Dysarthria and broader motor speech deficits in Dravet syndrome

Samantha J. Turner, MSpPath
Amy Brown, PhD
Marta Arpone, MSc
Vicki Anderson, PhD
Angela T. Morgan, PhD*
Ingrid E. Scheffer, MBBS, PhD*

Correspondence to Dr. Scheffer: scheffer@unimelb.edu.au

ABSTRACT

Objective: To analyze the oral motor, speech, and language phenotype in 20 children and adults with Dravet syndrome (DS) associated with mutations in *SCN1A*.

Methods: Fifteen verbal and 5 minimally verbal DS patients with *SCN1A* mutations (aged 15 months-28 years) underwent a tailored assessment battery.

Results: Speech was characterized by imprecise articulation, abnormal nasal resonance, voice, and pitch, and prosody errors. Half of verbal patients had moderate to severely impaired conversational speech intelligibility. Oral motor impairment, motor planning/programming difficulties, and poor postural control were typical. Nonverbal individuals had intentional communication. Cognitive skills varied markedly, with intellectual functioning ranging from the low average range to severe intellectual disability. Language impairment was congruent with cognition.

Conclusions: We describe a distinctive speech, language, and oral motor phenotype in children and adults with DS associated with mutations in *SCN1A*. Recognizing this phenotype will guide therapeutic intervention in patients with DS. ***Neurology*® 2017;88:743–749**

GLOSSARY

CCS = Complexity of Communication Scale; **DS** = Dravet syndrome; **GEFS+** = genetic epilepsy with febrile seizures plus; **ID** = intellectual disability; **MV** = minimally verbal; **V** = verbal; **VNS** = vagal nerve stimulator.

Dravet syndrome (DS) is an infantile-onset developmental epileptic encephalopathy with poor outcome. Typically, a 6-month-old infant presents with febrile hemiclonic status epilepticus in the setting of reputedly normal development, and then develops multiple seizure types over the next 4 years, with developmental slowing from 1–2 years of age.[1] More than 80% of cases have mutations of the sodium channel gene *SCN1A*. Intellectual disability (ID) is usual, with almost all patients having severe ID.

Speech and language function in adults and children with DS has not been specifically characterized. Three pediatric studies have examined language (understanding and use of words) in the context of a broader neuropsychological battery and include *SCN1A* positive and negative cases.[2–4] The results are varied, ranging from cohorts with severe ID and severe language impairment to others with mild to moderate ID and borderline to average naming and comprehension.

In terms of speech (how speech sounds are produced or articulated), dysarthria and speech planning difficulties have been reported anecdotally.[2,4–6] Oral motor skills have not been investigated.

We aimed to determine whether there was a characteristic developmental speech, language, and oral motor phenotype in children and adults with DS associated with mutations in *SCN1A*. Recognition of progressive patterns of dysfunction will inform diagnosis and guide therapeutic intervention.

Supplemental data at Neurology.org

*These authors contributed equally to this work.

From the Department of Paediatrics, The University of Melbourne (S.J.T., M.A., V.A., A.T.M., I.E.S.), and Department of Psychology (V.A.), The Royal Children's Hospital; Neuroscience of Speech Group, Clinical Sciences Theme (S.J.T., A.T.M.), Australian Centre for Child Neuropsychological Studies (A.B., M.A., V.A.), Murdoch Childrens Research Institute, Melbourne; Epilepsy Research Centre, Department of Medicine (I.E.S.), The University of Melbourne, Austin Health; and Florey Institute of Neuroscience and Mental Health (I.E.S.), Melbourne, Australia.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

METHODS Patients attending a DS clinic were invited to participate; the entire cohort comprised 26 patients with the electroclinical features of DS and an *SCN1A* mutation. Three families refused and 3 were unavailable during the study. Diagnosis was confirmed by a pediatric neurologist with expertise in DS (I.E.S.). All *SCN1A* mutations were located in highly conserved regions or reported to alter protein expression or function.

