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ORIGINAL ARTICLE

Adaptive behaviour in adolescents and adults with Dravet syndrome

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Abstract

Aim: To explore the feasibility of using an adaptive behaviour profile (ABP) assessment generated from a well-known measure—the Vineland Adaptive Behavior Scales, Second Edition (VABS-II)—as an instrument for outcome measures in adolescents and adults with Dravet syndrome.

Method: We administered the VABS-II to 35 adolescents and adults with Dravet syndrome (15 males; mean age 24 years, SD 8 years, range: 12–46 years) and collected epilepsy history and neurological features at the time of assessment. We conducted a cross-sectional analysis of VABS-II raw scores and performed cluster analysis to identify different subgroups. We then explored possible relationships between clinical and epilepsy features, ABPs, and age.

Results: Most participants obtained the minimum standard scores in the various VABS-II subdomains, while the raw score analysis outlined interindividual and intraindividual differences among skills. We found two subpopulations: one with a 'lower' ABP and one with a 'higher' ABP, corresponding respectively to individuals in whom myoclonic seizures or generalized spike-and-wave activity were present ('complete phenotype') or absent ('incomplete phenotype') on electroencephalography.

Interpretation: This study further delineates the natural history of Dravet syndrome. The assessment of an ABP through the VABS-II raw score analysis provides a means by which to illustrate profiles of adaptive behaviour in adolescents and adults with Dravet syndrome but shows limitations related to poor sensitivity in measuring fine clinical details. There is a need for new and more specific tools to monitor patients with developmental and epileptic encephalopathies.

Developmental and epileptic encephalopathies (DEEs) are a group of diseases characterized by developmental impairment and phases of plateauing or regression induced by epileptic activity that contribute to cognitive outcomes.[1] It is a complex and heterogeneous group, with wide variability of impaired functioning, primarily due to genetic alteration.[2]

Dravet syndrome is a well-known type of DEE caused by congenital mutations in the *SCN1A* gene.[1,3] Symptom onset is in the first year of life with convulsive seizures and status epilepticus in otherwise typically developing infants. During childhood, drug-resistant epilepsy occurs together with developmental slowing, leading to cognitive impairment.

This original article is commented on by Meskis on pages 732–733 of this issue.

Abbreviations: ABP, adaptive behaviour profile; ARS, adjusted raw score; DEE, developmental and epileptic encephalopathy; VABS-II, Vineland Adaptive Behavior Scales, Second Edition.

Language disturbances, motor disorders, and social and behavioural issues complete the clinical picture.

In Dravet syndrome, and in DEEs in general, targeted treatment aims to not only reduce seizure burden but also establish appropriate rehabilitation interventions aimed at preventing and minimizing comorbidities, which largely contribute to exacerbation of the clinical picture. Reduction of comorbidities is also a need frequently expressed by the caregivers and families of affected individuals.[4, 5]

Rehabilitation planning is challenging for individuals with DEEs. Interventions are tailored to the individual according to both personal abilities and vulnerabilities, which can be long-lasting; therefore, treatment goals need to be modified according to the individual's age.

Assessment of cognitive ability alone does not provide enough useful information to highlight individual skills and competences, as well as planning and modifying a treatment programme over time. This is especially true for adults with DEEs, for whom IQ scores typically show a 'floor effect'. Conversely, the evaluation of abilities of daily life, communication, socialization, and motor skills is useful for identifying treatment targets and potentially monitoring response to an intervention.[6]

In this study, we sought to explore the utility of an adaptive behaviour profile (ABP) assessment for outcome measures in adolescents and adults with Dravet syndrome through the use of the Vineland Adaptive Behavior Scales, Second Edition (VABS-II).[7] While these features have been reported in the paediatric literature for Dravet syndrome, there is limited understanding of their presentation in adolescence and adulthood.[8,9] Therefore, the current study may contribute to the literature by further delineating the natural history of Dravet syndrome and provide suggestions regarding intervention targets and concrete goals through forward-looking rehabilitation programmes.

What this paper adds

- Most adults with Dravet syndrome obtained the minimum standard scores in the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) subdomains.
- The VABS-II raw score analysis showed interindividual and intraindividual variability.
- Individuals with myoclonic seizures and/or generalized spike-and-wave activity on electroencephalography showed a worse adaptive behaviour profile.

METHOD

The current investigation is a monocentric study conducted at the Child Neuropsychiatry Unit of the University Hospital of Verona, Italy.

The sample consisted of 35 individuals with a clinical diagnosis of Dravet syndrome, longitudinally followed since 1978 and examined at our centre from 2017 to 2021.

Epilepsy history was collected for each individual, including age and presence of fever at first seizure, age at first afebrile seizure, recurrence of convulsive status epilepticus, seizure type according to the 2017 International League Against Epilepsy classification,[10] and presence of reflex seizures.

