.42			0.37			0.12			0.21
Total behavior problems	0.01	−0.45		0.01	−0.06		0.95	0.79		0.05
Total HRQoL	−3.45	−4.64	−1.04	−0.21	−0.31	−0.54	1.82	1.80	0.23	0.55
Indirect(on HRQoL)										
Cognition	−1.94			−0.12			0.98			
Total behavior problems	−0.01	0.47		0.01	−0.03		0.99	0.84		
Total HRQoL										
Total										
Cognition	0.42			0.37						
Total behavior problems	0.01	−0.45		0.01	−0.06					
Total HRQoL	−5.40	−4.17	−1.04	−0.32	−0.34	−0.54				

Table 7
Qualitative results open questions — patients with DS.

Worried about	Mentioned	Proud of	Mentioned
Self-reliance/future	48%	Character: cheerful/happy	52%
Physical health	25%	Character: sweet/caring	45%
(Cognitive) development	25%	Development	22%
Psychological and behavioral problems	25%	Character: social	15%
Seizures/epilepsy	20%	Character: perseverance	11%
Communication/social contacts	16%	Likes to cuddle	7%

to 62.3% of patients with DS having a deviant score for attention problems. Furthermore, increased deviant scores on aggressive behavior (24.7%), withdrawn behavior (22.4%), and somatic problems (22.3%) were also found in patients with DS. These results are in line with findings of previous works, in which attention problems (and ADHD) came out as one of the main problems in patients with DS [13,20,21]. In addition, we compared patients with DS with the gp, as well as with patients with *SCN1A*-related epilepsy without DS, and found that even compared with the latter, differences were still large and significant. Differences in total behavior problems between patients with DS and patients with epilepsy without DS were also described in de Lange et al. [12] and, because these comorbidities can occur at a young age, it was suggested to involve them in the diagnostic process. Beyond that, the high prevalence of behavior problems in DS is worrisome, and active management of these problems might offer an opportunity for intervention and treatment. Problems with attention, for example, might respond to medical treatment or psychological/psychiatric assessment and therapy [43–45].

We found that behavior problems seem to remain quite similar across different ages. We only found a small decrease between the 6–17 year-olds and the adult category in total behavior problems and in the subscale attention problems. These results are partly in line with the results of previous work. In a cross-sectional study, Brunklaus et al. [13] found no differences in behavior problems across different age groups. Lagae et al. [21] however, found that behavior comorbidities increased slightly with age but plateaued or decreased in adults. It should be noted however, that the second age group (6–17 years) are children who are usually in school. During this period, patients with DS are functioning at a significantly lower level than their peers while still engaged in the community. Often, as they become adults, they are removed from the community more, and less interaction with typical peers occurs daily, which can influence the caregivers' responses to the checklist. Future longitudinal research with large sample sizes could provide more insight into the course of behavior problems over time.

4.2. HRQoL

Health-related quality of life was significantly lower for patients with DS compared with the gp. Physical and social functioning scores were especially low and decreased even more in the older age categories. Decreasing scores in HRQoL have been reported in patients with DS in other studies as well [13]. This could be due to a number of factors, such as disease progression with advancing age or because of parents becoming increasingly aware over time of the patients' disability and difference from their peers. It could also be related to other societal factors such as support systems or the fact that patients usually move out of their parents' home when they are older. On the other hand, the opposite was true for emotional functioning; patients with DS score relatively high on emotional functioning ($M = 70.5$), with even higher scores for the older patients. In addition, looking at the results of the qualitative questions, we see a similar picture; many parents describe their child as having a cheerful, happy, and sweet character. This finding seems somewhat contradictive, compared with the high prevalence of behavior problems and low perceived HRQoL in the other fields. However, Brunklaus et al. [13] found a similarly high score for patients with DS on emotional functioning ($M = 63.07$), and one could argue that problems with attention, which was the main behavior problem among patients with DS, do not necessarily mean patients cannot be sweet or happy. The interesting question here is whether or not the relatively high emotional functioning and cheerful and sweet character can be seen as one of the characteristics of DS? However, these characteristics could also be related to cognitive impairment, as some researchers have demonstrated before [46–49], or perhaps (partly) be a reflection of parents' love and affection for their child and a way to positively cope with the situation [50–52].