Standard protocol approvals, registrations, and patient consents. The study was approved by Austin Health Human Research Ethics Committee (Austin HREC H2011/04390). Written informed consent was obtained from all participants or their parents (for minors or those with ID). Consent covered use of video footage for publication.

Speech and language assessment. Two batteries were administered depending on the patient's ability (table 1). Standardized assessments were used where possible, for comparison with typically developing children.

The minimally verbal patients (MV) had little or no speech and were unable to cooperate with standardized assessment, while the verbal group (V) had conversational speech. Testing focused on oral motor, speech, and language skills.

Oral motor tasks and perceptual speech characteristics of conversational samples were independently rated by 2 speech pathologists (S.J.T., A.T.M.). The *SCN1A* mutation, psychological assessment results, medications, and seizure history were reviewed.

RESULTS The cohort comprised 20 patients with DS (11 female), with 15 in the V and 5 in the MV group (table 2). Median age was 11½ years (mean 13 years, range 15 months–28 years). Fifteen had de novo *SCN1A* mutations and 3 inherited mutations. Inherited mutations were from an unaffected mother (patient 10), a father with genetic epilepsy with febrile seizures plus (GEFS+; patient 15), and a mother (patient 20 here) with DS and a de novo *SCN1A* mutation (patient 7). Inheritance for 2 individuals (6, 18) could not be confirmed as their fathers were not available for testing.

In children under 2 years of age, development was normal. In older patients, cognitive skills varied markedly, with intellectual functioning ranging from low average (1) to borderline (1) to mild (5), moderate (2), and severe (9) ID. No pattern of performance was seen on verbal vs perceptual reasoning tasks. All patients were on antiepileptic drugs, with 17/20 taking 3 or more. Three individuals had a vagal nerve stimulator (VNS) (table 2).

Oral motor skills. See table 2 and video 1 (at Neurology.org). All 5 MV individuals showed impaired oral motor control apart from individual 2 who had independent jaw and tongue movement.[7]

Lip and tongue movement was reduced, asymmetrical, or poorly coordinated in 12/15 V individuals. Notably, 2/3 without impairment were the youngest patients in the cohort aged under 2 years. Lip retraction (say "ee") was generally within normal limits, while lip rounding (say "oo") was weak or asymmetrical. Two individuals (17 and 18) could not overcome an open mouth posture at rest to round the lips. Tongue protrusion, elevation, and lateral movement were also impaired, with 6 (8, 9, 11, 15, 16, 18) unable to elevate the tongue and 3 (16, 17, 18) showing involuntary tongue movement.

Overriding impaired motor programming and planning issues affected performance of speech motor and nonspeech oral motor tasks (table 2). Poor postural control of the trunk and head also affected lip and tongue movement.

Saliva control issues were prominent in 8/20 individuals, likely compounded by benzodiazepine therapy in 7 cases. Saliva control management included medication in 3 (3, 5, 18) and salivary duct surgery in 1 that was not beneficial (18). Mild dysphagia was reported in 5/20 individuals, including 1 with a VNS (17). Three had percutaneous endoscopic gastrostomy for nutrition (3, 4, 11).

Speech. See table 3 and video 2. All MV individuals had intentional communication. Three had potentially

Table 1 Comprehensive assessment battery

	Minimally verbal	Verbal
Oral motor skills	Early Motor Control Scales[7] (abnormal structure and function; predominant combined control-motor speech control subscales)	Early Motor Control Scales[7]—under 3 years or Verbal Motor Production Assessment for Children[15] (global motor control, focal oromotor control, sequencing subtests)—3 to 12 years or Frenchay Dysarthria Assessment, 2nd edition[16]—12 years and older
Speech	Behavioral sample: Complexity of Communication Scale[17]	Conversational speech sample Speech errors Dysarthria rating scale[18] Diagnostic Evaluation of Articulation and Phonology[19]
Language		Preschool Language Scales, 5th edition[20]—up to 7 years or Clinical Evaluation of Language Fundamentals, 4th edition[21]—5 to 21 years or Peabody Picture Vocabulary Test, 4th edition,[22] Expressive Vocabulary Test, second edition,[23] Test For Reception of Grammar, second edition[24]
Cognition	Clinical observation and attempt of formal cognitive assessment with Wechsler Abbreviated Scale of Intelligence, 2nd edition,[25] or Wechsler Intelligence Scale for Children, 4th edition, Australian Standardized Edition,[26] and Vineland Adaptive Behaviour Scales, 2nd edition,[27] for estimation of intellectual disability range	Bayley Scales of Infant and Toddler Development, 3rd edition,[28] or Wechsler Abbreviated Scale of Intelligence, 2nd edition,[25] and Vineland Adaptive Behaviour Scales, 2nd edition,[27] for estimation of intellectual disability range

