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Progressive Worsening of Gait and Motor Abnormalities in Older Adults With Dravet Syndrome

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Page 913

Abstract

Background and Objectives

Relative to the pediatric population, there is limited information about Dravet syndrome (DS) in adults. In addition to some of the gait abnormalities reported in children with DS (such as crouch gait and ataxia), adults with this condition have other gait and motor disturbances. Our primary objective was to examine gait and motor manifestations in adults with DS.

Methods

This study includes a prospective arm where 6 patients (mean age, 32 years) were examined through a modified version of the Unified Parkinson's Disease Rating Scale (mUPDRS) in 2014 and again in 2019. mUPDRS scores were assigned to gait, resting tremors, facial expression, arising from a chair, posture, and body bradykinesia. The cross-sectional arm includes mUPDRS testing in patients who were not evaluated in 2014 and an instrumental gait analysis (IGA). These cross-sectional tests were done in the 2019–2020 period. The IGA was performed using ProtoKinetics software with a gait mat built with sensors and 2 cameras capturing the sagittal and coronal planes. The IGA was performed in a group of 17 patients with DS (mean age, 31 years); the control group consisted of 81 healthy individuals, whose mean age was 62 years. Regression analyses were performed for the IGA and mUPDRS data.

Results

Five out of 6 participants evaluated prospectively over 5 years experienced worsening of their parkinsonian manifestations, including gait. Two patients (47 and 51 years of age) who were initially ambulatory could no longer walk 5 years later. The cross-sectional analysis of mUPDRS in a larger group of adults showed that worse scores for arising from a chair (p = 0.04), body bradykinesia (p = 0.01), and gait (p = 0.0003) were positively associated with age. The IGA cross-sectional arm revealed that all 17 adults with DS had abnormal gait measures in all domains tested. This group of patients performed worse than the healthy and older control group.

Discussion

Although seizures may decrease in older adults with DS, this prospective and cross-sectional study showed that their motor symptoms and gait become progressively worse as they age.

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Glossary

DEE = developmental and epileptic encephalopathy; **DS** = Dravet syndrome; **eGVI** = enhanced gait variability index. **IGA** = instrumental gait analysis; **mUPDRS** = modified Unified Parkinson's Disease Rating Scale; **PD** = Parkinson disease.

Dravet syndrome (DS) is a treatment-resistant developmental and epileptic encephalopathy (DEE) with onset in the first year of life.[1,2] More than 80% of patients with DS have pathogenic variants in the *SCN1A* gene.[2,3] *SCN1A* encodes the Nav1.1 protein, a voltage-gated sodium channel. One of the results of decreased levels or abnormal Nav1.1. protein is a decrease in GABAergic inhibition, leading to excessive excitation.[4-6] However, this protein is also expressed in other tissues. As such, it is not surprising that, in addition to seizures, patients also have slowing of cognitive development and gait problems.[2,7]

Relative to the pediatric population, there is limited information about DS in adults.[8-12] The majority of patients continue to have refractory seizures as adults, although their convulsive seizures can be restricted to sleep periods.[11,13] Myoclonic, atypical absence, and focal seizures with impaired awareness may decrease or disappear in adulthood.[8,10,11,13-15] Gait abnormalities have also been reported in a few adults.[10,14,16] These tend to differ from those reported in childhood.[17]

Parents and caregivers of adults with DS often comment that their adult child is losing certain previously acquired skills, including the ability to ambulate. To provide an objective assessment of these parental observations, we performed a prospective evaluation in a small group of patients and a cross-sectional evaluation of gait and parkinsonian manifestations in a larger group of adults with DS. We hypothesize that their gait and parkinsonian features will get worse with age.

Methods

Participants

Patients were identified at the Adult Epilepsy Genetics Clinic at Toronto Western Hospital between 2010 and 2020. Eligible participants had to have a clinical diagnosis of DS[18] and be 18 years of age or older. Because some adult patients did not have a well-characterized pediatric clinical history, we only included patients who also had genetic results showing pathogenic *SCN1A* or *GABRA1* variants in keeping with a DS diagnosis. Patients chronically exposed to antipsychotic medications were not eligible. For comparison, we used a control group consisting of 81 healthy individuals, whose mean age was 62 years.

