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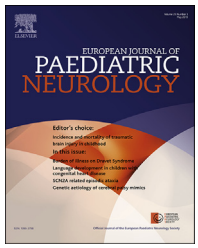

Review article

Gait deviations in patients with dravet syndrome: A systematic review

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ABSTRACT

Background: Dravet Syndrome is a rare developmental and epileptic encephalopathy characterised by epileptic seizures, cognitive impairment and motor disorders. Gait is markedly impaired and could benefit from targeted intervention to improve quality of life for patient and caregivers.

Objective: To establish the state of the art regarding gait deviations in patients with Dravet Syndrome.

Methods: A systematic search was performed in Pubmed, Web of Science, Science Direct and Embase. Studies that assessed gait deviations in patients diagnosed with Dravet Syndrome using clinical observation, video gait analysis or three dimensional (3D) gait analysis and reported gait characteristics, spatiotemporal or kinematic outcomes were included. Screening, quality assessment and data extraction were performed by independent reviewers.

Results: Out of a total of 478 citations, nine articles were included. The total study population had an age range from 2.5 to 47 years. Three studies used clinical observation, three studies video analysis and three studies 3D gait analysis. Crouch gait was observed in about half of the population next to a variety of other gait deviations such as parkinsonian and cerebellar gait. Other findings included abnormalities in spatiotemporal parameters and kinematics, passive knee extension deficits, skeletal malalignment and neurological signs.

Conclusions: A variety of gait characteristics was observed with crouch gait being the most reported gait pattern. Inconsistency in methods and findings from clinical and instrumented evaluation impede thorough understanding of the causal mechanism and evolution behind these deviations.

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Contents

1. Introduction

Dravet Syndrome, also called Severe Myoclonic Epilepsy of Infancy (SMEI), is a rare developmental and epileptic encephalopathy with an onset of severe epileptic seizures during the first year of life.[1] Prevalence is estimated between 1/15.000 and 1/40.000 and at least 80% of the patients have a mutation in the sodium channel type I alpha subunit, *SCN1A*.[2,3] Characteristics are drug resistant epileptic seizures, cognitive impairment and motor disorders.[2] Stagnation or decline in psychomotor development becomes evident before the age of two, with delayed development of gross and fine motor skills, language and cognitive abilities.[2,4,5] Gait is markedly impaired which tends to worsen with patients' age, making them lean on others or use a wheelchair for longer distances.[1,6,7] Hence gait problems aggravate the lack of independence and become a major concern for parents and caregivers.[8,9] While seizure control has been the principal issue in treatment of patients with Dravet Syndrome, attention to other problems such as gait disorders may as well improve quality of life for patient and caregivers.[10] Orthopaedic interventions and rehabilitation programs could address motor problems and improve walking abilities of patients. Detailed evaluation of motor function and more specifically gait examination may be performed to guide therapy planning and form an important part of the patients' follow-up.[11,12] Several methods for qualitative and quantitative gait examination exist. Clinical observation is usually performed during routine neurologic examination when a specialist observes the gait pattern of a patient. Video analysis refers to all methods that include video recording, which enables more repeatable examination, especially when standardized assessment tools are used.[13] Instrumented three dimensional (3D) gait analysis provides a more objective and reliable evaluation of gait.[14] In addition to registration of time- and distance-related aspects of gait (spatiotemporal parameters), it quantifies body segment and joint movements (kinematics) often combined with the forces that cause these movements (kinetics) and muscle activity during walking (electromyography). It remains unclear to what extent gait evaluations are performed in populations with Dravet Syndrome and how gait deviations are identified so far. Therefore, this literature review aims to provide an overview of all studies on evaluation of gait in patients with Dravet Syndrome.

2. Methods

2.1. Sources

This systematic literature review was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[15] The review protocol was predetermined and registered with the international prospective register of systematic reviews (PROSPERO, CRD42017070370). Three authors (AH, ITB and LW) performed a systematic search in four databases on May 23, 2018 with an update on October 24, 2018. The included databases were Pubmed, Web of Science, Science Direct and Embase. The search query "(dravet syndrome OR severe myoclonic epilepsy) AND (gait OR locomotion OR walking)" was adapted to the specific needs of each database, as reported in Table 1. EndNote X7™ (Clarivate Analytics) software was used to eliminate duplicates. A hand search for additional relevant publications was performed by consulting the reference lists of the included articles. If an article was not available, authors were contacted in order to obtain the manuscript.

