Independent walking and cognitive development in preschool children with Dravet syndrome

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[Abstract]

AIM To investigate the relation between cognitive and motor development in preschool aged children with Dravet syndrome, in particular between the age of independent walking and cognitive development.

METHOD Results of cognitive and motor developmental assessments and the age of independent walking were retrieved retrospectively from the medical records of 33 children (17 males, 16 females; mean age at last evaluation 33.2mo, SD 8.2mo, range 9–48mo) diagnosed with Dravet syndrome. Cognitive and motor developmental age, derived from the Bayley Scales of Infant Development Second and Third Edition or through standardized neurodevelopmental assessment, were converted into cognitive and motor developmental quotients. Multiple test scores per child were included.

RESULTS A strong positive relation was found between cognitive and motor developmental quotient (Pearson r=0.854; $p<0.001$) in 20 children (slope=0.75; 95% CI: 0.54–0.95). A later age of independent walking was associated with a lower cognitive DQ (28 children; $p<0.001$; slope=–1.01; 95% CI: –1.53 to –0.49). A higher cognitive developmental quotient was seen in children with an age at testing younger than 24 months. The cognitive developmental quotient of children with a delay in independent walking (>17.6mo) was significantly lower than those without a delay ($p=0.006$).

INTERPRETATION A strong relation exists between cognitive and motor development. Furthermore, the age of independent walking might be an important indicator of the development of children with Dravet syndrome.

What this paper adds

- Cognitive and motor development are strongly related in children with Dravet syndrome.
- Later age of independent walking is associated with worse cognitive development in children with Dravet syndrome.

[main text]

Dravet syndrome is a developmental epileptic encephalopathy, manifesting with long-lasting febrile and/or afebrile generalized or unilateral clonic seizures beginning in the first year of life.[1] It is associated with a mutation in the *SCN1A* gene in more than 80% of cases.[2] A delay in global development is seen from the second year of life.[3,4]

Global development can be divided into several domains: social-emotional, adaptive, communicative, cognitive, and motor development. All domains seem affected in children with Dravet syndrome. Their social-emotional development is characterized by behaviour disorders,[5] in particular aggressive behaviour,[6] attention deficits,[6–9] social problems[7,8] and hyperactivity.[8–10] Regarding adaptive development, a decline is seen until the age of 6 years with an improvement from the age of 10 years.[8,11,12] In the domain of communicative development, children with Dravet syndrome experience language difficulties,[5–8,10] mainly consisting of phonetic and phonological disorders.[6] Cognitive development appears seemingly typical until the age of 2 years, followed by a progressive decline that stabilizes at the age of 6 years.[3,4,6–9,11,13,14] On the other hand, abnormalities in visual function, a precognitive competence, can be observed before the cognitive decline at the age of 2 years[10,11] and extremely poor visuomotor skills are frequently reported.[3,6,14] A delay in motor development is described in the majority of children with Dravet syndrome from the age of 2 years, with

impairments in all motor domains (balance, coordination, visuomotor integration, power, and locomotion).[15] Walking disabilities are frequently observed[16–18] with an increase in the use of a wheelchair for community walking in adolescence.[16]

Dravet syndrome is challenging for the children as well as for their parents and caregivers.[17] The challenge is not only to manage the epilepsy, but also to cope with the developmental disorders, which can lead to a decrease in quality of life and independence of the child.[4] A great variability is seen in the long-term outcome of motor and cognitive disabilities.[1] Factors such as age at seizure onset and type of genetic mutation may play an important role, but also the use of contraindicated medication can contribute to this outcome.[19] Hence, it remains difficult to provide parents with a clear prognosis concerning the development of their child. It is also unclear how the different developmental domains are related to each other in children with Dravet syndrome. A strong relation between walking disability and cognitive outcome in patients with *SCN1A*-related seizure disorders after the age of 4 years has been reported.[16]

The World Health Organization emphasizes the importance of monitoring a child's global development through key motor milestones, which can help in detecting developmental delays.[20] Independent walking is one of these key motor milestones that can be easily observed by parents and caregivers; even retrospectively, this milestone is usually remembered by the parents.[21] In Dravet syndrome, where a developmental delay is commonly seen after the age of 2 years, it might be interesting to monitor this milestone. Our previous study showed that 11 out of 25 children with Dravet syndrome achieved independent walking after the 99th centile (17.6mo) of the World Health Organization norm.[15] This raises the question whether independent walking could be a possible prognostic factor in the development of children with Dravet syndrome. However, before independent walking can be

investigated as a prognostic factor, it is necessary to know how this milestone of early motor development is related to the other developmental domains, such as cognitive development.

