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RESEARCH ARTICLE

Comorbidities and predictors of health-related quality of life in Dravet syndrome: A 10-year, prospective follow-up study

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Abstract

Objective: Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy, leading to reduced health-related quality of life (HRQOL). Prospective outcome data on HRQOL are sparse, and this study investigated long-term predictors of HRQOL in DS.

Methods: One hundred thirteen families of *SCN1A*-positive patients with DS, who were recruited as part of our 2010 study were contacted at 10-year follow-up, of which 68 (60%) responded. The mortality was 5.8%. Detailed clinical and demographic information was available for each patient. HRQOL was evaluated with two epilepsy-specific instruments, the Impact of Pediatric Epilepsy Scale (IPES) and the Epilepsy & Learning Disabilities Quality of Life Questionnaire (ELDQOL); a generic HRQOL instrument, the Pediatric Quality of Life Inventory (PedsQL); and a behavioral screening tool, the Strength and Difficulties Questionnaire (SDQ).

Results: Twenty-eight patients were 10–15 years of age (0–5 years at baseline) and 40 were ≥16 years of age (≥6 years at baseline). Patients 0- to 5–years-old at baseline showed a significant decline in mean scores on the PedsQL total score ($p = .004$), physical score ($p < .001$), cognitive score ($p = .011$), social score ($p = .003$), and eating score ($p = .030$) at follow-up. On multivariate regression, lower baseline and follow-up HRQOL for the whole cohort were associated with worse epilepsy severity and a high SDQ total score ($R^2 = 33\%$ and 18%, respectively). In the younger patient group, younger age at first seizure and increased severity of epilepsy were associated with a lower baseline HRQOL ($R^2 = 35\%$). In the older age group, worse epilepsy severity ($F = 6.40$, $p = .016$, $R^2 = 14\%$) and the use of sodium-channel blockers were independently associated with a lower HRQOL at 10-year follow-up ($F = 4.13$, $p = .05$, $R^2 = 8\%$).

Significance: This 10-year, prospective follow-up study highlights the significant HRQOL-associated cognitive, social, and physical decline particularly affecting

younger patients with DS. Sodium channel blocker use appears to negatively impact long-term HRQOL, highlighting the importance of early diagnosis and disease-specific management in DS.

KEYWORDS

comorbidity, Dravet syndrome, HRQOL, *SCN1A*, severe myoclonic epilepsy of infancy, SMEI

1 | INTRODUCTION

Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy that typically presents in the first year of life with prolonged febrile and afebrile, generalized tonic–clonic or focal clonic epileptic seizures in children with no pre-existing developmental difficulties. Other seizure types, including myoclonic, focal, and atypical absence seizures, appear between the ages of 1 and 4 years.[1] The epilepsy is usually refractory to standard anti-seizure medications, and cognitive, behavioral, and motor impairments emerge from the second year of life. The majority of tested cases (over 85%) are caused by pathogenic variants in the *SCN1A* gene that result in the dysfunction of neuronal voltage-gated sodium channels.[2–6] The estimated incidence of DS is 1 in 15 500 to 1 in 40 000 live births.[5,7–9]

The assessment of health-related quality of life (HRQOL) in children with epilepsy has gained acceptance as a measure of the effect that chronic disease exerts on an individual's physical, social, and mental well-being.[10–12] A comprehensive study assessing HRQOL in patients with DS demonstrated a severe negative impact relative to normative data for matched age groups.[13] This study drew attention to the need for treatment to focus on a multidisciplinary team approach addressing the wider aspects of physical and mental well-being. Among the strongest independent predictors of poor HRQOL were epilepsy severity, the presence of myoclonic seizures, and early age at onset of seizures, underscoring the potential importance of more effective anti-seizure treatment options for children with DS. Indeed, recent research confirmed that patients with DS have lower HRQOL than the general population and other patients with epilepsy.[14,15] Studies have found that high seizure frequency was significantly related to a lower HRQOL[16] and a greater burden of comorbidities, especially motor and speech.[14] The same study reported that 21% of infants included had been exposed to the sodium channel–blocking drugs carbamazepine or oxcarbazepine and emphasized the need for early diagnosis and more effective antiepileptic medications to reduce the seizure burden in DS.

