Epilepsy & Behavior 158 (2024) 109958

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Research Paper

A tool for Dravet syndrome-associated neuropsychiatric comorbidities evaluation (DANCE)

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ARTICLE INFO

Keywords:
Dravet syndrome
Comorbidities
Neuropsychiatric
Quality of life

ABSTRACT

Background: Dravet syndrome (DS) is a rare and severe form of epilepsy that begins in infancy, which is primarily caused by pathogenic variants in the *SCN1A* gene. DS is characterized by prolonged and frequent drug-resistant seizures, as well as developmental delays and behavioral problems. The identification of these comorbidities is based on clinical interview and relies on healthcare professionals (HCPs) experience.
Methods: We assembled a group of expert HCPs and caregivers to create a screening checklist for assessing DS-Associated Neuropsychiatric Comorbidities (DANC). The checklist includes questions related to cognitive and psychiatric domains, motor skills, and the impact of DS on families' daily lives. We administered the checklist to 24 caregivers of DS patients from Belgium, France, and Spain. After piloting, we obtained feedback from expert HCPs and caregivers to refine the checklist.
Results: DS patients showed a wide array of neuropsychiatric symptoms related to DS. The most common cognitive domains reported were attention difficulties and multitasking problems (18/24 caregivers), and impulsivity (17/24), while the most common psychiatric symptoms were temper tantrums (14/24), mood swings (13/24) and autism spectrum disorder (12/24). Balance and coordination problem have been reported in almost all patients with a statement of only 4/23 with complete mobility. Most patients were dependent on others for self-care and eating, and presented sleeping disturbances. Caregivers reported high levels of stress in the family unit, both between siblings and parents. Results show that the main concerns of parents were the behavior and the cognition of the person with DS. The quantitative feedback results showed good-to-very good scores on usefulness, ease of completion, clarity and comprehensiveness of the checklist.
Conclusions: This pilot study suggests that the DANCE checklist could be a useful screening tool in daily practice for neuropsychiatric comorbidities facilitating their diagnosis and treatment, and empowering both caregivers and patients.

1. Introduction

1.1. Dravet syndrome clinical manifestations and burden

Dravet syndrome (DS) was initially referred to as "severe myoclonic epilepsy of infancy" (SMEI) but was later named after Dr Dravet [1], who first described it in 1978. DS is a rare and severe form of epilepsy that begins in infancy, and it affects an estimated 1 in 15,700 to 1 in 40,000 people worldwide [2–4]. *SCN1A* mutations are found in 85 % of patients [4,5], leading to a loss of function of the ion channel $Na_v1.1$ in GABAergic interneurons. This disruption induces a reduction in the inhibitory tone of the central nervous system [4,6]. DS usually manifests

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https://doi.org/10.1016/j.yebeh.2024.109958
Received 16 May 2024; Received in revised form 19 July 2024; Accepted 19 July 2024
Available online 26 July 2024

between the ages of 4 and 12 months with tonic-clonic or generalized clonic seizures, however, as time passes, seizures may be less frequent while cognitive, motor, and behavioral impairment, as well as other comorbidities, become more evident [9,6]. DS is also characterized by a 10–15 % risk of sudden unexpected death in epilepsy (SUDEP) [7–9], especially in patients aged under 10 [10–12].

Individuals with DS experience delays in reaching developmental milestones; cognitive impairment, including memory and attention deficits; as well as difficulty with communication and learning; behavioral problems such as hyperactivity, impulsivity and autistic spectrum traits; gait and motor problems related to coordination and balance intellectual disability; gastrointestinal problems and dyssomnia [11,13–18]. To date, the cognitive impairment seems the results of both the genetic component and the seizure burden. However, the underlying mechanisms of behavioral disturbances remain to be better understood. Higher seizure frequency was associated with the occurrence of more comorbidities and lower intelligence quotient (IQ), however the current studies focusing on this relationship show contrasting results [11,12].

The neuropsychiatric comorbidities have a significant impact on the quality of life (QoL) of individuals with DS and their families. The disease burden of DS includes not only the physical symptoms, but also the emotional and social impact of the condition [19]. As a result, caregivers may often experience emotional and financial strain due to providing a high level of care for the individual with DS [20,21].

