ORIGINAL CONTRIBUTION

Progressive Gait Deterioration in Adolescents With Dravet Syndrome

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Objective: To characterize changes in gait by age in patients with Dravet syndrome.

Design: Prospective, cross-sectional study.

Setting: Tertiary children's hospital.

Patients: Twenty-six subjects with Dravet syndrome, aged 2 to 34 years. Twenty-three patients had mutations of the sodium channel α1 subunit gene, *SCN1A*.

Interventions: Assessment via video gait analysis, physical examination of the lower limbs, use of the Functional Mobility Scale, and radiographs of the pelvis and feet.

Main Outcome Measures: Classification of the sagittal gait pattern and foot posture, assessment of muscle extensibility and joint range, and rating of functional mobility.

Results: Children aged 0 to 5 years had a normal or near-normal gait, whereas 5 of 10 children aged 6 to 12 years and 8 of 9 children aged 13 years or older had crouch gait. Physical examination showed that with increasing age, passive knee extension ($P=.008$) and hip extension ($P=.003$) decreased, external tibial torsion ($P=.007$) and pes planovalgus ($P=.05$) increased, and increased hip internal rotation did not show age-related change ($P=.27$). The Functional Mobility Scale showed universal independent walking over 5 and 50 m; however, adolescents showed wide variation in their ratings over 500 m, indicating mobility ranging from wheelchair use to independent walking ($P=.02$).

Conclusions: Children with Dravet syndrome show progressive gait deterioration in the second decade of life, with crouch gait and skeletal malalignment comprising increased femoral neck anteversion, external tibial torsion, and pes valgus. These age-related changes have a significant impact on mobility and independence in the community setting.

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SOME CHILDREN AND YOUNG adults with severe epilepsies develop slowly progressive gait disturbances, although this has not been well characterized. Dravet syndrome, also known as severe myoclonic epilepsy of infancy, is a severe epileptic encephalopathy due to mutations of the gene encoding the α1 subunit of the sodium channel, *SCN1A*, in more than 70% of cases. It has a characteristic electroclinical evolution with onset at age 6 months, typically with febrile status epilepticus, followed by frequent convulsive seizures and the emergence of other seizure types after 1 year.[1,2] Development is normal in the first year of life and then plateaus; regression may occur. Attention has focused on the first 5 years of life when seizures are at their most severe with recurrent episodes of status epilepticus and developmental slowing occurs. However, little attention has been paid to the evolution of the motor deficits with age.

The early neurological examination findings in children with Dravet syndrome are usually normal; however, in the original description, Dravet[1] noted pyramidal tract signs and ataxia. To our knowledge, the nature and course of changes in gait by age have not been studied. We aimed to characterize the age at onset, nature, and trajectory of gait dysfunction in individuals with Dravet syndrome.

METHODS

This was a prospective, cross-sectional study of a consecutive cohort of children, adolescents, and adults with Dravet syndrome re-

Table 1. Demographic Data of Subjects With Dravet Syndrome

Patient No./Age, y	*SCN1A* Mutation	Mutation Type
1/2.5	V806fsX817	Truncation
2/4.3	K1313fsX1319	Frameshift truncation
3/4.4	G950E	Missense
4/4.5	IVS4 + 1G>A	Splice site
5/4.8	R613X	Nonsense truncation
6/5.6	IVS10-1G>C	Splice site
7/5.9	IVS14 + 2T>A	Splice site
8/6.3	I1545V	Missense
9/6.8	E1008X	Truncation
10/7.3	L1660P	Missense
11/7.4	F14fsX91	Truncation
12/8.9	Del exon21-26	Exon deletion
13/9.1	K1846fsX1856	Truncation
14/9.1	Negative	
15/10.4	IVS4 + 5G>A	Splice site
16/11.0	A1326P	Missense
17/11.5	Negative	
18/13.3	R1886X	Truncation
19/13.5	E1881D	Missense
20/17.1	W1812X	Truncation
21/17.4	F575fsX622	Truncation
22/17.9	P37fsX91	Truncation
23/21.0	F1707V	Missense
24/22.6	V944E	Missense
25/23.3	R222X	Truncation
26/34.4	Negative	

cruited through our previous studies of Dravet syndrome.[3] Ethical approval was obtained from the Ethics in Human Research Committee at the Royal Children's Hospital, Melbourne, Victoria, Australia. Written informed consent was obtained from all patients, their parents, or legal guardians.