Prospective outcome data on HRQOL in DS are sparse. In this longitudinal, 10-year, prospective follow-up study our aim was to identify specific short- and long-term comorbidities and disease-related predictors for HRQOL in DS. We anticipate that this will facilitate treatment planning in DS and allow us to better recognize the needs of patients and their families.

Key points

- Greater epilepsy severity and increased behavioral difficulties were significant predictors of lower health-related quality of life (HRQOL) for the whole cohort at baseline and at 10-year follow-up.
- The use of sodium channel blockers (SCBs) leading to increased seizure frequency at initial assessment was predictive of lower HRQOL in the older group at follow-up.
- Significant HRQOL-associated cognitive, social, and physical decline particularly affects younger patients with Dravet syndrome (DS).
- Early diagnosis and management of DS appear to be especially important in mitigating factors that negatively impact long-term quality of life in patients with DS.

2 | MATERIALS AND METHODS

This is a longitudinal, 10-year, prospective follow-up study from 2010 to 2020. Cases were initially identified from referrals between November 2005 and February 2010 to the *SCN1A* molecular genetic diagnostic service based at the Royal Hospital for Children in Glasgow, UK. Referring clinicians completed a structured referral form for every patient. This detailed the epilepsy phenotype and developmental status measured on a scale from 1 (representing a normal development) to 5 (indicating profound learning disability). Information relating to the use of anti-seizure medication was also recorded by the referring clinician. Study participants were asked to complete four postal questionnaires: the Epilepsy & Learning Disability Quality of Life Questionnaire (ELDQOL), the Impact of Pediatric Epilepsy Scale (IPES), the Pediatric Quality of Life Inventory (PedsQL), and the Strength & Difficulties Questionnaire (SDQ). The ELDQOL enabled

parents to rate epilepsy severity on a four-point scale ("mild," "moderate," "somewhat severe," or "very severe") calculated as the average response. The SDQ is a brief behavioral screening questionnaire that includes 25 items on psychosocial attributes, each being rated by the parent as either "not true," "somewhat true," or "certainly true." A total behavioral difficulties score is generated from four scales of five items each including emotional symptoms, conduct problems, hyperactivity/inattention, and peer relationship problems; the higher the score the more difficulties are observed in that area. (Please refer to the original study for further details.[13]) The study design and assessment window were conceived prior to and independent of the coronavirus disease 2019 (COVID-19) pandemic.

As part of the prospective follow-up study we contacted the clinicians of 141 patients, 140 of which responded. In the 10 years since families were first contacted, 7 patients died and 10 were lost to follow-up. A further 10 patients developed non-DS *SCN1A*-related phenotypes (genetic epilepsy with febrile seizures plus [GEFS+], febrile seizures plus [FS+], and myoclonic atonic epilepsy [MAE]), which was not known at study start in 2010 due to the young age of these patients at the time. Of the remaining 113 patients contacted, 68 responded, equaling a response rate of 60.2%.

This study was approved by the Scotland A Research Ethics Committee (reference 08/MRE00/115), and informed consent was obtained from a parent or legal guardian.

2.1 | Data analysis

Patients with missing data were excluded from the relevant analyses. Paired-samples *t* tests were used to assess any significant differences between the means of the patients' questionnaire scores on initial baseline response and on follow-up in cross-sections of several age groups. Differences in continuous variables are given as mean (standard deviation, SD). Correlations between variables were calculated via Pearson's correlation coefficient *r* and the effect size of significant results was calculated using Cohens *D* to give an indication of the magnitude of change. Predictors of HRQOL were analyzed using a linear regression model. All analyses were performed using SPSS statistical software version 24.0 at a significance level of 5% (SPSS).