Currently there is no known cure for DS, treatments are mainly focused on managing symptoms and reducing the frequency and severity of seizures. Despite the use of multiple antiseizure medications (ASMs), most patients with DS continue to experience seizures. Therefore, other treatments such as the ketogenic diet and vagus nerve stimulation may be considered in some cases [1,4,22–25]. Treatment should not only be focused on seizure management, but also on neuropsychiatric comorbidities, which are sometimes underestimated, and a multidisciplinary approach should be applied [26,27]. While DS is not preventable given its genetic origins, a combination of early diagnosis, suitable treatment, and proactive measures to prevent seizures can improve the overall prognosis and well-being of individuals affected by DS.

1.2. The DANCE project

Given the array of challenges associated with DS, focusing only on the early diagnosis and seizure management is not providing a comprehensive patient care. Unfortunately, the epilepsy phenotype might hide the cognitive and the behavioral issues. Therefore, recognizing non-seizure outcomes is crucial for a holistic approach. For these reasons we developed a checklist for the DS-Associated Neuropsychiatric Comorbidities Evaluation or DANCE, similarly to what was done for tuberous sclerosis complex-associated neuropsychiatric disorders (TAND) [28]. The DANCE project seeks to develop a tool to help both the clinicians and the affected families to easily identify comorbidities and assess their severity, as well as to know how these symptoms affect QoL of patients and caregivers. The goals of the checklist are (1) early, consistent and systematic identification of DANC, (2) providing effective treatment and management of the condition and its comorbidities, and (3) guide healthcare teams and caregivers in personalized intervention and management of the disease. This work presents the pilot study, which assesses the first goal. Goals 2 and 3 will be evaluated in future project phases.

2. Materials and methods

2.1. Checklist design

After a thorough bibliographic review on DS diagnosis and DANC, a focus group was convened, consisting of seven experts including neurologists, neuropsychologists, and patient advocacy group (PAG) representatives. HCPs and caregivers were provided with an online version of the checklist in English and requested to offer iterative qualitative feedback.

Subsequently, a pilot study was conducted with 24 DS caregivers from Belgium, France, and Spain completing the initial version of the checklist in English. The caregivers who participated in this study residing in Belgium, France, and Spain were English speakers. Upon completion, caregivers were asked to provide quantitative feedback by rating the questionnaire on a scale from 1 to 5, assessing its comprehensiveness, clarity, ease of completion, and overall usefulness.

Following the pilot study, a second focus group was organized, involving HCPs, PAG representatives, and caregivers who participated in the pilot phase. This session was dedicated to gathering qualitative feedback to further refine the checklist. The refined version of the checklist can be found in the supplementary material.

The checklist was designed with user-friendly questions, nevertheless, the option to seek assistance from HCPs should be readily accessible. The questionnaire is for the most part close-ended. Multiple choice questions (MCQs), forced-choice questions, trichotomous, and rating questions have been employed. Each question is tailored to avoid non-response.

The study was conducted in compliance with the Declaration of Helsinki. The protocol was reviewed by the ethical committee of the Hospital de la Santa Creu i Sant Pau. All participants received information about the study and provided written informed consent. Personal data were dissociated from the results in compliance with the EU General Data Protection Regulation (GDPR).

2.2. Statistical analyses

Data analyses and graphical representations were carried out using GraphPad 8.0.1. Continuous variables were represented as mean and standard deviation and categorical variables were represented as frequencies. Bar graphs and pie chart were created by counting the number of occurrences for each variable. The scatter dot plot was represented using Microsoft Excel, linear regressions and correlation analyses (Spearman correlation coefficient r) were performed in GraphPad 8.0.1 where the R^2 and p-values were calculated.

3. Results

3.1. The DANCE checklist

The questionnaire is divided into 7 sections: (1) Demographic information about the patient and the caregiver; (2) Patient's cognition and behavior; (3) Patient's motor skills; (4) Patient's daily life; (5) QoL of the family; (6) Expression of concern and worries; (7) Feedback on the questionnaire.