4.3. Relations between seizure frequency, cognition, behavior, and HRQoL

We also investigated the variables and their relationships in a conceptual model using a path analysis. We saw that cognitive impairment and behavior problems both independently predicted a lower HRQoL, with behavior problems being the most significant predictor. These results are in line with findings of Brunklaus et al. [13], who found that among several epilepsy-related factors, behavior problems were the strongest predictors of poorer HRQoL. In addition, we saw that seizure frequency did not have a direct effect on HRQoL but only indirect: the effect was completely mediated by cognitive impairment. However, there are two important side notes that we want to mention here. Firstly, all patients with DS have intractable epilepsy with (relatively) frequent seizures. When comparing with the general epilepsy population, whose seizure frequency ranges from mild to severe, the lack of differentiation among patients with DS may play a role in the lack of effect of seizure frequency. Secondly, in our path analysis, we placed seizure frequency at the beginning, with cognition, behavior, and HRQoL following from that. However, the cause of DS is genetic, which means that the *SCN1A* mutation and sodium channel impairment is really the origin. The relationship between seizure frequency and cognition might therefore, (in part) be a reflection of a worse genetic deficit leading both to more frequent seizures and worse cognition. However, adding mutation type to the model did not show significant relationships with epilepsy severity and/or cognition and did not improve the fit of the model to the data (data not shown). Future research is needed to gain more insight into the genetic and nongenetic factors influencing the separate aspects of DS.

Both seizure frequency and cognitive impairment have been shown to be associated with lower HRQoL in previous work. Sabaz et al. [53], for example, showed that children with refractory epilepsy and intellectual disability had lower overall HRQoL than those with epilepsy and normal intelligence. Even though cognition and behavior are also known to be closely linked (behavioral difficulties tend to increase as IQ decreases [54]), in our path model, we did not find a significant relationship between the two. Perhaps, this could be related to the nature of a path analysis, which has the tendency to give insignificant results with relatively small sample sizes. However, we did not find a correlation either: among our participants, there was no significant difference in behavior problems between the 5 different levels of cognitive impairment. In sum, our results show that cognitive impairment and behavior problems are both independent predictors of poorer HRQoL in patients with DS (with behavior problems as the strongest predictor), and seizure frequency is only indirectly related to HRQoL, through cognitive impairment. These results show clearly the importance of focusing on

behavior problems, rather than just epilepsy related factors, to increase patients' QoL.

4.4. Relations between subscales of behavior and HRQoL

We also investigated associations between different subscales of behavior problems and different functioning scales of HRQoL. The most problematic scores of patients with DS on behavior problems and HRQoL (i.e., attention problems and social functioning) also showed the highest correlations. Behavior problem total score was most related to social functioning, and HRQoL total score was most related to attention problems. Furthermore, correlations between subscales showed that problems with attention, aggression, and withdrawn behavior seem most related to social functioning. Somatic problems and anxiety/depression, on the other hand, were most related to emotional functioning. The latter correlation is probably due to the fact that patients with DS did not show many problems with anxiety/depression and did not show much difficulty with emotional functioning either.

Regarding both physical functioning and school/work functioning, attention problems were most related. Finally, behavior problems seem to be much more related to psychosocial than to physical functioning, and even somatic problems were significantly related to psychosocial but not to physical functioning.

To our knowledge, there has not been an extensive investigation of different subscales of both behavior problems and HRQoL and their associations in patients with DS. From the strength of the correlations, we can see that social functioning is another aspect in DS to worry about. The strong relationship with attention could be an indication that attention problems are one of the things that play a role in social relationships and social functioning of patients with DS. Scores of social functioning were low for patients with DS and tended to decrease even more in older age categories. In addition, parents described that social relationships (or the lack thereof) were one of the things they mostly worry about. Even though preservation of social skills has been noted in DS in some studies [3], others found that peer relationship problems are one of the main issues that patients with DS seem to struggle with [13,20]. Social skill deficits seem independently associated with epilepsy, especially in children with early-onset epilepsy [55]. A high prevalence of autism and/or autistic-like traits among patients with DS has also been reported in many studies [19,21,22,56]. Social deficits seem to continue into adulthood, increasing social isolation and exerting a negative impact on QoL [57,58]. Support and guidance of social problems in patients with DS might offer an opportunity for intervention. However, an important and interesting consideration to keep in mind is that all the measures we (and other researchers as well) administered were rated by parents. One could argue that 'problems' with social relationships are in fact perceived by parents but do not necessarily mean that patients themselves perceive them as such. Nevertheless, it is something that parents worry about a lot, so extra attention on this subject is important.

Other aspects that parents worry about mostly concern the future and self-reliance of their child. They worry about where he or she can stay in the future, when he or she moves out of their home, and whether he or she will be taken care of properly and lovingly. Previous research on this topic highlights the parents' major concerns regarding accommodation, future support and guardianship, and formal supports in the community [59]. Parents might not have enough confidence in the system or experience difficulty in finding appropriate accommodation for their child [60,61]. There is an important opportunity for healthcare institutions to diminish parents' worries and provide a safe and loving home for patients with DS. Research in this area is important as well. Studies over the years have shown the superiority of small-scale settings over large ones for example. A recent review about different residential settings for people with intellectual disability showed that smaller, more personalized, community-based services generally offered better outcomes in terms of many important life aspects such as adaptive skills, abilities and competence, overall QoL, and social life compared with larger settings. It is important to inform parents about these issues.