2.2. Study selection

The screening procedure in two phases was performed independently by three researchers (AH, ITB and LW). A priori formulated in- and exclusion criteria were applied to titles and abstracts in the first phase following the PICOS approach.[16] In case of uncertainty or if no abstract was available, the full texts were obtained for the second screening phase. Studies were included when the population (P) consisted of human patients diagnosed with Dravet Syndrome without any age limit. As intervention (I), an assessment of gait by means of clinical observation, 2D video gait analysis or instrumented 3D gait analysis had to be performed. No comparison group (C) was required. Articles that had an outcome (O) in terms of gait characteristics, spatiotemporal parameters, kinematics, kinetics or electromyography were included. Original research using any type of study is considered relevant to answer the research question, therefore all study designs (S), except for books, reviews and meta-analyses were included. Occasional and subjective reports on gait problems in studies with a focus on genetics, pharmacology or behavioural problems were excluded. Language knowledge of the authors was restricted to English, Dutch, French and German. Articles in other languages were not included.

Table 1 – Detailed search queries per database.

Database	Search details
Pubmed	(("epilepsies, myoclonic" [MeSH Terms] OR ("epilepsies" [All Fields] AND "myoclonic" [All Fields]) OR "myoclonic epilepsies" [All Fields] OR ("dravet" [All Fields] AND "syndrome" [All Fields]) OR "dravet syndrome" [All Fields]) OR (severe[All Fields] AND ("epilepsies, myoclonic" [MeSH Terms] OR ("epilepsies" [All Fields] AND "myoclonic" [All Fields]) OR "myoclonic epilepsies" [All Fields] OR ("myoclonic" [All Fields] AND "epilepsy" [All Fields]) OR "myoclonic epilepsy" [All Fields]))) AND (("gait" [MeSH Terms] OR "gait" [All Fields]) OR ("locomotion" [MeSH Terms] OR "locomotion" [All Fields]) OR ("walking" [MeSH Terms] OR "walking" [All Fields])) AND "humans" [MeSH Terms]
Web of Science	TS = ((dravet syndrome OR severe myoclonic epilepsy) AND (gait OR locomotion OR walking))
ScienceDirect	("dravet syndrome" OR "severe myoclonic epilepsy") AND (gait OR locomotion OR walking)
Embase	((dravet AND syndrome) OR (severe AND myoclonic AND epilepsy)) AND ('gait'/exp OR gait OR 'locomotion'/exp OR locomotion OR 'walking'/exp OR walking)

2.3. Data extraction and risk of bias

Data were extracted by the same three researchers (AH, ITB and LW) using a structured table including study design, population characteristics (number of participants, age, gender, diagnosis), measurement instruments and protocols and results on gait analysis and secondary outcomes. Risk of bias assessment was independently performed by two researchers (LW and PVdW) and the results were discussed until agreed upon. The Newtcastle-Ottawa assessment Scale for cohort studies (NOS) was adapted for cross-sectional studies, selected from previous adaptations.[17] A maximum of five stars could be earned in two categories: selection and outcome (e-appendix).

3. Results

3.1. Study selection

A total of 583 citations were identified in Pubmed (n = 83), Web of Science (n = 36), Science Direct (n = 330) and Embase (n = 134). After deduplication, 478 potentially relevant citations were screened. Eight citations were manually added for full text screening, of which none were found to be eligible. Full text assessment of thirty articles revealed nine articles that met the inclusion criteria (Fig. 1).

3.2. Study characteristics

Three full-length articles,[7,18,19] two short notes[20,21] and four conference abstracts[22–25] were included. All studies used cross-sectional study designs. Two patient cohorts reappear in different studies. Rilstone et al. (2012), Fasano et al. (2014) and Aljaafari et al. (2017) included patients from the Hospital for Sick Children, Toronto, Canada[18,20,21] and Hallemans et al. (2016), Wyers et al. (2017) and Verheyen et al. (2018) from the Antwerp University Hospital, Belgium.[22,24,25] The other research groups were situated in Australia,[7] France[19] and Italy.[23] Patients with an age range from 2.5 to 47 years were included. Six studies examined mainly children and adolescents, whereas the other three included only adults (Table 2).

