Psychiatric and cognitive phenotype of childhood myotonic dystrophy type 1

MARIE DOUNIOL[1] | AURÉLIA JACQUETTE[2] | DAVID COHEN[1,3] | NICOLAS BODEAU[1] | LINDA RACHIDI[1] | NATHALIE ANGEARD[2] | JEAN-MARIE CUISSET[4] | LOUIS VALLÉE[4] | BRUNO EYMARD[2] | MONIQUE PLAZA[1,3] | DELPHINE HÉRON[2] | JEAN-MARC GUILÉ[5]

1 Department of Child and Adolescent Psychiatry, Groupe-Hospitalier Pitié-Salpêtrièr, Paris. **2** Institute of Myology and Department of Genetics, Groupe-Hospitalier Pitié-Salpêtrièr, Paris. **3** Institute of Intelligent Systems and Robotics, Université Pierre et Marie Curie, Paris. **4** Paediatric Neurology, Hôpital Roger Salengro, Centre Hospitalier Régional Universitaire de Lille, Lille. **5** Child and Adolescent Psychiatry, Centre Hospitalier Universitaire d'Amiens, Université d'Amiens, Amiens, France.

Correspondence to Professor David Cohen at Département de Psychiatrie de l'Enfant et de l'Adolescent, Université Pierre et Marie Curie, AP-HP, Hôpital Pitié-Salpêtrière, 47–83, Boulevard de l'Hôpital, 75651 Paris Cedex 13, France. E-mail: david.cohen@psl.aphp.fr

This article is commented on by Kledzik and Dunn. To view this paper visit http://dx.doi.org/10.1111/j.1469-8749.2012.04392.x

PUBLICATION DATA
Accepted for publication 2nd May 2012.
Published online 00th Month 2012.

ABBREVIATIONS

ASD	Autism spectrum disorder
CTG	Cytosine–thymine–guanine
DM1	Myotonic dystrophy type 1

AIM To investigate the psychiatric and cognitive phenotype in young individuals with the childhood form of myotonic dystrophy type 1 (DM1).

METHOD Twenty-eight individuals (15 females, 13 males) with childhood DM1 (mean age 17y, SD 4.6, range 7–24y) were assessed using standardized instruments and cognitive testing of general intelligence, visual attention, and visual–spatial construction abilities.

RESULTS Nineteen patients had repeated a school grade. The mean (SD) Full-scale IQ was 73.6 (17.5) and mean Verbal IQ was significantly higher than the mean Performance IQ: 80.2 (19.22) versus 72.95 (15.58), p=0.01. Fifteen patients had one or more diagnoses on the DSM-IV axis 1, including internalizing disorders (phobia, n=7; mood disorder, n=6; other anxiety disorders, n=5) and attention-deficit–hyperactivity disorder, inattentive subtype (n=8). Twelve out of 22 patients had alexithymia (inability to express feelings with words and to recognize and share emotional states). Cognitive testing found severe impairments in visual attention and visual–spatial construction abilities in four out of 18, and 14 out of 24 patients respectively. No diagnosis was correlated with the transmitting parent's sex or with cytosine–thymine–guanine (CTG) repeat numbers. Patients with severe visual–spatial construction disabilities had a significantly longer CTG expansion size than those with normal visual–spatial abilities (p=0.04).

INTERPRETATION Children and adolescents with childhood DM1 have frequent diagnoses on DSM-IV axis 1, with internalizing disorders being the most common type of disorder. They also have borderline low intelligence and frequent impairments in attention and visual–spatial construction abilities.

Myotonic dystrophy type 1 (DM1) is the most frequently inherited neuromuscular disease, with autosomal dominant transmission. The estimated incidence is one in 8000 people.[1] DM1 is a progressive neuromuscular disorder caused by the expansion of a cytosine–thymine–guanine (CTG) trinucleotide repeat. The unstable CTG repeat sequence is located in the 3′ untranslated region of the dystrophia myotonica-protein kinase (*DMPK*) gene on the long arm of chromosome 19. In the general population, the CTG repeat ranges from five to 37 units, whereas in DM1 it exceeds 50 units and can increase to several thousand units. Progressive expansion of CTG amplification appears unstable and is biased towards amplification. It explains both the anticipation phenomenon observed in DM1 pedigrees and the variable clinical expression among affected individuals.

DM1 is classified according to clinical manifestations, severity, and age at onset.[2] Four types of DM1 are distinguished: (1) a mild form with cataracts and minimal muscular or no symptoms with onset in middle or older age; (2) a typical form with neuromuscular symptomatology with onset in adolescence or early adult life; (3) a childhood form with learning disability/learning difficulties often prominent before the age of 10 years but with mild or absent neuromuscular signs at onset; and (4) a congenital form with hypotonic cerebral palsy, facial diplegia, respiratory and feeding problems, as well as mild to moderate intellectual disability in survivors.

Although DM1 is relatively frequent, very limited data (12 case reports and seven studies) exist on the cognitive and psychiatric phenotypes of the childhood form.[3] Most studies evaluate general cognitive abilities, and few studies provide a systematic assessment of DSM-IV axis 1 psychiatric disorders.[4,5] All of the studies confirmed the high prevalence of DSM-IV axis 1 diagnoses, but some data were controversial.