Table 2 Patient details and results of oral motor and language assessment (n = 20)

	Minimally verbal, individual (sex)					Verbal, individual (sex)				
	1 (F)	2 (F)	3 (M)	4 (M)	5 (M)	6 (F)	7 (F)	8 (F)	9 (F)	10 (F)
SCN1A mutation[a]	R946C DN	S128X DN	E1008X DN	F14SfsX78 DN	K38NfsX54 DN	c.602+1 G>A	R222X I, Ma	M960R DN	R613X DN	F256TfsX3 I, Ma
Age at onset	6 wk	3 mo	5.5 mo	4.5 mo	2.5 mo	5.5 mo	6 wk	2.5 mo	6 mo	4.5 mo
ASD	X	√	√	X	X	X	X	X	X	X
AEDs at assessment	VPA, CZP, STP	VPA, TPM, CZP	VPA, TPM, AZM, CZP	VPA, CLB, TPM, STP	STP, CLB, TPM, VPA, LEV, VNS	VPA, CLB, TPM	VPA, TPM	VPA, CZP, LEV, TPM	VPA, TPM, CLB	TPM
Age at assessment	6 y 2mo	9 y 3 mo	12 y	12 y 8 mo	24 y	15 mo	15 mo	4 y 6 mo	5 y 2 mo	6 y
Cognition[b]	Severe ID	Severe ID[c]	Severe ID	Severe ID	Severe ID	95[c]	90	60[c]	75	67
Language										
Receptive[d]	NC	NC	NC	NC	NC	100	100	74	69	48[c]
Expressive[d]	NC	NC	NC	NC	NC	85	105	68	68	50[c]
Dysphagia	X	X	PEG—nutrition	PEG—nutrition	X	X	X	X	X	X
Oral motor and speech motor										
Drooling	X	X	√	√	√	X	X	X	X	X
Lips: rounding, retraction	Can say "ee"	Can smile	Can smile	Can smile, say "ee"	Can smile	Can smile	Can say "ee"	Rounding Abn	N[e]	N
Tongue: elevation, protrusion, lateral	NS	Can elevate /s/	NS	Can elevate /t/,/d/	NS	Can elevate /t/,/d/	Can elevate /d/,/l/	Elevation, lateral Abn[e]	Elevation Abn	N
Multiple movement: blow + smile, a-m-u, ka-la	NC	NC	NC	NC	NC	NC	NC	Abn	Abn	Abn
Motor planning/programming	NC	NC	NC	NC	NC	NC	NC	VSeq[f]	VSeq[f]	VSeq[f]
VMPAC	—	—	—	—	—	—	—	VGlobal[f]	—	VGlobal[f]
	—	—	—	—	—	—	—	VFocal[f]	VFocal[f]	VFocal[f]
Other publications	—	29	30,31	30,31	31,32	—	—	—	—	—