The VABS-II[7] was administered as an interview by a trained neuropsychologist to the caregivers of 10 adolescents (12–18 years) and 25 adults (>18 years) with Dravet syndrome between 2017 and 2021. The VABS-II is largely used in clinical practice with individuals with intellectual disability, including adults and individuals with DEEs.[8, 11, 12] The questionnaire explores the ABP from birth to 90+ years of age through four domains: communication (receptive, expressive, and written communication skills); daily living skills (personal, domestic, and community interaction skills); socialization (interpersonal relationships, play and leisure time, and coping skills); and motor skills (gross and fine). A composite score is also provided, summarizing the individual's skills in all four domains. Higher scores suggest higher adaptive functioning, while lower scores suggest lower adaptive functioning.

Standard scores (mean = 100, SD = 15) were reported for all individuals. Of note, standard scores were not calculated for the motor skills domain on the VABS-II due to a ceiling effect over the age of 6 years. Adaptive levels were derived from standard scores, differentiating the following groups: low (standard score = 20–70); moderately low (standard score = 71–85); adequate (standard score = 86–114); moderately high (standard score = 115–129); and high (standard score = 130–160).

To explore the ABP more deeply, we divided each participant's raw score by their age-expected raw score in all domains to obtain a percentage. We then conducted a cross-sectional analysis of VABS-II scores for the whole sample, considering both standard scores and adjusted raw scores (ARS).

Seizure frequency at the time of VABS-II administration was assessed from a seizure diary maintained by caregivers. Concomitantly, the presence/absence of ataxic gait, cortical myoclonus, pyramidal signs, and parkinsonism/bradykinesia was obtained through a complete neurological examination. Language ability was also tested during the medical visit and classified into four categories: absent; single words; short sentences; and simple conversations/normal. The existence of autistic traits was assessed during the course of clinical observation and through specific questions to caregivers.

After generating a descriptive analysis of the entire cohort's VABS-II data and electroclinical variables, we used a data-driven approach to explore potential differences in the population, that is, a two-step cluster analysis. A two-step cluster analysis is an exploratory tool implemented in SPSS v25.0 (IBM Corp., Armonk, NY, USA) designed to reveal

natural groupings (or clusters) within a data set.[13] It uses a distance measure to separate groups and then a probabilistic approach to choose the optimal subgroup model.[14] This analysis was performed separately using VABS-II ARS and electroclinical variables to identify subgroups with different ABPs (independently from electroclinical variables) and subgroups with different epilepsy phenotypes (independently from the VABS-II data). The number of clusters was determined automatically.

We then compared groups based on the cluster results to explore possible relationships between epilepsy features and ABPs. We compared variables not used in the respective cluster analysis, including outcome variables, using cluster membership as a grouping variable, by means of analysis of variance, Mann–Whitney *U* test, or Fisher's exact test respectively for continuous or categorical variables, as appropriate.

We further investigated the possible influence of age at test administration on VABS-II results by means of Spearman's rank correlation analysis. Finally, a descriptive analysis of the ABPs of the adult population was performed, reporting the most common well-mastered skills and vulnerabilities.

Ethical approval was not required by the institution's research ethics committee. Participants' caregivers gave written informed consent for the publication of the following results.

RESULTS

Demographic and clinical features

The sample consisted of 35 individuals (15 males; mean age 24 years, SD 8 years, range: 12–46 years) born between 1972 and 2008. *SCN1A* gene test revealed pathogenic variants in 31 out of 32 tested individuals.

Median age at first seizure was 5 months (range = 2–11 months). The first seizure occurred during fever in 17 individuals (median = 6 months; range = 3–11 months) and without fever in 18 individuals (median = 4 months; range = 2–9 months) (Figure S1). Prolonged convulsive seizures were experienced by most individuals (n = 29). Common seizure types were focal onset non-motor seizures (n = 30) and hemiclonic seizures (n = 28). Twenty-four individuals had absence seizures and 19 individuals experienced absence status epilepticus. Twenty-two individuals exhibited myoclonic seizures. Reflex seizures occurred in 19 individuals, 16 individuals experienced reflex seizures triggered by flashing lights, and 12 individuals experienced self-triggered reflex seizures. At ABP assessment, the age of individuals ranged between 12 years and 46 years (median = 20 years).

Seizures occurred daily/almost daily in three individuals (median = 26 years; range = 15–34 years), weekly in nine individuals (median = 31 years; range = 18–38 years), monthly in 12 individuals (median = 18 years; range = 12–46 years), were sporadic in four individuals (median = 20 years; range = 16–27 years), and were absent in seven individuals (median = 20 years; range = 13–32 years).

Twenty-six individuals showed tonic/tonic–clonic/tonic vibratory seizures; four had focal seizures and one (15 years) still showed myoclonic and absence seizures.

At neurological examination, ataxic gait was seen in 21 individuals (median = 21 years; range = 13–46 years) and was absent in 14 individuals (median = 20 years; range = 12–38 years). Cortical myoclonus was found in 21 individuals (median = 26 years; range = 14–46 years) and was not seen in 14 individuals (median = 19 years; range = 12–38 years). Parkinsonism/bradykinesia was observed in eight individuals (median = 19 years; range = 13–36 years) and was absent in 27 individuals (median = 21 years; range = 12–46 years). Pyramidal signs were seen in seven individuals (median = 34 years; range = 26–46 years) and were absent in 28 individuals (median = 19 years; range = 12–37 years).