Since both cognitive and motor developmental disorders can be recognized early, this study will investigate the relation between cognitive and motor development, focusing on the association between the age of independent walking and cognitive development. We hypothesize that motor and cognitive development are positively related and that acquisition age of independent walking is negatively related to cognitive development in children with Dravet syndrome. Investigating this relationship can give more information about the development of children with Dravet syndrome and might be a first step to further prognosis setting concerning the child's development.

METHOD

Study design and setting

Data were collected from the medical records of patients, referred to the University Hospital of Antwerp between February 1985 and September 2019. Data were obtained retrospectively from a longitudinal study (The Path of Dravet)[4] as well as prospectively from patients that are participating in the T-GaiD (Treatment of Gait disorders in children with Dravet syndrome) project, recruited through Stichting Dravetsyndroom the Netherlands/Flanders between January 2017 and September 2019. Motor development of the included patients has been described previously.[15] In the present study the relationship with cognitive development was analysed. The study was approved by the ethics committee of Antwerp University Hospital (15/47/497). Results are reported according to the STROBE guidelines.[22]

Participants

Inclusion criteria were: (1) diagnosis of Dravet syndrome according to the International League Against Epilepsy classification,[23] confirmed by genetic testing, and (2) data on both motor and cognitive development in the medical records until the age of 48 months. Patients with a mutation in genes other than *SCN1A* were excluded. Written informed consent for participation and publication was obtained for all participants from the parent or legal guardian.

Patient characteristics were collected from the medical records: year of birth, sex, type of *SCN1A* mutation, and, where available, age at seizure onset and duration of contraindicated medication use (defined as sodium channel blockers: carbamazepine, lamotrigine, oxcarbazepine, phenytoin, vigabatrin, lacosamide).

Outcome variables

Primary outcome variables were cognitive and motor developmental age, converted into developmental quotients (developmental quotient= 100 x [developmental age/chronological age]) and acquisition age of independent walking, expressed in months. Cognitive developmental ages were derived from the Bayley Scales of Infant Development, Second Edition or the Bayley Scales of Infant and Toddler Development, Third Edition, and motor developmental ages from Bayley Scales of Infant Development, Second Edition or through standardized neurodevelopmental assessment (Appendix S1). Multiple test scores per child obtained at different time points were included. The age of independent walking was retrieved from the medical records or obtained through parental interview.

To investigate the relation between cognitive and motor development, cognitive and motor assessments had to be within a time range of 3 months.

For the association between age of independent walking and cognitive development, the cognitive results were divided into three categories according to the chronological age at

the moment of cognitive testing (CAT I <24mo, CAT II 24–35mo, and CAT III >35mo). The reason for this categorization was that cognitive results were assumed to be approximately typical in the beginning, deteriorating during the second year of life.[3,6–9,11,13,14]

Statistical analysis

Cognitive and motor developmental quotient were normally distributed, thus Pearson's rank correlation coefficient was used to test the association between them. A linear mixed model for repeated measurements was fitted with motor developmental quotient as dependent variable and cognitive developmental quotient as fixed effect. Personal identifier was entered as random intercept, to correct for the non-independence between observations from the same individual.

To model the association between age of independent walking and cognitive developmental quotient, accounting for the age at testing, a linear mixed model for repeated measurements was fitted with cognitive developmental quotient as the dependent variable, and fixed effects age of independent walking (continuous variable) and age at testing (3-level categorical variable). A random intercept for personal identifier was included.

To know if the association between cognitive developmental quotient and age of independent walking was different between the three age categories, the interaction between those two variables was tested by adding the product between category and age of independent walking to the model. Since this interaction term was not significant (p=0.84), a model was fitted with only the main effects of age of independent walking and age at testing.

A Mann–Whitney U test was used to verify the difference in cognitive developmental quotient at last evaluation between children with Dravet syndrome with a delay in acquisition age of independent walking (>17.6mo)[20] and those without a delay.

Other analysis with patient characteristics investigated the correlation between age at seizure onset (non-normal distribution) and both age of independent walking and cognitive developmental quotient, using Spearman's rank correlation coefficient.