	Verbal, individual (sex)									
	11 (M)	12 (F)	13 (M)	14 (F)	15 (M)	16 (M)	17 (F)	18 (M)	19 (M)	20 (F)
SCN1A mutation[a]	D1416H DN	R101Q DN	c.602+1G>A DN	I1545V DN	A239T I, P	A1326P DN	F575SfsX48 DN	F1707V	V944E DN	R222X DN
Age at onset	6 mo	5 mo	5 mo	8.5 mo	6 mo	6 mo	7 mo	3 mo	7 mo	6 mo
ASD	√	X	X	X	√	X	X	X	X	X
AEDs at assessment	CLB, VPA, TPM, STP	VPA, CLB, TPM, LEV	STP, CLB, TPM, LEV, CZP	STP, VPA, TPM	VPA, TPM, CLB	CZP, VPA, TPM, VNS	VPA, STP, CLB, VNS	CLB, VPA, TPM, LTG	STP, VPA, CLB	LEV
Age at assessment	6 y 8 mo	9 y 5 mo	10 y 9 mo	11 y 7 mo	14 y 6 mo	17 y 4 mo	23 y 10 mo	27 y 2 mo	27 y 11 mo	28 y 5 mo

Continued

Table 2 Continued

	Verbal, individual (sex)									
	11 (M)	**12 (F)**	**13 (M)**	**14 (F)**	**15 (M)**	**16 (M)**	**17 (F)**	**18 (M)**	**19 (M)**	**20 (F)**
Cognition[b]	46	46[c]	Severe ID	68[c]	48[c]	Severe ID[c]	56	40	Severe ID	87
Language										
Receptive[d]	50	58	33	58	Unable to finish	55	45	20	NC	PPVT 76 TROG 71
Expressive[d]	50	53	26	61		48	59	20	NC	84
Dysphagia	√PEG	X	√	X	√	X	√	√	X	X
Oral motor and speech motor										
Drooling	X	X	X	X	√	√	√	√	√	X
Lips: rounding, retraction	Abn[e]	N	Abn[e]	N	FDA-2: retraction 7, alternate 6	FDA-2: retraction 9, alternate 6	FDA-2: retraction 5, alternate 3	FDA-2: retraction 7, alternate 3[e]	NC	FDA-2: retraction 8, alternate 8
Tongue: elevation, protrusion, lateral	Elevation, lateral Abn[e]	N	Abn[e]	Lateral Abn[e]	Trunk control inhibited movement	FDA-2: protrusion 3, elevation 1, lateral 2	FDA-2: protrusion 4, unable to finish	FDA-2: protrusion 6,[e] elevation 1, lateral 5[e]	NC	FDA-2: protrusion, elevation, lateral 9
Multiple movement: blow + smile, a-m-u, ka-la	Abn	Abn	Abn	Decreased lip movement	Abn	Abn	Abn	Abn	NC	N
Motor planning/ programming	Abn	VSeq[f]	VSeq[f]	VSeq 95th percentile	Abn, groping	Abn	Abn	Abn	NC	N
VMPAC	VGlobal[f]	VGlobal[f]	VGlobal[f]	VGlobal[f]	—	—	—	—	—	—
	VFocal[f]	VFocal[f]	VFocal[f]	VFocal[f]	—	—	—	—	—	—
Other publications	—	—	31	30,31	30	31	30,31	30,31,33	30,31,33	30,31,33,34

Abbreviations: Abn = abnormal; AED = antiepileptic drug; ASD = autism spectrum disorder; AZM = acetazolamide; CLB = clobazam; CZP = clonazepam; DN = de novo; FDA-2 = Frenchay Dysarthria Assessment, 2nd ed (scores 7 or below correspond to less than 1% of the normative sample); I = inherited; ID = intellectual disability; LEV = levetiracetam; LTG = lamotrigine; Ma = maternal; N = normal; NC = not able to cooperate with testing; NS = not shown; P = paternal; PEG = percutaneous endoscopic gastrostomy; PPVT = Peabody Picture Vocabulary Test; STP = stiripentol; TPM = topiramate; TROG = Test for Reception of Grammar; VFocal = VMPAC Focal Oromotor Control; VGlobal = VMPAC Global Motor Control; VMPAC = Verbal Motor Production Assessment for Children; VNS = vagal nerve stimulator; VPA = valproic acid; VSeq = VMPAC Sequencing.