Language was absent in five individuals (median = 26 years; range = 13–34 years). Of the remaining individuals, one individual produced isolated words (26 years), 16 individuals used only short sentences (median = 24 years; range = 12–46 years), and 13 individuals exhibited normal language or sustained a simple conversation (median = 19 years; range = 14–32 years).

Autistic features were observed in eight individuals (median = 30 years; range = 13–46 years). Complete data are shown in Figure 1.

VABS-II questionnaire results

Standard scores

The adaptive behaviour composite score was in the low range for 32 out of 35 individuals. In particular, 5 out of 10 adolescents and 21 out of 25 adults obtained the minimum composite score (standard score = 20, 26 out of 35 individuals). No significant difference was found between the average composite scores of adolescents (standard score = 29.6) and adults (standard score = 27.9) ($p > 0.05$) (Figure 2a).

Communication scores were in the low range for 31 out of 35 participants (mean standard score = 31.8; minimum = 20, maximum = 109) (Figure 2b). In the daily living and socialization domains, 32 out of 35 individuals were rated in the low range (daily living mean standard score = 34.4, minimum = 20, maximum = 103; socialization mean standard score = 30.2, minimum = 20, maximum = 100) (Figure 2c,d). No significant differences emerged between the subscale scores for adolescents and adults ($p > 0.05$).

Adjusted raw scores

The highest ARS were obtained in the subdomains of fine motor ability (median = 74.6%; minimum = 23.6%, maximum = 104%), gross motor ability (median = 73.8%; minimum = 48.8%, maximum = 100%), expressive communication (median = 72.2%; minimum = 5.6%,

