Received: 25 July 2018 | Revised: 27 September 2018 | Accepted: 30 September 2018

DOI: 10.1002/epi4.12281

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia Open® Open Access

Autism spectrum disorder and cognitive profile in children with Dravet syndrome: Delineation of a specific phenotype

Lisa Ouss[1,2] | Dorothee Leunen[1,2] | Jacques Laschet[1] | Nicole Chemaly[1] | Giulia Barcia[3] | Emma M. Losito[1] | Aveline Aouidad[4] | Zoe Barrault[1] | Isabelle Desguerre[1] | Delphine Breuillard[1] | Rima Nabbout[1]

[1]Reference Centre for Rare Epilepsies, Department of Pediatric Neurology, Necker Enfants Malades Hospital, APHP, Paris Descartes University, Imagine Institute, Paris, France

[2]Child Psychiatry Unit, Necker Enfants Malades Hospital, Paris, France

[3]Department of Medical Genetics, Necker Enfants Malades Hospital, APHP, Paris, France

[4]Department of Child and Adolescent Psychiatry, APHP, Pitié-Salpêtrière Hospital, Paris, France

Correspondence
Rima Nabbout, Reference Center for Rare Epilepsies, Necker Enfants Malades Hospital, Paris, France.
Email: rimanabbout@yahoo.com

Summary

Objective: We aimed to assess a cohort of young patients with Dravet syndrome (DS) for intellectual disability (ID) and autism spectrum disorder (ASD) using standardized tools and parental questionnaires to delineate their specific profiles.

Methods: We included 35 patients with DS aged 24 months to 7 years, excluding patients with a developmental age (DA) <18 months (n = 5). We performed specific tests adapted for ID (Psychoeducational Profile, Third Edition [PEP-3]), in addition to the Child Development Inventory (CDI) and Vineland Adaptive Behavior Scales, Second Edition (VABS-II) questionnaires. We used 2 standardized tools for ASD: the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) and the Autism Diagnostic Interview-Revised (ADI-R). We compared the with parental questionnaires and the VABS-II, and with ASD characteristics.

Results: PEP-3 subscales showed pathologic development in all but one patient (97%): ID in 23 of 30 (77%), and borderline cognitive functioning in 6 of 30 (22%). Eleven patients (39%) had ASD and 2 (7%) had a Social Communication Disorder (SCD) diagnosis. We found no difference between PEP-3 and CDI categorization except for fine motor skills. We found significant negative correlations between ADOS-2 and PEP-3 for the majority of scores. For patients aged older than 50 months, 2 groups emerged (ASD/no ASD) with significant difference in DA. The logistic regression for ASD diagnosis explained by VABS-II showed a significant effect for Socialization, Motor Skills, and Adaptive Behavior.

Significance: We found a high prevalence of ID in patients with DS. ID is characterized by expressive and comprehensive communication deficits in addition to visuospatial difficulties. ASD showed a specific profile with a relative preservation of social skills, emphasizing a possible underdiagnosis. Parental questionnaires can provide a good assessment of cognitive profile and might allow the difficulty of addressing cognitive scales in DS to be overcome. The profile of ID and ASD should help to establish early adapted rehabilitation programs and emphasizes the global

need for care beyond seizures in DS and other developmental epileptic encephalopathies.

KEYWORDS
autism spectrum disorder, cognitive scales, epileptic encephalopathy, intellectual disability, Parents' questionnaires

1 | INTRODUCTION

Dravet syndrome (DS) is a rare childhood epilepsy characterized by pharmacoresistant seizures that begin usually in the first year of life. DS is a developmental early onset epileptic encephalopathy with moderate to severe intellectual disability (ID), motor impairment, and behavioral/psychiatric disturbances.[1–3]

DS has a typical developmental trajectory with almost normal development in the first year of life. A cognitive slowing usually appears between the second and the third years of life and stabilizes around the age of 6 years.[1,2,4] Fifty-eight percent to 100% of patients show ID extending from mild to profound.[4–8]

Neuropsychological phenotypes of patients with DS are heterogeneous, but there is evidence that visual functions are impaired early and show a persistent delay over time.[1,3,9] Nonverbal Wechsler scores are usually worse than verbal skills.[10–12] Motor disabilities, particularly fine motor skills and gait disturbances, are also frequently reported.[4,7,13,14]

Most of DS patients develop language but with pronounced dysfunctions such as oral motor impairment, dysarthria, speech planning difficulties, and expressive language deficits.[3,4,7,10,11,13,15] Complex cognitive ability deficits, such as categorization and executive disorders, have also been reported.[4,12,13] The causes of these cognitive dysfunctions are still unknown, but underlying genetic dysfunction seems to play a key role.[2,3]

Autism spectrum disorder (ASD) features have been reported in patients with DS but were defined as « autistic traits » without using standardized tools. Depending on the type of assessment (Table 1), rates of "autistic traits" vary from 8.3% to 61.5%.[4,6,16–20] Most studies have reported lack of verbal communication, with 10%-79% of patients showing social problems, such as poor peer relationships, being withdrawn, lack of emotional reciprocity, social rules problems, or excessive familiarity.[6,18,19,21–23] Restricted and unusual interests, like obsessions, perseverations, or self-stimulations, are reported in 24%-69%.[6,18,19,24] Neophobia,[6,19] adherence to routines and sensory particularities, are less described.[18,25]

Only one study assessed ASD in children with DS using standardized tools: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR) and the International Classification of Diseases, Tenth Revision (ICD-10) criteria, the Childhood Autism Rating Scale (CARS) diagnosis tool, and the Autism Behavior Checklist (ABC),[6] but without any gold standard diagnosis tool (Autism Diagnostic Interview-Revised [ADI-R] or Autism Diagnostic Observation Schedule, Second Edition [ADOS-2]). Yet, it is known that the combination of an expert clinician evaluation with ADI-R and ADOS-2 is the most efficient approach to performing an accurate diagnosis of ASD.[26] Finally, characterization of developmental and behavioral phenotypes in patients with DS remains challenging in clinical practice due to the child's fatigability, time-consuming evaluations, and the need for expert teams and tools adapted to severe cognitive and behavioral disorders that are lacking to date.

Key Points

- We report a high rate of ID and ASD in this series of DS patients aged from 2- to 7-years-old
- Parental reports for cognitive assessment such as CDI are effective in DS
- Patients with DS present a specific ASD profile with relative preservation of social skills

This study aimed to (1) delineate ASD and ID profiles in young children with DS using adapted gold standard tools, and (2) test a battery of cognitive assessment, with parental questionnaires and cognitive tests, in order to identify a rapid, reproducible, and sensitive tool to evaluate the cognitive abilities in children with DS.

2 | MATERIALS AND METHODS

2.1 | Patients

We enrolled 35 consecutive patients with DS followed at our center, age 24 months to 7 years, from 2013 to 2017. We excluded patients with a developmental age (DA) <18 months. This study had the approval of our institution's ethics committee.

2.2 | Cognitive and adaptive assessment

The cognitive assessment was performed by 2 neuropsychologists (DL, ZB) and included a standardized observational examination (Psychoeducational Profile, Third Edition; PEP-3)[27] using both cognitive and behavioral subscales for all patients. In addition, patients' parents filled out a questionnaire (Child Development Inventory [CDI][28]; French version, IDE[29]) and underwent a parent interview (Vineland Adaptive Behavior Scales, Second Edition [VABS-II],[30] French Adaptation ECPA).