Patients with Dravet **s**yndrome (or DS) experience significant neurodevelopmental plateauing with emergence of behavioral and social difficulties in the first 5 years of life.[8] The cohort was, therefore, split into patients younger than 6 years of age at referral, and those equal/older than 6 years of age, in order to determine whether there might be a difference in factors impacting HRQOL at different ages. These patient groups are also referred to in this article as the under 16-years-old and over 16-years-old at follow-up.

To identify predictors of HRQOL we performed two separate linear regression analyses. In order to identify baseline predictors of HRQOL, the first regression analysis was performed with the PedsQL generic core total score as the dependent variable to determine whether any factors present at baseline might enable a prediction of HRQOL in patients 10 years later, at follow-up. The second regression was performed with the follow up (FU) PedsQL score as the dependent variable. Baseline factors, that is, variables measured at the time of referral, were tested as possible predictors in both the baseline and long-term follow-up model and included the following: gender, age at first seizure (months), presence of different seizure types (Table S1), age at onset of different seizure types (months), developmental status (normal, mild, moderate, severe, profound), acquired motor disorder (yes/no), autistic features (yes/no), electroencephalography (EEG) abnormalities in year 1 (yes/no), mutation type (truncating/missense), sodium channel blockers increasing seizure frequency (yes/no), epilepsy severity (as per ELDQOL), and behavioral difficulties (as per SDQ).

3 | RESULTS

The questionnaire package was completed and returned by 68 of the 113 families contacted for the follow-up study. All patients had a pathogenic variant in *SCN1A*. A detailed demographic and phenotypic description of the cohort at baseline is illustrated in Table S1, showing that there is no marked difference between responders and non-responders. The overall mortality is 7 of 120 patients (5.8%).

Of the 68 patients, 28 were 10–15 years of age at follow-up and 40 were 16 years or older at the time of follow-up. There was no significant difference in age at first seizure between groups: 5.8 (SD 2.7) vs 5.7 (SD 2.3) months. There was a difference in developmental status at baseline between the older and younger groups. At baseline, the younger group was found to be less disabled, with a mean developmental status score of 2.0 (SD 0.8) vs a score of 3.5 (SD 0.9) for the older children ($p < .0001$).

3.1 | Comparing the cohort at baseline and at follow-up

In a comparative evaluation between baseline and follow-up measures of PedsQL, IPES, and SDQ across younger

and older patients with DS, we compared the baseline and follow-up scores of the whole cohort with normative PedsQL population data (Table 1).[17] Subsequently, we also divided the entire sample into two age groups, whose scores were then compared separately: those between the ages of 0 and5 years at the time of initial referral and those who were 6 years of age and older at time of initial referral. Patients were included only if they had scores for both the baseline and the follow-up measurement on each separate test. Data are mean ± standard deviation (SD), unless otherwise stated. The scores for all scales were normally distributed across both age groups as assessed by visual observations of normal *Q-Q* plots and Kolmogorov-Smirnoff tests. Only three outlier scores were observed: one outlier for the PedsQL cognition score for children <16 years of age at follow-up and two outliers for the IPES score for <16 years of age. Inspection of their values did not reveal them to be extreme and they were kept in the analysis.

Normative PedsQL population data means were consistently higher compared to patients with DS, indicating notably better HRQOL in controls compared to patients with DS (Table 1). Among patients with DS there were significant changes in mean scores between baseline and at follow-up, for several tests for the whole cohort and for the younger group of patients who were 0–5 years of age at baseline (therefore <16-years-old at follow-up; Table 1). For the group of patients who were 6 years of age or older at baseline, there was no significant decrease in mean score at follow-up.