Severe ID = standardized assessment attempted but valid score could not be obtained; IQ estimated to be less than 40. Three individuals (6, 7, 20) showed no oral motor impairment; 2 were unable to finish the assessment due to fatigue (17) and a seizure during testing (11). Individual 19 did not cooperate with the assessment.

[a] Nomenclature according to Claes et al. (Hum Mutat 2009).[35]

[b] Scores indicate full-scale IQ (Wechsler Intelligence Scale for Children–IV, Wechsler Abbreviated Scale of Intelligence–II; mean 100, SD 15) or ID ranges based on Vineland Adaptive Behaviour Scales scores and full-scale IQ results if available.

[c] External clinical assessment.

[d] Normative data—mean 100, SD 15; scores 70 and below: <2 SD below the mean.

[e] Motor planning difficulty.

[f] Below fifth percentile.

Table 3 Perceptual speech assessment in verbal patients with conversational speech (n = 13[a])

	Frequency		Severity, n		
	n	%	Mild	Moderate	Severe
Respiration					
Breath support for speech	13	100	4	7	2
Audible inspiration	6	46	2	4	
Forced inspiration/expiration	4	31	2	2	
Grunt at end of expiration	0	0			
Voice					
Intermittent breathiness	10	77	10		
Wetness	5	38	4	1	
Strain-strangled	4	31	2	2	
Hoarseness	3	23	3		
Glottal fry	3	23	3		
Harshness	0	0			
Pitch					
Variation of pitch (monopitch)	10	77	7	3	
Steadiness of pitch (tremor)	10	77	8	2	
Pitch level	8	62	7	1	
Excessive fluctuation of pitch	6	46	2	3	1
Pitch breaks	5	38	3	2	
Loudness					
Maintenance of loudness	8	62	7	1	
Loudness level (overall loudness)	6	46	6		
Variation of loudness (monoloud)	6	46	6		
Excessive loudness variation	5	38	4	1	
Articulation					
Precision of consonants	13	100	6	5	2
Length of phonemes	13	100	7	6	
Precision of vowels	13	100	7	6	
Resonance					
Hyponasality	8	62	5	3	
Mixed nasality	2	15	1	1	
Hypernasality	1	8	1		
Prosody					
General stress pattern	13	100	4	9	
Phrase length	11	85	2	9	
General rate	10	77	6	4	
Maintenance of rate	8	62	8		
Prolonged intervals	8	62	6	2	
Rate fluctuations	3	23	2	1	
Short rushes of speech	3	23	2	1	
Intelligibility					
Overall intelligibility	12	92	5	4	3

[a] The 2 youngest individuals in the verbal group (patients 6 and 7) aged 15 months did not have conversational speech.

communicative behavior (Complexity of Communication Scale [CCS] score 7b) such as eye contact, gesture, vocalization (1, 5), or using an adult's hand as a tool (3) regarded as nonsymbolic communication. Two (2, 4) had symbolic communication (CCS score 10), using single words recognized by an unfamiliar observer.

In the V group, conversational speech intelligibility was severely impaired in 3 (16, 18, 19), moderately impaired in 4 (11, 13, 15, 17), mildly reduced in 5 (8, 9, 10, 12, 14), and normal in 1 (20). All had inadequate breath support for speech. Speech was typified by imprecise articulation of consonants and vowels, abnormal nasal resonance, breathy or strain-strangled voice, low pitch, and prosodic errors (e.g., excess stress on unstressed parts of speech, slow rate, short phrases). Sound errors included voicing errors, distortion of fricatives /s, z, ʃ/, affricates /tʃ, dʒ/ and /l/, delayed phonological processes (final consonant deletion, gliding, fronting, stopping, cluster reduction, /f/ for /θ/, /d/ for /ð/) and atypical phonological processes (backing, replacing sounds with /j/ or /h/, insertion of schwa vowel). The vocal quality of individuals 16 and 17 may be attributed to VNS functioning; however, their voice was similar to patients without a VNS.