For PEP-3, results are reported in developmental levels based on percentiles (Adapted Level -percentile rank, >89; Mild Level percentile rank, 75-89; Moderate Level percentile rank, 25-74; and Severe Level percentile rank, <25). In addition, we calculated developmental quotients (DQs) from the DA to enable comparison between patients' scores. Then we calculated mean DQ for cognitive scales for each patient. DQs were also calculated for CDI scales. For VABS-II, standardized scores are reported. Children older than 6 years were excluded from motor assessment, as there is a ceiling score at 6 years for this item. DQ categorization is the following: normal, DQ 115-85; high risk of delay, DQ 84-70; and very high risk of delay, DQ <70.

2.3 | Autism spectrum disorder diagnosis and profiles

Autism spectrum disorder (or ASD) diagnosis was performed combining (1) a systematic psychiatric examination by the expert (LO) to assess clinically the ASD symptoms and Diagnostical and Statistical Manual of Mental Disorders, Fifth Revision (DSM-5) criteria[31] with 2 diagnosis gold standard tools: a parental interview (ADI-R)[32] and an observational tool (ADOS-2).[33]

The DSM-5 [31] defines the following ASD criteria: deficits in all 3 of the Social Communication (SC) criteria (deficits in socioemotional reciprocity; in nonverbal communicative behavior; and in developing, maintaining, and understanding relationship), and at least 2 of the 4 criteria listed under Restricted and Repetitive Behaviors (RRBs: stereotyped or repetitive movements or use of objects; insistence on sameness; restricted or fixed interests; hyper or hyporeactivity to sensory inputs).

The Autism Diagnostic Interview-Revised (or ADI-R) is a semi-structural parental autism diagnosis questionnaire that assesses 3 domains: Communication, Social Interaction, and RRBs. An algorithm of subscore combination defines thresholds for ASD for each domain.

The Autism Diagnostic Observation Schedule (or ADOS-2) is composed of 4 modules that are adapted to age and verbal communication level. The test consists of a set of situations or games that are videotaped to observe the child in situations requiring play and social behavior. Five domains are evaluated: Communication, Social Interaction, Play, Repetitive Behaviors, and Other Behaviors (hyperactivity, anxiety, and so on). In addition, ADOS-2 provides a severity score. Videos were coded by 2 trained specialists (LO, DB). ADOS-2 was proposed when (1) patients showed clinical autistic symptoms at psychiatric examination and/or (2) at least one socialization or communication ADI-R domain reached the threshold for ASD.

Children who had DSM-5 criteria for ASD and pathologic scores in all ADI-R and ADOS-2 domains, were diagnosed with ASD. Children who had DSM-5 criteria for Social Communication Disorder (SCD) and pathologic scores in ADI-R and ADOS-2 domains, but not for RRBs, were classified as SCD. Children without abnormalities or with abnormalities in only some domains of DSM-5 were rated "no ASD diagnosis." In the case of discrepancies between DSM-5 criteria and ADI-R and ADOS-2 thresholds, the final diagnosis was provided by the expert.[26]

2.4 | Statistical analysis

JMP v.12 software (SAS Institute Inc.) was used for all statistical procedures.

Cohort descriptive statistics were done for age, gender, and for scores for the questionnaires and scales performed. The effect of age on the test and questionnaire scores or results was assessed using analysis of variance (ANOVA) by the slope test (leverage) of the linear fit. Contingency analyses were made by the chi-square test for likelihood. Most of the numerical data were expressed as scores showing no normal distribution; therefore nonparametric tests were used for the analyses comparing only scores. Using multivariate analysis, the correlations between the different evaluated scores were determined and tested on the Spearman's rank-order correlation coefficient Rho.

Group comparisons were achieved by Student's *t* test (one tailed) or by one-way ANOVA with subsequent Wilcoxon test, or by logistic regression depending on the role of the categorical and numerical variables.

For all analyses, the differences were considered statistically significant if the *P*-value was below 0.05. The significances were further coded as follows: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

3 | RESULTS

We enrolled 35 children with DS diagnosis. Five were excluded, having DA of<18 months. Thirty patients were included: 18 girls (60%) and 12 boys (40%). They were ages 26 to 91 months (mean age 63.2 months; median age 64.5 with quartiles of 46.8 and 78.0 months). Patients' demographic and clinical data are reported in Table 2. All patients had PEP-3 scale evaluation; 28 (93%) had psychiatric examination. Twenty-six parents (86%) filled out the CDI questionnaire and 28 (93%) the VABS-II.

TABLE 1 Description of "autistic features" in patients with Dravet syndrome (DS) in the literature

	No. patients	Age (y)	Assessment instruments	% ASD	Autistic traits %	Social problems %	Communication/ language disorders	No play with toys %	Restricted interests RI, Repetitive behavior %	Hyperactivity, attention problems %	Other
Nabbout et al. (2009)[3]	28	11 (4-24)	Clinical evaluation	NA	46.4	NA	No language 53.6, few words 32.1, short sentences 14.3	NA	NA	22.2	NA
Ragona et al. (2011)[2]	26	5-19	Clinical evaluation	NA	15.4	NA	NA	NA	NA	83.3; 69.2	NA
Dravet et al. (2011)[21]	NA	NA	Clinical evaluation	NA	NA	No play with peers	Language delay	Yes	NA	Attention	NA
Ceulemans et al. (2011)[16]	60/24	NA	Vineland	8.3	NA	NA	NA	NA	NA	Yes	NA
Genton et al. (2011)[17]	24	20-50	Clinical evaluation	25	NA	NA	Language impairment 100	NA	NA	NA	NA
Chieffo et al. (2011)[4]	12	Survey 2-6 y	Griffith's dev. scale	8.3	NA	NA	NA	NA	NA	NA	NA
Brunklaus et al. (2011)[22]	163	7.2	SDQ, PedsQL	NA	NA	Peer relationship 75	NA	NA	NA	Attention 66	Conduct problem 33
Skluzacek et al. (2011) (2005 cohort)[18]	65	7.7 (<1-36)	Clinical evaluation	18	40	Withdrawn 18	Echolalia 18, no language 48, language delay 68	14	Self-stimulation 26, perseveration 35, obsessions 24	20	Excessive familiarity 47
Skluzacek (2011) (2009 cohort)[18]	86	7.7 (<1-36)	Clinical evaluation	21	33	10	Echolalia 24, no language 28, language delay 83	30	Self-stimulation 20, perseveration 52, obsessions 40	34	Excessive familiarity 56
Li et al. (2011)[6]	37	9.3 (2.8-12.3)	DSM-IV-TR, ICD-10, ABC, CARS	24.3	97.3 at least one feature	Emotional reciprocity 27	Speech delay 91.9: language regression 10.8	NA	Adherence to routine 32.4, restricted interests 55	NA	54.1 short temper
Villeneuve et al. (2013)[23]	21	6-20	Vineland	NA	100 at least one feature	Gaze, friendships, social rules	91% verbal IQ < 60	NA	Unusual + restricted interests	Opposition/ provocation	Excessive familiarity

continued

Table 1 *continued*

	No. patients	Age (y)	Assessment instruments	% ASD	Autistic traits %	Social problems %	Communication/ language disorders	No play with toys %	Restricted interests RI, Repetitive behavior %	Hyperactivity, attention problems %	Other
Berkvens et al. (2015)[19]	13	34.7 (18-60)	AVZ-R, SGZ, TVZ	61.5	NA	69.2	84.6	69.2	Stereotyped use, adherence to routine 46.1; restricted interests 69.2	None	Self-mutilation
Rosander et al. (2015)[20]	42	7 (1-17)	Play observations, parental interview	36	16	7	NA	NA	NA	NA	NA
Villas et al. (2017)[24]	220	8 (0.9-32)	Parental survey	NA	67	53	Language delay 84	49	68	50	Excessive familiarity 57