The checklist begins with a brief introductory segment, then follows a demographic data segment where data about the patient and the interviewee are collected. The second part of the checklist is focused on cognition and behavior. Here, the caregiver outlines the performance of the patient in the following areas: language, intelligence quotient (IQ) or developmental quotient (DQ) depending on the age of the patient, cognitive and psychiatric symptoms. Since not all patients received an official IQ or DQ evaluation, choices were given ranging from normal intellectual ability to profound intellectual disability. The third segment deals with motor skills of the patient. Information on mobility, balance, coordination, gait, ataxia, and parkinsonism is entered. The fourth section of the checklist aims to know how well the patient can take care of themselves in daily activities, their eating habits, and their sleep hygiene. The fifth part of the checklist aims at assessing how the parents' and siblings' daily life has changed due to DS. In the sixth part, the caregiver is required to give their grading of worry on cognition, behavior, motor skills, daily life, eating, sleeping patterns of the patient and daily life of the family. The questions follow a rating in a scale of 1 to 10. Finally, the interviewee provides quantitative feedback about the

questionnaire, rating on comprehensiveness, clarity, ease of completion and usefulness in a scale from 1 to 5.

3.2. Demographic data

We interviewed 24 caregivers of people with DS from Belgium, France and Spain in the pilot phase. The patients' ages ranged from 0.67 to 24 years old, with a mean ± SD of 10.87 ± 7.20 years old (Fig. 1A). Parents reported that the person with DS had no other sibling (6/24), one other sibling (9/24), two other siblings (2/24) or more (7/24) living in the same home with the patient.

3.3. Cognition and behavior of DS patients

The DANCE checklist initially assesses language skills of the persons with DS. Analyzing DS patients above 2 years of age (n = 23), only 2 caregivers reported normal or fluent language abilities, while 13/23 reported simple language, 3/23 reported the patients producing few single words (less than twenty), while the remaining 5/23 reported the patients being non-verbal (Fig. 1B). Seventeen out of twenty-three caregivers reported to have or have had language evaluation and language support from an HCP.

When inquired about the IQ or DQ score, 8/24 patients did not answer because they did not have a formal evaluation or because they could not estimate the IQ or DQ. Out of the caregivers who answered, 3/16 patients were reported to have normal intellectual ability (mean age = 5.9 years, range = 0.67–10 years), while the others presented lower IQ or DQ ranging from mild to profound intellectual disability. Importantly, only 15/24 caregivers reported to have had a formal evaluation of intelligence by a professional using neuropsychological tests. As expected, the IQ/DQ evaluation was robustly correlated to the language abilities of the patients (Spearman r = −0,8399; p-value = 0.0001).

Other cognitive and behavioral outcomes were evaluated (Fig. 2A). The most common in DS patients were attention difficulties and multitasking problems (reported by 18/24 caregivers), impulsivity (17/24), repetitive behaviors (16/24), inflexibility (16/24) and visuospatial skills issues (16/24). We also asked the caregivers if the person with DS had received any diagnosis for these domains. Out of 24 parents, 5 said they had not received a formal diagnosis for any of the domains that were evaluated before. Moreover, 6/24 parents said they had received no professional support for treating cognitive symptoms, and they were evenly distributed across the three countries.

Next, the questionnaire inquired about psychiatric aspects of the patients (Fig. 2B). The most commonly reported were temper tantrums (14/24), mood swings (13/24) and autism spectrum disorder (12/24). We also inquired if the patients had a formal diagnosis (15/24, with 5 patients in each country) or have had psychiatric support (12/24). Of the 12 DS patients who lacked psychiatric support, 5 were from Spain, 4 from France, and 3 from Belgium.

3.4. Motor skills of DS patients

During the analysis of motor abilities, one patient who was under the age of two years was excluded to prevent confusing typical developmental milestones with mobility issues associated with DS. As shown in Fig. 3A, only 4/23 patients were reported to have complete mobility while 12/23 presented some difficulties, 4/23 need significant support and 3/23 need a wheelchair. Due to the high burden of the disease on mobility, most patients (20/23) received physical therapy. The most common mobility impairments were balance and coordination problems (21/23), followed by ataxia (14/23), crouch gait (9/23), and parkinsonism (7/23) (Fig. 3B). As the results indicate, some of the DS patients who were reported to be completely mobile, still experience balance and coordination problems.

3.5. Daily life of DS patients

Regarding the daily life of the patients, no DS patient was independent in self-care. Patients were reported to be dependent on others for their daily life activities (18/24) or to have some self-care skills (6/24).

We considered tasks such as eating and sleeping as the main domains to evaluate daily life independency. Regarding eating, 7/24 DS patients were able to eat independently, 8/24 patients were dependent on others while 9/24 presented some self-care skills during eating. Most patients (16/24) were reported to eat a normal quantity of food, however they were very selective with the type of food (16/24). When asked about swallowing problems, most caregivers (19/24) did not report them.