Patients were included if they had a confirmed diagnosis of Dravet syndrome based on electroclinical features. This included both the classical and borderline forms, as we have previously shown that separation of these entities is not clinically significant.[2,3] Each child attended the Hugh Williamson Gait Laboratory for 2-dimensional video gait analysis (VGA), physical examination, rating of functional mobility, and radiography of the lower limbs. All data were collected by a physiotherapist (J.M.R.) with experience in pediatrics and gait analysis.

The VGA was conducted with the child walking barefoot along a 10-m walkway within the gait analysis laboratory. Views were obtained according to the laboratory's standardized protocol of split-screen sagittal and coronal views, full sagittal view, sagittal view from the midthigh to the floor, full coronal view, and coronal view from the midcalf to the floor. The sagittal gait pattern was assessed from the VGA and classified as normal, variable, or crouch gait.[4,5] Crouch gait was defined as increased hip and knee flexion and ankle dorsiflexion throughout the stance phase. The sagittal gait patterns of true equinus, jump gait, and apparent equinus[4] were not seen in this cohort. The reliability of this classification of sagittal gait patterns in spastic diplegic cerebral palsy has been established based on either sagittal kinematics or VGA.[4]

A standardized physical examination[6] was conducted to assess joint range, muscle length, bony rotational alignment, muscle tone,[7] spasticity, and ligamentous integrity.[8] Foot posture was classified as within normal limits, mild indicating pes planus, or moderate to severe signifying pes planus with abductus and valgus. Muscle strength could not be assessed owing to limitations in the patients' cognitive ability. Radiographs of the hip (anteroposterior view) were taken to detect whether hip dysplasia was present. Foot radiographs (standing anteroposterior and lateral) were taken and quantitatively measured by the objective radiological criteria established by Davids et al,[9] which have shown good reliability in children without[9] and with[10] pathology. One parameter for the hindfoot, midfoot, and forefoot was measured, which correlates best with the clinical evaluation of pes planus. The greater the lateral talocalcaneal angle, the more valgus and abducted is the hindfoot; the greater the naviculocuboid overlap, the more pronated is the midfoot; and the greater the talo–first metatarsal angle, the more planus is the midfoot/forefoot. Inspection of spinal alignment was part of the standardized physical examination.

Ratings of mobility and function were undertaken using the Functional Mobility Scale[11,12] and the Gillette Functional Assessment Questionnaire.[13] The age at which the child commenced independent walking was noted.

For analysis, the subjects were divided into 3 age groups: birth to 5 years, 6 to 12 years, and 13 years and older. The groups were devised to determine whether deterioration in gait was related to particular periods and developmental stages of the children's lives, eg, prior to school entry vs midchildhood vs adolescence and adulthood. To compare mean outcomes for the different age groups, linear regression models to allow for measurements from the 2 limbs of the same subject were used.[14] Robust standard errors are inflated to take into account any excess correlation in measurements from the 2 limbs of the same patient. Comparisons across age groups in gait pattern, foot posture, radiology findings, and mobility status were described by odds ratios calculated from ordered logistic regression with robust standard errors. Stata version 7 statistical software (StataCorp LP) was used for statistical analysis.

RESULTS

Twenty-six individuals (52 limbs) with Dravet syndrome were evaluated. There were 15 males and 11 females, with a mean age of 11.6 years (range, 2.5-34.4 years). Seven individuals were aged 0 to 5 years, 10 were aged 6 to 12 years, and 9 were aged 13 years or older. Twenty-three subjects (88%) had an *SCN1A* mutation (**Table 1**). The mean (SD) age at the commencement of independent walking was 17 (5.1) months (range, 9-30 months). Twenty-three individuals (88%) had achieved independent walking by their second birthday. The age at attainment of independent walking did not differ between the 3 age groups.