ABC, Autism Behavior Checklist; AVZ-R, Pervasive Developmental Disorder in Mental Retardation scale-Revised; CARS, Childhood Autism Rating Scale; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders Revised, Fourth Edition; ICD-10, International Classification of Diseases, Tenth Revision; NA, not available; PedsQL, Pediatric Quality of Life Inventory; SDQ, Strength and Difficulties Questionnaire; SGZ, Maladaptive behavior scale for individuals with ID; TVZ, Temperament scale for individuals with ID.

3.1 | Cognitive assessment

3.1.1 | Psychoeducational Profile, Third Edition

The analysis of PEP-3 subscales showed pathologic developmental levels (mild, moderate, or severe levels) in the majority of patients. The Affective Expression (AE) scale was the least affected measure, with only 13 of 30 patients (43%) showing pathologic levels (Figure 1). Patients obtained worse scores with a moderate or severe developmental level—percentile rank <75 for Fine Motor (FM, 27/30 patients, 90%), Cognitive Verbal/Preverbal (CVPV, 24/30, 80%), Gross Motor (GM, 24/30), Visual Motor Imitation (VMI, 21/30, 70%), and Expressive Language (EL, 19/30, 63%) subscales (Figure 1).

DQs were calculated for the cognitive scales: EL (mean [m] = 48; 18-80), GM (m = 52; 29-89), FM (m = 56; 36-92), Receptive Language (RL, m = 57; 16-90), VMI (m = 57; 32-114), CVPV (m = 60; 26-97).

Considering mean DQ for cognitive scales for all 30 patients, one patient had no risk of delay (3%), 6 patients had a high risk of delay (20%), and 23 had a very high risk of delay (77%).

3.1.2 | Child Development Inventory

Twenty-six parents filled out the CDI. Twenty-one patients (81%) presented a very high-level risk of delay for the general scale (DQ < 70), 4 of 26 (15%) a high level risk (70 ≤ DQ < 85), and one patient (4%) was in the normal range (Figure 1). Patients with high risk or in the normal range were in the youngest group of patients (<50 months).

3.1.3 | VABS-II

Twenty-eight parents underwent the VABS-II interview. For the global score (adaptive behavior), standard scores ranged from 56 to 105 (mean = 75). Mean scores for each domain ranged from 71 (Motor Skills; 56-90) to 79 (Daily Living Skills; 59-115). Ten children were older than 6 years of age and were excluded from motor assessment (36%).

3.1.4 | Coherence of parental questionnaires/PEP-3 scale

The coherence between the CDI questionnaire and the PEP-3 was evaluated comparing the common domains for PEP-3 and CDI scales (DA). EL ($\rho = 0.76$, $^{***}P < 0.001$), RL ($\rho = 0.55$, $^{**}P = 0.002$), FM ($\rho = 0.59$, $^{**}P = 0.001$), and GM ($\rho = 0.7271$, $^{***}P = 0.001$) were significantly correlated. Furthermore, the CDI general score was significantly

TABLE 2 Genetic, seizure, and neurodevelopmental assessment data

No.	Age at inclusion (mo)	Gender	Mutation *SCN1A*	Exon/ intron	De novo/ heredity	Age at onset of seizure (mo)	Trigger	Seizures semiology	Status epilepticus at onset	Age at treatment introduction (mo)	Treatment	Autism	Delay (CDI)	Delay (PEP-3)
1	84	M	Negative	NA	NA	8	Fever	F	N	8	VPA, STP, CLB	No	++	++
2	33	M	c1165C3T	Exon 8	NA	5	Fever/Vac	GTC	Y	6	VPA, CLB, TPM, STP	No	NA	++
3	87	M	c.580G>A/p.Asp194Asn	Exon 4	De novo	9	Fever	GTC	N	NA	VPA, CLB, STP	No	++	++
4	64	F	c.4219C>T/p.Arg1407X	Exon 21	NA	9	Fever	TC right	Y	12	VPA, TPM	ASD	++	++
5	65	M	p.lys868Asn C.2604G>C	Exon 15	Mother	6	Fever	GTC	N	8	VPA, CLB, TPM	No/SCD	++	+
6	91	M	c.473+1G>A	Intron 3	De novo	4	Fever	GTC	Y	4	VPA	No	++	++
7	50	M	c.2360T>G/p.Met787Arg	Exon 13	De novo	9	Fever/Vac	F	Y	13	VPA, CLB, STP	ASD	+	+
8	45	F	c.2836C>T/p.Arg946Cys	Exon 15	De novo	6	Fever	GTC	N	8	VPA, CLB, STP	No	++	++
9	71	F	Negative	NA	NA	6	Fever	Atonic, GTC	N	7	TPM, VPA, CLB, CZP	ASD	++	++
10	35	F	c.4476+1_4476 +5del	Intron 23	De novo	6	Fever	GTC	N	6	VPA, CLB, STP	No	++	++
11	62	M	Negative	NA	NA	13	Fever	GTC	N	20	VPA, TPM, STP	No	++	++
12	58	F	Negative	NA	NA	10	Fever	F, GTC, pattern sensitivity myoclonia	N	16	VPA, LEV, CLB	NA	++	+
13	35	F	c.568T>C/p.Trp190Arg	Exon 4	De novo	7	Fever	F	Y	10	VPA, CLB	No	+	−
14	26	M	c.5734C>T p.(Arg1912*)	Exon 26	De novo	2	Vac	GTC	N	4	VPA	No	++	+
15	77	F	c.1378C>T/p.GIn460	Exon 10	De novo	10	No	GTC	N	10	VPA	No	++	++
16	64	F	Negative	NA	NA	5	No	C	Y	13	VPA, CLB, STP	NO/SCD	++	++
17	57	M	c.2951T>G/p.Leu984Arg exon 16; (c.4339-34_4339-30delTggta intron 22 variant)	Exon 16	De novo	6	Fever	GC	N	6	VPA, CLB, STP	ASD	NA	++