Inquiries about sleep revealed that most patients do not have difficulties falling asleep (16/24), however more than one third of patients wake up early (9/24). Seven patients were reported to wake up because of seizures while 9/24 did wake up without them. Interestingly, only 1/24 patient was reported to suffer sleep apnea, however 8/24 caregivers were not sure about this domain, therefore this data is worth being further investigated at a clinical level (Fig. 4A). In fact, 19/24 patients did not receive a polysomnography study and 17/24 did not receive sleep support. Sleep medication was taken by 7/24 patients. As an outcome which could impact the daily life of both patients and families, caregivers were asked to report whether if the patient slept in the same room (10/24) or in the same bed (7/24) with the caregivers or if the patient slept under the supervision of an alarming system (7/24) (Fig. 4B).

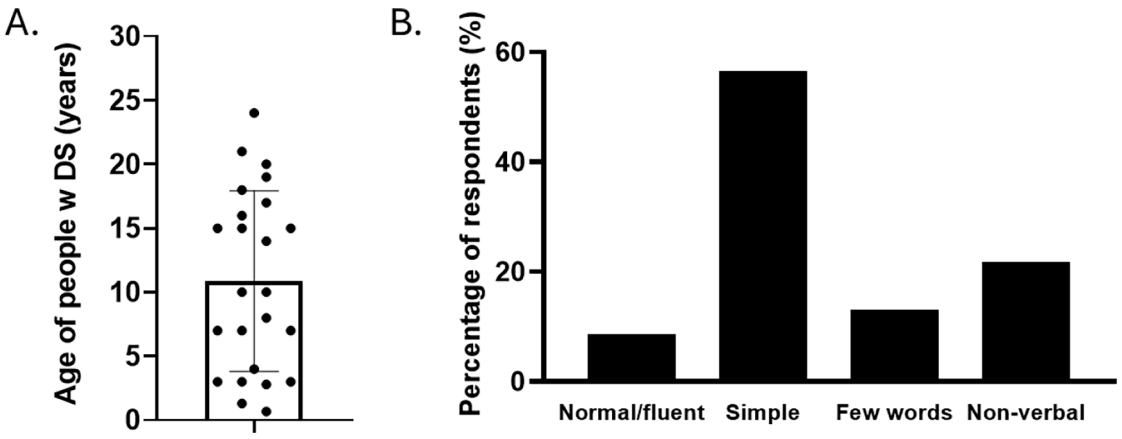

Fig. 1. Demographic and language characteristics of DS patients in the pilot phase. A. Age distribution of DS patients (n = 24). B. Language level of DS patients. The language level is assessed as the number of words produced by the patient (n = 23). The percentage of respondents is represented.