Language. Thirteen patients cooperated with language testing. Severely impaired receptive and expressive language (>2 SD below the mean) was seen in 9/13, a severe expressive deficit in patient 8 (receptive moderate), and moderately impaired receptive language in patient 20. The 2 youngest patients scored in the average range at age 15 months (table 2).

DISCUSSION A distinctive speech and language phenotype was found in 20 patients with DS associated with *SCN1A* mutations. Oral motor impairment was common, compounded by poor postural control of the trunk, neck, and head. Motor planning and programming difficulties were striking. Speech was characterized by imprecise articulation of consonants and vowels, abnormal nasal resonance, breathy or strain-strangled voice, and errors in pitch and prosody. Language impairment involving receptive and expressive language was seen in all bar the 2 youngest children. Nonverbal individuals had intentional communication.

Our language findings were more severe than previously reported in 2 earlier studies, which found borderline to average comprehension (9/12 and 9/9 children) and naming (8/12 and 4/9 children).[3,4] This disparity is likely due to past studies including children of a younger age range (up to 13 years of age) and with better cognitive profile. Further, around half of previously reported patients had *SCN1A* mutations. Our findings are comparable to a cohort aged up to 16 years, in which 3/20 children had preserved language.[2]

We found a trend towards a more severe speech phenotype in adults than children, with 3/4 of verbal adults being moderately to severely unintelligible. Current therapeutic regimens for DS are more targeted than in the past, which may lead to amelioration of speech impairment. The oldest adult had very mild impairments in respiration, articulation, phonation, and prosody; however, her phenotype is distinct from the rest of the cohort, as she had normal speech intelligibility, no oral motor impairment, and normal intellect, which is rare in DS. The youngest girls, aged 15 months, presented with age-appropriate language and oral motor skills, which likely reflects the typical developmental trajectory of DS, with normal development slowing in the second year of life.

Interestingly, 5 patients (aged 6–27 years) reported mild dysphagia, similar to the frequency reported in older adults from their fourth decade (5/22 patients).[5] Larger numbers of patients are needed to determine whether there is a correlation between the severity of the speech phenotype and features such as age, type and inheritance of *SCN1A* mutation, seizure types, and medication. Looking at cognitive outcome more broadly, previous studies have shown no correlation of *SCN1A* mutation class, age at seizure onset, type, and number, and MRI abnormalities.[8,9]

The voltage-gated sodium channel $Na_V1.1$, encoded by *SCN1A*, is found in brain regions important for speech and language function including the cerebellum, sensory motor cortex, basal ganglia, hippocampus, middle temporal gyrus, and middle frontal gyrus.[10] Hyperexcitability due to loss of function of GABAergic inhibitory interneurons expressing $Na_V1.1$ underlies seizures in DS.[11] Abnormal inhibition may also be important for speech and language function in DS. Interestingly, abnormal excitation due to mutations in the excitatory glutamate receptor subunit gene *GRIN2A* is associated with motor speech impairment in epilepsy-aphasia syndromes.[12] Studies in milder *SCN1A* phenotypes such as GEFS+ may clarify the role of sodium channels in speech and language impairment.

Moreover, structural changes in speech and language brain regions have been reported and include precentral gyrus, cerebellum, brainstem, corpus callosum, corticospinal tracts, and association fibers (left inferior fronto-occipital fasciculus, left uncinate fasciculus),[13] and influence phenotypic heterogeneity.

Understanding the speech and language phenotype in DS is crucial to planning early intervention. Targeted dysarthria therapy has been successful in other pediatric populations with mild to severe dysarthria[14] and could potentially also improve speech intelligibility of verbal patients with DS.

AUTHOR CONTRIBUTIONS

S.J.T., A.T.M., and I.E.S. designed the study and wrote the manuscript. A.T.M., I.E.S., and V.A. supervised the study. S.J.T. and A.T.M. performed phenotypic analysis. A.B. and M.A. performed most standardized developmental/intellectual functioning assessments.

ACKNOWLEDGMENT

The authors thank the families for their participation in this study; Associate Professor Nancy Brady for use of the Complexity of Communication Scale; Deborah Hayden and Brookes Publishing for permission to use the prepublication version of the Early Motor Control Scales; and Natalie Bryant and Annie Roten for assistance with filming assessments.