All results were analysed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA), except for the linear mixed model that was analysed with JMP Pro version 14.0 (SAS Institute Inc., Cary, NC, USA, 1989–2019). Significance was set as $p<0.05$.

RESULTS

Participants

Medical records of 64 patients diagnosed with Dravet syndrome were screened. Two patients had a mutation in another gene (*HCN1A*, *SCN2A*) and were excluded. Twenty-seven more patients were excluded: 16 had no outcome on either cognitive or motor development and 11 had only assessments after the age of 48 months. Of the remaining group, two children were tested with a cognitive test battery other than Bayley Scales of Infant Development, Second Edition or Bayley Scales of Infant and Toddler Development, Third Edition and were also excluded (Figure S1). There were 33 children remaining (mean age at last evaluation 33.2mo, SD 8.2mo; total age range 9–48mo; 17 males, 16 females).

For 20 children (mean age at last evaluation 26.4mo, SD 8.7mo) a standardized cognitive and motor test was completed within a time range of 3 months. Multiple assessments per child were included, leading to 31 cognitive and 31 motor assessments.

The acquisition age of independent walking was known in 28 children, for which 72 standardized cognitive tests were collected (mean age at last evaluation 34.1mo, SD 7.8mo).

Characteristics of all included children and developmental quotient at last evaluation are presented in Table 1.

Relation between cognitive and motor developmental quotients

A strong positive relation was found between cognitive and motor developmental quotient (r=0.854; p<0.001) in 20 children with Dravet syndrome and is presented in Figure 1.

A significant effect of cognitive developmental quotient was observed (p<0.001), with a slope of 0.75 (95% CI: 0.54–0.95), meaning that a one-unit increase in cognitive developmental quotient is associated with an average increase of 0.75 in motor developmental quotient. Variance between individuals accounted for 61%, whereas variance within individuals accounted for the remaining 39% of the total variance.

Relation between age of independent walking and cognitive outcome

The cognitive results of 28 children with Dravet syndrome were divided into three categories according to the age at the time of cognitive testing: CAT I (<24mo) consisted of 26 results obtained from 18 children, CAT II (24–35mo) comprised 31 results from 23 children, and CAT III (>35mo) included 15 results from 10 children.

The relation between age of independent walking and cognitive developmental quotient is presented in Figure 2. Age of independent walking was significantly associated with cognitive developmental quotient (p<0.001; slope=–1.01 with 95% CI: –1.53 to –0.49), indicating that a later age of independent walking is associated with a lower cognitive developmental quotient. In addition, there was a significant difference in outcome between the three categories (p<0.001). Post hoc analysis using Tukey's correction for multiple testing indicated that CAT I had a significantly higher cognitive developmental quotient compared to the two other categories, whereas CAT II and CAT III did not significantly differ.

Out of 28 children, 16 had a delay (>17.6mo) in acquisition of independent walking. Mann–Whitney *U* test showed a significant difference in cognitive developmental quotient at last evaluation between children with a delay in age of independent walking and those without (p=0.006).

Figure 3 compares all cognitive developmental quotient of children with a delayed age of independent walking to those without a delay. Most of the children in both groups show a steep fall during the first 24 months. The group of children without a delay achieved a cognitive developmental quotient at last evaluation between 59.0 and 100.0, whereas the children with delay show a more variable cognitive outcome, ranging from 28.9 to 87.1 at last evaluation.

Additional analyses

Age at seizure onset (mean=5.7mo; range=3–11mo) was obtained from 26 children. A significant negative correlation between age at seizure onset and age of independent walking was found (ρ=-0.575; p=0.004). No significant correlation was found between age at seizure onset and cognitive developmental quotient (ρ=0.220; p=0.280).

DISCUSSION

This study aimed to investigate the relation between cognitive and motor development, in particular the association between age of independent walking and cognitive development. Cognitive and motor development were strongly related: a later age of independent walking was associated with a worse cognitive development in children with Dravet syndrome.

The strong positive relation between cognitive and motor development supports previous findings, that is, a co-activation of the neocerebellum and dorsolateral prefrontal

cortex showing that motor and cognitive functions are closely related in both typically developing children and children with developmental disorders.[24] Our results suggest that children with severe cognitive impairments are more likely to display severe motor impairments. Furthermore, a worse cognitive development is seen in children who achieve independent walking at a later age. Even when children are tested before the age of 24 months, where a larger variability in cognitive developmental quotient is seen, the association between this motor milestone and cognitive development remains consistent, suggesting that a developmental delay can be seen before the age of 2 years.