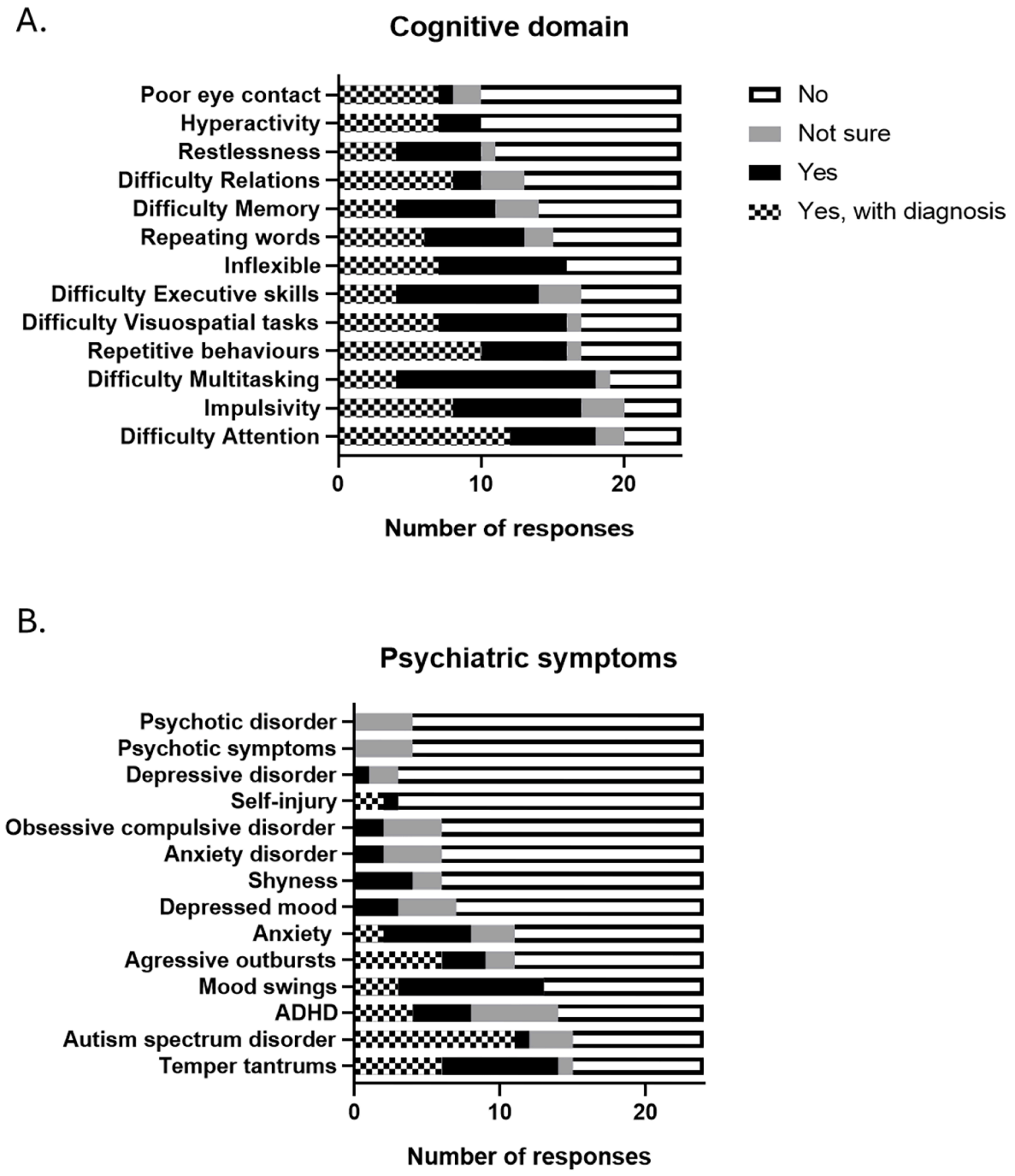

Fig. 2. Cognitive and psychiatric symptoms in DS patients as reported by caregivers (n = 24). A. Bar chart showing the prevalence of cognitive symptoms. B. Bar chart showing the prevalence of psychiatric symptoms. Caregivers were asked to answer whether if the cognitive or psychiatric symptom was present ("Yes", black) and if they have had a diagnosis ("Yes, with diagnosis", black and white checks). Other possible responses were "Not sure" (grey bar) or "No" (empty bar).

3.6. Impact of DS on families' daily life

Due to the high burden of DS on caregivers and siblings, aspects of the daily life of the whole family were assessed. As shown in Fig. 5A, 18/24 caregivers reported high levels of stress between parents leading to significant relationship difficulties and 14/24 caregivers reported stress within the family, including siblings, who were reported to have their life completely changed (19/24). We also asked if family life had been significantly altered because of DS, and 22/24 caregivers answered affirmatively. As shown in Fig. 5B, the most altered aspects of daily life were parents' work (20/24), and parents' leisure and social time (19/24).

In addition, the caregivers were asked to evaluate how much DS changed, bothered, troubled, and distressed the family on a scale from 1 to 5 with a result of 4.21 ± 0.78 (mean ± SD). Fifteen families out of twenty-four received psychological support. As a result, the mother was the most common family member to have had psychological support (13/15), followed by sibling(s) (6/15) and the father (3/15).