continued

Table 2 *continued*

No.	Age at inclusion (mo)	Gender	Mutation *SCN1A*	Exon/ intron	De novo/ heredity	Age at onset of seizure (mo)	Trigger	Seizures semiology	Status epilepticus at onset	Age at treatment introduction (mo)	Treatment	Autism	Delay (CDI)	Delay (PEP-3)
18	90	M	c.5040delC/p. Met1681Cysfs X1714	Exon 26	De novo	4	Fever	Hemicorporal	N	10	VPA, CLB, STP	ASD	++	++
19	57	F	NA	NA	NA	3	No	GTC	Y	3.5	Br, VPA, CLB, STP	No	NA	++
20	91	M	c.2792G>A/p.Arg931His	Exon 15	De novo	5	Fever	GTC	Y	5	VPA, CLB, STP	ASD	++	++
21	78	F	c.5209A>T (p.Lys1737*)	Exon 26	De novo	7	Fever	GTC	Y	8	VPA, STP, CLB	ASD	++	++
22	46	M	c.1129C>T/p.Arg377X		NA	6	Fever	GTC	Y	8	VPA, CLB	NA	−	+
23	40	F	c.3213del (p.Asp1072llefs*8)	Exon 16	De novo	7	Fever	Right hemiclonic	Y	8	LEV, VPA, CLB, TPM	No	+	+
24	78	F	c.4757delG/p. Gly1586GlufsX5	Exon 25	NA	3	Fever	GTC	N	6	VPA, CLB, STP	ASD	++	++
25	47	F	c.1849A>T/p.Arg617X	Exon 11	De novo	6	No	F	N	10	VPA, STP, CLB	No	+	++
26	70	F	c.455C>T/p.Pro1519Ser	Exon 24	Mother	9	No	GTC	Y	10	VPA, CLB	ASD	++	++
27	77	F	c.235G>T.Asp 79Tyr	Exon 1	Mosaicism mother	8	Fever	GTC	N	NA	CLB, VPA, STP	ASD	NA	++
28	69	M	c.974A>G/p.Tyr325Cys	NA	NA	7	Fever	GTC	Y	7	VPA	No	++	++
29	67	F	Negative	NA	NA	7	Fever	T	NA	NA	VPA, STP, CLB	ASD	++	++
30	81	F	c.602+1G>A i	Intron 4	De novo	9	Fever	GTC	Y	12	VPA, STP, CLB	No	++	++

ASD, Autism Spectrum Disorder; BR, potassium bromide; C, clonic seizures; CLB, clobazam; CZP, clonazepam; FS, focal seizures; GC, generalized clonic seizures; GTC, generalized tonic-clonic seizures; LEV, levetiracetam; M, myoclonic; NA, not available; SCD, Social Communication Disorder; STP, stiripentol; TC, tonic-clonic seizures; TPM, topiramate; Vac, vaccination; VPA, sodium valproate; (−), no risk of delay; (+) = high level risk of delay, DQ <85; (++) very high risk of delay, QD <70 (categorization of delay were obtained with mean PEP-3 cognitive DQ).

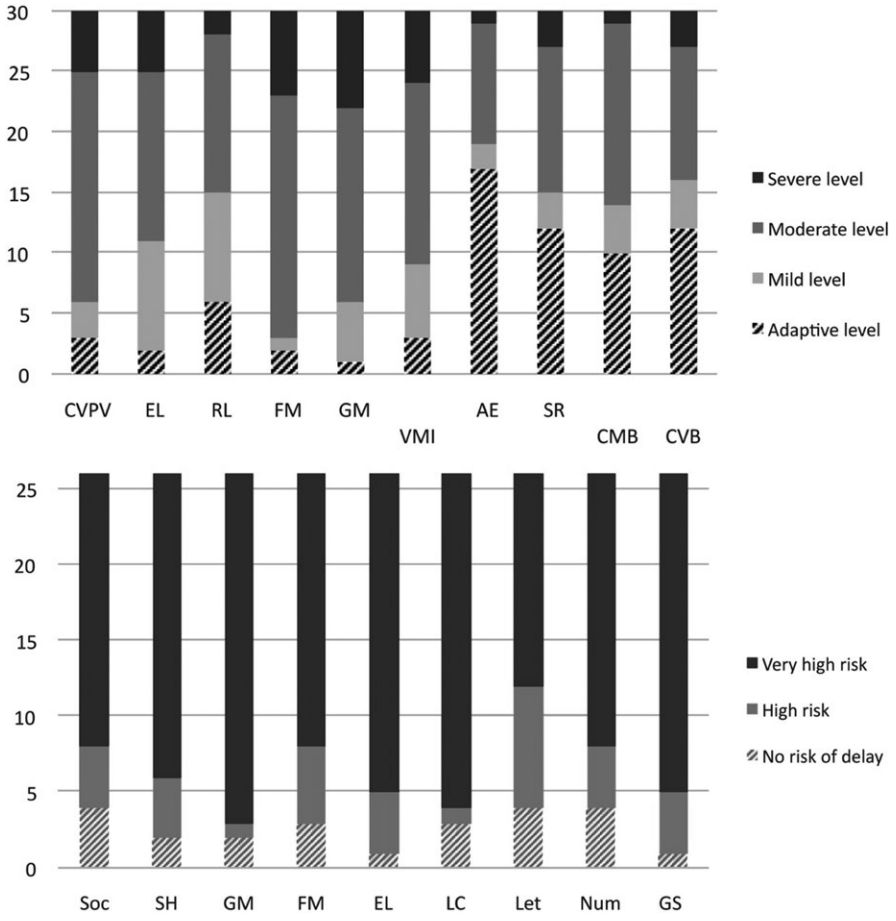

FIGURE 1 Upper graph—proportion of patients for each developmental level of PEP-3 scale according to the subscales. CVPV, Cognitive Verbal/Preverbal; EL, Expressive Language; RL, Receptive Language; FM, Fine Motor; GM, Gross Motor; VMI, Visual Motor Imitation; AE, Affective Expression; SR, Social Reciprocity; CMB, Characteristic Motor Behaviors; CVB, Characteristic Verbal Behaviors. Lower graph: Proportion of patients for each developmental level of the CDI scale according to the subscales. Soc, Social; SH, Self Help; GM, Gross Motor; FM, Fine Motor; EL, Expressive Language; LC, Language Comprehension; Let, Letters; Num, Numbers; GS, General Scale

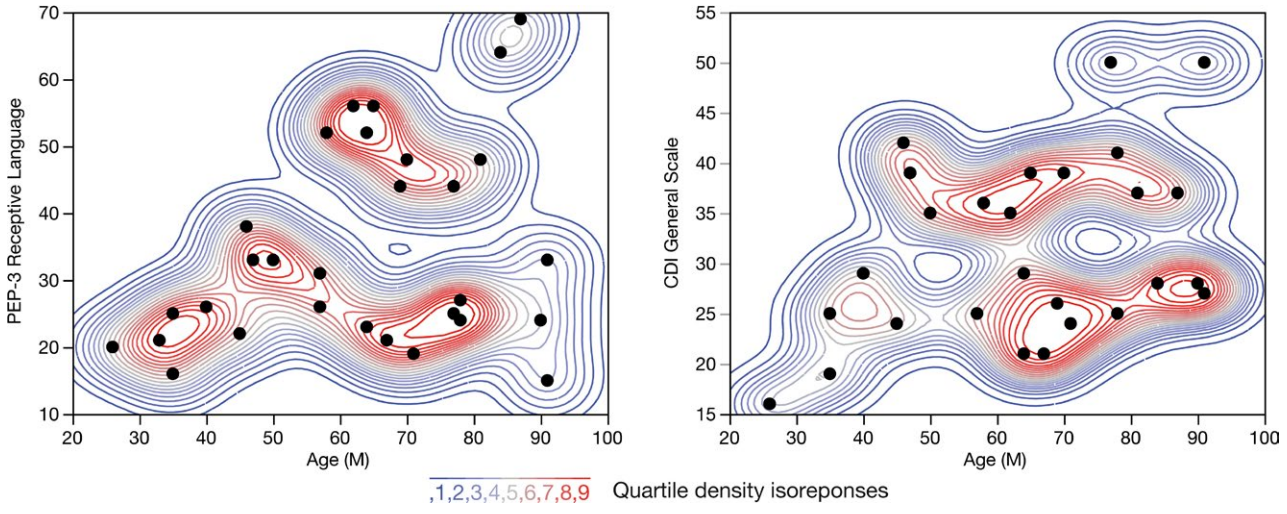

FIGURE 2 Nonparametric density plot of bivariate analyses of the variables "PEP-3 Receptive Language" and "CDI General Scale" with respect to Age (M = months)