ID	Age	EPILEPSY FEATURES											NEUROLOGICAL FEATURES AT VABS-II QUESTIONNAIRE							VABS-II SCORES																	ADAPTIVE BEHAVIOUR PROFILE	EPILEPSY PHENOTYPE
																				STANDARD SCORES				ADJUSTED RAW SCORES (% of the age-expected)														
																									Communication			Daily Living			Socialization			Motricity			
		Age at epilepsy onset (months)	First seizure during fever	Age at first afebrile seizure (months)	Convulsive status epilepticus	Hemiclonic seizures	Non-motor focal onset seizures	Absence seizures	Absence status epilepticus	Myoclonic seizures	Photosensitivity	Self-induced seizures	Cortical myoclonus	Ataxic gait	Pyramidal signs	Parkinsonism/ bradikinesia	Autistic traits	Seizure type	Language	Seizure frequency	Composite	Communicaton	Day-living	Socialization	Composite	Receptive	Expressive	Written	Person	Domestic	Community	Interpersonal relationships	Play and leisure	Coping skills	Gross motor skills	Fine motor skills		
1	12y 8m	3	Y	4	Y	Y	Y	Y	Y	Y	Y							F, TC	oo	●●	58	46	70	72	79	68	74	65	85	93	55	70	84	85	92	100	High	Complete
2	13	5	Y	5	Y					Y							Y	-	oo	-	32	45	44	42	76	78	84	67	79	50	63	64	74	65	90	99	High	Incomplete
3	13y 1m	2		2	Y	Y	Y	Y	Y	Y				Y		Y		F	oo	●●	20	25	27	21	58	75	60	33	61	60	34	51	76	32	76	75	Low	Complete
4	13y 2m	3		3	Y	Y											Y	TC	-	●●	20	20	36	32	52	80	51	9	55	100	19	67	60	33	60	57	Low	Incomplete
5	14y 7m	4	Y	7	Y	Y	Y	Y					Y					TC	ooo	●●	25	31	47	35	67	78	74	38	76	70	56	64	74	41	75	78	High	Incomplete
6	14y 9m	4		4		Y	Y	Y		Y	Y		Y	Y				TC	oo	●●	20	20	20	20	52	58	53	22	49	47	22	41	69	24	84	86	Low	Complete
7	15y 9m	3		3	Y		Y	Y	Y	Y	Y	Y	Y	Y			Y	A, M, TC	oo	●●●●	20	20	20	20	57	70	75	52	56	33	37	41	40	58	79	67	Low	Complete
8	16y	4	Y	10		Y	Y											TC	ooo	●●	31	43	52	36	76	88	82	70	76	69	65	62	76	47	86	102	High	Incomplete
9	17y 6m	4		4	Y	Y	Y						Y	Y				-	ooo	-	50	71	70	34	87	100	98	81	89	100	74	92	76	44	94	104	High	Incomplete
10	17y	10	Y	15	Y	Y	Y	Y	Y									F	ooo	●●	20	31	30	20	79	80	85	83	83	18	85	60	85	64	95	102	High	Incomplete
11	18y	6	Y	14	Y	Y	Y	Y	Y	Y	Y		Y	Y		Y		TC	ooo	●●●	20	20	20	20	54	55	74	12	60	27	30	58	58	9	80	82	Low	Complete
12	18y 6m	4		4	Y	Y	Y							Y		Y		TC	ooo	●●	79	88	61	100	85	100	98	88	93	44	56	93	92	34	76	100	High	Incomplete
13	19	4	Y	5	Y	Y	Y	Y	Y	Y	Y		Y	Y		Y		TC	oo	●●	20	20	20	20	51	80	58	26	44	6	16	49	73	22	73	75	Low	Complete
14	19y 6m	9		9		Y	Y						Y	Y				-	ooo	-	20	34	20	20	51	80	78	70	65	6	41	29	40	1	58	71	Low	Incomplete
15	20y	8	Y	10	Y		Y	Y			Y		Y	Y				F, TC	oo	●●●	20	23	29	20	66	93	71	52	73	48	33	59	71	23	83	89	Low	Incomplete
16	20y 1m	5		5	Y	Y	Y	Y	Y	Y			Y	Y		Y		TC	oo	●●	20	20	21	20	59	60	71	50	66	15	44	53	68	19	68	83	Low	Complete
17	20y 2m	6	Y	34		Y	Y											-	ooo	-	72	109	67	58	90	100	100	100	95	56	67	86	94	31	100	100	High	Incomplete
18	20y 3m	6		6	Y	Y	Y											TC	ooo	●	20	20	20	20	59	55	78	56	76	6	40	70	66	15	63	71	Low	Incomplete
19	21y	6	Y	10	Y	Y	Y	Y	Y	Y	Y	Y		Y				TC	-	●	20	20	20	20	30	60	19	12	35	21	15	37	10	7	55	49	Low	Complete
20	24y	3	Y	4	Y	Y	Y	Y	Y	Y	Y	Y		Y				-	ooo	-	20	20	50	20	73	88	78	60	85	58	58	61	58	21	100	90	High	Complete
21	26y	5		5	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		TC	o	●●●●	20	20	20	20	36	48	41	8	52	19	6	47	21	5	70	54	Low	Complete
22	26y 1m	5	Y	5	Y		Y	Y	Y	Y	Y		Y	Y			Y	TC	-	●●●	20	20	20	20	14	15	6	0	12	4	0	21	7	0	55	24	Low	Complete
23	27y	6	Y	14		Y	Y						Y					TC	ooo	●	20	20	34	20	68	95	82	52	76	42	64	57	37	29	74	81	Low	Incomplete
24	29y	7	Y	84														-	ooo	-	55	49	103	61	94	100	97	84	94	96	92	84	100	30	100	100	High	Incomplete
25	29y	4		4	Y	Y	Y	Y	Y	Y		Y	Y					TC	oo	●●●	20	20	20	20	48	55	75	4	62	10	8	68	29	12	83	64	Low	Complete
26	31y	4	Y	5	Y		Y	Y		Y			Y	Y	Y			TC	-	●●●	20	20	20	20	41	65	44	8	59	38	13	40	34	9	69	58	Low	Incomplete
27	32y	11	Y	60	Y		Y											-	ooo	-	72	77	82	87	93	100	98	90	90	69	91	86	100	36	99	100	High	Incomplete
28	32y 6m	9		9	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y				TC	oo	●●	20	20	20	20	44	65	58	0	45	29	15	46	52	17	65	49	Low	Complete
29	34y	3		3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	TC	oo	●●●	20	20	20	20	39	65	55	6	66	35	5	37	13	7	68	43	Low	Complete
30	34y 6m	3		3	Y	Y	Y	Y	Y	Y		Y	Y	Y	Y	Y	Y	TC	-	●●●●	20	20	20	20	23	28	17	0	29	8	1	29	10	4	63	49	Low	Complete
31	36y 7m	6		6	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y		TC	oo	●●●	20	20	20	20	34	63	49	6	42	0	0	32	39	4	66	49	Low	Complete
32	36y 7m	8	Y	15	Y	Y		Y	Y	Y	Y		Y	Y				TC	oo	●●●	20	20	20	20	52	68	71	20	72	29	25	53	19	21	64	71	Low	Complete
33	37y 6m	4		4	Y	Y	Y	Y		Y	Y	Y	Y	Y				TC	oo	●●	20	20	20	20	42	68	72	18	39	21	25	45	31	10	49	46	Low	Complete
34	38y	9		9	Y	Y	Y	Y	Y	Y		Y			Y		Y	TC	oo	●●●	20	20	20	20	44	55	59	12	63	4	26	53	19	15	55	63	Low	Complete
35	46y	5	Y	8	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	TC	oo	●●	20	20	20	20	40	60	63	16	49	8	16	46	32	16	54	38	Low	Complete
			51%		83%	80%	89%	69%	54%	63%	46%	34%	60%	60%	20%	23%	23%																					
Median	20y	5		5																	20	20	20	20	53,9	68	72	33	65	33	33	53	58	21	74	75		
Q1	17y	4		4																	20	20	20	20	43	60	56	10	51	13	15	43	31	10	63	55		
Q3	31y	6		10																	23	33	46	33	74	84	80	66	78	57	57	66	75	34	85	94		