The majority of children aged 0 to 5 years (6 of 7 individuals) had a normal gait pattern. Five of the 10 children aged 6 to 12 years showed crouch gait ($P = .002$). By age 13 years, most adolescents (8 of 9 individuals) were in crouch gait ($P = .001$) (**Figure 1** and **Figure 2**). Ataxia, defined by a wide-based gait, was rarely observed in the cohort.

Changes in the physical examination findings with age are shown in **Table 2**. Physical examination of the sagittal plane showed that with increasing age, mean passive knee extension decreased and contracture began to develop. The mean hip extension decreased in adolescence and the mean popliteal angle increased across the 3 age groups. In the transverse plane, the mean passive hip internal rotation was increased in all age groups. Although the increased femoral neck anteversion decreased after 6 years, it was still increased with respect to values for typically developing children. External tibial

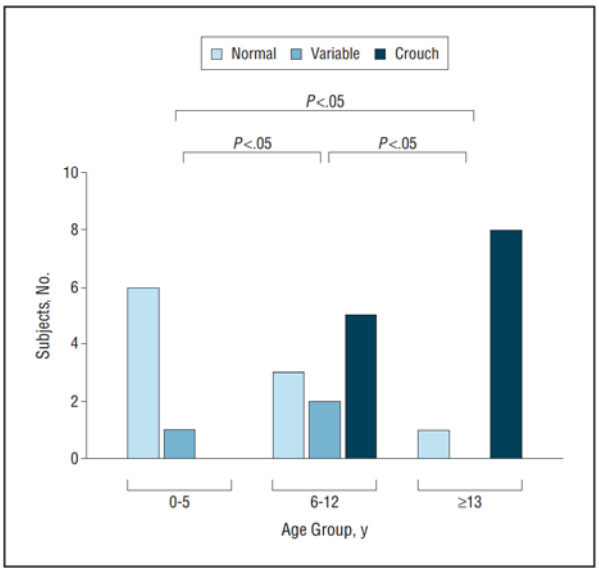

Figure 1. Change in gait patterns across age groups. As subjects became older, fewer walked with a normal gait pattern and more walked in crouch gait.

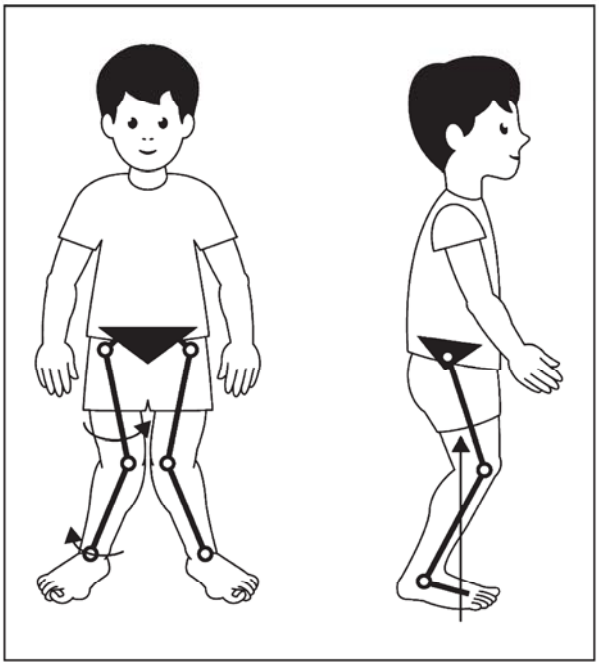

Figure 2. Crouch gait is characterized by increased hip and knee flexion and ankle dorsiflexion in the sagittal plane throughout the stance phase and is accompanied by bony malalignment in the transverse plane of medial femoral torsion, lateral tibial torsion, and planoabductovalgus of the feet.

torsion, as measured by the bimalleolar axis, was significantly increased in the group aged 13 years and older compared with the other age groups. Compared with the group aged 0 to 5 years, those aged 13 years and older showed 8 times greater odds (95% CI, 1.0-65.3; $P = .05$) of worsening foot deformity (pes planus with abductovalgus). Ligamentous laxity was found in 6 subjects, only 1 of whom walked in crouch gait. Hypertonicity as measured by the Modified Ashworth Scale[7] and spasticity as measured by the Tardieu Measure[15] were not observed.