Furthermore, parents reported psychological and behavioral problems more often than epilepsy specific factors as their main worries in the open response. This confirms the results of our path analysis in which we found that behavior problems seem to have a larger effect on HRQoL than epilepsy, cognitive and seizure-related factors. The study of Villas et al. [56] also reported parents' main concerns in an open response; speech/communication, cognitive and behavior problems, and long-term care were in the top 5 of parents' main concerns. However, the difference was that Villas et al. [56] asked parents for their main concerns *after seizure control*. We found that parents actually seem to worry about behavior problems more than they worry about seizure control.

4.5. Strengths and limitations

In this study, we have evaluated several disease characteristics, behavior problems, and HRQoL in a relatively large sample of 85 patients with DS and 31 patients with *SCN1A*-related epilepsy without DS from different ages. To our knowledge, we are the first to investigate both the behavior and HRQoL subscales, compared with the gp and patients with epilepsy without DS, and explore the complex relationships of these variables in a conceptual model.

Nevertheless, our study suffered from some limitations. Even though our sample consisted of patients from different ages, which made it possible to investigate the effect of age and compare results of children and adults, it was still a cross-sectional study. We were only able to compare older and younger patients with each other, not changes within the patient. Future prospective studies on a cohort of patients with DS might give a better insight into behavior and HRQoL in individual patients over time.

Another limitation, as mentioned before, is the fact that all questionnaires were rated by parents. Although parents are often the ones closest to the patients, their perception may differ from the patient's real experience [62]. However, because of the cognitive impairment of patients with DS, it is difficult to obtain reliable data directly from the patients, and parent-rated questionnaires seem to be the best alternative in such cases [63,64].

Furthermore, the group of patients without DS we used for comparison was smaller than the group of patients with DS (31 to 85), and the patients without DS were considerably older than the group of patients with DS. This could have biased the outcome of the comparison.

4.6. Practical implications and directions for future research

Despite these limitations, the results of this study generate new insights, practical implications, and directions for future research. Considering the fact that most problems seem to occur in difficulties with attention and social life, these areas could be highlighted during clinical consults and during intervention and information to parents. Problems with attention and aggression might respond to medical treatment or psychological/psychiatric assessment and therapy [43–45]. Other important aspects to consider are the concerns of parents, which seem to be mostly related to long-term care, overall health, cognitive development, and behavioral problems.

Future research could investigate the possible risk factors for behavior problems in patients with DS. Our results showed that seizure frequency and cognitive impairment apparently do not effect behavior problems in patients with DS. These results are remarkable, and future research should investigate this further. To our knowledge, risk factors for behavior problems have not been studied in DS yet. There has been some research on risk factors affecting cognition in patients with DS though, which found that antiepileptic drugs with cognitive side effects, especially in heavy multiple-drug therapy, and the restrictions

that children with severe epilepsy inevitably undergo could be related to cognitive impairment [65]. Future research could investigate whether these factors influence behavior problems as well.

In research on other epilepsy syndromes and epilepsy in general, a number of risk factors have been identified for behavior problems, including both biological/epilepsy factors (younger age at seizure onset, type and frequency of seizures, cognitive impairment, temporal or frontal lobe onset, and antiepileptic medications [66]) and social factors (mostly related to the family environment and parenting [67,68]). Some reports indicate that seizure variables and the use of polytherapy are associated with increases in symptoms whereas other studies have not found this relationship [69]. Studies investigating both seizure/epilepsy variables and family variables commonly show that family variables have a greater influence on child behavior [66,70] and that maladaptive parenting (possibly caused by the struggle to cope with the situation of having a child with epilepsy) was the strongest predictor of behavior problems 3 to 4 years after diagnosis of epilepsy [71]. However, recent prospective studies of children with new-onset seizures show that child behavior problems can precede the onset of epilepsy, which suggests that behavior problems in children might contribute to disrupting the family environment, indicating a complex and bidirectional relationship between the family environment/parenting and behavior problems [67,72]. These findings provide inspiration for future research on behavior problems in patients with DS as well. When we can identify and understand possible causes and risk factors for behavior problems, it will be easier to design and evaluate appropriate interventions and assist families in coping with the situation.

4.7. Conclusion

Our results emphasize the high prevalence of behavioral problems in DS and the significant impact this has on QoL, independent of epilepsy-related problems. Active management of behavioral problems in patients with DS might offer an opportunity for intervention and should be considered as part of the management plan. Future research is needed to identify possible risk factors for behavior problems.

Acknowledgments

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2018.11.029.

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