FIGURE 1 Demographic features, epilepsy characteristics, neurological outcome, Vineland Adaptive Behaviour Scales, Second Edition (VABS-II) scores, and cluster memberships. Key to symbols: –, absent; ○, single words; ○○, short sentences; ○○○, simple conversations/normal; ●, sporadic; ●●, monthly; ●●●, weekly; ●●●●, daily/almost daily. Abbreviations: A, absences; F, focal; M, myoclonic; Q1, lower quartile; Q3, upper quartile; T, tonic/tonic–clonic/tonic vibratory; Y, yes

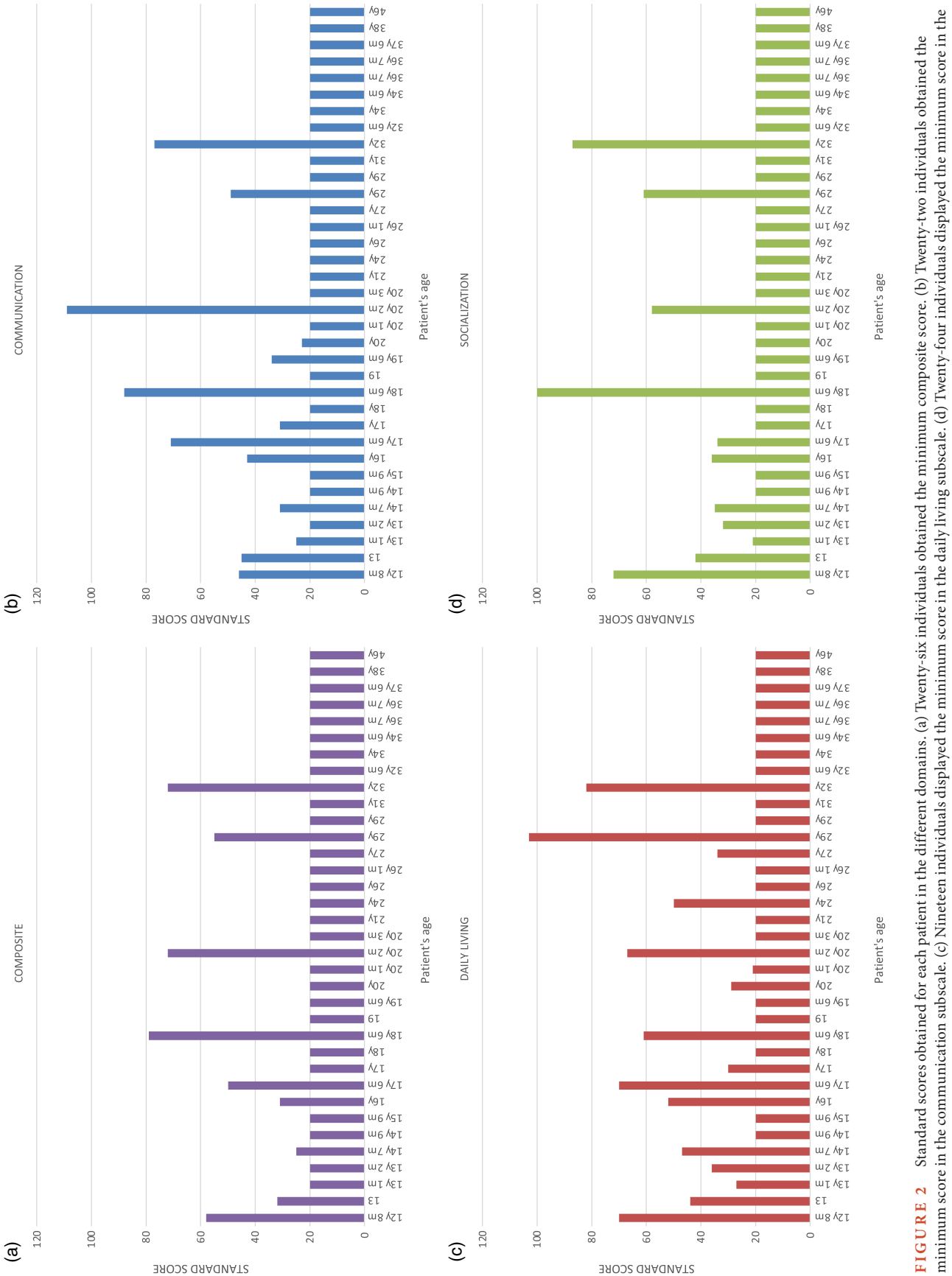

FIGURE 2 Standard scores obtained for each patient in the different domains. (a) Twenty-six individuals obtained the minimum composite score. (b) Twenty-two individuals obtained the minimum score in the communication subscale. (c) Nineteen individuals displayed the minimum score in the daily living subscale. (d) Twenty-four individuals displayed the minimum score in the socialization subscale