Study Design

One arm of the study consisted of 6 patients who were prospectively studied over a period of 5 years. Their gait and motor manifestations were evaluated through the modified Unified Parkinson's Disease Rating Scale (mUPDRS). The results of their first evaluation were published in 2014[14]; their second evaluation, done in 2019, is reported here. Another group of 12 adults with DS (not previously evaluated) was studied in a cross-sectional manner using mUPDRS. Finally, 17 adults (including some of those who participated in the prospective study) were evaluated with instrumental gait analysis (IGA). The cross-sectional evaluations (mUPDRS and IGA) were done during 2019 and 2020.

Modified Unified Parkinson's Disease Rating Scale

The mUPDRS has been validated for patients with DS.[14,19] The measures evaluated include right and left upper limbs resting tremor, facial expression, arising from a chair, gait, posture, and body bradykinesia. The maximum possible mUPDRS points is 4 for each measure, leading to a potential 28 total points. mUPDRS evaluations were assessed by movement disorder specialists in 2014 (A.F.) and again in 2019–2020 (A.F. and C.G.).

Instrumental Gait Analysis

A formal gait assessment was completed on the Zeno Walkway Gait Analysis System (ProtoKinetics). This system has sensors built into the gait mat and uses 2 video cameras 90° apart, providing a sagittal and coronal view. Each patient was asked to walk on the mat for 6 feet, back and forth, for 2 attempts. The ProtoKinetics software (PKMAS) was adopted to extract the following measures: ambulation time (seconds), cadence (steps/min), double support percentage (% of time of gait spent on both feet), double support time (amount of time [seconds] of gait spent on both feet), gait cycle (begins at heel strike of one foot and continues until the heel strike of the same foot [seconds]), gait velocity (the time it takes to travel a specified distance [cm/s]), number of steps, right/left step length asymmetry (ratio of right to left step length), short/long step time asymmetry (ratio of right to left step time), single/double time ratio (the time spent on 1 foot vs 2 feet), stance percentage (% of gait spent in stance phase), stance time (time spent in stance phase [seconds]), step length (cm), stride width (cm), swing percentage (% spent in swing phase), and enhanced gait variability index (eGVI) (fluctuation of gait measures between steps). This information can provide clinicians objective data about their patients' gait.

A chart review was performed in 2019–2020 to determine the seizure type and frequency in these participants (eTable 1, links.lww.com/WNL/B947).

Data Analysis

All data analyses were performed in GraphPad Prism 9.1.2. The gait analysis and mUPDRS scores were analyzed using the Spearman rank order correlation for associations between age and gait measures.

Table 1 Study Tasks Completed by 21 Participants

Patient ID	IGA in 2019	mUPDRS completed in 2014	mUPDRS completed in 2019
1		x	
2		x	
3	x	x	x
4	x	x	x
5		x	
6	x	x	x
7	x	x	
8	x	x	
9	x		x
10	x	x	x
11	x	x	x
12		x	x
13	x		x
14	x		x
15	x		x
16	x		x
17	x		x
18	x		x
19	x		
20	x		
21	x		
Total	17	11	13

Abbreviations: IGA = instrumental gait analysis; mUPDRS = modified Unified Parkinson's Disease Rating Scale.

Table 2 Genetic Findings

Patient ID	Gene variant	Mutation type
1	c.1090A>C	Missense
2	c.5018T>A	Missense
3	c.3985C>T	Frameshift
4	c.5488_5489delCA	Frameshift
5	c.1090A>C	Missense
6	c.2792G>A	Missense
7	c.3517+2T>C	Splice site
8	c.912_913dupTT	Frameshift
9	c.2946+1G>T	Splice site
10	c.4168G>A	Missense
11	c.563A>T	Missense
12	c.4900delC	Frameshift
13	c.1028+1G>A	Splice site
14	c.664C>T	Nonsense
15	c.4762T>C	Missense
16	c.3705+4A>T	Splice site
17	c.4427_4435dupACCTGTTTA	Frameshift
18	c.524C>T	Missense
19	c.3661G>C	Missense
20	c.4374C>A	Missense
21[a]	c.865A>G	Missense

[a] This patient has a *GABRA1* mutation.