Although low cognitive developmental quotient is seen in children of all age categories, a difference was found between cognitive developmental quotient in children aged younger than 24 months (CAT I) and children aged 24 to 48 months (CAT II, CAT III), showing an increase in developmental delay from the age of 2 years as described in the literature.[3,4,6–9,11,13,14] Since no loss of acquired skills has been reported, the increase in developmental delay seems more likely to represent an arrest of cognitive development, followed by an increasing discrepancy between developmental age and chronological age, rather than a regression.[13]

Children with Dravet syndrome have a decline in global development during the first 4 years of life that stabilizes around the age of 6 years.[3] Our data included children until the age of 48 months, covering the most important period of cognitive and motor development. To confirm if our findings may give an indication of the long-term developmental outcome, further longitudinal research is mandatory.

Children with a delay in independent walking had a significantly lower cognitive developmental quotient than children without a delay. These results emphasize the importance of monitoring motor milestones in a child's development. In Dravet syndrome the acquisition age of independent walking might be an additional indication of the severity of the phenotype

that would be easy to apply in clinical practice. The present study shows that it is strongly advisable to monitor this milestone in children with Dravet syndrome and to focus attention on those who show such a delay, as they might benefit from early developmental therapy.

The strong relationship between motor and cognitive development is seen in all patients, regardless of their epileptic history, supporting literature that suggests that the sodium channel dysfunction plays an important role in the developmental delay in the different domains.[7,10,13,25] The contribution of the epilepsy and the anticonvulsant therapy to the developmental outcome is still not known. In the past sodium channel blockers (contraindicated medication) were frequently used as anticonvulsant therapy, which tend to aggravate seizures in Dravet syndrome and might have negatively influenced cognitive outcome.[4,19,26,27] Although in the present study only limited results on contraindicated medication use were available (Table 1), they suggest that children with an earlier year of birth used contraindicated medication for a longer period.

A correlation was found between age at seizure onset and age of independent walking: the earlier seizure onset occurs, the later children learn to walk independently. This raises the question if an early onset and later age of independent walking would characterize a more severe phenotype. Later age of independent walking suggests worse cognitive development, but no correlation could be found between age at seizure onset and cognitive development. These findings are not conclusive because of the small sample size, but are in line with current knowledge on Dravet syndrome.[9,10] Combining the age of independent walking with the genetic data, seizure onset, and epileptic features might give an extra dimension in defining the phenotype. This needs to be further investigated through prospective longitudinal research from the onset of the disease.

Limitations of the study

Although Bayley Scales of Infant Development, Second Edition and Bayley Scales of Infant and Toddler Development, Third Edition are strongly correlated, a difference exists between both scores that could have an effect on the outcome.[28,29] Our data consisted of only six scores derived from Bayley Scales of Infant and Toddler Development, Third Edition and excluding these results led to a similar outcome with an even stronger association. In addition to Bayley Scales of Infant Development, Second Edition, motor developmental age was also gained through neurodevelopmental assessment, obtained by a trained clinician using a standardized form, to ensure all assessments were standardized.

The reliability of retrieving the age of independent walking retrospectively through parental interview might be questionable. Literature shows that parental recall of this motor milestone is often accurate and reliable[21,30] and our results were similar to earlier findings.[31] Because of the retrospective nature of the study, a possible selection bias emerges. Children with suspected developmental problems are more likely to undergo developmental assessment at an early age. However, typical developmental quotient results were also present in this study, and when comparing cognitive developmental quotient of the 14 children that were excluded (because of missing motor developmental data) with the included children, no significant difference could be found (Mann–Whitney *U* test, p=0.415).

The sample size used in our study was rather small, as a result of the rarity of the disease. However, children were recruited from two different institutions in Belgium and the Netherlands, increasing the representativeness of the sample. Only children with Dravet syndrome and a mutation in the *SCN1A* gene were included, limiting the application in alternative genetic mutations of Dravet syndrome. In the broader spectrum of *SCN1A* gene mutations, walking disabilities are almost never observed in patients without Dravet syndrome.[16] Although more benign *SCN1A*-related disorders do not benefit from this study,

screening for a delay in independent walking can be useful for distinguishing mild from more severe disorders, such as Dravet syndrome. Given the retrospective nature of the study, the influence of anticonvulsant therapy and seizure frequency and severity on the development of children with Dravet syndrome remains difficult to determine.