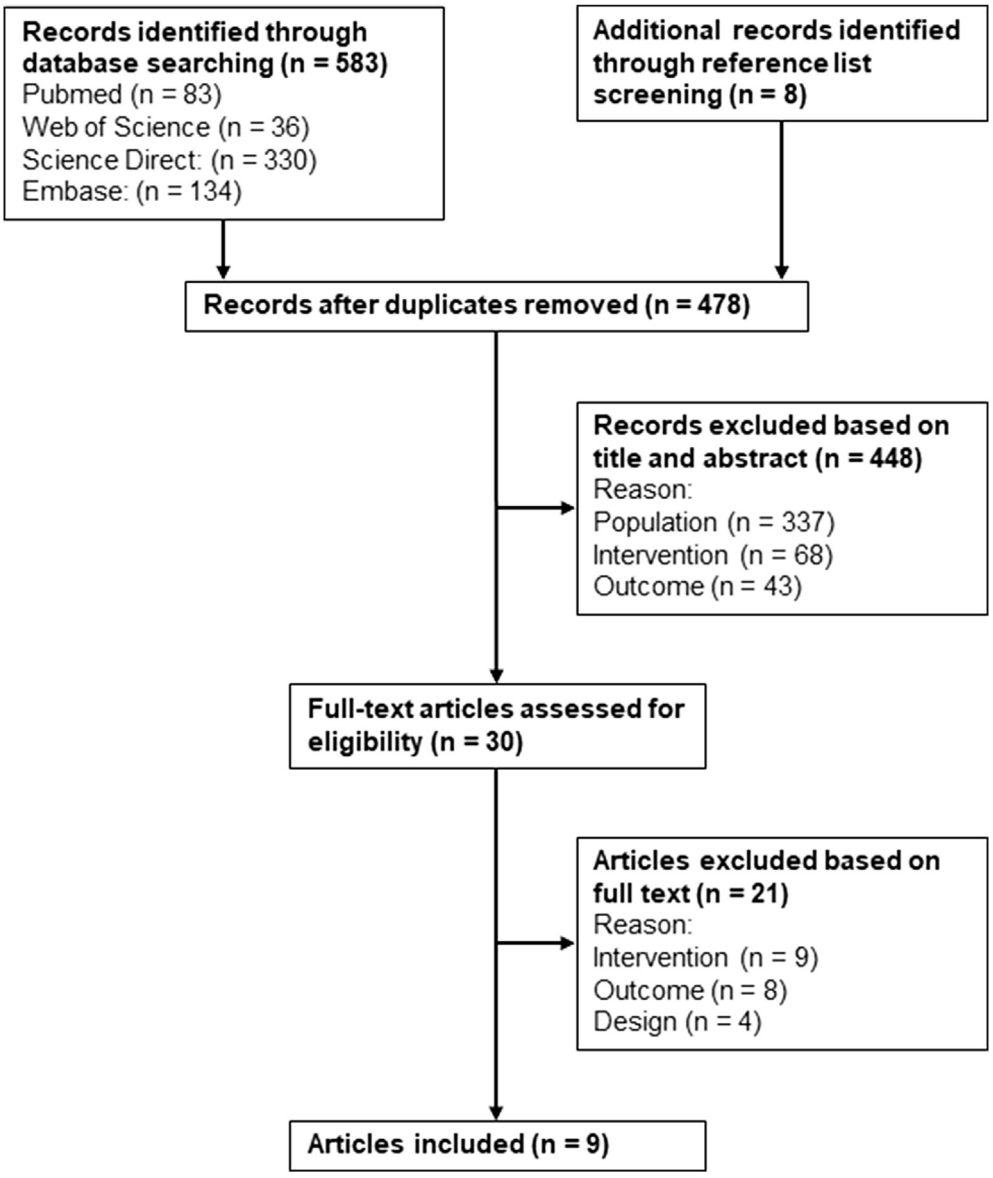


Fig. 1 – Study selection process.

3.3. *Risk of bias*

The quality of the studies varied between two and four stars on a total of five (Table 2). All studies earned a star for representativeness of the sample, with three studies reporting a consecutive cohort and five studies using non-random sampling. Since no study justified the sample size, no stars were earned on this item. All but two studies described the ascertainment of diagnosis and earned a star. Outcome assessments and statistical tests were variable between all studies, explaining most of the variability in total number of stars (e-appendix).

3.4. *Primary outcome*

Gait was the primary outcome of this review and was assessed using different methods. Three studies evaluated gait by means of clinical observation,[18,19,21] three studies used video analysis[7,20,23] and three studies performed instrumented 3D gait analysis[22,24,25] (Table 2). Three types of outcomes on gait were described in the included studies. First, rather qualitative descriptions of gait patterns will be discussed, followed by descriptions of spatiotemporal parameters and finally gait kinematics. Since kinetics and EMG were not reported in the included studies, this will not be discussed.