3.7. Expression of concern and worries

Furthermore, we evaluated the caregivers' most significant concerns (Fig. 6A). On a scale from 0 to 10, the most severe concerns were the patients' behavior (mean ± SD=8.75 ± 1.22), cognition (8.58 ± 2.00),

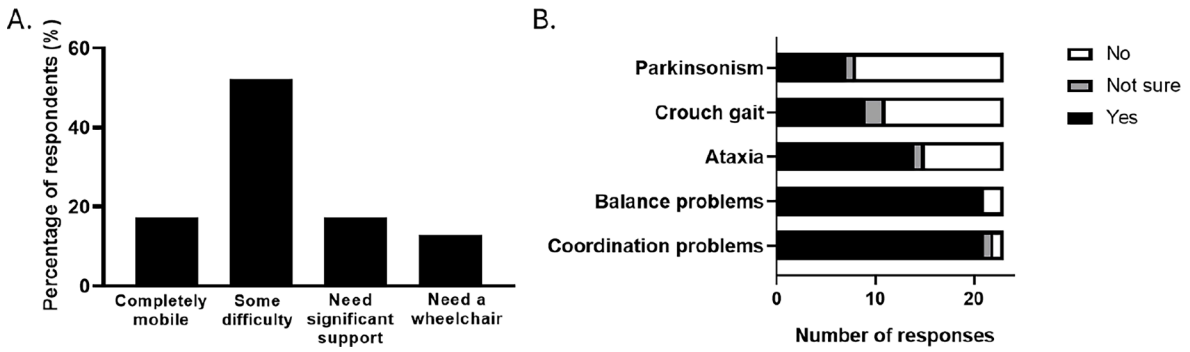

Fig. 3. Mobility features of DS patients (n = 23). A. Bar graph representing the percentage of patients who are completely mobile, have some mobility difficulties, need significant support or are completely dependent and need a wheelchair. B. Bar chart representing the prevalence of several mobility symptoms. Caregivers were asked to indicate whether if the symptom was present ("Yes", black bar), if they were "Not sure" (grey bar) or if it was not present ("No", empty bar).

Fig. 4. Sleep hygiene of DS patients (n = 24). A. Prevalence of sleeping problems in DS patients. B. Location where the person with DS sleeps and use of seizure alarm system. Caregivers were asked to indicate whether if the symptom was present ("Yes", black bar), if they were "Not sure" (grey bar) or if it was not present ("No", empty bar).

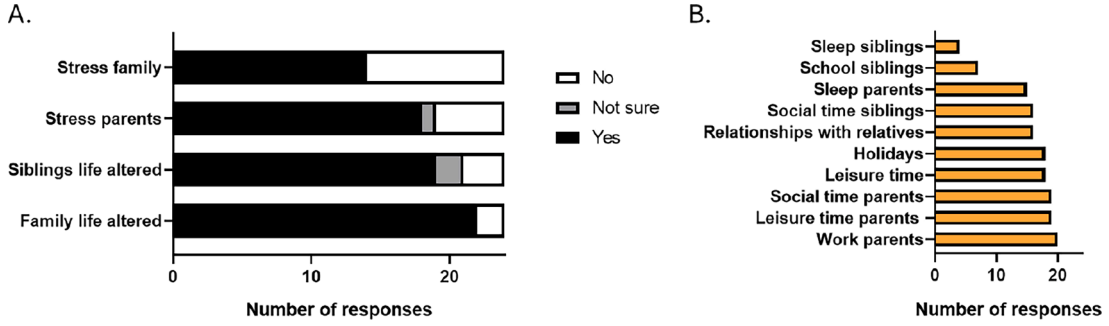

Fig. 5. Daily life of families affected by DS (n = 24). A. Bar chart representing the prevalence of daily life alterations in different domains such as the whole family life, the life of siblings, the presence of stress between parents or in the whole family, including siblings. Caregivers were asked to indicate whether if the symptom was present ("Yes", black bar), if they were "Not sure" (grey bar) or if it was not present ("No", empty bar). B. Domains where daily life is altered as reported by caregivers of persons with DS.

and the daily life of patients (8.50 ± 2.11) and family (8.29 ± 2.20). While worries about motor skills of the patient (7.63 ± 2.34), eating (7.25 ± 2.15) and sleeping (6.38 ± 2.95) were less important, as reported by the caregivers. Interestingly, the caregivers' mean concern ranges from 5 to 10, confirming that DS imposes a significant burden on caregivers. As shown in Fig. 6B, when we correlate the mean concern expressed by the parents with the number of cognitive and psychiatric diagnoses in the patients (linear regression $R^2 = 0.0461$), the correlation is not significant, meaning that the number of domains diagnosed does not does not well reflect the concerns of caregivers (Spearman r = 0.2764; p-value = 0.1911). The mean concern was also analyzed in relation to the age of the patient, revealing no correlation between the