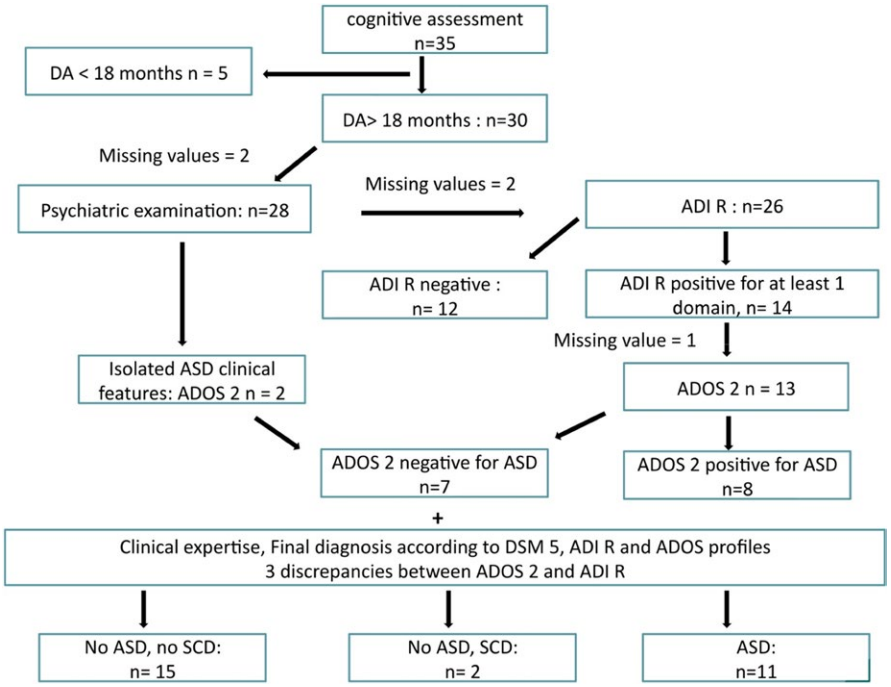

FIGURE 3 Flow chart for diagnosis of autism spectrum disorder

correlated with all of the PEP-3 cognitive variables: CVPV ($\rho = 0.6367$, ***$P = 0.001$), EL ($\rho = 0.7515$, ***$P < 0.001$), RL ($\rho = 0.6272$, ***$P = 0.001$), FM ($\rho = 0.5618$, **$P = 0.002$), GM ($\rho = 0.6322$, ***$P = 0.001$), and VMI ($\rho = 0.5431$, **$P = 0.003$).

The chi-square test showed no difference between PEP-3 and CDI categorization among very high risk of delay categorization for receptive communication ($P = 0.49$), expressive communication ($P = 0.75$), and gross motor ($P = 0.03$). The categorization for fine motor showed differences ($P = 0.010$), with a higher number of very high risk of delay for PEP-3 compared to the CDI parental questionnaire.

The VABS-II global adaptive behavior score was significantly correlated with PEP-3 DQ for GM ($\rho = 0.6033$, ***$P < 0.001$), FM ($\rho = -0.5211$, **$P = 0.004$), VMI ($\rho = -0.5108$, **$P = 0.005$), EL ($\rho = -0.4837$, **$P = 0.009$), RL ($\rho = -0.3848$, *$P = 0.04$), and Characteristic Verbal Behavior scores (CVB, $\rho = -0.3902$, *$P = 0.04$), but not with CVPV ($\rho = -0.337$, $P = 0.07$), AE ($\rho = -0.3154$, $P = 0.10$), Social Reciprocity (SR, $\rho = -0.1768$; $P = 0.36$), and Characteristic Motor Behavior (CMB, $\rho = -0.2409$; $P = 0.21$) scores.

3.1.5 | Link between cognitive and adaptive levels with patient's age

Age of patient at assessment was not linked to the PEP-3 DA for RL, VMI, and FM, whereas it was with CVPV ($\rho = 0.4109$; *$P < 0.05$), EL ($\rho = 0.4154$; *$P < 0.05$), and GM ($\rho = 0.3694$; *$P < 0.05$).

Nevertheless, for the RL and CDI General Scale, from 50 months of life, 2 distinct populations emerged (Figure 2): a first group with increasing DA over chronological age, and the second showing a stagnation of DA through chronologic age.

Child Development Inventory (or CDI) scores were not correlated with age, except for Letters ($\rho = 0.4692$, *$P = 0.01$), and Numbers subscales ($\rho = 0.4869$, **$P = 0.01$).

VABS-II Socialization (*$P = 0.01$), Daily Living Skills (*$P = 0.01$), Motor Skills (**$P = 0.001$), and Adaptive Behavior (*$P = 0.02$) domains were negatively correlated with age, whereas the Communication domain did not reach statistical significance ($P = 0.10$).

3.2 | Autism spectrum disorder assessment

3.2.1 | Descriptive data

Twenty-eight patients had a psychiatric examination (Figure 3). Twenty-six had ADI-R. The 2 patients who did not have ADI-R were younger than 3 years and had no ASD symptoms according to the DSM-5. Fourteen patients reached the threshold for at least one ADI-R domain (54%). Fifteen had ADOS-2, 13 after the ADI-R and 2 after detecting ASD isolated clinical features on psychiatric examination. Figure 3 shows the different ASD assessment scales and the results obtained in this cohort.

According to the DSM-5 classification and ADI-R and ADOS-2 (Figure 3), 11 patients showed ASD (39%) and 2 had an SCD diagnosis (7%). The 15 remaining patients (54%) had neither ASD nor SCD.