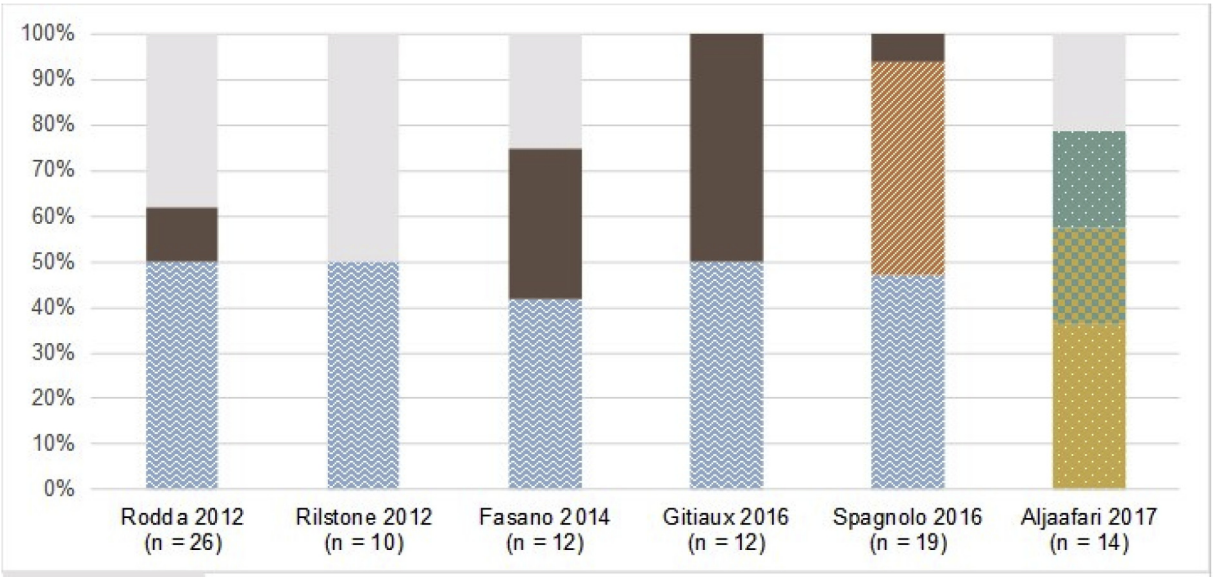
3.4.1. *Gait pattern description*

Based on clinical observation[18,19,21] and video analysis,[7,20] various gait patterns were described, as shown in Fig. 2. The terminology used for this description was not always defined. Rodda et al. (2012) observed a normal or variable sagittal plane gait pattern in children up to five years. Between ages six and twelve, half of the patients had

Table 2 – Description of included studies.

First Author	Year	Journal, article type	City, Country	Sample size	Age range	Gender m/f	Diagnosis	Method of gait analysis	Additional investigation	Study quality
Rodda[7]	2012	Arch Neurol, full length article	Melbourne, Australia	26	2.5–34.4 years (median 9.1)	15/11	Clinical	Video analysis	Clinical examination, FMS, radiography	****
Rilstone[18]	2012	Epilepsia, full length article	Toronto, Canada	10	18–47 years (median 24.5)	4/6	Genetic	Clinical observation	Clinical examination, genetic screening, seizure counts	***
Fasano[20]	2014	Neurology, short communication	Toronto, Canada	12	20–43 years (median 24.5)	4/8	Genetic	Video analysis	Clinical examination, mUPDRS	****
Gitiaux[19]	2016	Neurology, full length article	Paris, France	12	2–17 years (median 7.5)	8/4	Genetic	Clinical observation	Clinical examination, NCS, needle EMG	**
Spagnolo[23]	2016	Gait & Posture, conference abstract	Padua, Italy	19	Mean 12.8	Not reported	Genetic	Video analysis	WeeFIM	***
Hallemans[22]	2016	Gait & Posture, conference abstract	Antwerp, Belgium	13	Mean 8.11, SD 2.1 years	6/7	Clinical	3D gait analysis	Clinical examination	****
Aljaafari[21]	2017	Epilepsia, short communication	Toronto, Canada	14	20–46 years (median 27.5)	5/9	Genetic	Clinical observation	Clinical examination, mUPDRS	***
Wyers[24]	2017	Gait & Posture, conference abstract	Antwerp, Belgium	16	3–22 years (mean 12.4)	Not reported	Not reported	3D gait analysis	Clinical examination	***
Verheyen[25]	2018	Gait & Posture, conference abstract	Antwerp, Belgium	29	3–24 years (mean 13.3)	Not reported	Not reported	3D gait analysis	Clinical examination	***

m = male, f = female, SD = standard deviation, 3D = three dimensional, FMS = Functional Mobility Scale, mUPDRS = modified Unified Parkinsons's Disease Rating Scale, NCS = nerve conduction study, EMG = electromyography, WeeFIM = Functional Independence Measures for Children.
*Stars earned on the adapted Newcastle–Ottawa quality assessment Scale.



Normal	Normal gait (Rodda, Rilstone, Fasano)
	No parkinsonian gait, no cerebellar gait (Aljaafari)
Other	Variable, not specified (Rodda)
	Small or shuffling steps, en bloc turns, "slapping to the floor" steps, irregular, reduced or absent arm swinging, tip toe gait, frequent stops, wide base, long steps or festination (Fasano)
	Gait disturbances, not specified (Gitiaux)
	Hyperextension of the knee (Spagnolo)
Cerebellar	Cerebellar gait, not specified (Aljaafari)
	Both parkinsonian gait and cerebellar gait (Aljaafari)
Parkinsonian	Parkinsonian gait, not specified (Aljaafari)
Normal knee, altered ankle	A pattern characterized by normal knee kinematics but altered ankle kinematics with increased plantarflexion in preswing (Spagnolo)
Crouch	Increased hip and knee flexion and ankle dorsiflexion throughout the stance phase (Rodda)
	The presence of knee and hip flexion during stance or gait (Rilstone)
	Crouch, not specified (Fasano, Gitiaux)
	Flexed knee associated with possible alterations of ankle kinematics (Spagnolo)