3.2 | Baseline and long-term predictors of HRQOL

Increased epilepsy severity and a higher SDQ total score indicating greater behavioral difficulties were associated with lower HRQOL for the whole cohort at both baseline and follow-up (Tables 2 and 3). At baseline, the strongest predictor of a lower baseline HRQOL was greater epilepsy severity ($\beta = -.416$), followed by a higher SDQ score ($\beta = -.395$). Together these two independent variables accounted for 33% of the variation in HRQOL (adjusted R^2; Table 2). Baseline lower HRQOL in the younger patient group was most strongly associated with greater epilepsy severity ($\beta = -.525$) followed by a younger age at first seizure ($\beta = -.412$). Together these two independent variables accounted for 35% of the variation in HRQOL (adjusted R^2; Table 2).

These factors were no longer associated with lower HRQOL at follow-up. Behavioral difficulties recorded at the time of follow-up were, however, related to HRQOL in this younger group, with a higher SDQ score at follow-up being associated with a lower HRQOL at follow-up ($F(1, 27) = 21.434$, $p < .001$; Table 3). This is similar to the findings at baseline for the older group, confirming the importance of behavioral factors as key predictors of HRQOL.

In the older patient group, the use of sodium channel blockers (SCBs) leading to increased seizure frequency at initial assessment was associated with a lower HRQOL at 10-year follow-up ($F(1, 34) = 4.13$, $p = .05$). Epilepsy severity at baseline was also independently associated with lower follow-up HRQOL in the older patient group ($F(1, 33) = 6.40$, $p = .016$). Both factors were independent predictors of lower HRQOL at 10-year follow-up (Table 3).

4 | DISCUSSION

In this study we prospectively evaluated the health-related quality of life (or HRQOL) in patients with DS over a 10-year follow-up period. We found that increased epilepsy severity was associated with lower HRQOL for the whole cohort, both at baseline and at follow-up. This suggests that the severity of epilepsy early on in the disease course continues to affect quality of life at the 10-year follow-up. This effect was greatest in the older patient group, where epilepsy severity was independently associated with lower HRQOL at follow-up. In contrast, in the younger group, epilepsy severity was predictive of lower HRQOL at baseline alone and not at follow-up. It may be that the patients in the younger group, having benefited from an earlier diagnosis, were managed more appropriately at an early stage of the disease. A younger age at first seizure was also associated with lower baseline HRQOL in the younger patient group, but this association was no longer evident at follow-up. This might be related to the disease course, with a relatively rapid progressive decline over the first 5–6 years followed by a plateauing in terms of seizure severity and frequency.[18] The lack of any long-term impact of age at first seizure on HRQOL in the younger group might also reflect the earlier implementation of appropriate treatment plans relative to the older group, as they received an earlier genetic diagnosis, which may lead to improved treatment and reduction in seizure frequency.[19,20]

In the older patient group, reported SCB use leading to increasing seizure frequency was independently associated with lower HRQOL on follow-up 10 years later. This further highlights the importance of controlling the frequency of seizures early on by avoiding inappropriate medication, which is known to lead to clinical worsening.[21] In this regard, the importance of early diagnosis cannot be understated; indeed, it has been speculated that delayed diagnosis may explain a high incidence of seizures in patients >12 years of age.[22] Furthermore, a study on parent-reported experiences in 46 different countries

TABLE 1 Whole cohort and <16 years old at follow-up.