Data were collected over more than 30 years. Over this time span, anticonvulsant therapy in Dravet syndrome has been refined, with the avoidance of contraindicated medication, which could have had an influence on the developmental outcome of the children. Because of the small sample size and the polytherapy, no conclusions can be drawn on the influence of anticonvulsant therapy or contraindicated medication.

Conclusion

A strong relation exists between cognitive and motor development in preschool aged children with Dravet syndrome. The motor milestone of independent walking might be an important indicator of the development of children with Dravet syndrome. Further prospective longitudinal research is necessary to confirm that this motor milestone may be considered as a prognostic marker of the child's development and hereby could improve developmental therapy guidelines.

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Figure 1: Correlation between motor and cognitive developmental quotients in children with Dravet syndrome aged 9–48 months. Each symbol represents an individual.

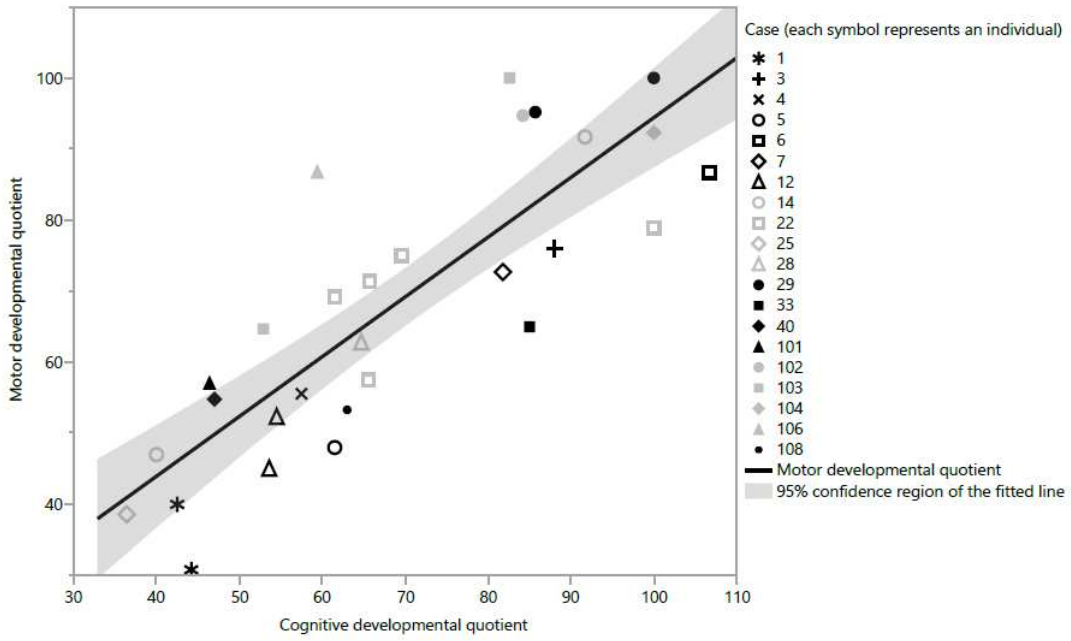

Figure 2: Correlation between age of independent walking in months and cognitive developmental quotient in children with Dravet syndrome according to the age at cognitive testing.

