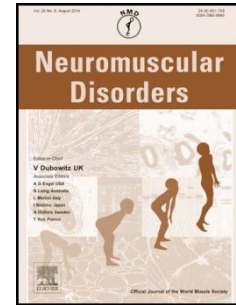


PII: S0960-8966(17)31337-8
 DOI: <https://doi.org/10.1016/j.nmd.2017.12.006>
 Reference: NMD 3493

Received date: 28-9-2017
Accepted date: 8-12-2017

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Childhood onset-form of Myotonic Dystrophy type 1 and Autism Spectrum Disorders: Is there comorbidity?

N Angeard^{1,4,*}, E Huerta¹, A Jacquette², D Cohen³, J Xavier³, M Gargiulo^{4,5}, L Servais⁴, B Eymard⁴, D Héron²

¹ Inserm U1129, Paris, France; Paris Descartes University, Sorbonne Paris Cité, France; CEA, Gif sur Yvette, France

² Centre de Référence "Déficiences intellectuelles", Département de Génétique et INSERM U 975, Groupe Hospitalier Pitié-Salpêtrière, APHP, Paris, France

³ CNRS UMR 7222 Institut des Systèmes Intelligents et Robotiques, et Service de Psychiatrie de l'Enfant et de l'Adolescent, Groupe Hospitalier Pitié-Salpêtrière, APHP, Paris, France

⁴ Institut de Myologie, Groupe Hospitalier Pitié-Salpêtrière, APHP, Paris, France.

⁵ Laboratoire de Psychologie Clinique et Psychopathologie (EA 4056), Université Paris Descartes, Sorbonne Paris Cité, Institut de Psychologie, Boulogne, France.

* Corresponding author

E-mail address: nathalie.angeard@parisdescartes.fr (Nathalie Angeard)

Inserm U1129, Université Paris Descartes- Sorbonne Paris Cité, 71 avenue Edouard Vaillant, 92100 Boulogne-Billancourt, France

Fax number: 33 1 42 19 28 74

Manuscript: 3149 words

Highlights

- Identifying the Childhood DM1 neuropsychological profile
- Highlighting the psychiatric symptoms specific to the childhood DM1
- Implementing optimal screening even before neuromuscular signs have appeared

Abstract

Myotonic dystrophy type 1 (DM1) is a multisystemic disorder with neuromuscular symptoms and brain dysfunctions. Depending on the phenotypic expression, the degree of cognitive impairment remains heterogeneous, ranging from moderate to severe intellectual disability in the congenital form, to executive, visuospatial and personality dysfunction in the adult-onset form. Studies exploring the cognitive or psychiatric impairments in the childhood form of DM1, characterized by an age of onset between one and ten years, uneventful pre and post natal history and normal development the first year of life, are scarce and show conflicting results in regard to a comorbid diagnosis of Autism Spectrum Disorders (ASD). The aim of the current review is to summarize diagnostic criteria and update the state of the debate regarding comorbidity. Evidence from 9 studies collected in Pubmed database (representing a total of 175 cases) focusing on clinical, neuropsychological and neuroimaging domains in Childhood DM1 is considered and similarities or differences between Childhood DM1 and ASD are identified. Highlighting what is known about the neurocognitive features specific to the childhood-onset form of DM1 could help (1) propose early screening regarding socio-emotional and attentional/executive functions or (2) implement therapeutic programs based on reinforcement of executive skills or social cognition.

Key words: Myotonic Dystrophy Type 1, childhood-onset form, Autism Spectrum Disorders, comorbidity, neuropsychological profiles, Social Communication Disorder.

Running Title: Childhood DM1 and ASD comorbidity

Introduction

Myotonic dystrophy type 1 (DM1) is an autosomal dominant genetically transmitted neuromuscular disease that causes myotonia, progressive muscular dystrophy and **multiorgan** disorders (cardiac, digestive system, *etc.*). It is caused by an abnormal repetition of the cytosine-thymine-guanine (CTG) triplet of the DMPK gene located on chromosome 19q13.3. The number of repeats varies from one person to another, with an average between 5 and 37 CTG's in a healthy subject, and between 50 and 2000 in the DM1 population [1].