Scales	*N*	Normative controls[a], mean ± SD	*t* test of controls vs baseline mean		DS baseline, mean ± SD	DS FU, mean ± SD	*t* test of baseline vs FU		
			T	*p*-Value			*t*	*p*-Value	Cohen *D*
Whole cohort									
PedsQL total	**55**	**84.61 ± 11.19**	**20.47**	**<.001**	**44.49 ± 18.34**	**38.60 ± 18.51**	**2.318**	**.024**	
Physical	**65**	**89.06 ± 12.27**	**23.311**	**<.001**	**39.68 ± 28.84**	**27.05 ± 26.37**	**4.221**	**<.001**	
Emotional	60	**78.28 ± 15.54**	**5.272**	**<.001**	63.28 ± 18.68	58.84 ± 20.33	1.639	.106	
Social	61	**86.82 ± 15.42**	**20.112**	**<.001**	40.43 ± 24.58	35.81 ± 23.31	1.161	.250	
School	48	**81.52 ± 16.09**	**17.858**	**<.001**	36.81 ± 21.05	38.77 ± 18.94	−0.618	.540	
Cognitive	57	–	–		23.07 ± 23.98	20.76 ± 21.34	0.719	.475	
Speech	46	–	–		30.28 ± 25.25	30.71 ± 29.01	−0.121	.904	
Eating	**63**	–	–		**55.97 ± 25.97**	**49.44 ± 27.80**	**2.236**	**.029**	
IPES	49	–	–		24.17 ± 6.59	23.08 ± 7.76	0.899	.373	
SDQ total	62	–	–		16.64 ± 5.67	16.37 ± 4.89	0.457	.649	
<16 years old at follow-up									
PedsQL total	**24**	**84.61 ± 11.19**	**13.791**	**<.001**	**51.21 ± 20.500**	**39.94 ± 16.380**	**3.193**	**.004**	**0.65**
Physical	**27**	**89.06 ± 12.27**	**12.772**	**<.001**	**53.93 ± 28.441**	**30.63 ± 26.448**	**4.773**	**<.001**	**0.92**
Emotional	27	**78.28 ± 15.54**	**4.518**	**<.001**	67.96 ± 20.951	63.66 ± 19.061	1.014	.320	N/A
Social	**28**	**86.82 ± 15.42**	**19.246**	**<.001**	**47.79 ± 27.574**	**32.44 ± 21.522**	**3.208**	**.003**	**0.61**
School	24	**81.52 ± 16.09**	**11.900**	**<.001**	43.08 ± 23.511	41.56 ± 17.293	0.304	.764	N/A
Cognitive	**24**	–	–		**35.17 ± 29.451**	**20.49 ± 23.082**	**2.761**	**.011**	**0.56**
Speech	10	–	–		40.90 ± 32.199	43.13 ± 40.873	−0.216	.834	N/A
Eating	**27**	–	–		**60.22 ± 26.873**	**49.63 ± 27.207**	**2.294**	**.030**	**0.44**
IPES	23	–	–		23.80 ± 7.89094	24.68 ± 6.79927	−0.483	.634	N/A
SDQ total	28	–	–		16.25 ± 6.80210	16.54 ± 5.440	−0.334	.741	N/A

Note: All bold values highlight statistically significant results.

Abbreviations: DS, Dravet syndrome; FU, follow-up; IPES, Impact of Pediatric Epilepsy Scale; PedsQL, Pediatric Quality of Life Inventory; SDQ, Strength and Difficulties Questionnaire; *t*, *t* test.

[a]Summarized data from UK published norms for the PedsQL Core including 665 healthy children (Upton et al.[17]).

TABLE 2 Univariate and multivariate regression analysis for predictors of HRQOL at baseline.

		Univariate regression			Multivariate regression			
Predictor variables	***B***	**ΔR^2**	***F***	***p*-Value**	**β**	**ΔR^2**	***t***	***p*-Value**
Whole cohort ($n = 68$)								
Epilepsy severity (mild to very severe)	−10.603	.187	13.657	.001	−.416	Overall model = 0.33	−3.765	<.001
SDQ total score (baseline)	−1.743	.217	16.477	<.001	−.395		−3.568	.001
Patients (0–5) ($n = 28$)								
Epilepsy severity (mild to very severe)	−11.914	.184	6.192	.021	−.525	Overall model = 0.35	−3.035	.007
Younger age at first seizure	2.646	.091	3.198	.088	.412		2.382	.027
Patients ≥6 years old ($n = 40$)								
SDQ total score (baseline)	−1.760	.169	7.509	.010				

Note: Whole cohort ($n = 68$), in patients 0–5 ($n = 28$) and in patients ≥6 years old ($n = 40$).