For example, some groups found that internalizing disorders (mood or anxiety disorders) were the most frequent, whereas one group, mixing both congenital and childhood DM1, found that nearly 20% of patients with DM1 had an autism spectrum disorder (ASD).[6] Attention-deficit–hyperactivity disorder (ADHD) was found in 17 to 35% of patients, with most having the inattentive subtype;[7] however, children were also described as hypotonic, slow, and showing somnolence.[8] Vigilance disorders were also observed in the adult form of DM1 years after disease onset.[9,10] Therefore, the link between clinical attention impairment and sleep or vigilance disorder raises many questions, such as whether the ADHD inattentive subtype is misdiagnosed as a form of vigilance disorder, and whether, conversely, vigilance problems are related to a severe attention deficit. Another hypothesis for the misdiagnosis of ADHD inattentive subtype might be the disorder called sluggish cognitive tempo, which is currently discussed in the area of ADHD neurocognition.[11]

For cognitive ability, the mean Full-scale IQ of individuals with the childhood form of DM1 was globally assessed in the borderline range, 69 to 80,[11] but a significant discrepancy was found between IQ scales, with Performance IQ being lower than Verbal IQ.[12,13] Furthermore, admixture analysis of the IQ distribution showed that childhood DM1 might be subdivided into two subgroups according to IQ scores. The first group exhibited mild intellectual disability, and more frequently maternal inheritance and longer expansion, whereas the second group displayed borderline normal intelligence, and more frequently paternal inheritance and shorter expansion.[3] In both groups, analyses of the Wechsler subscale scores showed severe deficits for many individuals in the Object Assembly and Block Design tests, suggesting a visual–spatial deficit.[12] The evidence of reading disability without phonological deficit in childhood DM1 also suggested a visual–spatial deficit.[13] However, so far, no study has assessed psychiatric phenotype, attention, and visual–spatial construction ability in the same individuals with DM1.

The aims of the present study were as follows: (1) to assess diagnoses on DSM-IV[14] axis 1 in individuals with childhood DM1, using semi-structured instruments and clinical interviews; (2) to explore, using validated rating scales, several clinical dimensions (anxiety, depression, impulsivity, somnolence, and alexithymia [inability to express feelings with words and to recognize and share emotional states]) that are of importance for differential diagnoses; (3) to explore, using cognitive testing, attention and visual–spatial construction ability; and (4) to assess whether CTG repeat expansion size and transmission mode are correlated with the above findings, as these two variables have been shown to be significantly associated with general cognitive ability.[4–7,12,15]

What this paper adds

- Psychiatric phenotype is frequent in childhood DM1, with internalizing disorder and ADHD inattention subtype being the most prevalent.
- Cognitive impairment includes visual attention and visual–spatial construction impairments, even in participants with normal intelligence.

METHOD

Participants

The study was conducted between June 2009 and June 2010. The local ethics committee of the Pitié-Salpêtrière Hospital approved the study. Forty-seven individuals and their families were invited to participate in the study. Twenty-eight individuals participated after written informed consent was obtained from patients and their caregivers (for minors only). We found no significant difference for age and sex distribution between included participants and those who declined participation. However, participants included had a higher IQ despite similar ranges (mean 73.7 [SD 17.6], range 42–129; vs 62.5 [16.2], 50–114).

The participants were recruited from the Pitié-Salpêtrière Institute for Muscle Diseases and the Department of Neuro-Paediatrics at Lille University Hospital, France. The inclusion criteria were as follows: (1) a confirmed molecular diagnosis of DM1; (2) age at onset between 1 year and 10 years; (3) an uneventful pre- and neonatal history; and (4) normal development during the first year of life. The participants were divided into two subgroups according to age at assessment: one group of children and adolescents before the age of 18 years (n=11) and one group of young adults between 18 and 24 years (n=17).

Procedure and instruments

All patients and their parents (if minors) received by post several questionnaires that they completed at home. Additionally, the patients were assessed by a child psychiatrist using semi-structured instruments, and a psychologist conducted cognitive testing (see below). Sociodemographic data, medical history, medical records, and genetic data were also reviewed. Of note, all patients already had developmental, genetic, and neurological assessments during the diagnosis procedure.

Diagnoses on DSM-IV axis 1 were assigned after assessment with validated semi-structured interviews appropriate for age. The measures used included the Mini-International Neuropsychiatric Interview (MINI) for adults[16] and the Dominic-R, a computerized questionnaire for children and adolescents.[17–19] In addition, the children were screened for ADHD, using the whole ADHD section of the Diagnostic Interview Schedule for Children IV, short version.[20] For adults, patients completed the Adult ADHD Self-Report Scale,[21] which is a valid scale for evaluating adults for ADHD.[21] Also, we screened for ASD using the Autism Mental Status Examination (ASME).[22] In case of scores of 5 or more, parents were interviewed to assess ASD with the Autism Diagnostic Interview-Revised.[23] We used a best-estimate procedure to assign diagnoses on DSM-IV axis 1, based on the clinical interview and the semi-structured interviews (MINI or Dominic-R; Diagnostic Interview Schedule for Children IV, short version or Adult ADHD Self-Report Scale; Autism Diagnostic Interview-Revised).