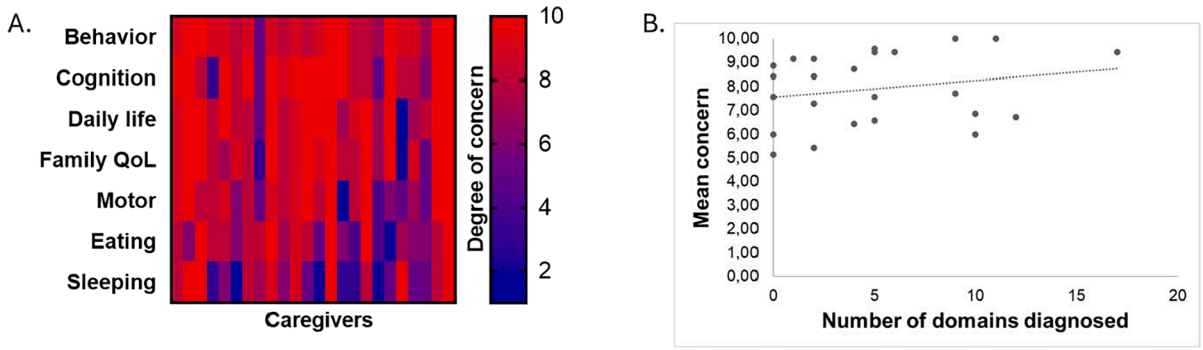

Fig. 6. Concerns and worries of DS caregivers (n = 24). A. Heatmap of the concerns' ratings by DS caregivers. Each column represents a caregiver, and each row represents a concern. Ratings range from low concern (1, blue) to high concern (10, red). B. Scatter plot of the number of cognitive and psychiatric diagnoses in each DS patient versus the mean concern rating by their caregiver. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

two variables (Spearman r = −0,0646; p-value = 0.7641).

3.8. Feedback on the questionnaire

Finally, we asked caregivers to provide quantitative feedback about the questionnaire from 1 to 5 on comprehensiveness (mean ± SD 4.25 ± 0.79), clarity (4.04 ± 0.86), ease of completion (4.46 ± 0.83) and usefulness (4.47 ± 0.59). This feedback, together with a focus group with HCPs and caregivers, allowed for the refinement of the questionnaire.

4. Discussion

This pilot study confirms the significantly high occurrence of comorbidities in individuals with DS, along with a substantial burden of neuropsychiatric symptoms affecting both patients and caregivers. In addition, we identified a broad spectrum of neuropsychiatric comorbidities, affecting language, cognitive and psychiatric functions, as well as self-care abilities. This underscores the profound impact of the condition on the daily lives of both the individuals with DS and their families. The study also highlighted the considerable stress experienced by siblings and parents, coupled with their concerns regarding the behavior and cognitive abilities of the family member with DS.

Interestingly, our data suggest that the number of cognitive and psychiatric domains diagnosed do not reflect the concerns of the caregivers. This may be due to the inherent subjectivity of this tool, or it may indicate a discrepancy between the caregiver's opinion and the NHS capacity to evaluate the patient's cognitive and psychiatric condition. Since DANC are often not formally diagnosed, these findings could pave the way for future studies aimed at quantifying the NHS's ability to diagnose DANC and analyzing the discrepancies between caregivers' concerns and official evaluations. The checklist was designed as previously described, emphasizing the significance of these domains. This is supported by natural history or prospective studies that evaluate the occurrence of comorbidities and disease burden. It was recently shown that DS patients older than 2 years present language and communication delays, and developmental stagnation [29]. Similar results were obtained for behavior in other studies, where more than 60 % of the children above the age of 12 years had behavioral problems [30]. Speech impairment was also observed in more than 65 % of patients [31]. Other studies showed that, although epilepsy severity decreased with age, comorbidities were more apparent including autistic features, behavioral problems and motor problems [32]. In addition, recent sleep studies showed disturbed sleep patterns in DS patients, independent of seizure frequency [33]. For these reasons the checklist was designed to have different sections encompassing cognition and behavior, motor skills and daily life (including sleeping and eating habits).