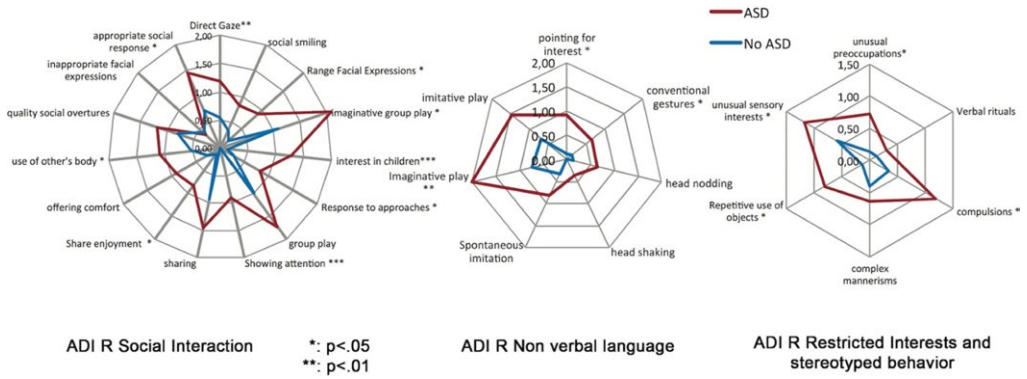

FIGURE 4 Comparison of ADI-R 3 subscores between Dravet syndrome (DS) children with autism spectrum disorder (ASD; in red) and DS children without ASD (in blue)

3.2.2 | Comparison of ASD/non-ASD children for ADI-R

To confirm the clinical phenotype of DS children, we compared means of ADI-R subscores between those who fulfill the criteria for ASD and those who did not (Figure 4). In both groups, the social interaction profile of DS children is heterogeneous ("star" profile in Figure 4). However, DS patients with ASD showed a significantly higher impairment of direct gaze (***$P = 0.004$), range of facial expressions (*$P = 0.04$), imaginative group play (*$P = 0.01$), interest in children (**$P = 0.001$), response to approaches (*$P = 0.04$), showing attention (**$P < 0.001$), share enjoyment (*$P = 0.02$), use of others' body (*$P = 0.03$), and appropriate social response (*$P = 0.01$; Figure 4). In the nonverbal language domain, DS patients with ASD showed significantly more difficulties in imaginative play (**$P = 0.008$), pointing (*$P = 0.04$), and conventional gestures (*$P = 0.02$). In the RRB domain, DS patients with ASD showed significant differences in unusual preoccupations (*$P = 0.02$), compulsions (*$P = 0.03$), repetitive use of objects (*$P = 0.02$), and unusual sensory interests (*$P = 0.04$). However, unusual sensory interests have been found in 47% of the patients with no ASD (7/15).

3.2.3 | Correlation between ADI-R domains and ADOS-2 severity scores, and according to age at assessment

None of ADI-R domains and ADOS-2 severity score were correlated, but there was a trend between the Reciprocal Social Interaction ADI-R subscore and the ADOS-2 severity score ($P = 0.07$). The age at assessment was correlated positively with the Reciprocal Social Interaction domain of ADI-R (*$P = 0.01$), and Communication domain (*$P = 0.03$), but not with RRBs. However, the ADOS-2 severity score was not linked to age.

3.2.4 | Correlation between ASD and cognitive assessment

We found significant negative correlations between ADOS-2 severity score and each PEP-3 score (DQ; bivariate analysis) for RL ($R^2 = 0.233396$, ***$P < 0.001$), CVPV ($R^2 = 0.190286$, **$P = 0.001$), EL ($R^2 = 0.062743$, **$P = 0.005$), FM ($R^2 = 0.163454$, *$P = 0.01$), GM ($R^2 = 0.085568$, *$P = 0.01$), and VMI ($R^2 = 0.055015$, *$P = 0.04$).

When we divided the group of DS patients (ASD vs [non ASD + SCD]), there were significant differences in the PEP-3 cognitive DQs between the 2 groups (Student's unilateral *t* test) in RL (***$P < 0.001$), VMI (**$P = 0.001$), CVPV (**$P = 0.002$), GM (**$P = 0.002$), FM (*$P = 0.02$), and EL (*$P = 0.04$), with higher DQ for no ASD + SCD patients. Both groups showed differences for all behavioral PEP-3 developmental levels: SR (***$P < 0.001$), CVB (**$P = 0.006$), AE (**$P = 0.01$), and CMB (*$P = 0.01$; Wilcoxon test).

Logistic regression for ASD diagnosis with PEP-3 scores (DQ) showed significant effects for RL (**$P = 0.004$), CVPV (*$P = 0.01$), GM (*$P = 0.02$), and VMI (*$P = 0.02$); and with behavioral PEP-3 scales: SR (**$P = 0.007$), CVB (*$P = 0.01$), AE (*$P = 0.01$), and CMB (*$P = 0.02$), but failed to reach significance for EL, FM, and CMB.

For patients older than 50 months of age, 2 groups emerged (ASD/no ASD; Figure 2). The two groups showed a difference at Student's unilateral *t* test for PEP-3 scores (DQ) in RL (***$P < 0.001$) and CVPV (**$P = 0.007$). The 2 groups showed differences for all behavioral PEP-3 developmental levels for SR (**$P = 0.005$), CVB (*$P = 0.02$*), CMB (*$P = 0.04$), and AE (*$P = 0.04$; Wilcoxon test).

Logistic regression for ASD diagnosis explained by cognitive PEP-3 scores (DQ) in patients older than 50 months showed significant effects for RL (*$P = 0.01$) and CVPV

(*$P = 0.03$), and for 3 behavioral PEP-3 developmental levels: SR (*$P = 0.01$), CVB, (*$P = 0.03$), and AE (*$P = 0.04$).

3.2.5 | Links between ASD and adaptive behavior (VABS-II)

The logistic regression for ASD diagnosis explained by VABS-II showed a significant effect for Socialization (*$P = 0.01$), Motor Skills (*$P = 0.01$), and Adaptive Behavior (*$P = 0.048$), but no significant effect on Communication ($P = 0.09$) and Daily Living Skills ($P = 0.07$).

3.3 | Correlations between medical variables and neuropsychiatric features

3.3.1 | Medical variables and cognitive features

We explored a possible link between the presence of the *SCN1A* mutation, the age at onset of seizure (in months), and status epilepticus at onset, with cognitive delay (cognitive delay: DQ <70 based on mean DQ for cognitive scales) and PEP-3 cognitive subscales (PEP-3 DQs).

Only the age at onset of seizures showed a trend for statistical significance for Expressive Language DQ (simple linear regression, ANOVA F test: $P = 0.055$) and RL DQ ($P = 0.056$): patients with higher DQs had later onset. All other P-values for PEP-3 DQ and cognitive delay were above 0.14.

3.3.2 | Medical variables and ASD features

We also explored the possible link between the medical and genetic variables with ASD variables (ASD diagnosis, ADOS-2 severity score). No significant P-values were found (all $P > 0.22$).

4 | DISCUSSION

We report a high prevalence of ASD in our cohort: 11 (39%) if we exclude SCDs according to DSM-5 and 13 (46%) ASD when we include SCDs, according to the ICD-10. This rate is relevant considering the use of 2 gold standard scales but might be underestimated, as we excluded the children presenting a DA less than 18 months.

The occurrence of ASD in DS is controversial. Guzzettta[25] does not mention autistic traits. Ceulemans et al[16] and Villeneuve et al[23] concluded that children with DS do not present ASD, as the socialization scale of the VABS-II is almost always better when compared to the overall results of the scale. This assumption often leads to ASD being underdiagnosed and prevents patients from benefitting from structured and adapted care. In addition, we found a significant correlation between the VABS-II socialization subscale and ASD, suggesting that the preservation of the VABS's socialization score reported[23] might apply to patients with DS as a group but not for the subgroup of DS patients with ASD.