Several clinical dimensions were quantified using validated scales. We used either the Children's Depression Inventory or the Beck Depression Inventory, according to the age of the patient, to assess and score depression. The Children's Depression Inventory[24] measures depressive symptoms in

children and adolescents aged 7 to 18 years (total scores range from 0–54). The Beck[25] Depression Inventory measures depressive symptoms in adults (total scores range from 0 to 63). Depression in adults was also assessed by a clinical hetero-assessment, using the Hamilton[26] Depression Rating Scale. To assess anxiety, we used the Spielberger[27] State-Trait Anxiety Inventory, which consists of two sets of questions measuring the level of anxiety as a current state and as a personality trait. We used the Toronto Alexithymia Scale[28] to assess alexithymia. Total scores range between 20 and 100, with higher scores indicating a higher tendency towards alexithymia. For the French version of the scale,[29] cut-off scores have been established, with total scores greater than 56 indicating the presence of alexithymia and scores less than 44 indicating a definite absence of alexithymia. Clinical dimensions related to the ADHD construct were also investigated. We used either the Lecendreux[30] (for children) and Epworth[31] (for adults) scales to assess vigilance and somnolence. The Lecendreux somnolence scale for children measures the severity of somnolence, if present. The Epworth Sleepiness scale is an instrument intended to measure daytime sleepiness in adults.[31] In addition, we used the Eysenck[32] Impulsivity self-report questionnaire to assess impulsivity. The parents of children and adolescents completed the Conners[33] Test for Parents.

The patients were also given a cognitive assessment that included testing of general cognitive abilities, using the Wechsler Intelligence Scale for Children in 11 participants and the Wechsler Adult Intelligence Scale in 17 participants.[34,35] The patients also completed the Conners Continuous Performance Test, a 20-minute computerized test that measures visual attention, impulsivity, and fatigability.[36] After a training phase to introduce the instructions, the patient is asked to press the space bar while seeing letters appearing at a different pace, except when an 'X' appears. The test yields several measures of attention. The reaction time standard error is a measure of response speed consistency. The higher the reaction time standard error, the greater the response inconsistency, the lower the sustained attention is. This measure is consistently reported as well correlated with attention-deficit disorders.[37,38] Two other measures examine change in reaction time at the different interstimulus intervals. These measures detect the patient's capacity to respond even when the stimulation is lowered by a presentation of the letters at a slower rate. They are a reflection of the patient's arousal. In addition, the standard error by block detects changes in response consistency over the duration of the test. The test is split into several blocks, and reaction time standard errors are calculated for each block. High values of the standard error by block indicate a loss of sustained attention as the test progresses.[38]

Finally, we used the SAMUEL[39] to assess visual–spatial construction abilities. The SAMUEL is a computerized task that consists of rebuilding a figure using pieces with visual–spatial cues. During the training phase, the participant is asked to rebuild a known image (Fig. 1a). The task itself uses abstract and geometric figures, based on Gestalt rules (Fig. 1b). It includes two levels of increasing difficulty, using four pieces and, later, nine pieces. Given the difficulties encountered by DM1 individuals, we report here only the percentage of correct trials for each task.

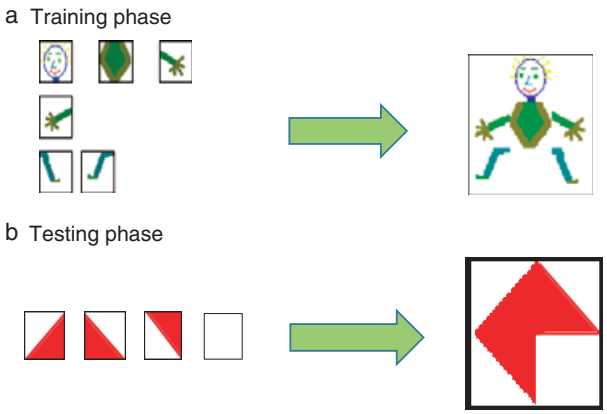

Figure 1: Illustration of the SAMUEL test during the (a) training and (b) testing phases. The SAMUEL[39] assesses visual–spatial construction abilities. It is a computerized task that consists of rebuilding a figure using pieces with visual–spatial cues. During the training phase, the participant is asked to rebuild a known image (e.g. a body [a]). The task itself uses abstract and geometric figures, based on Gestalt rules (b). It includes two levels of increasing difficulty, using four pieces and, later, nine pieces.

Statistical analysis

When different scales were used, depending on the age of the patient (Children's Depression Inventory/Beck Depression Inventory and Lecendreux/Epsworth), we created a binary variable based on the two initial scales and their thresholds. R software, version 2.12.2 for Windows (http://www.r-project.org), was used to analyse the data. Because of the small sample size, non-parametric tests were used in case the data were not normally distributed. In that case, a Mann–Whitney *U* test was used to analyse differences between groups. When the hypothesis of normality was verified, Student's *t*-test was preferred. Contingency tables were analysed using Fisher's exact test. The relationship between quantitative variables was tested using Pearson's and Spearman's correlations. All tests were two-tailed and conducted at a 5% significance level, except for the verbal and performance subtests, which were conducted at a 1% significance level.