STUDY FUNDING

S.J.T. is supported by National Health and Medical Research Council (NHMRC) Postgraduate Scholarship (101777), Australian National University Gowrie Scholarship, and Speech Pathology Australia Nadia Verrall Memorial Research Grant. V.A. is supported by NHMRC Senior Practitioner Fellowship (2010–2019). A.T.M. is supported by NHMRC Career Development Award (607315, 2010–2015) and Practitioner Fellowship (1105008, 2016–2020). I.E.S. is supported by NHMRC Program Grant (628952, 2011–2015; 1091593, 2016–2020) and Senior Practitioner Fellowship (1006110, 2011–2015; 1104831, 2016–2020). The project is also supported by Australian Research Council Discovery Project (DP120100285) to A.T.M. and I.E.S.

DISCLOSURE

S. Turner, A. Brown, M. Arpone, V. Anderson, and A. Morgan report no disclosures relevant to the manuscript. I. Scheffer serves on the editorial boards of *Neurology*® and *Epileptic Disorders*; may accrue future revenue on a pending patent re: Therapeutic compound; has received speaker honoraria from Athena Diagnostics, UCB, GSK, Eisai, and Transgenomics; has received funding for travel from Athena Diagnostics, UCB, and GSK; and receives/has received research support from the NHMRC, ARC, NIH, Health Research Council of New Zealand, March of Dimes, the Weizmann Institute, CURE, US Department of Defense, and the Perpetual Charitable Trustees. Go to Neurology.org for full disclosures.

Received June 9, 2016. Accepted in final form November 23, 2016.

REFERENCES

1. Dravet C, Bureau M, Oguni H, Cokar O, Guerrini R. Dravet syndrome (severe myoclonic epilepsy in infancy). In: Bureau M, Genton P, Dravet C, et al, eds. Epileptic Syndromes in Infancy, Childhood and Adolescence, 5th ed. Montrouge, France: John Libbey Eurotext Ltd.; 2012: 125–156.
2. Casse-Perrot C, Wolff M, Dravet C. Neuropsychological aspects of severe myoclonic epilepsy in infancy. In: Jambaque I, Lassonde M, Dulac O, eds. The Neuropsychology of Childhood Epilepsy. New York: Plenum Press/Kluwer Academic; 2001:131–140.
3. Battaglia D, Chieffo D, Siracusano R, et al. Cognitive decline in Dravet syndrome: is there a cerebellar role? Epilepsy Res 2013;106:211–221.
4. Chieffo D, Battaglia D, Lettori D, et al. Neuropsychological development in children with Dravet syndrome. Epilepsy Res 2011;95:86–93.
5. Catarino CB, Liu JY, Liagkouras I, et al. Dravet syndrome as epileptic encephalopathy: evidence from long-term course and neuropathology. Brain 2011;134:2982–3010.
6. Genton P, Velizarova R, Dravet C. Dravet syndrome: the long-term outcome. Epilepsia 2011;52(suppl 2):44–49.
7. Hayden D, Wetherby AM, Cleary JE, Prizant BM. Early Motor Control Scales: Prepublication Version. Baltimore: Paul H. Brookes Publishing Co.; 2011.