Two series reported the prevalence of ASD in patients with DS at 23.9%[6] in children and 61.5%[19] in adults. The underestimation of ASD in the pediatric series could be related to a relative preservation of the communicative skills.[16,23] Adult patients were clinically diagnosed with autism, but had preserved social skills, with a discrepancy between *regular* autistic features, and the inappropriate familiarity with strangers.[19] The relative preservation of social smiling in our series and the fact that 17 of 30 patients had adapted Affective Expression on PEP-3, show that children with DS and ASD show more pro-socials features than expected for a typical case of autism and explain again the underestimated prevalence of ASD in previous reports. Although communicative skills are partly preserved, patients present qualitatively unadapted social behaviors. A similar phenotype has been described in patients with ASD due to de novo genetic etiologies compared to patients with ASD and no genetic abnormalities.[34]

In our series, 23 of 30 patients (77%) presented ID. We used the PEP-3 scale, since it is designed especially for "hard to assess" children. Classical intelligence scales (Wechsler scales) are challenging and poorly adapted for patients with ASD, and with ID in general. On PEP-3, cognitive deficits were higher than behavioral disturbances, showing a genuine cognitive delay before the age of 7 years. Expressive language, gross motor, and fine motor scales showed the lowest DQ mean scores. Visuomotor and fine motor development were not correlated with age at assessment, showing a stagnation of the acquisitions and slow improvement of the performances, as described previously.[9,12] Although gait impairment is reported[35] we showed an improvement of gross motor scales over age.[3,7] This emphasizes the need for adapted rehabilitation.

Language was delayed, with a discrepancy between receptive and expressive domains; the latter was more affected. This sensorimotor integration deficit might be explained by the dorsal stream impairment hypothesis also proposed for the visuomotor skill impairment in DS.[36,37] However, expressive skills are better in older patients, suggesting a possible dynamic of acquisition in this domain, whereas RL skills did not show this age-related pattern.

Verbal/Preverbal cognitive scales, as well as prescholar acquisition with letter and number acquisitions, showed better scores in older patients. This suggests a nonprogressive disorder with a potential for improvement and learning, as reported in a smaller previous longitudinal study.[3]

Parents' questionnaires (IDE) in our cohort showed high consistency with psychologist's assessment for cognitive

development. We found a high consistency between parents' assessment of cognitive skills (IDE) and the domains of the PEP-3, except for fine motor evaluation. This validates the usefulness of these questionnaires and allows us to propose them as promising tools to evaluate children with DS when the PEP-3 tool is challenging to use with patients with certain characteristics (excessive behavior disorder, child fatigability, or interruption with seizures, and so on). These questionnaires can be considered as an easy primary evaluation tool that may be extended to use in other early onset epilepsies syndromes with ID.

The correlation between ASD and ID in DS has been proposed previously[6,19] and was found to be significant also in our cohort. DS patients with ASD presented greater cognitive deterioration than patients without ASD, and ASD severity was linked with ID severity. RL deficit seemed the most significantly correlated with ASD. This particular cognitive feature is to be emphasized, as previously more attention had been given to visuospatial[4,9–12,25]and expressive language impairments.

We encountered 2 distinct populations of children with DS after the age of 50 months (Figure 2): one with cognitive impairment and ASD, and the other with less cognitive impairment and no ASD. The absence of ASD patients in the youngest group (maybe because children children under 18 months of DA had not been included in the study) could also partly explain this divide. It is challenging to define the onset of first ASD symptoms, due to the confounding factor of ID. In our cohort, age at assessment was linked with reciprocal social interaction at ADI-R. It is possible that problems with social interactions increase with age, due to a specific phenotype in social cognition, or because of a consequence of instrumental problems, especially executive function (EF). This age of 50 months, corresponding to the beginning of the preschool years, is a key period for the development of EF and attention.[38] We could hypothesize that cognitive and adaptive tasks are too demanding regarding EF for children with DS. This is consistent with the dysexecutive syndrome hypothesis.[23] These 2 groups have to be confirmed with a larger sample and a longitudinal study.

The links between ID and ASD are not fully understood. ID and ASD are suspected to be partly linked to the genetic underlying disease and not exclusively related to epilepsy.[3] Nevertheless, we did not find any significant link between the presence of ASD and ID, and age at onset, status epilepticus at onset, and the presence of *SCN1A* mutation. The nearly significant trend with age at onset and language features is relevant with the early maturation of language brain networks. A genetic common pathway for seizures, ID, and ASD is reported in many genetic conditions[39] and might be partly relevant for DS where the impairment of the sodium channel *SCN1A* function can explain not only the seizures but also the ASD and the ID.[40] This hypothesis has to be confirmed in a larger sample.

The high rate and the atypical phenotype of ASD in DS found in this series have major clinical implications. This finding supports the necessity to use standardized tools such as ADI-R and ADOS-2 for ASD diagnosis. This diagnosis should allow personalized and targeted interventions on specific difficulties in order to decrease the severity of associated ASD comorbidity and its possible impact on cognitive development.

4.1 | Study limitations

This study had some limitations. The number of patients in both groups before and after 50 months was not similar and did not allow to confirm a significant difference between the two groups and a cut-off age at 50 months. We did not assess the number of seizures, as we had incomplete data. We faced other limitations due to the instruments and the scores we used. Because we used 3 ADOS-2 modules, we could not perform a comparison on ADOS-2 items but used comparison scores to assess severity scores. The motor scores of the VABS-II showed a ceiling effect at 6 years. Finally, patients were followed in the same tertiary center, and this might have generated a patient group that was more severely affected.

5 | CONCLUSION

The present study indicates a high prevalence of ID and a high rate of ASD, showing a specific profile (relative preservation of social skills) in this cohort of DS. The use of parental questionnaire can provide a good assessment of cognitive profile and could help overcome the difficulty of addressing cognitive scales. This cognitive evaluation is of major importance as patients with severe ID are more at risk for ASD. A global cognitive survey is recommended early, addressing language skills, and particularly receptive skills, which are linked to autistic disorders. Specific rehabilitation programs (motor and logopedic) for patients with ASD, focusing specifically on RL and alternative communication methods, should be introduced and implemented.

The diagnosis and the phenotyping of ASD is another critical step in evaluating patients with DS. Insights into core processes of ASD and links between ASD and ID are needed, as we know that early interventions with infants and with their parents[41] improve outcomes of autistic features. The role of the sodium channel disorder on the cognitive outcome and on ASD is highly suspected[40,42] but we should also question the impact of nondiagnosed ASD on patients' cognitive development and outcome. This methodology should be extended to other early onset developmental epileptic encephalopathies

in order to better delineate the phenotype of these diseases beyond seizures but also to better define the endpoints to propose to evaluate future therapies.

ACKNOWLEDGMENT

We are thankful to the patients and their families for their participation to this work.