In DM1 patients, the size of the repeat is unstable and is correlated with the severity of the symptoms. An anticipation phenomenon can be observed, as the symptoms become more serious and appear earlier across generations [2]. **According to the international myotonic dystrophy network (IDMC; [3]), five phenotypes can thus be identified: 1) the late-onset form (symptomatic *pauci*); 2) the adult form which associates neuromuscular symptoms and myotonia, difficulties masticating, swallowing and speaking, cardiac and gastrointestinal disorders, cataract and central nervous system impairment that might cause cognitive and social adaptation disorders; 3) the juvenile form with age at onset between 11 and 20 and which is characterized by school and mating problems; 4) the childhood-onset form with learning difficulties and/or academic delay that frequently appear before the age of 10 as initial presentation, with few if any neuromuscular symptoms; and finally 5) the congenital form, often diagnosed *in utero* along with hydramnios and a diminution of fetal movements.**

Symptoms may include generalized hypotonia, severe swallowing difficulties, respiratory distress, facial diplegia and moderate to severe intellectual disability (ID).

In addition to the neuromuscular symptoms and multisystemic diseases, psychiatric disorders have recently been reported. Studies that assessed the adult form of DM1 reveal frequent avoidant personality disorders (20%), the main characteristics of which are social inhibition and anxiety [4]. As far as the childhood onset-form is concerned, the studies focusing on this aspect are quite recent and the data available address contradictory results. Internalizing disorders, such as anxiety and mood disorders as well as attention deficit disorder, diagnosed in 17 to 35% of the DM1 patients [5-6], are the most prevalent. Swedish researchers [7] have underlined autistic spectrum disorders (ASD), however these data have not been confirmed by recent French data [5].

The coexistence of two or several diseases or disorders in one given patient raises the question of their clinical impact in terms of therapeutic indications. Diagnosing a specific DM1 psychiatric phenotype may be of critical importance, as the therapeutic directives are more efficient if the symptoms are taken into consideration as part of a disorder rather than in an isolated manner. As far as the question of the presence or absence of ASD in the childhood form of DM1 is concerned, one can consider the stakes are high, as evidencing a comorbidity would encourage professionals to track early signs (*e.g.*, the emergence of shared-attention capacities), and would also favor the implementation of an adequate therapeutic approach.

To investigate possible link between DM1 and ASD, we will review the literature following two axes 1) a synthesis of the papers pointing out the psychiatric and cognitive disorders observed in childhood DM1 patients, but also a critical analysis of the studies in which the presence of an ASD has been explored in this population, and 2) a comparison between cognitive profiles and brain functioning specific to each one of these two pathologies.

Psychiatric disorders in the childhood form of DM1

As far as the presence of psychiatric disorders associated with DM1 is concerned, one observes an important prevalence of emotional and behavior disorders in the childhood phenotype (28.5% in Steayert *et al.*'s study [6], 42% in Goosens *et al.*'s [8], 32% in Echenne *et al.*'s [9]). Attention deficit disorder without hyperactivity, phobia, mood disorder, anxiety and alexithymia are the most frequently diagnosed psychological disorders [5-6]. Nonetheless, except for the description of isolated clinical cases [10], the analysis of the studies bearing on the presence or absence of comorbidity between DM1 and ASD sheds light on contradictory results. Ekström's group [7] has evaluated 57 children and adolescents from Swedish care centers presenting different phenotypes [adult/classic (n=2), childhood (n=18) or congenital (n=37) forms] and shows that 36% of the cohort presents an ASD, usually comorbid with severe ID (Intellectual Disability) associated to the congenital form.

Other studies that describe the psychiatric and cognitive profile of the childhood form of DM1 have not found the same prevalence of ASD. Thus, in a retrospective study, Echenne *et al.* [9] mention only one subject out of 38 (2,6%) fulfilling the DSM-IV criteria for ASD diagnosis. Similarly, in the article published by Steyaert *et al.* [6], only one subject out of 16 (6,2%) obtains a significant evaluation in the CARS (Child Autism Rating Scale). More recently, Douniol's group [5] has evaluated 28 subjects with the childhood form of DM1 and failed to obtain clinically significant scores according to the AMSE (Autism Mental Status Examination).

These contradictory results may be due to, on the one hand, the phenotypic heterogeneity of the cohorts (congenital and childhood forms studied together, although the

deficits emerge at very different developmental stages), but also to the heterogeneous levels of cognitive impairment (with IQs ranging from severe ID to normal efficiency) (Table 1).