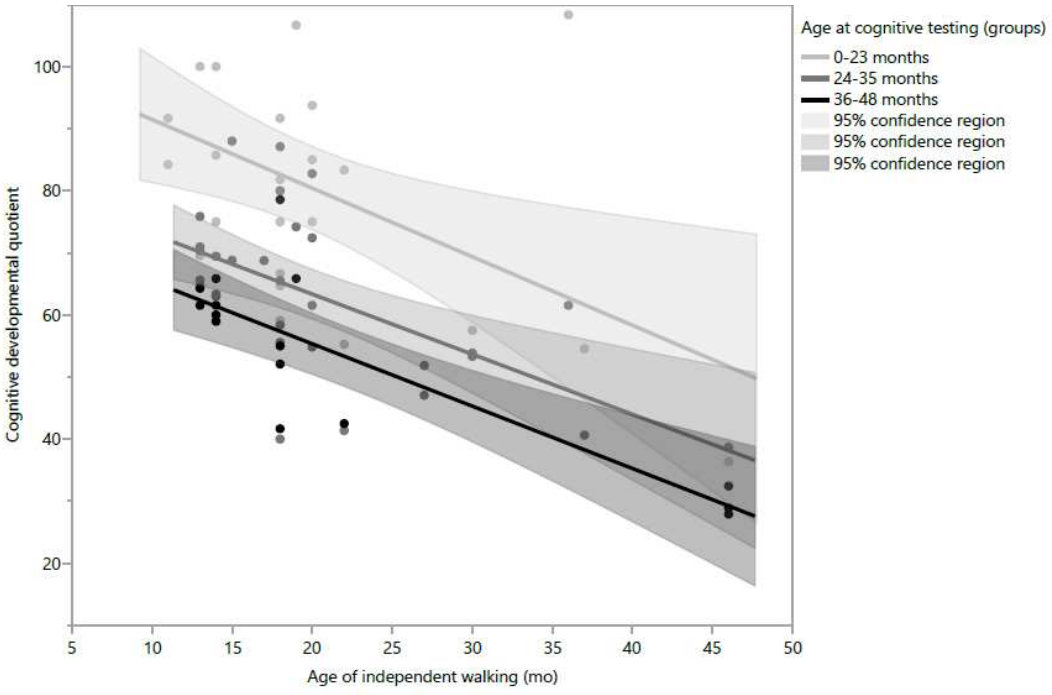

Figure 3: Comparison of longitudinal follow-up of cognitive developmental quotients in children with Dravet syndrome with a delayed age of independent walking to those without a delay.