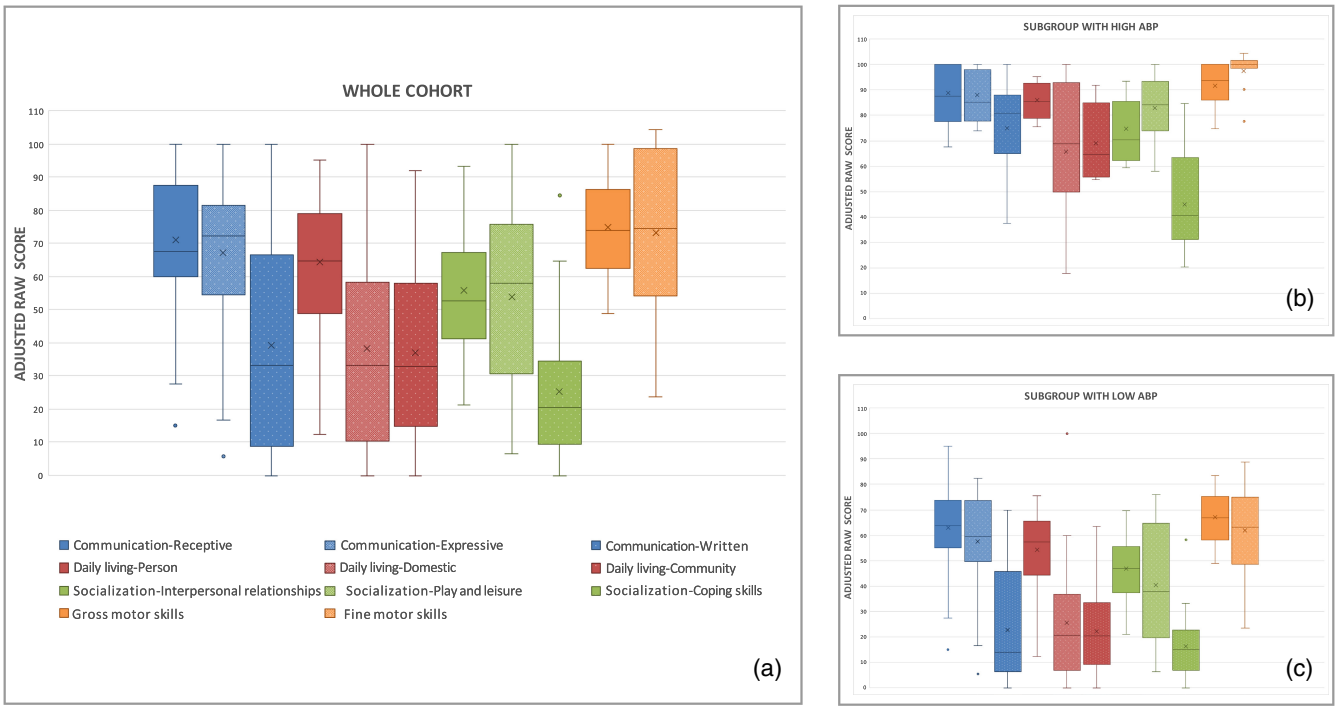

FIGURE 3 Adjusted raw score distribution for the whole cohort (a) and in the subgroups with high (b) and low (c) adaptive behaviour profiles (ABPs)

maximum = 100%), and receptive communication (median = 67.5%; minimum = 15%, maximum = 100%).

The lowest ARS were achieved in written communication (median = 33.3%; minimum = 0%, maximum = 100%), domestic daily living skills (median = 3.3%; minimum = 0%, maximum = 100%), community daily living skills (median = 33%; minimum = 0%, maximum = 92%), and coping skills, that is, behavioural and emotional skills utilized across different social situations (median = 33%; minimum = 0%, maximum = 92%). Complete results are shown in Figure 1.

Adaptive behaviour profile cluster analysis

The two-step cluster analysis based on the ARS identified two subgroups with different ABPs (cluster membership is shown in Figure 1). The first group ($n = 11$), which we named 'higher ABP', demonstrated a higher level of functioning and the mean composite ARS was 81.8% (minimum = 67.1%, maximum = 93.6%). The second group ($n = 24$), named 'lower ABP', consisted of individuals with a lower level of functioning (mean composite ARS = 46.3%; minimum = 13.7%, maximum = 67.9%).

ARS were significantly different across all subscales between these two groups ($p < 0.001$ in all subscales) (Figure 3). Main differences emerged in communication-written (mean = 75% vs 22.7%), daily living-community (69.2% vs 22.2%), socialization-play and leisure (83% vs 40.5%), daily living-domestic (65.7% vs 25.7%), and fine motor skills (97.6% vs 62.1%).

No differences were found between the two groups with regard to sex ($p = 0.43$), while seizure frequency ($p = 0.004$) and age were higher in the group with lower ABP (median = 26 years vs 17 years 6 months, $p = 0.036$).

Epilepsy phenotype cluster analysis

A data-driven, two-step cluster analysis based on epilepsy features revealed two distinct subgroups (cluster membership is shown in Figure 1).

The first group included 20 individuals. All had myoclonic and absence seizures. Most had absence status epilepticus ($n = 18$), seizures triggered by flashing lights ($n = 15$), and self-induced seizures ($n = 12$). This group also exhibited a lower age at first seizure (mean = 4.85 months) and at first afebrile seizure (mean = 6.1 months), and a higher probability of first seizure without fever ($n = 12$).