Insert here Table 1

Whereas the population studied by Douniol [5] is mainly comprised of subjects affected with the childhood form of DM1 and having an average IQ of 73.5, a mere 32% of the population studied by Ekström *et al.* [7] had the childhood-onset form, and an IQ ranging from 35 to 59 (89% of the cohort). All in all, in the Swedish study, only 3 childhood DM1 patients fulfill the criteria of an ASD diagnosis (16.7%).

Another important element concerns the comorbidity between ID and ASD, found again in Ekström *et al.*'s study [7] (33.3% of the ASD subjects suffer from ID). ID is both a disorder that is frequently associated with ASD, and also one of its differential diagnosis for the severe and profound cognitive deficits; the struggles concerning this distinction are often mentioned in the literature [11].

Finally, despite the sensitivity of the diagnostic [ADI-R (Autism Diagnostic Interview-Revised)] or screening (AMSE) tools used in the two studies mentioned above, the considerable heterogeneousness of the symptoms in ASD and their variability add further complication to a correct diagnosis. Clinical experience shows that diagnosis based on the combination of information from the parents, clinical history and clinical observations are significantly more stable across time [12] than those obtained from one single tool. Douniol *et al.* [13] had already mentioned this issue when presenting two clinical cases in which the symptoms associated to the childhood phenotype, such as late language acquisition, hypotonia and social withdrawal, may be considered as signs of autism in young DM1 patients, unconfirmed later.

The large variability of expression of symptoms among the ASD children population (absence of language in most ASD children, while others will develop sophisticated language; some children present self-harm behaviors or extreme aggressiveness while others do not; social impairments may also vary considerably) is also found in DM1 subjects. Thus, in the analysis conducted by Ekström *et al.* [7], four groups are constituted: 1) Autistic disorder (individuals fulfilling the DSM-IV diagnostic criteria), 2) “Autistic-like” condition (patients who present at least four, but not all the DSM-IV diagnostic criteria), 3) Asperger (according to DSM-IV) and 4) non-autistic. According to the authors, the most frequently symptoms in their DM1 child population concern the field of social relations and, to a lesser extent, limited and repetitive interests and behaviors. Of note, no subject has self-harm behaviors. The patients are described as friendly but withdrawn, not using language spontaneously during social interactions (no initiation of interaction but contingent response), the predominant impairments occurring in the field of communication and social interactions. With the currently developing diagnostic criteria based on DSM-V, DM1 patients presenting autistic signs may not anymore be diagnosed as suffering from ASD but rather “social (pragmatic) communication disorders,” as this is the field in which symptoms are predominant.

Cognitive functioning in the childhood form of DM1

Studies bearing on the cognitive functioning of DM1 subjects shed light on a correlation between DM1 phenotype and severity of the disease [9]. Indeed, in the congenital form, a (moderate to severe) ID is often associated with an IQ of 40-60 in about 60% of the cases. In the childhood form, the results remain quite heterogeneous, with IQs varying between 42 and 114, and a bi-modal distribution [14]. Douniol *et al.* [13] tried to understand

the variability in the distribution of IQs by conducting an analysis of the various existing studies. Starting from the bi-modal distribution, they distinguished two phenotypes within the childhood form: a first sub-group characterized by mild to moderate ID, delay in language and motor acquisition, major learning difficulties, daytime sleepiness associated with vigilance disorders and a mainly maternal transmission of the disease; a second sub-group with normal/subnormal cognitive efficiency, dissociation between IQ scales (with mainly Verbal IQ > Performance IQ), moderate learning difficulties, attentional weakness and visual constructive impairments and a mainly paternal transmission mode.

As far as the study of more specific cognitive functions is concerned, capacities for visual attention and visual constructive function seem to be particularly impaired [5,15]. This fact largely accounts for the learning difficulties in reading observed in DM1 patients with normal intelligence [5]. Discrepancies between verbal and visual memory were noted by Angeard *et al.* [15], with results significantly lower when it comes to encoding visual information. Deficits in auditory-verbal working memory as well as in attentional processes were also mentioned [5, 14-15]. Other executive functions, such as inhibition and flexibility, were evaluated without providing conclusive results due to inadequate tools.