RESULTS

For the study, we recruited 28 participants aged 7 to 24 years. The distribution of males and females was equivalent (13 and 15 respectively) as well as the distribution of children and adults (11 and 17 respectively). Although we had more maternal than paternal transmission, the difference was not significant. Table I summarizes patients' sociodemographic, genetic, and clinical characteristics. Patients with DM1 had poor academic achievement: 19 had repeated a school grade (this is common practice in France for children who are not making adequate progress), 11 received special education outside the

Table I: Sociodemographic, genetic, and clinical characteristics in study participants with childhood myotonic dystrophy type 1 (*n*=28)

Sociodemographic data	
Age: mean (SD), range, y:mo	17:3 (4:6), 7:0–24:0
<18y vs ≥18y, *n*	11 vs 17
Male vs female, *n*	13 vs 15
School delay, *n*	19
Special education program, *n*	11
Unemployment (for adults only), *n*	17
Genetic assessment	
CTG repeats: mean (SD)	656.4 (326.4)
Inheritance: maternal vs paternal, *n*	17 vs 11
DSM-IV axis 1 diagnosis, *n*	
Current mood disorder (MDE or dysthymia)	6
Phobias	7
Other anxiety disorders	5
ADHD (DISC-IV + ARSS)	8
Oppositional defiant disorder	5
One or more axis 1 diagnosis	15
Dimensional measures	
BDI (adults), mean (SD)	20.1 (4.9)
HDRS (adults), mean (SD); *n*>HDRS cut-off	3.6 (3.8); 3
CDI (minors), mean (SD); *n*>CDI cut-off	15.8 (8.3); 3
STAI A trait, mean (SD); *n*>cut-off	34.3 (12.8); 6
STAI B state, mean (SD); *n*>cut-off	41 (13.5); 4
AMSE, mean (SD); *n*>cut-off	1.29 (1.46); 0
TAS 20,[a] mean (SD); *n*>cut-off	57.0 (9.2); 12

[a]*n*=22. CTG, cytosine–thymine–guanine; MDE, major depressive episode; ADHD, attention-deficit–hyperactivity disorder; DISC-IV, Diagnostic Interview Schedule for Children IV, short version; ARSS, Adult ADHD Self-Report Scale; BDI, Beck Depression Inventory; HDRS, Hamilton Depression Rating Scale; CDI, Children's Depression Inventory; STAI, Spielberger State-Trait Anxiety Inventory; AMSE: Autism Mental Status Examination; TAS, Toronto Alexithymia Scale.

Table II: Cognitive characteristics and attention-deficit–hyperactivity disorder (ADHD) dimension in participants with childhood myotonic dystrophy type 1 (*n*=28)

WISC-III or WAIS-III	
Full-scale IQ mean (SD)	73.6 (17.55)
Verbal scale IQ mean (SD)	80.2 (19.2)
CPT-II (visual attention) (*n*=18), *n*	
ADHD Confidence Index[a]	4
CPT-II variables[b]	
Omissions	3
Commissions	2
Variability	3
Hit RT	6
Hit RT SE	6
Attentiveness 'd'	3
Hit RT Block Change	2
Hit SE Block Change	5
Hit RT ISI Change	5
Visual–spatial/constructive abilities SAMUEL test (*n*=24), *n*	
Complete failure	*n*=11
Successful four figures (*n*=13)	*n*=12
Successful nine figures (*n*=13)	*n*=10
ADHD dimensions,	
Somnolence: >cut-off,[c] *n*	4
Eysenck impulsivity: mean (SD)	8.9 (3.8)
CPT-II ADHD: >cut-off,[d] *n*	2
Adult ADHD Self-Report Scale: >cut-off, *n*	4

[a]Confidence Index>50. [b]T scores>60. [c]Lecendreux (minors) or Epworth (adult) scales. [d]Minors only. CPT-II, Conners Continuous Performance Test (2nd edition); Hit RT, reaction time; Hit RT SE, reaction time standard error; Hit RT Block Change, standard error by block; Hit SE Block Change and Hit RT ISI Change, changes in reaction time at the different interstimulus intervals; WISC-III, Wechsler Intelligence Scale for Children; WAIS-III, Wechsler Adult Intelligence Scale, 3rd edition; ADHD, attention-deficit–hyperactivity disorder.

regular educational system, and 17 of the adults were unemployed or sponsored through disabled persons' aid.

In all, 15 patients had one or more diagnoses on DSM-IV axis 1. Most had an internalizing disorder such as phobia (*n*=7), current mood disorder (major depressive episode or dysthymia, *n*=6), or other anxiety disorder (*n*=5). The frequency of oppositional defiant disorder was also relatively high (*n*=5). We found no psychosis and none of the patients had a clinically significant score on the Autism Mental Status Examination. We found eight individuals with ADHD, all with the inattentive subtype. Quantitative assessment of depressive and anxious symptomatology found the same number of patients with scores above scale threshold. Specifically, using the Spielberger State-Trait Anxiety Inventory and a cut-off defined according to norms in the general population,[40] four patients were clinically anxious, and six showed traits that were consistent with clinical anxiety. Of 22 patients, 12 had alexithymia, defined as a score 56 or more on the TAS.

For clinical dimensions related to the ADHD construct (Table II), the average of the Eysenck impulsivity score was normal (mean=8.9), but six patients showed significant impulsivity with a cut-off defined according to norms in the general population.[33] None of the patients showed hyperactivity, and only four had clinical somnolence. A subgroup of 18 patients was given the Conners Continuous Performance Test to assess visual attention. The number (percentage) of patients with significantly elevated T scores (T>60) for each of the variables of interest was as follows: reaction time standard error, *n*=6; reaction time, *n*=6; the standard error by block, *n*=5; and change in reaction time at the different interstimulus intervals, *n*=5.