The second group included 15 individuals. A small number had myoclonic seizures ($n = 2$; $p < 0.001$), absence seizures ($n = 4$; $p < 0.001$), absence status epilepticus ($n = 1$; $p < 0.001$), seizures triggered by flashing lights ($n = 1$; $p < 0.001$), and self-induced seizures ($n = 0$; $p = 0.002$). When compared to the first group, this group had a slightly higher age at first seizure (mean = 6.07 months, $p = 0.117$) and at first afebrile seizure (mean = 18 months, $p = 0.033$), with a lower probability of first seizure without fever (34.3%, $p = 0.191$).

The differences that emerged between these two groups are consistent with the division of Dravet syndrome into two subtypes proposed by some authors: one subtype with a 'complete phenotype', which corresponds to our first

subgroup, and another subtype in which key features, such as myoclonic seizures or generalized spike-and-wave activity on electroencephalography, are missing ('incomplete phenotype'), corresponding to our second group.[15]

No significant differences were found between the two groups for focal seizures, convulsive status epilepticus, and hemiclonic seizures ($p > 0.05$).

The complete phenotype was related to worse outcomes at last assessment, including major language impairment ($p = 0.004$), higher seizure frequency ($p = 0.002$), and ataxic gait ($p = 0.019$). Furthermore, individuals with the complete phenotype also demonstrated worse outcomes in terms of ABP: 18 out of 20 individuals belonged to the group with lower ABP, while 11 out of 15 individuals with the incomplete phenotype fell within the group with higher ABP ($p = 0.003$).

Correlation with age

There was a significant correlation between age and composite raw score ($p = 0.006$, Spearman's rank coefficient = −0.45), as well as between age and adjusted composite raw score ($p = 0.002$, Spearman's rank coefficient = −0.51). In particular, this worsening trend of both composite raw scores ($p = 0.012$, Spearman's rank coefficient = −0.55) and adjusted composite raw scores ($p = 0.004$, Spearman's rank coefficient = −0.61) was present in individuals with the complete phenotype. For this subsample, a significant inverse relationship between age and raw scores emerged across several subscales: communication-written; daily living-domestic; daily living-community; socialization-play and leisure; socialization-coping skills; gross motor skills; and fine motor skills ($p < 0.05$). Conversely, no significant decreases were noted in the raw scores of individuals with the incomplete phenotype (Figure S1).

Most common vulnerabilities and well-mastered skills

A descriptive analysis of the ABPs of adults was performed, dividing individuals with complete and incomplete phenotypes. For this analysis, an individual item on the VABS-II was considered as 'passed' if the participant received a score of 1 (behaviour is sometimes or partially performed) or 2 (behaviour is usually or habitually performed). 'Vulnerabilities' were defined as abilities unconsolidated by 90% or more individuals, while 'well-mastered skills' were defined as abilities consolidated by 90% or more individuals. Results are shown in Appendix S1.

DISCUSSION

With the current study's goal of expanding knowledge about the natural history of DEEs, we investigated the ABPs of a sample of adolescents and adults with Dravet syndrome, the best-known and best-studied DEE.

The analysis of adaptive behaviour through the VABS-II was useful to outline an operating profile and identify treatment targets for rehabilitative interventions. However, as already suggested by Berg et al.,[11] this measure shows some limitations when applied to individuals with DEEs, mostly related to poor sensitivity in measuring fine clinical details and capturing small longitudinal changes that these individuals can show in response to shifts in treatment or disease course.

Most of the individuals, and in particular the adults, obtained the minimum score for composite standard scores and subscales (score = 20), producing the so-called floor effect. This finding confirms what has been previously reported in the literature regarding the poor long-term outcome of Dravet syndrome[3, 16–21] but provides little information regarding interindividual and intraindividual variability and does not permit the delineation of a functional profile. Conversely, a raw score analysis outlined some differences among skills, with greater abilities in the areas of motricity and verbal communication, and major problems in the areas of daily living skills, written communication, and behavioural and emotional control. This profile partially diverges from those previously reported for children with Dravet syndrome, in which communication capacity was lower than socialization capacity.[8] Like our findings, abilities of daily life were considerably impaired in childhood.[8] Further studies should be conducted with adolescents and adults affected by other genetic DEEs to continue investigating the specificity of this profile.