DISCLOSURE

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

REFERENCES

1. Cassé-Perrot C, Wolff M, Dravet C. Neuropsychological aspects of severe myoclonic epilepsy in infancy. In: Jambaqué I, Lassonde M, Dulac O, editors. Neuropsychology of childhood epilepsy [Internet]. Springer US; 2001 [cited 2017 Jun 21]. p. 131–40. (Advances in Behavioral Biology). Available from http://link.springer.com/chapter/10.1007/0-306-47612-6_14
2. Ragona F, Granata T, Bernardina BD, et al. Cognitive development in Dravet syndrome: a retrospective, multicenter study of 26 patients. Epilepsia. 2011;52:386–92.
3. Nabbout R, Chemaly N, Chipaux M, et al. Encephalopathy in children with Dravet syndrome is not a pure consequence of epilepsy. Orphanet J Rare Dis. 2013;8:176.
4. Chieffo D, Battaglia D, Lettori D, et al. Neuropsychological development in children with Dravet syndrome. Epilepsy Res. 2011;95:86–93.
5. Ragona F, Brazzo D, De Giorgi I, et al. Dravet syndrome: early clinical manifestations and cognitive outcome in 37 Italian patients. Brain Dev. 2010;32:71–7.
6. Li B-M, Liu X-R, Yi Y-H, et al. Autism in Dravet syndrome: prevalence, features, and relationship to the clinical characteristics of epilepsy and mental retardation. Epilepsy Behav. 2011;21:291–5.
7. Caraballo RH, Fejerman N. Dravet syndrome: a study of 53 patients. Epilepsy Res. 2006;70:231–8.
8. Olivieri G, Battaglia D, Chieffo D, et al. Cognitive-behavioral profiles in teenagers with Dravet syndrome. Brain Dev. 2016;38:554–62.
9. Chieffo D, Ricci D, Baranello G, et al. Early development in Dravet syndrome; visual function impairment precedes cognitive decline. Epilepsy Res. 2011;93:73–9.
10. Chieffo D, Battaglia D, Lucibello S, et al. Disorders of early language development in Dravet syndrome. Epilepsy Behav. 2016;54:30–3.
11. Battaglia D, Chieffo D, Siracusano R, et al. Cognitive decline in Dravet syndrome: is there a cerebellar role? Epilepsy Res. 2013;106:211–21.
12. Ricci D, Chieffo D, Battaglia D, et al. A prospective longitudinal study on visuo-cognitive development in Dravet syndrome: is there a "dorsal stream vulnerability"? Epilepsy Res. 2015;109:57–64.
13. Acha J, Pérez A, Davidson DJ, et al. Cognitive characterization of children with Dravet syndrome: a neurodevelopmental perspective. Child Neuropsychol. 2015;21:693–715.
14. Gitiaux C, Chemaly N, Quijano-Roy S, et al. Motor neuropathy contributes to crouching in patients with Dravet syndrome. Neurology. 2016;87:277–81.
15. Turner SJ, Brown A, Arpone M, et al. Dysarthria and broader motor speech deficits in Dravet syndrome. Neurology. 2017;88:743–9.
16. Ceulemans B. Overall management of patients with Dravet syndrome. Dev Med Child Neurol. 2011;53:19–23.
17. Genton P, Velizarova R, Dravet C. Dravet syndrome: the long-term outcome. Epilepsia. 2011;52:44–9.
18. Skluzacek JV, Watts KP, Parsy O, et al. Dravet syndrome and parent associations: the IDEA League experience with comorbid conditions, mortality, management, adaptation, and grief. Epilepsia. 2011;52:95–101.
19. Berkvens JJL, Veugen I, Veendrick-Meekes MJBM, et al. Autism and behavior in adult patients with Dravet syndrome (DS). Epilepsy Behav. 2015;47:11–6.
20. Rosander C, Hallböök T. Dravet syndrome in Sweden: a population-based study. Dev Med Child Neurol. 2015;57:628–33.
21. Dravet C. The core Dravet syndrome phenotype. Epilepsia. 2011;52:3–9.
22. Brunklaus A, Dorris L, Zuberi SM. Comorbidities and predictors of health-related quality of life in Dravet syndrome. Epilepsia. 2011;52:1476–82.
23. Villeneuve N, Laguitton V, Viellard M, et al. Cognitive and adaptive evaluation of 21 consecutive patients with Dravet syndrome. Epilepsy Behav. 2014;31:143–8.
24. Villas N, Meskis MA, Goodliffe S. Dravet syndrome: characteristics, comorbidities, and caregiver concerns. Epilepsy Behav. 2017;74:81–6.
25. Guzzetta F. Cognitive and behavioral characteristics of children with Dravet syndrome: an overview. Epilepsia. 2011;52(Suppl 2):35–8.
26. Charman T, Gotham K. Measurement issues: screening and diagnostic instruments for autism spectrum disorders–lessons from research and practise. Child Adolesc Ment Health. 2013;18:52–63.
27. Schopler E. Psychoeducational profile: PEP-3; TEACCH individualized psychoeducational assessment for children with autism spectrum disorders. Austin, TX: Pro-ed; 2005.
28. Ireton H, Glascoe FP. Assessin children's development using parents' reports: the child development inventory. Clin Pediatr (Phila). 1995;34:248–55.
29. Duyme M, Zorman M, Tervo R, et al. French norms and validation of the Child Development Inventory (CDI): Inventaire du Développement de l'Enfant (IDE). Clin Pediatr (Phila). 2011;50:636–47.
30. Sparrow SS, Balla DA, Cicchetti DV. Vineland-II adaptive behavior scales. Crowley, TX: AGS Publishing; 2005.
31. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC; 2013.
32. Lord C, Rutter M, Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord. 1994;24:659–85.
33. Lord C, Rutter M, DiLavore PC, et al. Autism diagnostic observation schedule: ADOS-2. Los Angeles, CA: Western Psychological Services; 2012.
34. Bishop SL, Farmer C, Bal V, et al. Identification of developmental and behavioral markers associated with genetic

abnormalities in autism spectrum disorder. Am J Psychiatry. 2017;174:576–85.
35. Rodda JM, Scheffer IE, McMahon JM, et al. Progressive gait deterioration in adolescents with Dravet syndrome. Arch Neurol. 2012;69:873–8.
36. Rauschecker JP. Ventral and dorsal streams in the evolution of speech and language. Front Evol Neurosci. 2012;4:7.
37. Atkinson J, Braddick O. Visual attention in the first years: typical development and developmental disorders. Dev Med Child Neurol. 2012;54:589–95.
38. Carlson SM, Davis AC, Leach JG. Less is more: executive function and symbolic representation in preschool children. Psychol Sci. 2005;16:609–16.
39. Moss J, Howlin P, Oliver C. The assessment and presentation of Autism Spectrum Disorder and associated characteristics in individuals with severe intellectual disability and genetic syndromes. In: Burack JA, Hodapp RM, Iarocci G, Zigler E, editors. The Oxford handbook of intellectual disability and development. Oxford, MI: Oxford Library of Psychology, Oxford University Press, 2011; p. 275–302.
40. Han S, Tai C, Westenbroek RE, et al. Autistic-like behaviour in Scn1a+/− mice and rescue by enhanced GABA-mediated neurotransmission. Nature. 2012;489:385–90.
41. Green J, Charman T, Pickles A, et al. Parent-mediated intervention versus no intervention for infants at high risk of autism: a parallel, single-blind, randomised trial. Lancet Psychiatry. 2015;2:133–40.
42. Tatsukawa T, Ogiwara I, Mazaki E, et al. Impairments in social novelty recognition and spatial memory in mice with conditional deletion of Scn1a in parvalbumin-expressing cells. Neurobiol Dis. 2018;112:24–34.

How to cite this article: Ouss L, Leunen D, Laschet J, et al. Autism spectrum disorder and cognitive profile in children with Dravet syndrome: Delineation of a specific phenotype. *Epilepsia open*. 2019;4:40–53. https://doi.org/10.1002/epi4.12281