Other cognitive dimensions included Full-scale IQ and the SAMUEL test. These findings are also summarized in Table II. The mean (SD) individual Full-scale IQ was in the borderline range (73.6 [17.55]), with a significant discrepancy between the mean (SD) Performance IQ (72.95 [15.58]) and the mean (SD) Verbal IQ (80.2 [19.22]) (t=3.64, p=001). Twenty-four patients were also given the SAMUEL test to assess their visual–spatial construction ability; four refused to be assessed. Notably, 11 showed very severe impairment in visual constructive ability, as demonstrated by the fact that they did not pass the first level of the test (four figures) and could not finish it. For those who did not abandon the test (*n*=13), all but one passed the four-figure level, and only 10 passed the nine-figure level. In total, 14 participants were not able to finish the two levels, showing severe visual–spatial construction impairments.

Given previous data showing a correlation between clinical severity and genetic characteristics, to assess whether psychiatric or cognitive phenotype was correlated with mode of transmission or CGT repeat size, we performed univariate analyses (Table III). Given the sample size, these analyses should be regarded as exploratory as the lack of statistical power prevents

Table III: Correlation between psychiatric phenotype and (1) cytosine–thymine–guanine (CTG) repeat and (2) transmission mode (maternal vs paternal)

	CTG repeat	Transmission mode
DSM-IV axis 1 diagnosis		
Current mood disorder (MDE or dysthymia)	t=−0.3, df=26 (p=0.775)	OR=1.4 (0.2; 18.2) (p=1)
Phobias	t=1.3, df=26 (p=0.218)	OR=0.8 (0.1; 7.2) (p=1)
Other anxiety disorders	t=−0.7, df=26 (p=0.521)	OR=1 (0.1; 13.7) (p=1)
ADHD	t=1.7, df=9 (p=0.093)	OR=0.5 (0; 52.2) (p=1)
Oppositional defiant disorder	t=−0.9, df=26 (p=0.376)	OR=1 (0.1; 13.7) (p=1)
Dimensional instruments		
BDI or CDI record (n=28)	Pearson's r=−0.07 (−0.4; 0.3) (p=.737)	t=−0.5, df=14.1 (p=0.61)
HDRS (adults, n=17)	Spearman ρ=0.16 (−0.4; 0.6) (p=0.53)	U=39 (p=0.807)
STAI A trait	Pearson's r=−0.13 (−0.5; 0.3) (p=0.518)	U=7 (p=0.727)
STAI B state	Pearson's r=0.06 (−0.3; 0.4) (p=0.772)	U=10 (p=0.906)
TAS 20 (n=24)	Pearson's r=−0.13 (−0.5; 0.3) (p=0.57)	U=76 (p=0.304)
Somnolence (Lecendreux or Epworth scale)	t=1.3, df=26 (p=0.214)	OR=0.3 (0; 6.4) (p=0.672)
Eysenck impulsivity	Pearson's r=0.12 (−0.3; 0.5) (p=0.537)	U=62 (p=0.141)
AMSE total score	Spearman ρ=0.25 (−0.1; 0.6) (p=0.21)	U=94 (p=1)
IQ		
Full-scale IQ mean (SD)	Pearson's r=−0.51 (−0.7; −0.2) (p=0.008)	t=1.1, df=24 (p=0.28)
Verbal scale IQ mean (SD)	Pearson's r=−0.33 (−0.7; 0.1) (p=0.123)	t=0.6, df=21 (p=0.51)
ADHD dimensions		
CPT-II scores (visual attention) (n=18)		
ADHD Confidence Index	Pearson's r=0.2 (−0.3; 0.6) (p=0.432)	U=44.5 (p=0.772)
Omissions	Pearson's r=0.28 (−0.2; 0.7) (p=0.261)	U=48 (p=0.504)
Commissions	Pearson's r=0.24 (−0.3; 0.6) (p=0.348)	U=40.5 (p=1)
Hit RT	Pearson's r=0.08 (−0.4; 0.5) (p=0.738)	U=39 (p=0.965)
Hit RT SE	Pearson's r=0.3 (−0.2; 0.7) (p=0.226)	U=50 (p=0.408)
Attentiveness	Pearson's r=0.33 (−0.2; 0.7) (p=0.17)	U=43 (p=0.829)
Hit RT Block Change	Pearson's r=0.32 (−0.2; 0.7) (p=0.195)	U=39 (p=0.965)
Hit SE Block Change	Pearson's r=0.16 (−0.3; 0.6) (p=0.533)	U=50 (p=0.408)
Visual–spatial ability (SAMUEL test)		
Complete failure vs four figures vs nine figures	t=−2.2, df=22 (p=0.04)	OR=1.5 (0.2; 10.7) (p=0.947)

MDE, major depressive episode; ADHD, attention-deficit–hyperactivity disorder; BDI, Beck Depression Inventory; HDRS, Hamilton Depression Rating Scale; CDI, Child Depression Inventory; HDRS, Hamilton Depression Rating Scale; STAI, Spielberger State-Trait Anxiety Inventory; TAS, Toronto Alexithymia Scale; AMSE, Autism Mental Status Examination; CPT-II, Conners Continuous Performance Test (2nd edition); Hit RT, reaction time; Hit RT SE, reaction time standard error; Hit RT Block Change, standard error by block; Hit SE Block Change, change in reaction time at the different interstimulus intervals; OR, odds ratio.

any definitive conclusion. We found no association or correlation between the mode of transmission, CTG repeat size, and each clinical dimension or DSM-IV diagnosis. Full-scale IQ was correlated with CTG number repeat but was not associated with transmission mode. SAMUEL success rates and abandon rates were not associated with IQ scores or transmission mode. However, success on the complete SAMUEL test was associated with shorter CTG repeat size.