Data Access and Data Availability

The corresponding author takes full responsibility for the data, the analyses and interpretation, and the conduct of the research; has full access to all of the data; and has the right to publish any and all data, separate and apart from the guidance of any sponsor. Anonymized data not published within this article will be made available by request from any qualified investigator.

Standard Protocol Approvals, Registrations, and Patient Consents

Written consent was obtained from all patients' caregivers. Ethics approval was granted by the University Health Network Research Ethics Board.

Results

Twenty-nine patients were eligible for the study. Given the COVID-19 pandemic, several patients' caregivers declined to come to the hospital for this study. As a result, 18 patients were evaluated with mUPDRS (6 of them were part of the prospective study and were evaluated twice, 5 years apart [results of the first evaluation were published previously[14]]); 17 patients completed the IGA (Table 1). The age range was 18–51 years and mean age was 31.81 ± 9.6 years. A breakdown of the pathogenic variants is reported in Table 2. This group of adults with DS displayed a tendency to have a decrease in seizure frequency, as this group averages 2.4 convulsions per week. They also had mainly nocturnal convulsions in adulthood. Six out of 21 patients in this study were seizure-free for at least a year before the assessments were performed. Cognition was not formally evaluated, as all patients experienced moderate or severe intellectual disability. Cranial nerves were evaluated to the extent the participants collaborated for evaluation and we noted no abnormalities.

Modified Unified Parkinson's Disease Rating Scale

In the prospective group, we observed a worsening of mUPDRS scores over a 5-year span in 5 of 6 patients (Table 3).

Table 3 mUPDRS Scores in 6 Patients Completed in 2014 and 2019

Patient number and age at first (F) and second (S) assessment, y	Resting tremor, L	Resting tremor, R	Facial expression	Arising from chair	Gait	Posture	Body bradykinesia	Total
3								
(F) 24	0	0	3	1	2	1	3	10
(S) 29	0	0	2	1	1	1	1	6
4								
(F) 23	0	0	1	0	0	0	1	2
(S) 28	1	1	1	0	1	0	0	4
6								
(F) 34	0	0	3	4	2	1	3	13
(S) 39	0	0	3	2	2	4	3	14
10								
(F) 42	0	0	2	4	3	3	3	15
(S) 47	0	0	3	4	4[a]	4	3	18
11								
(F) 23	0	0	3	0	1	1	1	6
(S) 28	1	1	3	0	1	1	2	9
12								
(F) 46	0	0	2	4	3	1	3	12
(S) 51	0	0	1	4	4[a]	1	4	14

Abbreviation: mUPDRS = modified Unified Parkinson's Disease Rating Scale.
[a] Score 4 means these patients are no longer able to ambulate.

The only patient who improved was patient 3, who was started on levodopa after the first assessment. The 2 older patients (ages 47 and 51 at the last evaluation) were ambulatory at their first assessment in 2014, but they were no longer able to walk in 2019 when the second assessment was done. These 2 patients also received levodopa after their first evaluation, but this medication was discontinued after the patients stopped walking.

In the cross-sectional group, 12 patients were evaluated with mUPDRS only once, between 2019 and 2020. We observed a significant correlation between worse scores and older age for body bradykinesia ($p = 0.01$), gait ($p = 0.0003$), arising from a chair ($p = 0.04$), and total score ($p = 0.0004$) (Figure 1).