Fig. 2 – Percentage and definition of observed gait patterns in the included population per first author.

developed a crouch gait pattern, defined by increased hip and knee flexion and ankle dorsiflexion throughout the stance phase. In the subgroup of 13 years and older, eight out of nine patients walked in crouch. No definition of the variable gait pattern was reported, but the authors mentioned that ataxia, defined by wide-based gait, was rarely observed in the cohort.[7] Rilstone et al. (2012) observed crouch gait, defined by the presence of knee and hip flexion during stance or gait in five out of ten patients, progressively worsening with age. None of their patients exhibited gait ataxia.[18] Fasano et al. (2014) recognized crouch gait without further specification, and other gait abnormalities such as small or shuffling steps, en-bloc turns and "slapping to the floor" steps.[20] In the study of Gitiaux et al. (2016), all patients showed gait disturbances and children older than six exhibited crouch gait, not further specified. No exact number

of patients with this gait pattern was reported, but six out of twelve patients were older than six indicating that about half of the population exhibited crouch gait.[19] Spagnolo et al. (2016) identified two evenly distributed patterns: crouch gait and a pattern characterized by normal knee joint motion but increased ankle plantarflexion in preswing.[23] Furthermore, they observed forward lean of the trunk with anterior pelvic tilt in half of their population and knee hyperextension in one patient.[23] Aljaafari et al. (2017) observed parkinsonian gait and cerebellar gait in their population without reporting the definitions used. Parkinsonian gait, but not cerebellar gait, was significantly more present in their cohort of patients with Dravet Syndrome as compared to Lennox-Gastaut Syndrome.[21]

3.4.2. *Spatiotemporal parameters*

Several parameters can be calculated based on spatial and temporal measurements of gait. Also qualitative descriptions will be discussed in this paragraph, since only two authors reported spatiotemporal parameters. Fasano et al. (2014) based their findings on video observation and described small steps in seven out of twelve patients, long steps in one and a wide base in one other.[20] Hallemans et al. (2016) reported spatiotemporal parameters calculated through instrumented 3D gait analysis. A lower walking velocity (1.03 ± 0.25 m/s), smaller strides (0.93 ± 0.21 m), higher cadence (67 ± 10 strides/min) and longer duration of stance (61 ± 3%) were observed in children with Dravet Syndrome compared to age-matched typically developing children.[22]

3.4.3. *Kinematics*

Kinematics study the position and motion of body segments and joints in the three anatomical planes. The participants from the Antwerp study cohort were tested using instrumented 3D gait analysis and compared to age-matched typically developing children based on mean kinematic parameters,[22] mean kinematic time profiles[24] and Gait Profile Scores[25] (Table 3).

Mean pelvic internal rotation and external hip rotation were significantly increased.[22] Concerning the hip, increased flexion was found at initial contact,[22] during stance[24] and in swing,[22] as well as increased adduction in midstance.[22] Increased knee flexion was measured in different parts of the stance phase[22,24] and in swing.[22] At the level of the ankle, increased dorsiflexion in stance,[22] around push-off[24] and in swing[22] were observed, as well as overall increased external rotation of the ankle.[24] In both studies, the standard deviations around the means were large.[22,24]

The kinematic time profiles of different joints were combined to calculate Gait Profile Scores[26] in the study of Verheyen et al. (2018). The authors considered scores as deviations when they exceeded two standard deviations of the scores in a reference group of typically developing children. Deviations were found in four out of twenty-nine patients for sagittal plane kinematics (combination of pelvis, hip, knee and ankle) and in five patients for coronal plane kinematics (pelvis and hip). For transverse plane kinematics (pelvis, hip and foot), deviations were found in fifteen patients.[25]

Table 3 – Deviations in gait kinematics.

	Sagittal plane				Coronal Plane			Transverse Plane		
			Dravet	TD			Dravet	TD	Dravet	TD
Kinematic parameters: Significantly different joint (peak) angles ($\alpha = 0.05$)[22]	Hip flexion	IC	42° ± 8°	37° ± 2°	Hip adduction	MSt	9° ± 2°	7° ± 2°	Pelvis internal rotation	4° ± 2°
		Sw	44° ± 8°	36° ± 2°					Hip external rotation 9° ± 3°	−14° ± 12°
	Knee flexion	IC	15° ± 10°	8° ± 7°					18° ± 13°	
		LR	31° ± 7°	19° ± 3°						
		Sw	64° ± 8°	60° ± 3°						
	Ankle dorsiflexion	MSt	18° ± 3°	11° ± 3°						
		TSt	3° ± 5°	−17° ± 10°						
Kinematic time profiles: Significantly different phases of the gait cycle ($\alpha = 0.05$)[24]	Hip flexion		ca. 40–60%GC						Ankle external rotation	ca. 0–100 %GC
	Knee flexion		ca. 30–50 %GC							
	Ankle dorsiflexion		ca. 55–70 %GC							
Gait Profile Scores: scores exceeding 2SD of TD[25]	4/29 patients (14%)				5/29 patients (17%)				15/29 patients (51%)	
	Total score: 13/29 patients (45%)									

TD = typically developing children, IC = initial contact, MSt = midstance, Sw = swing, LR = loading response, TSt = terminal stance, %GC = percentage of the gait cycle, SD = standard deviation.