Table 2. Comparisons of Physical Examination Parameters for Subjects With Dravet Syndrome Across Age Groups

	Degree of Movement on Physical Examination, Mean (SD)		
Parameter	0-5 y	6-12 y	≥13 y
Sagittal plane			
Hip extension	15 (2)	15 (3)	7.5 (5)[a]
Knee extension	6.2 (3)	3.1 (2)[b]	−2 (7)[c]
Popliteal angle	2.5 (6)	13 (11)[b]	35 (14)[a]
Dorsiflexion, knee 90°	39 (9)	32 (7)	22 (10)[a]
Dorsiflexion, knee 0°	33 (8)	19 (8)[b]	10 (12)[c]
Transverse plane			
Hip internal rotation	66 (9)	58 (9)	58 (17)
Femoral neck anteversion	30 (3)	22 (5)[b]	23 (6)[c]
Bimalleolar axis	21 (7)	24 (9)	31 (7)[a]

[a] $P < .05$ between the group aged 0 to 5 years and the group aged 13 years and older and between the group aged 6 to 12 years and the group aged 13 years and older.
[b] $P < .05$ between the group aged 0 to 5 years and the group aged 6 to 12 years.
[c] $P < .05$ between the group aged 0 to 5 years and the group aged 13 years and older.

Table 3. Comparisons of Lateral Radiograph Parameters for Subjects With Dravet Syndrome Across Age Groups

	Degree on Lateral Radiograph, Mean (SD)		
Parameter	0-5 y	6-12 y	≥13 y
Hindfoot, talocalcaneal angle	42 (12)	52 (7)	61 (8)[a]
Midfoot, naviculocuboid overlap	36 (17)	54 (12)[b]	80 (12)[a]
Forefoot, talo–first metatarsal angle	11 (10)	19 (8)	35 (8)[a]

[a] $P < .05$ between the group aged 0 to 5 years and the group aged 13 years and older and between the group aged 6 to 12 years and the group aged 13 years and older.
[b] $P < .05$ between the group aged 0 to 5 years and the group aged 6 to 12 years.

Dyskinetic or dystonic movement patterns were not seen. In-shoe orthotics were worn by 11 of 26 subjects (42%).

Mild, flexible or postural kyphosis was noted as part of the crouch gait posture in adolescents and young adults only (group aged ≥13 years). However, no fixed spinal deformities were noted. No radiographs of the spine were considered necessary because of the absence of significant or fixed deformities on clinical examination.

Radiology showed mild hip dysplasia (without subluxation) with no variation across age groups. Foot radiographs showed a significantly increased talocalcaneal angle and talo–first metatarsal angle on radiographs of the weight-bearing lateral foot in the adolescent and older age group (aged ≥13 years). Naviculocuboid overlap exhibited increases with advancement in age group ($P = .03$ for patients aged 0-5 years vs 6-12 years; $P = .001$ for patients aged 6-12 years vs ≥13 years) (**Table 3**).

On the Functional Mobility Scale, subjects rated 5 or 6 (independent walking) for 5 and 50 m in all age groups. However, adolescent and adult subjects showed wide

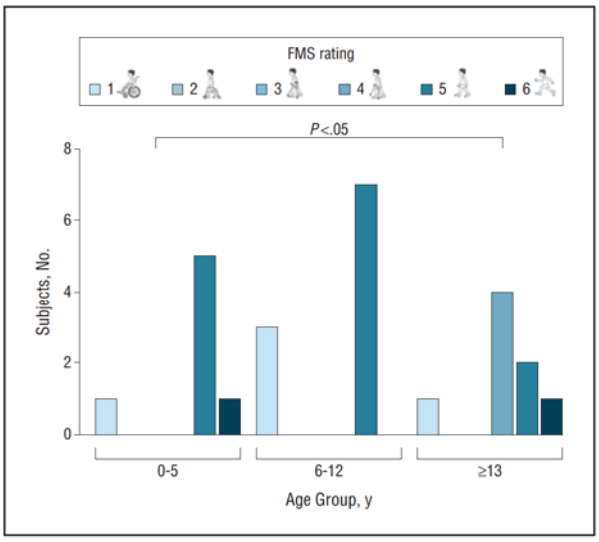

Figure 3. Change in mobility status over 500 m across age groups as measured by the Functional Mobility Scale (FMS). By age 13 years or older, fewer subjects were independent walkers and more were either leaning on another person for support (rating 4) or using a wheelchair (rating 1).