DISCUSSION

At the time of investigation, most of the patients had repeated a school grade and many patients required special education, confirming previous studies that highlight this major issue even when patients have minor neurological symptoms or motor impairment.[4] Average Full-scale IQ was in the borderline intelligence range (IQ 70–80), and nearly half of the patients had a mild intellectual disability (IQ 50–70). Verbal IQ was significantly superior to Performance IQ, which has been reported in previous studies.[4,12] For psychiatric phenotype, half of the patients had one or more DSM-IV axis 1 diagnoses, including internalizing disorders, ADHD inattentive subtype, and oppositional defiant disorder. These results confirm the findings of Goosens et al.,[4] who reported that up to 60% of childhood patients with DM1 had a psychiatric diagnosis, as assessed by the Dutch version of the Diagnostic Interview for Children and Adolescents-Revised. Notably, both categorical and dimensional investigation confirmed that ADHD in patients with childhood DM1 is characterized by a high rate of attention difficulties and a low rate of hyperactivity, if any. In addition, most patients had alexithymia. Anxiety and depression could be partly explained by the severe impairment in terms of academic achievement and social interactions. The 'invisible' disease has severe consequences. Although we found a high rate of patients with phobias, the average level of anxiety was normal according to Spielberger State-Trait Anxiety Inventory (French norms). We hypothesized that alexithymia and the inability to recognize their own emotional state and the feelings of others could explain the high prevalence of oppositional defiant disorder found in our sample as well as in that of Echenne et al.[15] However, in the current sample, none of the patients with oppositional defiant disorder showed significant alexithymia.

Specific cognitive testing evidenced frequent severe visual attention and visual–spatial construction impairments. Cognitive profiles of the patients were heterogeneous: some patients presented all the difficulties that were assessed (intellectual deficit, visual–spatial impairment, and attention deficit), whereas others had normal intelligence and visual attention

deficit or visual–spatial construction impairment only. In addition, all of the patients who completed the SAMUEL test performed it slowly. No diagnosis was correlated to the transmitting parent's sex or to CTG repeat numbers. Patients with severe visual–spatial construction disability had a significantly longer CTG expansion size, as did those with lower IQ, which has been found in previous studies.[4,5,13,15,41,42]

These results confirm previous hypotheses of authors who suspected visual–spatial dysfunction based on (1) Wechsler Intelligence Scale for Children profile (very low scores on Object Assembly and Block Design[12,41,42]) and (2) specific reading and spelling impairments in patients with childhood DM1 and no intellectual disability (no phonological deficit, severe impairment in searching for information in a television programme).[13] These results are also in line with recent studies that reported a high rate (82%) of ocular motor abnormalities (alliterated conjugate eye movements), as well as visual function pathologies (low visual acuity, hyperopia, or astigmatism) in childhood DM1.[43,44] All these abnormalities could affect the development of the visual system and the ability to learn to read.

We did not find any individual with ASD in our sample, which confirms most of the other published studies,[4,5,7,15] with the exception of Ekström et al.[6] who described a high rate (35%) of ASD in childhood DM1. The discrepancy could be explained by at least four factors. (1) Our sample size was too small to draw any conclusion about the prevalence of ASD in the sample, and the discrepancy between studies may be due to chance or recruitment bias. (2) The high prevalence of children with a congenital form of DM1 and the high prevalence of intellectual disability in the sample of Ekström et al. Indeed, although we had a very low AMSE mean score, low score ranges (Table I), and no patient above the clinical threshold, we found a higher AMSE mean score in patients with intellectual disability compared with those who had normal intelligence (mean 2.2 [SD 1.5] vs 0.77 [1.2] respectively; t=39, p=0.009). (3) The patients with ASD in the study by Ekström et al. were described as not presenting classic autism but rather an 'autistic spectrum' with no stereotypies and correlating with severity of DM1 and intellectual disability. Indeed, during ASME, none of the patients had repetitive behaviours/stereotypy and unusual sensitivities. (4) There might be a symptomatic continuity between social phobia/alexithymia found in our sample and withdrawal/autism spectrum found in the sample of Ekström et al. As we did not use the Autism Diagnostic Interview-Revised parental interview systematically, we cannot exclude ASD diagnoses at the age of 5 years because the language delay associated with intellectual disability, hypotonia, and social withdrawal may contribute to an 'autistic-like' presentation in young patients with DM1 (see case 1 in Douniol et al.[3]).

Finally, both standardized evaluation for DSM-IV diagnoses (Mini-International Neuropsychiatric Interview, Dominic-R, ADHD section of the Diagnostic Interview Schedule for Children IV, short version) and cognitive assessment (Conners Continuous Performance Test), found the same rates for ADHD of nearly a third. All of the patients with a diagnosis of ADHD had the inattention subtype with no hyperactivity. Moreover, Conners Continuous Performance Test subscores indicated slowness (reaction time) and fatigability (score standard error by block) in nearly a third of the participants. Cognitive impairment (inattention, slowness, and fatigability) involved a larger population than those with an ADHD diagnosis because five participants showed visual attention deficit with no clinical diagnosis of ADHD. Therefore, the disorder called sluggish cognitive tempo should be investigated with appropriate instruments in further research,[11] as well as hearing attention, given the abnormalities in visual development.[44] The low rate of somnolence (present in only four patients) contradicts the hypothesis of continuity between somnolence and attention deficit. The rate of excessive daytime sleepiness is lower than the rates observed in adults (nearly 30%) according to Yu et al.[45]