Abbreviations: *B*, unstandardized coefficient; *F*, *F*-test; HRQOL (PedsQL total score), health-related quality of life; SDQ, Strength and Difficulties Questionnaire; *t*, *t* test; β, standardized coefficient; ΔR^2, adjusted *R* square.

TABLE 3 Univariate and multivariate regression analysis for predictors of HRQOL at follow-up.

		Univariate regression			Multivariate regression			
Predictor variables	***B***	**ΔR^2**	***F***	***p*-Value**	**β**	**ΔR^2**	***t***	***p*-Value**
Whole cohort ($n = 68$)								
Epilepsy severity (mild to very severe)	−8.860	.121	9.498	.003	−.354	Overall model = 0.18	−3.023	.004
SDQ total score (baseline)	−1.095	.077	6.115	.016	−.267		−2.286	.026
Patients (0–5) ($n = 28$)								
FU SDQ total score	−2.307	.431	21.434	<.001				
Patients ≥6 years old ($n = 40$)								
Epilepsy severity (mild to very severe)	−10.612	.137	6.40	.016				
SCB increasing seizure frequency	−12.689	.082	4.13	.050				

Note: Whole cohort ($n = 68$), in patients 0–5 years old at baseline ($n = 28$) and in patients ≥6 years old at baseline ($n = 40$).

Abbreviations: *B*, unstandardized coefficient; *F*, *F*-test; FU, follow-up; HRQOL (PedsQL total score), health-related quality of life; SCB, sodium channel blocker; SDQ, Strength and Difficulties Questionnaire; *t*, *t* test; β, standardized coefficient; ΔR^2, adjusted *R* square.

reported delayed diagnosis as a fundamental challenge, with at least 50% of families not receiving a diagnosis for their child with DS for >3 years. Many of these patients were misdiagnosed and were commonly treated with SCBs (frequently carbamazepine and lamotrigine),[14,23] which have been postulated as causal factors in the exacerbation of the disease course.[8,24,25] Conversely, the use of anti-seizure treatment plans specifically tailored to patients with DS can lead to improvements in seizure reduction. In 2000 Chiron et al.[26] found that adding stiripentol to valproate and clobazam in children with DS led to more than a 50% reduction in tonic–clonic seizures in 71% of participants. The addition of cannabidiol to standard anti-seizure treatment in a study of 120 children and young adults with DS and drug-resistant seizures resulted in a greater reduction in convulsive seizure frequency than placebo.[27] More recently, fenfluramine has been associated not only with a reduction in seizure frequency in up to 70% of patients[28,29] but also with improvement in global impression and QOL scores,[30] suggesting that appropriate pharmaceutical treatment might have a positive impact on HRQOL. Further studies are needed to determine the impact on HRQOL of anti-seizure medications used in patients with DS patients.

Our 10-year, prospective HRQOL data corroborate previous cross-sectional analyses, revealing that as well as a worse HRQOL in patients with DS compared to the general population, HRQOL in older patients is rated lower than in younger patients.[13] Given the significant decline in PedsQL total score, physical score, cognitive score, social score, and eating score in the younger group over the follow-up period of our study, it is likely that this previously observed result reflects disease progression and not simply ascertainment bias. Indeed, the first 5–6 years of life represent a progressively worsening phase with a widening gap compared to developmentally normal peers, in particular in terms of cognitive function and behavioral problems,[31,32] which stabilize

thereafter.[33] Up to two thirds of children with DS have been found to score in the abnormal range for behavioral or conduct disorders.[8,22,34,35] We found that a worse baseline SDQ score was predictive of poorer HRQOL at 10-year follow-up, which corroborates findings from other studies regarding the crucial role played by behavioral factors in the HRQOL of patients with DS[23,34,36,37] and is consistent with the possibility that behavioral problems, in particular when observed at a young age, may reflect a more severe disorder.[14,34] Given the increasing recognition that seizures are not the main cause of the comorbidities in DS,[38,39] but that their severity is affected by the underlying *SCN1A* channelopathy,[18,40,41] it remains to be seen whether new precision therapies that target the underlying channelopathy might not only improve seizure control but also affect the presence and severity of comorbidities.[21,41]