Regardless of the DANC impact on families and patients, neuropsychiatric evaluation is time-consuming and needs specialized staff, and as a result, these comorbidities may remain underdiagnosed and may not be addressed adequately. During the diagnostic process, HCPs may use several validated scales to assess comorbidities [34–39], however, to date, there are no specific questionnaires that comprehensively assess the complexity of DANC. For this reason, the DANCE checklist was developed as an easy and objective tool for DANC screening, with the goals to minimize the limitations of currently available diagnostic tools for DS and standardize the clinical evaluation by guiding the examination to be consistent for every patient.

This study presents limitations such as subjective nature of the questionnaire. The responses to the checklist may be influenced by the patient's cognitive or emotional state at the time of answering, which can distort the picture of the disease and its severity. The questionnaire relies on the caregiver's testimony, rather than the patient's self-report, which may not reflect the symptoms that are intrinsic to the patient. Therefore, the presence of experienced HCPs may be essential to obtain more objective information and resolve any doubts from the caregiver. These difficulties are inherent to the assessment of DS comorbidities, as many patients have low IQ/DQ and are unable to perform a self-assessment of their neuropsychiatric symptoms. Also, the questionnaire was developed in English, which may have induced a language-based bias. However, the recruited caregivers were English speakers and they received assistance from HCPs in completing the questionnaire. In the next steps of this project, the survey will be translated-back-translated into several different languages. Another limitation is that in this work we present the results from a pilot study with a limited number of questionnaires. In the future, the checklist will be extended to other HCPs and PAGs in different countries. By extending its use, the final version of the questionnaire will be validated, to propose a reliable tool for DANC evaluation.

Additionally, the pilot study presented in this work focused solely on achieving the first goal of the DANCE project: developing a tool for the early, consistent, and systematic identification of DANC. In the next phases of the project, we will implement the second and third goals: providing effective treatment and management of the condition and its comorbidities, and guiding healthcare teams and caregivers in personalized intervention and disease management. With a DANC evaluation based on the tool developed in this work, families affected by Dravet syndrome will be empowered and have increased awareness, enabling more informed conversations with their neurologist. Simultaneously, a systematic evaluation will assist HCPs in managing and treating DANC. Initiating comprehensive treatment for DS promptly is only possible if an early diagnosis is achieved. Novel treatment modalities are currently being investigated, including gene therapy approaches [40], that hold the potential to prevent or slow down disease progression, however, their effectiveness depends on a prompt and accurate follow-up of seizure frequency and duration, and comorbidities evolution. The DANCE checklist can serve as a valuable, screening, and follow-up tool,

and as such can be used in a complementary fashion to other screening tools. In addition, the checklist can also serve as a home-based questionnaire to assess the QoL of patients and their caregivers.

5. Conclusions

We expect that the DANCE checklist will contribute to easily screen neuropsychiatric comorbidities in patients with DS. We anticipate that the questionnaire will help identifying distinctive DS comorbidities patterns, facilitating a more objective process of diagnosis. Additionally, the use of this tool could facilitate prompt interventions, reducing the societal and economic impact of the disease.

Moreover, the checklist holds the potential to monitor patients longitudinally, especially when assessing the impact of various treatment interventions, both pharmacological and non-pharmacological. Through such longitudinal studies, valuable insights can be gained, enabling safe and efficacious combinations of treatments.

Ethical publication statement

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.

Funding sources

This study has been conducted independently by the authors with a funding by Biocodex.

CRediT authorship contribution statement

Simona Giorgi: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation. **Stéphane Auvin:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Conceptualization. **An-Sofie Schoonjans:** Methodology, Investigation. **Eulalia Turón:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Irene Sánchez-Miranda:** Investigation. **Antonio Gil-Nagel:** Writing – review & editing, Methodology, Investigation. **Lieven Lagae:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation, Conceptualization. **José Ángel Aibar:** Writing – review & editing, Supervision, Software, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JAA and SG, as president and scientific director of Fundación Síndrome de Dravet, have received grants and/or financial support from GW Pharma, Zogenix, Ovid Therapeutics, Encoded Therapeutics, Biocodex, Praxis, Stoke, Takeda, UCB, Epygenix, Jazz Pharmaceuticals and StrideBio to help carry out research projects or provide consulting services. The honoraria have always been donated directly or indirectly to the Fundación Síndrome de Dravet. The other authors have stated that they had no interests that might be perceived as posing a conflict or bias.

Acknowledgments

The authors would like to thank the families and caregivers who participated in the pilot study by completing the survey.

The other authors have stated that they had no interests that might be perceived as posing a conflict or bias.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2024.109958.

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