Our results should be understood in the context of the following study limitations. (1) Although the sample included only patients with childhood DM1, there was some heterogeneity in the ages of the patients and recruitment bias. (2) We had to use different instruments for children, adolescents, and adults. (3) The large age range may skew the results, despite the absence of a correlation between age and the study results. Indeed, DM1 tends to worsen with age. (4) We could not give all the cognitive tasks to all of the patients because of patient refusal, mainly because of fatigability. (5) We only studied visual attention. Given the visual–spatial construction impairment, we wonder whether hearing attention is impaired as well. (6) We did not have a matched comparison group, and cognitive and clinical assessments were not blind to diagnosis. (7) Finally, given the prevalence of DM1, the sample size was limited and statistical comparison should be regarded as exploratory. Specifically, the lack of statistical power prevents any definitive conclusion on the correlation between clinical severity and genetic characteristics (Table III).

Despite these limitations, we consider that school difficulties encountered by children and adolescents with DM1 should be a focus of early care. Learning difficulties could be explained by the multiplicity and the importance of cognitive deficits, even in children with normal intelligence. These deficits, including attention deficit, fatigability, and visual–spatial construction disability, can result in reading and spelling difficulties as well as mathematical impairment. Children with childhood DM1 deserve more specialized school adaptation, and research should investigate treatments. First, stimulants should be investigated for treating attention deficit and/or vigilance impairment. Given that DM1 is a multi-system disease that includes cardiac risk, this risk needs to be specifically explored and monitored.[46] Second, given the prevalence of learning difficulties, language remediation and reading therapy should be considered as well. Finally, emotional aspects of personality should be taken into account; traits such as anxiety, depressive reactions, and an inability to decode feelings may contribute to difficulty in social integration and should improve with psychotherapy and/or social skills training.

In conclusion, the findings confirm the importance of psychiatric and cognitive symptoms in the childhood form of DM1. These difficulties have a severe impact on school integration and academic achievements, and include visual attention and visual–spatial construction impairments. Therapeutic approaches should be investigated, including stimulant medication and focused cognitive remediation.

ACKNOWLEDGEMENTS

We thank the children, adolescents, young adults, and their parents for participating in the study. The work was supported by the Association Française contre les Myopathies (number 11,839).