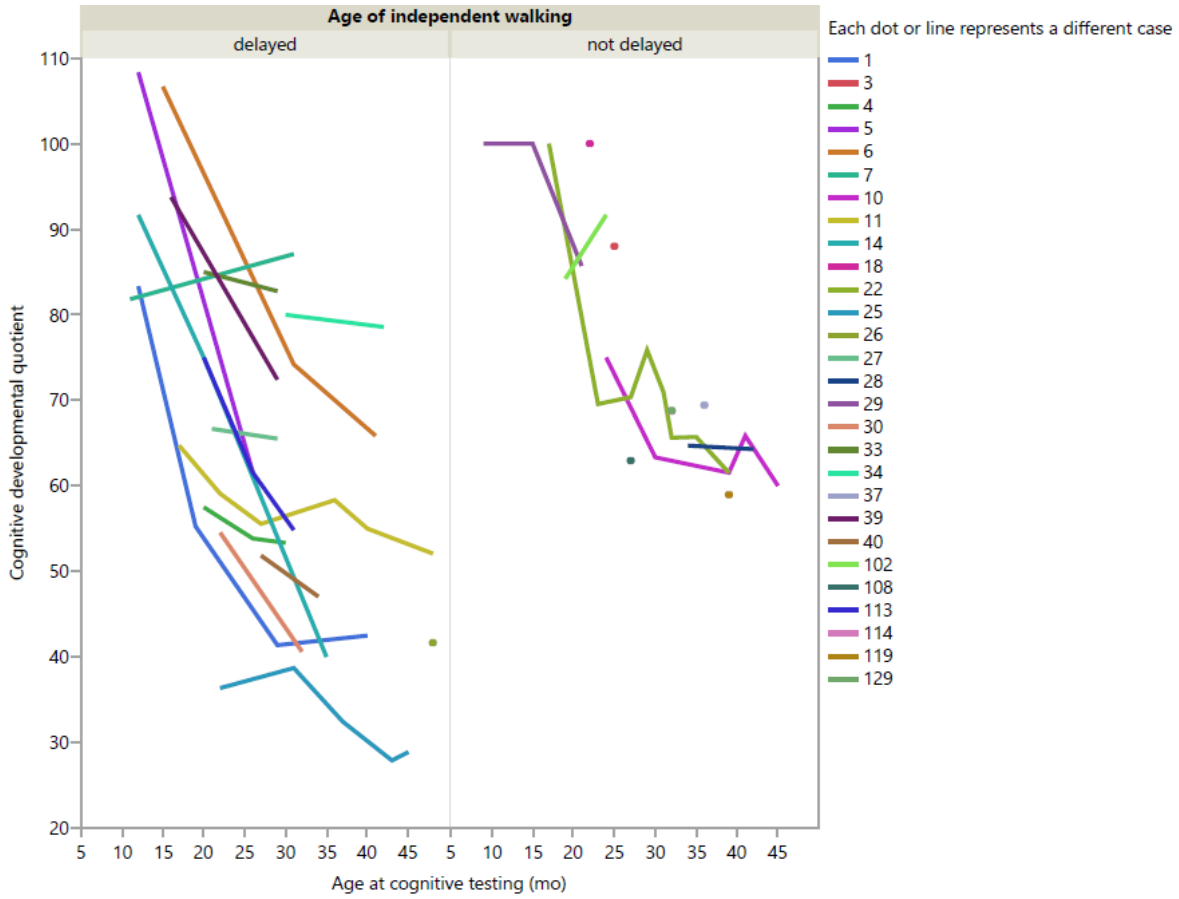

Table 1: Characteristics of the included children (*n*=33) and their developmental quotients (DQ) at last evaluation

Year of birth	*SCN1A* mutation	De novo	Sex (m/f)	Age at last evaluation (mo)	Cognitive DQ	Motor DQ	Age of independent walking (mo)	Age at seizure onset (mo)	Duration contraindicated medication (mo)	Case
1984	Double missense	Yes	M	32	68.8		15	11	Unknown	129
1986	Nonsense	Yes	F	34	52.9	64.7		6	Unknown	103
1986	Missense	Unknown	F	39	59.0		14		Unknown	119
1988	Frameshift	Yes	M	13	100.0	92.3			Unknown	104
1989	Missense	Yes	F	31	54.8		20		Unknown	113
1992	Frameshift	Yes	F	24	91.7	94.7	11	4	Unknown	102
1993	Missense	Yes	M	28	53.6	45.0		4,5	12	12
1993	Missense	Yes	F	48	41.7		18	6	>24	26
1994	Splice site	Yes	M	39	61.5	69.2	13	5	>24	22
1994	Nonsense	Yes	M	32	68.8		17		Unknown	114
1999	Frameshift	Yes	M	48	52.1		18	6	2	11
1999	Missense	Unknown	M	34	47.1	54.8	27	3	15	40
2000	Nonsense	Yes	F	45	60.0		14	7	0	10
2000	In-frame deletion	Yes	F	45	28.9	38.6	46		Unknown	25
2000	Type unknown	Unknown	M	28	46.4	57.1			Unknown	101
2001	Frameshift	Yes	F	31	87.1	72.7	18	4,5	5	7
2002	Missense	Yes	M	22	100.0		13	8	1	18
2003	Missense	Yes	F	30	53.3	55.6	30	3	18	4
2004	Missense	Yes	M	37	59.4	86.8		9	Unknown	106
2008	Frameshift	Yes	M	40	42.5	40.0	22	6	0	1
2008	Nonsense	Yes	F	35	40.0	47.0	18	5	1	14
2009	Nonsense	Yes	M	41	65.9	86.7	19	3	1	6
2010	Missense	Yes	F	26	61.5	48.0	36	4	0	5
2010	Nonsense	Yes	M	29	82.8	65.0	20	5	1	33
2011	Nonsense	Yes	M	25	88.0	76.0	15	7	0	3
2011	Missense	Yes	M	27	63.0	53.3	14	6	0	108
2012	Type unknown	Yes	M	42	78.6		18	6	0	34
2013	Frameshift	Yes	F	36	69.4		14	6	0	37
2014	Missense	Yes	M	29	65.5		18	6	0	27
2014	Nonsense	Unknown	F	42	64.3	62.8	13	8	Unknown	28
2014	Nonsense	Yes	F	21	85.7	95.2	14	6	0	29
2014	Missense	Unknown	F	32	40.6		37	4	0	30
2016	Type unknown	Unknown	F	29	72.4		20		Unknown	39
			M=17; F=16	Mean=33.2; SD=8.2	Mean=63.9; SD=17.9	Mean=65.3; SD=18.4	Median=18; IQR=14–20	Median=6; IQR=4.5–6		

SUPPORTING INFORMATION

Appendix S1: Items examined during neurodevelopmental assessment

Neurodevelopmental assessment
Supine - Visual contact - Auditory contact - Tactile contact - Head - Upper limbs - Grasping - Trunk (asymmetry) - Pelvis (asymmetry) - Lower limbs
Stimulation from supine to prone and vice versa
Active rolling
Prone position
Pull to sit
Supported sitting
Sitting without support
Reflexes/ reactions
Position on hands and knees/ Crawling
Kneeling on both knees
Standing/ walking
Mobility
Breathing
Commentary

Figure S1: Flowchart participants and available data