3.5. *Secondary outcomes*

Various secondary outcomes related to motor problems were reported in the included articles. The most relevant will be discussed in the next paragraphs and consisted of the evaluation of musculoskeletal integrity, neurologic signs and activities and participation.

3.5.1. *Musculoskeletal integrity*

Physical examination for passive joint range of motion and skeletal alignment was performed in five studies[7,19,22,24,25] and radiographs were taken to detect foot deformities in one.[7] Three authors reported passive knee extension deficits in a minority of the patients.[7,19,24] 'Flessum of the knees' was observed by Gitiaux et al. (2016) in three out of twelve patients[19] and mild hamstrings shortening by Wyers et al. (2017) with popliteal angles between 50° and 70° short to full extension in six out of fifteen patients.[24] In the study of Rodda et al. (2012), passive knee extension angles decreased and popliteal angles increased with increasing age. Mean angles in the oldest age group (adolescents, age ≥13) revealed only mild deficits (knee extension −2±7°, popliteal angle 35 ± 14° short to full extension).[7] Indications for hypermobility were documented as 'ligamentous laxity' in six out of twenty-six patients,[7] 'hyperlaxity' in one out of twelve patients[19] and excessive passive ankle dorsal flexion (≥25°, knee 90°) in nine out of sixteen patients.[24] Passive ankle dorsiflexion angles were higher (age 0-5 y: mean 39 ± 9°; age 6-12 y: mean 32 ± 7°, knee 90°) in younger children compared to adolescents (mean 22 ± 10°, knee 90°).[7] Femoral anteversion was only slightly increased in three studies with values up to 30°.[7,22,24] Other malalignments consisted of external tibial torsion (bimalleolar axis of 31 ± 7° in the ≥13 years subgroup)[7] and pes planovalgus (eight times greater odds in patients aged 13 years and older,[7] pes valgus in three out of twelve patients[19] and pes planovalgus in thirteen out of sixteen patients[24]). Femoral anteversion and tibial torsion did not correlate with the severity of the gait deviations in the transverse plane.[25]Three lateral radiographical parameters in the ≥13 years age group were larger than one standard deviation above the mean of normal references and significantly increased in older compared to younger children ($p < 0.05$). These parameters were hindfoot abductovalgus (mean talocalcaneal angles 61 ± 8°, compared to normative values 49 ± 6.9°), midfoot pronation (mean naviculocuboid overlap angle 80 ± 12°, norm 47 ± 13.8°) and forefoot planus (mean talo-first metatarsal angle 35 ± 8°, norm 13 ± 7.5°).[7,27] Muscle strength measurements were not reported in the included studies. Moreover, three authors stated that muscle testing was not possible due to reduced cooperation or cognitive abilities of their participants.[7,18,20]

3.5.2. *Neurological signs*

Neurological examination was discussed in five articles.[7,18–21] Spasticity was only present in four cases out of the fourteen patients from Toronto[18,20,21] and not observed in other studies.[7,19] Cerebellar dysfunction was assessed in two studies. Although no patients had gait ataxia in the study of Rilstone et al. (2012), they did show cerebellar signs such as dysarthria in six out of ten and intentional tremor in four out of ten adult patients.[18] Gitiaux et al. (2014) on the contrary did not observe tremor, adiadochokinesia or dysmetria, but reported ataxia without specification in five out of ten younger patients.[19] Parkinsonism was investigated in the study group from Toronto using a modified Unified Parkinson's Disease Rating Scale (mUPDRS, score between 0 and 76, higher values indicating more severe parkinsonism) with scores between 0 and 25 as a result, significantly correlated with age ($\rho = 0.61$, $p = 0.03$).[20,21] Parkinsonian features such as antecollis, bradykinesia and cogwheel rigidity were present in at least eleven of their fourteen cases.[20,21] Rodda et al. (2012) did not use a Parkinson rating scale, but noted postural kyphosis as part of the crouch gait posture in adolescents and young adults.[7] Gitiaux et al. (2014) on the other hand stated that none of the patients presented with extrapyramidal signs.[19] Two patients received levodopa treatment and experienced improvement in slowness and rigidity.[20] When compared to Lennox-Gastaut syndrome, parkinsonian gait was significantly more present, but no significant difference in the severity of parkinsonism features was found.[20,21]

3.5.3. *Activities and participation*

At the level of activities and participation, Rodda et al. (2012) observed a large variation in scores on the Functional Mobility Scale (FMS) for walking distances over 500 m in adolescents and adults, with four patients leaning on others and one patient using a wheelchair. The Gillette Functional Assessment Questionnaire did not reveal any significant difference between age groups.[7] Out of the five patients who walked in crouch in the study of Rilstone et al. (2012), three needed support to walk distances over 50 m and two were not able to walk more than short distances of 5 m, necessitating the use of a wheelchair outside the home.[18] The mean total score on the Functional Independence Measures for Children (WeeFIM) in the study of Spagnolo et al. (2016) was 93 on a maximum of 126, indicating decreased independence.