However, it should be noted that the profile in the current study is characterized by a degree of interindividual variability. That is, we found two subpopulations exhibiting gross differences in their scores: one with a lower level of functioning (lower ABP) and one with a higher level of functioning (higher ABP). These two groups correspond respectively, with few exceptions, to individuals exhibiting epilepsy within the complete phenotype of Dravet syndrome (i.e. presence of myoclonic seizures or spike-and-wave activity) versus the incomplete phenotype of Dravet syndrome (i.e. absence of myoclonic seizures or spike-and-wave activity).[15]

This finding is consistent with what is already reported in the literature regarding worse outcomes for individuals with Dravet syndrome with the complete phenotype.[21, 22] In fact, in the current cross-sectional study, there was no correlation between age at test administration and VABS-II raw scores for individuals with the incomplete phenotype. This is comparable to other genetic DEEs, where a longitudinal decline of standardized scores is absent or due to slower progression.[12, 23] Conversely, in the subpopulation with the complete phenotype, an inverse relationship between age and both raw and standard scores emerged. Even in the motricity

domains, in which a ceiling effect is seen over 6 years in the general population, the raw scores of older individuals with the complete phenotype were lower than the raw scores of younger individuals. These data suggest a possible deterioration of fine motor skills in this subcohort, similarly to what has been previously reported for gait in Dravet syndrome.[24]

The differences we found between the two phenotypes can help guide forward-looking rehabilitative planning by focusing on realistically attainable goals.

For example, for individuals with the complete phenotype, treatment could aim to expand lexiconic and phonological abilities; in individuals with the incomplete phenotype, who are usually able to produce complete sentences and tell stories, treatment could instead focus on understanding more complex instructions, reading and writing of simple passages, and practising reading comprehension. As for personal autonomy skills, in individuals with the complete phenotype, rehabilitation could aim to improve personal hygiene skills, dressing/undressing, using simple kitchen utensils and appliances such as a microwave oven, and practising using money for small purchases. In individuals with the incomplete phenotype, the following interventions can be targeted: cleaning and tidying tasks; cooking simple foods on the stove; using money with the support of a calculator; and using public transport for short trips.

While several studies reported the potential efficacy of new antiseizure treatments started in adulthood and their possible effects on daily life,[25, 26] data regarding the implications of rehabilitation interventions in adulthood are lacking. This is a crucial issue since, despite being typically diagnosed in childhood, late diagnosis of Dravet syndrome (and other genetic DEEs) has been increasing in recent years.[27]

Similarly, the impact of rehabilitation withdrawal during adulthood is not well studied. Some cognitive and adaptive skills may be lost over time due to several reasons: school attendance stoppage with subsequent decrease in cognitive and operational stimuli; reduction in opportunities for socialization; interruption of sports and other recreational activities. Rehabilitation interventions are usually reduced during adulthood and most adult patients usually live in long-term care residential centres.[28–30]

The findings highlight the need for holistic care management for patients with DEEs. Quality of life was adversely influenced by seizures and multiple comorbidities, and differed in quality and severity; in some cases, they were disease-specific and may also vary considerably with age.[31] Therefore, in individuals with a DEE, the assessment of different functions should not be carried out in comparison to the general population. Rather, it is recommended that assessment should be specific for the underlying condition and tailored to the individual over time. This scenario implies the need for disease registries to define the natural history of each of these rare conditions and evaluate the response to pharmacological and/or rehabilitative therapies. These recommendations are also aligned with the requests of families and international agencies involved with DEEs.[4, 32]

Study limitations

The main limitation is the relatively small sample. Although the cohort for the current study has been followed longitudinally, only cross-sectional data for the ABP and neurological features have been presented in this paper.

Notably, the possible role of different pharmacological approaches that patients received over the course of their lives cannot be excluded in the finding of lower scores in older adults.

Furthermore, our data do not address other potential causes of impairment (e.g. crouched gait, slowed movements, perseveration, and psychiatric symptoms), which may highly impact everyday functioning and may be specific treatment areas. Thus, the possible impact of different environmental factors on these individuals is difficult to characterize and has not been considered because it was beyond the scope of the current study.

Conclusion

With the rising emerging potential for precision medicine, acknowledgement of the natural history of rare diseases is crucial to identify targeted interventions and new treatment options.[31–33]

This study shows that using VABS-II standard scores (i.e. comparison with the general population) in the assessment of global functioning of individuals with DEEs is not the optimal approach to outline the characteristics of these individuals, neither in terms of interindividual differences nor in the evaluation of changes over time. Conversely, the current study's deeper raw score analysis allowed for the exploration of both aims. Overall, there is a need for disease-specific tools, including a multidimensional approach in which interviews are accompanied by clinical evaluations to provide sufficient granular detail.

The current study confirms that, in Dravet syndrome, adaptive behaviour outcomes are generally poor; it also underlines differences between the two clinical phenotypes. These findings can help guide forward-looking rehabilitation programmes for individuals with Dravet syndrome by establishing realistic and reachable treatment goals.

The real impact of rehabilitation treatments in adults with DEEs is not currently known and should be the object of further studies. Furthermore, rehabilitation intervention measures and treatment targets should be included in transitional programmes for young patients with DEEs to the adult health care system.[33]

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DATA AVAILABILITY STATEMENT

The data that support the findings are partially included in the manuscript (Table 1). Complete data are not publicly

available due to the containing information that could compromise the privacy of research participants.

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SUPPORTING INFORMATION

The following additional material may be found online:

Appendix S1: Detailed description of most common vulnerabilities and well-mastered skills found in subgroups with 'complete phenotypes' and 'incomplete phenotypes'.
Figure S1: Distribution and trends by age of standard and adjusted raw scores in the different domains and subdomains.

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