Instrumental Gait Analysis

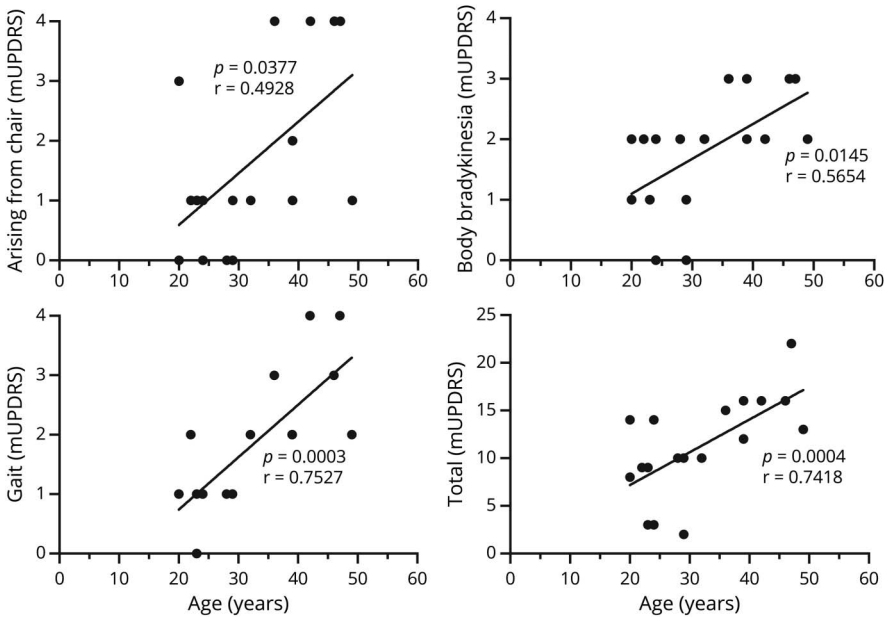
Seventeen patients with DS completed the IGA (cross-sectional evaluation done only once in 2020). The IGA results demonstrated that several gait measures were worse in older patients (Figure 2): double support percentage ($p = 0.0007$), double support time ($p = 0.02$), single/double time ($p = 0.003$), step length ($p = 0.0001$), stride length ($p = 0.0004$), stance percentage ($p = 0.01$), swing percentage ($p = 0.01$), and eGVI ($p = 0.04$). The following measures showed a trend towards worsening function with increasing age: ambulation time, gait cycle, number of steps, and gait velocity (eFigure 1, links.lww.com/WNL/B946). In all the gait modalities evaluated, the patients with DS (mean age 31 years) performed worse than the older healthy control group, whose mean age was 62 years.

Discussion

Although DS is well studied in the pediatric population, there is little information regarding DS in adulthood.[8-12] As such, we do not know how patients with DS age. In this study, it was observed that gait measures and parkinsonian symptoms were abnormal across all ages, but clearly worse in older patients, suggesting a progressive gait disorder. This progression was confirmed in a subgroup of patients studied prospectively. In the 5-year period that patients were followed, we found evidence of a decline in gait function and increase in parkinsonian manifestations, including 2 patients who were ambulatory in the first and were no longer able to walk in this second evaluation.

In the cross-sectional IGA, all gait measures evaluated were abnormal and worse in the older patients, in keeping with a progressive course. In addition, all gait measures were worse

Figure 1 Evaluation of Parkinsonian Symptoms in 2019–2020



Parkinsonian manifestations (arising from a chair, body bradykinesia, gait, and total modified Unified Parkinson's Disease Rating Scale [mUPDRS] score) are worse in older adults.