4. Discussion

The aim of this literature review was to establish the state of the art regarding the evaluation of gait deviations in patients with Dravet Syndrome. Although research on this subject is scarce, this systematic review in four databases provides an overview of peer reviewed articles and conference abstracts. Small sample sizes and large heterogeneity in patient ages and measurement methods make it difficult to draw a general conclusion. Wide age ranges in the included studies make it hard to separate stable features of the syndrome from age-dependent characteristics.

The most reported gait pattern was crouch gait, observed by the majority of authors in about half of the population. Crouch is a sagittal plane pattern defined as excessive ankle dorsiflexion with excessive hip and knee flexion during stance phase and is common in patients with spastic diplegic cerebral palsy.[28] The cause of crouch gait is multifactorial and may

include muscle weakness, spasticity, contractures or lever arm dysfunction.[29] Clinical examination findings on these factors were inconsistent in patients with Dravet Syndrome. Moreover, testing muscle strength is especially difficult due to low cognitive or behavioural capacities. Further investigation of muscle strength and bony deformities is needed to document possible causes of crouch gait in this population.

Large standard deviations around the mean kinematics in the studies of Hallemans et al. (2016) and Wyers et al. (2017) suggested differences in severity of deviations, with part of the observations situated within the normal range.[22,24] Furthermore, not only knee joint motion in the sagittal plane, but also ankle joint and transverse plane deviations should be evaluated in patients with Dravet Syndrome.[22–25]

Other observed patterns include parkinsonian and cerebellar gait, but no specification of this classification was provided.[21] Characteristics of parkinsonism such as levodopa responsive bradykinesia, shuffling gait, rigidity and trunk anteflexion were inconsistently described in mostly adult populations.[7,20,21] The observation of cerebellar signs or ataxia in patients with Dravet Syndrome is controversial. Depending on how authors define ataxia, different conclusions have been reported.[1,6,18,19,30] Ataxia-like clumsiness in toddlers lasts longer than expected,[6] which explains why ataxia was only observed in young children by one author[19] Other findings on cerebellar symptoms were contradictory.[18,19,21] Ataxia may temporarily appear after prolonged seizures and later become a constant part of a patient's motor problems.[1,30] It remains unclear whether true cerebellar ataxia is present in patients with Dravet Syndrome.[6] The large variety and lack of specification in terminology illustrates how difficult it is to formulate an accurate description of the gait pattern in patients with Dravet Syndrome.

It is not well understood how the gait deviations evolve from childhood to adulthood. Studies on children and adolescents focussed on deviations in joint range and alignment,[7,22–25] while in adult patients merely neurological aspects of gait were assessed.[18,20,21] A combination of all observations suggests that children younger than six years of age have a normal or variable gait pattern with possibly features of joint hypermobility and ataxia.[7,19] By adolescence (age $\geq$ 13), part of the patients have developed a flexed gait pattern with passive knee extension deficit and bony malalignment.[7] In adulthood, parkinsonian gait and extrapyramidal signs become evident.[20,21] Other neurological signs such as spasticity, dysarthria and intentional tremor are infrequently observed.[18,21] These observations can only cautiously be interpreted as an evolution in the gait deviations, since they are based on cross-sectional studies. Longitudinal studies are needed to document the evolution of gait in patients growing older.

Although the gait patterns may resemble those of patients with cerebral palsy, Parkinson's disease or cerebellar dysfunction, the pathophysiology in Dravet Syndrome is different and should be approached as such. Dravet Syndrome is primarily caused by loss-of-function mutations in the *SCN1A*-gene that encodes the voltage-gated sodium channel type-1 ($Na_v1.1$) largely distributed in the central nerve system.[1] Reduced function of GABAergic interneurons results in an imbalance of excitatory over inhibitory neurotransmission which causes epilepsy and co-morbidities.[31] Depending on the site or structure where the $Na_v1.1$ channels are expressed, different aspects of movement disorders are induced. Motor neuron dysfunction could partially explain the gait features with at first distal mild motor deficits followed by proximal (crouch-like) deficits.[19] Involvement of basal ganglia dysfunction on the other hand could explain levodopa responsive parkinsonism symptoms.[20] The vulnerability of the dopaminergic system to ageing[32] explains why parkinsonism was only described in adult populations, where it showed a clear correlation with age.[20] Deficits in cerebellar Purkinje neurons might cause ataxia,[33] but evidence for this mechanism in humans is lacking.[31] To understand the gait problems, we should think of Dravet Syndrome as a sodium channel interneuronopathy causing complex clinical presentations of varying nature.