8. Brunklaus A, Ellis R, Reavey E, Forbes GH, Zuberi SM. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. Brain 2012;135:2329–2336.
9. Villeneuve N, Laguitton V, Viellard M, et al. Cognitive and adaptive evaluation of 21 consecutive patients with Dravet syndrome. Epilepsy Behav 2014;31:143–148.
10. Whitaker WR, Faull RL, Waldvogel HJ, Plumpton CJ, Emson PC, Clare JJ. Comparative distribution of voltage-gated sodium channel proteins in human brain. Brain Res Mol Brain Res 2001;88:37–53.
11. Yu FH, Mantegazza M, Westenbroek RE, et al. Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy. Nat Neurosci 2006;9:1142–1149.
12. Turner SJ, Mayes AK, Verhoeven A, Mandelstam SA, Morgan AT, Scheffer IE. GRIN2A: an aptly named gene for speech dysfunction. Neurology 2015;84:586–593.
13. Perez A, Garcia-Penton L, Canales-Rodriguez EJ, et al. Brain morphometry of Dravet syndrome. Epilepsy Res 2014;108:1326–1334.
14. Pennington L, Parker NK, Kelly H, Miller N. Speech therapy for children with dysarthria acquired before three years of age. Cochrane Database Syst Rev 2016;7:CD006937.
15. Hayden D, Square P. The Verbal Motor Production Assessment for Children. San Antonio, TX: The Psychological Corporation; 1999.
16. Enderby P, Palmer R. Frenchay Dysarthria Assessment, 2nd ed. Austin, TX: PRO-ED; 2008.
17. Brady NC, Fleming K, Thiemann-Bourque K, et al. Development of the communication complexity scale. Am J Speech-Language Pathol 2012;21:16–28.
18. Murdoch BE. Dysarthria: A Physiological Approach to Assessment and Treatment. Cheltenham, UK: Stanley Thornes; 1998.
19. Dodd B, Hua Z, Crosbie S, Holm A, Ozanne A. Diagnostic Evaluation of Articulation and Phonology. London: Pearson Assessment; 2002.
20. Zimmerman I, Steiner V, Pond R. Preschool Language Scales, Australian and New Zealand Language Adapted Edition, 5th ed. Sydney: Pearson; 2011.
21. Semel E, Wiig E, Secord W. Clinical evaluation of language fundamentals. In: Australian Standardised Edition, 4th ed. Marrickville, Australia: Harcourt Assessment; 2006.
22. Dunn LM, Dunn DM. The Peabody Picture Vocabulary Test, 4th ed. Minneapolis, MN: NCS Pearson Inc.; 2007.
23. Williams KT. Expressive Vocabulary Test, 2nd ed. London: Pearson Assessment; 2007.
24. Bishop DJ. Test for Reception of Grammar, 2nd ed. London: Pearson Assessment; 2003.
25. Wechsler D. The Wechsler Abbreviated Scale of Intelligence, 2nd ed. London: Pearson; 2011.
26. Wechsler D. Wechsler Intelligence Scale for Children, Australian Standardised Edition, 4th ed. Sydney: Pearson Clinical and Talent Assessment; 2005.
27. Sparrow SS, Cicchetti DV, Balla DA. Vineland Adaptive Behavior Scales, 2nd ed. London: Pearson; 2005.
28. Bayley N. Bayley Scales of Infant and Toddler Development, 3rd ed. London: Pearson; 2005.
29. Carvill GL, Weckhuysen S, McMahon JM, et al. GABRA1 and STXBP1: novel genetic causes of Dravet syndrome. Neurology 2014;82:1245–1253.
30. Harkin LA, McMahon JM, Iona X, et al. The spectrum of SCN1A-related infantile epileptic encephalopathies. Brain 2007;130:843–852.
31. Rodda JM, Scheffer IE, McMahon JM, Berkovic SF, Graham HK. Progressive gait deterioration in adolescents with Dravet syndrome. Arch Neurol 2012;69:873–878.
32. Singh R, Andermann E, Whitehouse WP, et al. Severe myoclonic epilepsy of infancy: extended spectrum of GEFS+? Epilepsia 2001;42:837–844.
33. Jansen FE, Sadleir LG, Harkin LA, et al. Severe myoclonic epilepsy of infancy (Dravet syndrome): recognition and diagnosis in adults. Neurology 2006;67:2224–2226.
34. Vadlamudi L, Dibbens LM, Lawrence KM, et al. Timing of de novo mutagenesis: a twin study of sodium-channel mutations. New Engl J Med 2010;363:1335–1340.
35. Claes LRF, Deprez L, Suls A, et al. The *SCN1A* variant database: a novel research and diagnostic tool. Hum Mutat 2009;30:E904–20.