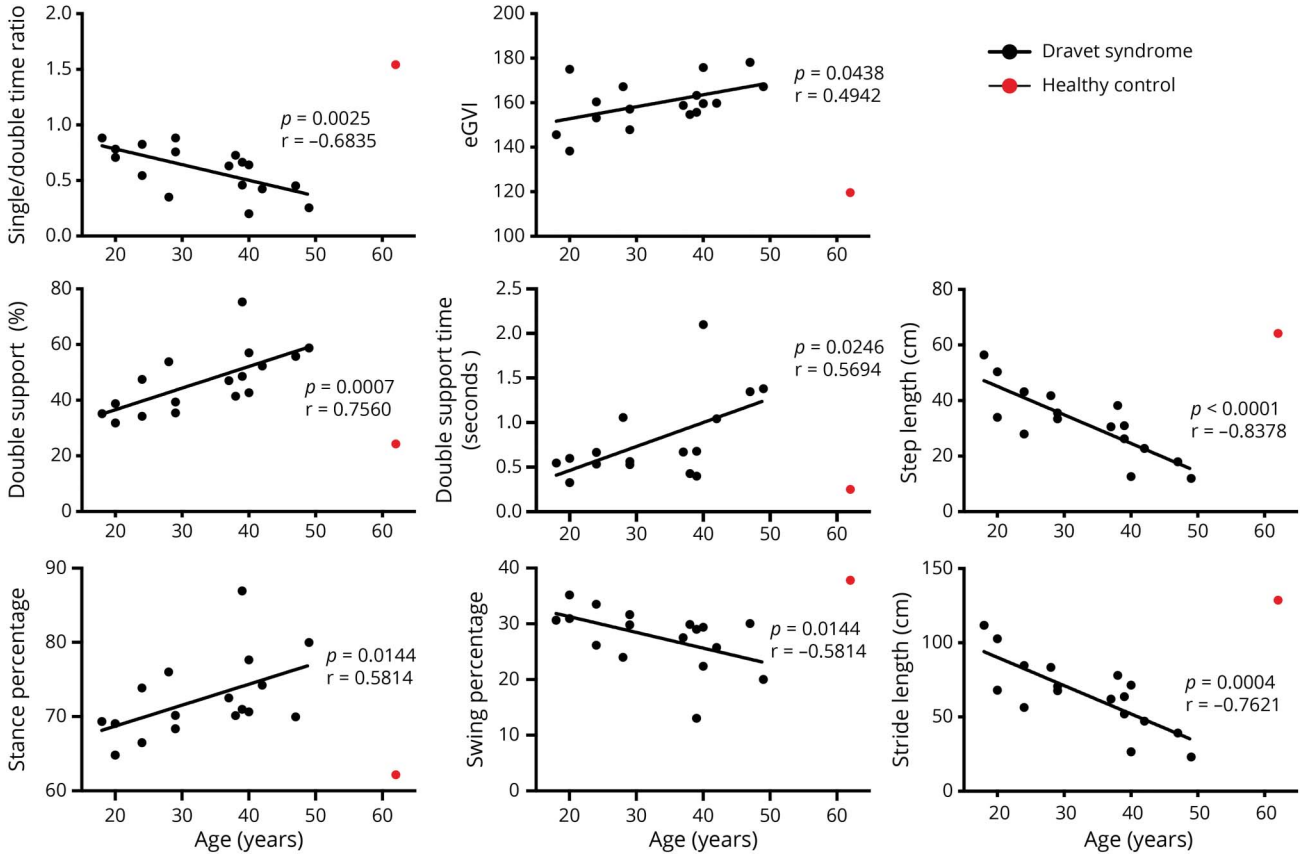
in the DS group compared with an older healthy control group (mean age of control group was double that of patients with DS). The IGA registered a combination of increase in gait velocity, decrease in single/double time ratio, increased number of steps, and increase in eGVI. These abnormal gait findings are in keeping with gait abnormalities of patients with Parkinson disease (PD).[20] The cadence and stride width in adults with DS was consistent across all ages, again aligning with the literature in PD, in which stride width and cadence were reported to have no apparent relationship with age in PD.[21-23] In addition, in both DS and PD there is a progressive worsening of bradykinetic gait features (step length and velocity).