The independence of a person with Dravet Syndrome is decreased, not only because of cognitive disabilities, but also due to walking difficulties. At least 15%–30% of the patients need support from a person to walk outside the house and up to 20% use a wheelchair.[7,18] The use of walking aids was not reported in this population. Clinicians should recognise the impact of the motor problems on daily activities and participation in society and address them with appropriate interventions. Treatment could include orthopaedic management of foot deformities and targeted physiotherapy programs, but evidence regarding intervention outcomes is lacking. The decision-making process should be guided by appropriate gait evaluation.[12]

Most descriptions of gait deviations were based on clinical observation or video analysis. The reliability of these methods highly depends on the experience of the assessor[34] and their results should be considered as subjective and qualitative descriptions of the gait pattern. Instrumented 3D gait analysis on the other hand is an objective and quantitative measurement tool. It is standard procedure in the treatment of patients with cerebral palsy where it adds an important value to clinical decision making.[35] However, its use in patients with Dravet Syndrome was only briefly documented in conference abstracts of the same research group and not reported in peer reviewed articles. Further research on kinematics of gait is needed for more profound documentation of the gait problems. There are currently no studies published on kinetics and electromyography during gait in this population. These aspects however are essential for better understanding of the underlying mechanism of pathological gait as they enable an integrated analysis of lever arm function and muscle activity covering the link between clinical examination findings and kinematic abnormalities.[36]

An explanation for the lack of 3D gait analysis studies in this population is the challenge of the assessment protocol itself. The complete assessment takes about two hours and is not only physically tiring, but also requires good cooperation of the participant.[37] Not all patients are able to comply with the test requirements because of cognitive or behavioural difficulties and thus appropriate data are hard to collect. Alternative methods exist that are more user friendly such as video gait assessment tools,[13] inertial sensors[38] or electronic walkways.[39] Future research is desirable to elaborate gait analysis protocols that offer standardized and reliable

measurements but are also easily applicable in patients with Dravet Syndrome and other patients with intellectual disabilities or behavioural problems.

The inclusion of conference abstracts in this review implied a weakness because they contain limited information on methods and results and are not peer reviewed. On the other hand, in the largely understudied area of this subject, inclusion of conference abstracts offered a more complete overview of the investigations that were performed. Two patient cohorts reappear in three studies each. These studies do not necessarily add new data but a different perspective on the same patients. Therefore the observations of Rilstone et al.,[18] Fasano et al.[20] and Aljaafari et al.[21] and the kinematic data from Hallemans et al.,[22] Wyers et al.[24] and Verheyen et al.[25] should not be accumulated to avoid overrepresentation of the same patients. Another limitation of this review was the moderate to low methodological quality of the included studies. Risk of bias was increased due to not mentioning the diagnostic criteria in two studies,[24,25] less repeatable outcome assessments in two other studies[19,21] and lack of statistical tests in three studies.[18,19]

5. Conclusion

This systematic review found evidence for the existence of a large variety of gait deviations in patients with Dravet Syndrome. A subgroup of patients seems to exhibit a crouch gait pattern, although possible causes such as muscle weakness, spasticity or contractures are rarely documented. The causal mechanism and pathophysiology of the gait deviations is still insufficiently understood. Progressive deterioration of gait, joint range and alignment and neurological signs is hypothesised and should be further investigated in longitudinal research. Clinicians should pay attention to evaluation and treatment of gait disorders in order to improve the patients' functional independence. Future research should ideally proceed with 3D gait analysis including kinetics and electromyography for increased insight in gait pathology. However, gait analysis protocols that are feasible and achievable in daily clinical practice need to be developed as well.

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Conflicts of interest

None declared.

Appendix 1 – Authors.

Name	Location	Contribution
Lore Wyers	University of Antwerp	Conception of the study, literature screening, data extraction, quality assessment, drafting and revising the manuscript, interpreting the data
Patricia Van de Walle	University of Antwerp	Conception of the study, quality assessment, drafting and revising the manuscript, interpreting the data
Aurélie Hoornweg	University of Antwerp	Literature screening, data extraction, drafting and revising the manuscript, interpreting the data
Ionela Tepes Bobescu	University of Antwerp	Literature screening, data extraction, drafting and revising the manuscript, interpreting the data
Karen Verheyen	University of Antwerp	Interpreting the data
Berten Ceulemans	University of Antwerp, Antwerp University Hospital	Interpreting the data; revising the manuscript for intellectual content
An-Sofie Schoonjans	University of Antwerp, Antwerp University Hospital	Interpreting the data; revising the manuscript for intellectual content
Kaat Desloovere	KU Leuven	Interpreting the data; revising the manuscript for intellectual content
Ann Hallemans	University of Antwerp	Conception of the study, drafting and revising the manuscript, interpretation of the data

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2019.03.003.

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