variation in their ratings for 500 m (score range, 1-6), indicating mobility ranging from wheelchair use to independent walking (95% CI, 0.4-0.8; $P = .02$) (**Figure 3**). There was no significant difference in the level of mobility between age groups on the Gillette Functional Assessment Questionnaire.

COMMENT

We examined the progressive deterioration in gait observed in patients with Dravet syndrome. Our subjects obtained independent walking at an age similar to those in other studies.[16,17] Various authors have described the gait in Dravet syndrome as ataxic[16-22] with estimates that 50% to 60% of subjects[18,21,22] have an ataxic gait, including 20% who exhibit mild pyramidal signs.[18] In addition, we noted extrapyramidal features in 4 of 14 adults with Dravet syndrome.[20] However, the evolution of the gait pattern in Dravet syndrome has not been subject to critical analysis. In this study, a biomechanical assessment of muscle extensibility, joint range, bony torsion, and ligamentous laxity has been coupled with a neurological assessment of muscle tone, spasticity, and movement patterns.

This study has shown that with increasing age, subjects with Dravet syndrome develop crouch gait. The rotational profiles of the hip, tibia, and foot reveal increasing lever arm dysfunction, which may contribute to the development of crouch gait.[23] In contrast to crouch gait in spastic diplegic cerebral palsy in which hip and knee contractures are substantial,[24] we found that contractures at the hip and knee are present but small. Hip dysplasia was mild and did not show evidence of worsening as the subjects aged, but foot deformity did worsen as previously described.[18]

Passive internal rotation of the hip was consistently increased throughout all age groups. This and the increased femoral anteversion and mild hip dysplasia may be the primary abnormalities that stimulate the development of increasing external tibial torsion and pes planus with abductovalgus deformity with increasing age. Increased femoral anteversion decreases the lever arm of the gluteus medius, and internal rotation of the hip can be an attempt to restore this.[25] However, internal rotation of the femurs will require the feet to be externally rotated with respect to the femurs for the feet to be aligned to the line of progression of the body. The external rotation of the feet with respect to the femurs can be gained by increasing external tibial torsion or deformation of the feet into a planoabductovalgus position.[26-28] This may explain the increasing external tibial torsion and foot deformity, particularly in adolescence. The ability of the knee to extend in the stance phase is compromised by increased external tibial torsion[29] or a foot posture of pes planus with forefoot abductus and hindfoot valgus,[30] as both decrease the magnitude of the ground reaction force that acts to extend the knee. The development of the increased external tibial torsion accompanied by foot deformity in the transverse plane may predispose the children and adolescents with Dravet syndrome to the development of crouch gait in the sagittal plane.

Crouch gait is one of the 4 sagittal gait patterns typically seen in spastic diplegic cerebral palsy.[4] Spasticity may be present in children with Dravet syndrome but is mild, consistent with the observation that crouch gait is not characterized by lower limb spasticity. Weakness in the antigravity lower limb muscles (gluteal muscles, quadriceps, gastrocnemius, and soleus), which act predominantly in the sagittal plane, is a major contributor to crouch gait. At the time of the adolescent growth spurt, muscles that have previously been able to support the body in the upright position may be disadvantaged if strength does not increase proportionally with the increase in body mass.[31] It is hypothesized that it may be the abnormal biomechanical alignment (increased medial femoral torsion, lateral tibial torsion, and pes valgus) coupled with weakness in the antigravity muscles acting in the sagittal plane that lead to the development of crouch gait in Dravet syndrome in adolescence.