Abnormal gait has long been reported in children and adolescents with DS, although parkinsonian features per se have not been reported in pediatric cohorts. Two studies in children with DS and young adults demonstrated that patients spend a significant increased amount of time in support stance, compared with typically developing peers.[24,25] Similarly to younger patients with DS, our older adult DS population also spent a significantly increased amount of time in stance, and this time was longer with older age, thus representing a compensatory mechanism for the antero-posterior instability typical of parkinsonian gait disorders.[26] Another common gait pattern observed in children and young adolescents with DS is a crouch gait with increased flexion of the knees, ankles, and hips.[17,27] In addition to the parkinsonian gait, a few of our adult patients also had crouched gait. Interestingly, a gait characterized by knee flexion has been described in patients with late stage PD.[28]

In the current study, a subgroup of adult patients with DS was evaluated prospectively, 5 years apart. At the first evaluation, using an mUPDRS, it was observed that adults with DS had parkinsonian gait (slow pace, small steps, en bloc turning, little to no arm swing, postural instability) and other motor parkinsonian features (bradykinesia, rigidity, antecollis, and camptocormia).[14,19] That group of patients was reevaluated with mUPDRS in 2019. The longitudinal data show that both gait and the other motor features have deteriorated over this 5-year period in all but 1 patient (patient 3). Two patients (patients 10 and 12) who had mUPDRS evaluation in 2014 are no longer walking in 2021. Their caregivers reported that in this period of 5 years, it became increasingly difficult to have them leave their wheelchair and even with support, their gait was too "unsafe." The patients also started to refuse any attempts to walk. Patients 10 and 12 were started on levodopa after their first mUPDRS evaluation at the ages of 42 and 46 years, respectively. However, this medication was stopped after 2 years in both cases, as the initial benefits observed after the addition of levodopa wore off. Patient 3 was also started on levodopa after the first mUPDRS evaluation, but she was only 24 years old at that time. Patient 3 continues to derive benefits from levodopa and she is the only one who improved in the second mUPDRS evaluation. The minimal clinically important difference for motor has been reported on average to be between 2.3 and 3.3 points for the UPDRS scale.[29,30] However, these studies were based on all scale items. Our study saw an average decrease of 2.2 points in 5 of 6 individuals.[29,30]

Our study has a few limitations. In particular, we had a limited sample size and were unable to enroll over a third of eligible patients. The COVID-19 pandemic was the primary cause precluding us from recruiting more patients to the hospital for their IGA and mUPDRS evaluations. This also limited the sample followed prospectively (from 11 patients in 2014 to 6 patients in 2019); however, even this limited sample provides

Figure 2 Instrumental Gait Analysis Shows That Gait Measures Are Worse in Older Patients and That Patients With DS Perform Worse Than Older Healthy Controls



The measures shown are all significantly worse with more advanced age in these adults with Dravet syndrome. Other evaluated measures that were not statistically significant are listed in eFigure 1 (links.lww.com/WNL/B946). eGVI = enhanced gait variability index.

information demonstrating the progressive nature of gait and motor deterioration in adults with DS. We also note that muscle weakness may be a potential confounding limitation in in the assessment of gait. Many patients with DS use wheelchairs to travel large distances. This may lead to a disuse of lower limbs musculature and in turn influence gait assessments.[31]

Factors such as contraindicated medications and delayed diagnosis can potentially affect adult outcomes. It was shown that long periods of contraindicated medication intake during the first 5 years of life are correlated with worse long-term cognitive outcomes of patients with DS.[32] It is unknown whether these contraindicated medications play a role in abnormal gait and motor manifestations and their progression. Almost all of the participants in this study (18/21 [85.7%]) were diagnosed in adulthood. It is likely that these patients have been misdiagnosed several times during their life. As a result, they could have been exposed to a variety of contraindicated medications for long periods of time.

This is the largest gait and motor analysis in an older adult DS population (mean age 31 years) and the first prospective study, to our knowledge, of a subgroup of these older patients. Taken altogether, the results show a progressive deterioration of gait and motor function as patients with DS age. It is unclear why such deterioration happens with age and further research should help explain not only why this happens but also if it is possible to slow or avoid this progression.

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Disclosure

D.M. Andrade serves on the medical advisory board of Dravet Syndrome Foundation and Stoke Therapeutics, is on the speakers bureau for Eisai and Biocodex, and has participated in investigator-initiated research for Biocodex and Dravet Syndrome Foundation. A.T. Berg is on the speakers bureau for Biomarin and the advisory board for Zogenix and Neurocrin. The remaining authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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