In this prospective series of patients with DS, we observed a 5.8% mortality after 10 years. This is within the range of previously reported values varying from 3.75% in parent-led databases to 17.5% in medical series, confirming that DS is associated with significant mortality.[23,42] Our rates are not as high as in other series. Ascertainment bias might play a role, as the majority of DS deaths tend to occur in early childhood, whereas our patients tended to be older, with the majority being 6 years of age or older at study onset.[23,42] The cause of death reported in our cohort appears to be similar to that of previous studies, with four of seven (57%) being attributed to sudden unexplained death in epilepsy (SUDEP).[23,42]

There are several limitations to this study. Nearly 40% of contacted carers/patients did not respond, thereby introducing a potential bias; however, there was no marked difference in demographic data between responders and non-responders. Comparing over 20 clinical and demographic characteristics among responders and non-responders (Table S1) we note the following differences: responders more frequently experienced a prolonged first seizure and although ~40% of patients with DS in both groups experienced status epilepticus, the age at onset appears earlier in the responders. We further observe that the age at which development was noted to be abnormal is younger in the non-responder group. These findings do not suggest that either responders or non-responders consistently present with a more severe disease phenotype.

Although patients had access to up-to-date treatment during the 10-year follow-up period, our results do not reflect the effects from newer anti-seizure medications such as cannabidiol or fenfluramine, as these treatments have only recently started to become available.

5 | CONCLUSIONS

Early diagnosis and management of DS, including avoidance of SCBs, appears to be especially important in mitigating factors that negatively impact long-term HRQOL in patients with DS. Indeed, the impact of epilepsy severity on baseline and follow-up HRQOL underscores the need for careful therapeutic strategies, including the use of second-line anti-seizure medication as advised in the latest European and international guidance.[43,44] This study highlights the significant HRQOL-associated physical, social, and cognitive decline, which particularly affects younger patients with DS. The high prevalence of behavioral problems in DS and their significant impact on quality of life, independent of epilepsy-related factors, emphasizes the need for active management and treatment of these difficulties and reinforces the importance evoked in previous studies,[45] of early intervention in order to mitigate the neurodevelopmental comorbidities that accompany Dravet syndrome.

AUTHOR CONTRIBUTIONS

Phoebe Makiello: Writing – Original Draft Preparation (lead), Writing – Review & Editing, Data Curation, Formal Analysis (lead), Visualization, Validation. Tony Feng: Visualization, Writing – Review & Editing. Benjamin Dunwoody: Investigation, Writing – Review & Editing. Felix Steckler: Investigation, Writing – Review & Editing. Joseph Symonds: Writing – Review & Editing. Sameer M. Zuberi: Conceptualization, Project Administration, Methodology, Writing – Review & Editing. Liam Dorris: Formal Analysis, Writing – Review & Editing. Andreas Brunklaus: Project Administration (lead), Conceptualization, Supervision, Writing – Review & Editing (lead), Funding Acquisition, Methodology, Resources, Validation.

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CONFLICT OF INTEREST STATEMENT

A.B. has received honoraria for presenting at educational events, advisory boards, and consultancy work for Biocodex, Jazz/GW Pharma, Encoded Therapeutics, Stoke Therapeutics, Nutricia, and UCB/Zogenix. S.M.Z. has received honoraria for presenting at educational events, advisory boards, and consultancy work for GW Pharma, Zogenix, Biocodex, Encoded Therapeutics, Stoke Therapeutics, and Nutricia. The remaining authors have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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