The mechanism for the increased femoral torsion in all of the age groups may be partly due to the mild delay in attainment of independent walking that in turn delays the application of force from the Bigelow ligament around the femoral neck, which in normal circumstances remodels and consequently decreases the high femoral anteversion present at birth.[26,30]

Problems with mobility in adolescence and adulthood have long been identified in Dravet syndrome.[22] Here, mobility was compromised at the community level from adolescence when many started to lean on others for support or to use a wheelchair for long distances. The decline in mobility is probably attributable to crouch gait. However, owing to the cognitive impairment of adolescents with Dravet syndrome, it is impossible to know whether they experience the disabling symptoms of knee pain and fatigue typically associated with habitual crouch gait in spastic diplegic cerebral palsy.[5,23,32]

The cause(s) of crouch gait in Dravet syndrome is not clear, so preventive measures are difficult to prescribe. If increased femoral anteversion is the precipitating fac-

tor, surgical correction prior to the development of compensatory external tibial torsion and foot deformity may be possible. If planus midfoot deformity is a precursor to the development of crouch gait, perhaps the instigation of in-shoe orthotics may prevent development of further foot deformity. However, many of the subjects in this study had been wearing in-shoe orthotics and crouch gait still occurred. Sagittal plane correction of short contracted muscles and fixed flexion deformities is not necessarily applicable to the patients with Dravet syndrome as contracture was not substantial, but lever arm correction of bony malalignment between the femur, tibia, and foot in the transverse plane may be appropriate. Such surgical intervention, involving a number of operations during 1 surgical session, may not be advisable owing to the limited cognitive abilities and varying levels of cooperation in subjects with Dravet syndrome, which may limit or prevent successful rehabilitation. However, in our institution, foot stabilization surgery to correct pes valgus was undertaken in a patient with Dravet syndrome older than 13 years and mobility was regained. There are other patients under careful consideration for surgical management, but to our knowledge there is no evidence to date regarding surgical outcomes for crouch gait in Dravet syndrome. Currently at our institution, patients are followed up closely for deterioration in gait and prescribed orthotic support (ankle foot orthoses) when needed and practical. Muscle weakness in spastic diplegic cerebral palsy can be addressed by programs of progressive resistance training,[33-37] but again this may be difficult in the patients with Dravet syndrome.

The strengths of our study were the prospective standardized collection of clinical, radiographic, and VGA data using protocols with good reliability.[4,6,9,11,12] The principal weakness of the study was the lack of kinematic data. Instrumented gait analysis requires a significant degree of cooperation from the patient for 2 to 3 hours. Children with significant intellectual disability, including those with Dravet syndrome, are unable to comply with the rigors of instrumented gait analysis. In particular, they tend to remove the retroreflected markers and fail to follow simple commands required to walk along the walkway and to achieve clean foot placement on the force plates for kinetic data.

A key question is whether the frequency of seizures, the number and quantity of antiepileptic drugs, and the nature of the *SCN1A* mutation influence the likelihood of developing a crouch gait. Of our adolescent and adult patients, 8 of the 9 cases had crouch gait. The 1 exception was a patient with Dravet syndrome with a nonsense mutation and normal intellect who has been previously characterized in depth.[38] She is the only one of our patients who has had long seizure-free periods and receives 1 antiepileptic drug. Given the rarity of her milder phenotype, a definite conclusion cannot be drawn regarding the impact of seizures, medication, and the type of mutation on the development of crouch gait.

As Dravet syndrome is usually caused by sodium-channel gene mutations, a key question is how sodium-channel dysfunction could lead to a gait disturbance. Crouch gait is not specific to patients with Dravet syndrome or sodium-channel mutations, but the high frequency in patients with Dravet syndrome and the characteristic progression during 2 decades of life in this now well-defined epileptic encephalopathy suggest that there may be a specific pathogenesis to unveil. The knockout *SCN1A* mouse shows ataxic abnormalities associated with impairment of the γ–aminobutyric acid (GABA)–ergic function of inhibitory neurons, the Purkinje cells of the cerebellum.[39] However, only young mice have been studied, so it is not known whether older mice develop a gait disturbance akin to that observed in humans with Dravet syndrome. Progress in understanding the pathogenesis and pathophysiology may allow preventive measures to be instituted.[40]

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