REFERENCES

1. Douniol M, Gargiulo M, Jaquette A, Heron D, Cohen D. Phénotype psychiatrique des maladies neuro-musculaires. *Neuropsychiatr Enf Adolesc* 2008; **56:** 63–72.
2. Harley HG, Brook JD, Rundle SA, et al. Expansion of an unstable DNA region and phenotypic variation in myotonic dystrophy. *Nature* 1992; **355:** 545–6.
3. Douniol M, Lanthier-Gazzano O, Jacquette A, et al. Psychiatric and cognitive phenotype in children and adolescents with myotonic dystrophy. *Eur Child Adolesc Psychiatry* 2009; **18:** 705–15.
4. Goossens E, Steyaert J, De Die-Smulders C, Willekens D, Fryns JP. Emotional and behavioral profile and child psychiatric diagnosis in the childhood type of myotonic dystrophy. *Genet Couns* 2000; **11:** 317–27.
5. Steyaert J, Umans S, Willekens D, et al. A study of the cognitive and psychological profile in 16 children with congenital or juvenile myotonic dystrophy. *Clin Genet* 1997; **52:** 135–41.
6. Ekström AB, Hakenäs-Plate L, Samuelsson L, Tulinius M, Wentz E. Autism spectrum conditions in myotonic dystrophy type 1: a study on 57 individuals with congenital and childhood forms. *Am J Med Genet B* 2008; **147:** 918–26.
7. Steyaert J, de Die-Smulders C, Fryns JP, Goossens E, Willekens D. Behavioral phenotype in childhood type of dystrophia myotonica. *Am J Med Genet* 2000; **96:** 888–9.
8. Quera Salva MA, Blumen M, Jacquette A, et al. Sleep disorders in childhood-onset myotonic dystrophy type 1. *Neuromuscul Disord* 2006; **16:** 564–70.
9. Romigi A, Izzi F, Pisani V, et al. Sleep disorders in adult-onset myotonic dystrophy type 1: a controlled polysomnographic study. *Eur J Neurol* 2011; **18:** 1139–45.
10. Laberge L, Bégin P, Dauvilliers Y, et al. A polysomnographic study of daytime sleepiness in myotonic dystrophy type 1. *J Neurol Neurosurg Psychiatry* 2009; **80:** 642–6.
11. Penny AM, Waschbusch DA, Klein RM, Corkum P, Eskes G. Developing a measure of sluggish cognitive tempo for children: content validity, factor structure, and reliability. *Psychol Assess* 2009; **21:** 380–9.
12. Angeard N, Gargiulo M, Jacquette A, Radvanyio H, Eymard B, Héron D. Cognitive profile in childhood myotonic dystrophy type 1: is there a global impairment? *Neuromuscul Disord* 2007; **17:** 451–8.
13. Cohen D, Plaza M, Angeard N, et al. Reading and spelling impairments in children and adolescents with infantile myotonic dystrophy. *J Neurolinguist* 2006; **19:** 455–65.
14. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th edn. Arlington, VA: American Psychiatric Association, 1994.
15. Echenne B, Rideau A, Roubertie A, Sébire G, Rivier F, Lemieux B. Myotonic dystrophy type I in childhood long-term evolution in patients surviving the neonatal period. *Eur J Paediatr Neurol* 2008; **12:** 210–23.
16. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; **59** (Suppl. 20): 22–33; quiz 34–57.
17. Smolla N, Valla JP, Bergeron L, Berthiaume C, St-Georges M. Development and reliability of a pictorial mental disorders screen for young adolescents. *Can J Psychiatry* 2004; **49:** 828–37.
18. Valla JP, Bergeron L, Bidaut-Russell M, St-Georges M, Gaudet N. Reliability of the Dominic-R: a young child mental health questionnaire combining visual and auditory stimuli. *J Child Psychol Psychiatry* 1997; **38:** 717–24.
19. Valla JP, Bergeron L, Smolla N. The Dominic-R: a pictorial interview for 6- to 11-year-old children. *J Am Acad Child Adolesc Psychiatry* 2000; **39:** 85–93.
20. Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME. NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. *J Am Acad Child Adolesc Psychiatry* 2000; **39:** 28–38.
21. Kessler RC, Adler L, Ames M, et al. The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. *Psychol Med* 2005; **35:** 245–56.
22. Grodberg D, Weinger PM, Kolevzon A, Soorya L, Buxbaum JD. Brief report: the autism mental status examination: development of a brief autism-focused exam. *J Autism Dev Disord* 2012; **42:** 455–9.
23. Lord C, Rutter M, Le Couteur A. Autism diagnostic interview-revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord* 1994; **24:** 659–85.
24. Kovacs M. The Children's Depression Inventory (CDI). *Psychopharmacol Bull* 1985; **21:** 995–8.
25. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961; **4:** 561–71.
26. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 1967; **6:** 278–96.
27. Spielberger CD, Lushene R, Vagg PR, Jacobs GA. Manual for the State-Trait Anxiety Inventory. Paolo Alto, CA: Consulting Psychologists Press, Inc, 1983.
28. Bagby RM, Parker JD, Taylor GJ. The twenty-item Toronto Alexithymia Scale—I. Item selection and cross-validation of the factor structure. *J Psychosom Res* 1994; **38:** 23–32.
29. Loas G, Fremaux D, Marchand MP. [Factorial structure and internal consistency of the French version of the twenty-item Toronto Alexithymia Scale in a group of 183 healthy probands.]. *Encephale* 1995; **21:** 117–22. (In French).
30. Carrot B, Lecendreux M. Évaluation d'une somnolence diurne excessive en psychopathologie de l'enfant et de l'adolescent. *Archives de Pédiatrie* 2011; **8:** 891–901.
31. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; **14:** 540–5.
32. Eysenck SBG, Easting G, Pearson PR. Age norms for impulsiveness, venturesomeness and empathy in children. *Pers Individ Diff* 1984; **5:** 315–21.
33. Goyette CH, Conners CK, Ulrich RF. Normative data on revised Conners Parent and Teacher Rating Scales. *J Abnorm Child Psychol* 1978; **6:** 221–36.
34. Wechsler D. WAIS-III Administration and Scoring Manual. San Antonio, TX: The Psychological Corporation, 1997.
35. Wechsler D. Échelle d'Intelligence pour Enfants et Adolescents III. Paris: Editions du Centre de Psychologie Appliquée, 1995.
36. Conners CK. Conners' Continuous Performance Test. Toronto, ON: Multi-Health Systems, 1995.
37. Abou Abdallah T, Guile JM, Menusier C, Plaza M, Cohen D. Corrélats cognitifs et relationnels associés aux troubles de l'attention avec/sans hyperactivité. *Neuropsychiatr Enf Adolesc* 2010; **58:** 293–7.
38. Egeland J, Kovalik-Gran I. Validity of the factor structure of Conners' CPT. *J Atten Disord* 2010; **13:** 347–57.
39. Rozencwajg P, Corroyer D, Altman P. Diagnostic du Fonctionnement Cognitif. Manuel d'Instructions. Cergy, Delta Expert, 2002.
40. Verge P, Baruffol E, Boulanger N, et al. Évaluation des conséquences psychologiques des catastrophes environnementales: une étude de faisabilité à partir des inondations de 1992 dans le Vaucluse (France). *Cahiers Santé* 1999; **9:** 313–8.
41. Angeard N, Jacquette A, Gargiulo M, et al. A new window on neurocognitive dysfunction in the childhood form of myotonic dystrophy type 1 (DM1). *Neuromuscul Disord* 2011; **21:** 468–76.
42. Ekström AB, Hakenäs-Plate L, Tulinius M, Wentz E. Cognition and adaptive skills in myotonic dystrophy type 1: a study of 55 individuals with congenital and childhood forms. *Dev Med Child Neurol* 2009; **51:** 982–90.
43. Ekström AB, Tulinius M, Sjöström A, Aring E. Visual function in congenital and childhood myotonic dystrophy type 1. *Ophthalmology* 2010; **117:** 976–82.
44. Aring E, Ekström AB, Tulinius M, Sjöström A. Ocular motor function in relation to gross motor function in congenital and childhood myotonic dystrophy type 1. *Acta Ophthalmol* 2012; **90:** 369–74.
45. Yu H, Laberge L, Jaussent I, et al. Daytime sleepiness and REM sleep characteristics in myotonic dystrophy: a case-control study. *Sleep* 2011; **34:** 165–70.