In the field of social cognition, a specific deficit of the affective component of theory of mind [16] and impaired facial emotion recognition [17] were reported in the adult form. In the childhood phenotype, only Douniol's study [5] provides results showing that a large proportion of the patients (12/22) present alexithymia (difficulty expressing feelings with words, or sharing emotions).

The subjects with ASD also constitute a heterogeneous group, in which the severity of the symptoms, the cognitive abilities and the adaptive functioning largely vary. Two poles are usually identified. Low-level ASD regroups subjects with an IQ<70, presenting a heterogeneous profile with deficits (e.g., language) and well-functioning domains (visual

constructive abilities as well as immediate and procedural memory [18]). In this sub-group, as is the case for dysphasic children, Verbal IQ is lower than Performance IQ. The other pole comprises subjects with a high-level ASD presenting maintained verbal language (with difficulties bearing mainly on social, pragmatic aspects) and often a more homogeneous global cognitive profile. Several specific cognitive deficits have been associated with ASD. In the field of social cognition, deficits in the theory of mind have been observed, impaired emotion recognition have been also mentioned [19], but with contradictory results, some authors suggesting that the impairment is linked with IQ, not a specific characteristic of ASD subjects [20]. Besides, executive deficits involving cognitive flexibility, planning, inhibition or working memory were also reported [21].

In spite of the heterogeneousness of the results, it is interesting to examine the differences and the similarities between the cognitive and socio-emotional profiles of patients suffering from DM1 and ASD. One thus notices that the global cognitive levels vary considerably in the two pathologies with the presence of an associated ID in both. However, a cognitive profile in terms of higher Verbal Comprehension abilities than Perceptive reasoning or visuo-spatial skills is more often associated with DM1 than with ASD.

As far as more specific cognitive functions are concerned, visual constructive abilities seem to be unaffected in ASD subjects, whereas they are very much impaired in DM1 subjects. There have been too few studies exploring executive functions and social cognition skills in the childhood form of DM1 to draw any conclusions. Thus, further investigation of these high-level functions will allow characterizing a specific executive profile in childhood DM1 and to compare it to the profile of ASD subjects.

Neuroanatomical and neurofunctional aspects

It has been well established that DM1 is a neuromuscular disease that also affects the central nervous system (CNS). The kinase protein, coded by the gene that is altered in DM1, was found at high levels in the cardiac, the skeletal muscles but also the brain [23]. The impact on the CNS varies according to the DM1 phenotype [24-25]. As previously mentioned, in the adult form the global cognitive functioning remains relatively stable, executive and visual spatial disorders, hypersomnia and apathy being the main complications [26]. In the childhood form, the global cognitive impairment varies, with frequently associated learning difficulties, whereas in the congenital form ID is one of the major elements of the disease. Besides, whereas the presence of medical and neurologic comorbidity is the rule in the ASD group with ID (for example epilepsy [27]), sometimes bordering on syndromic autism symptoms, it is the exception in DM1.

Using PET (Positron Emission Tomography), a hypoperfusion of the frontal and parietal lobes in DM1 classical form, as well as a significant correlation of hemodynamic measures with the performances at executive tests were evidenced. Similarly, anatomical magnetic resonance imaging (aMRI) studies revealed WM (White Matter) lesions (in particular in the temporal and periventricular regions), a cortical atrophy and ventricular dilations; a hypoplasia of the *corpus callosum* was also noted (57%). Studies bearing on the congenital and childhood forms reveal cortical atrophy, ventricular dilation and diffuse WM anomalies (Meola et al., [22]; [28]).

As far as anatomo-functional relations are concerned, the results remain contradictory. Using diffusion imaging (DTI) in a group of DM1 subjects (suffering from both congenital and childhood forms), Wozniak *et al.* [29] evidenced a significant correlation between the diffuse connectivity anomalies and (1) the global cognitive level but also (2) the degree of “everyday life” executive dysfunction [planning/organization and self-control, evaluated through the behavior rating inventory of executive functions (BRIEF)] reported by parents.

In ASD subjects, at the anatomical level, anomalies in the white and gray matters were also found. Brain growth is abnormal during early childhood followed with a progressive slacking with development [30]. This increased augmentation of the volume seems to be linked with a proliferation of white matter during the first months of life. With maturation, WM development slackens, and becomes inferior to that of control subjects [31]. This maturation pattern could provide an explanatory framework to the results showing lower levels of WM connectivity in autistic adolescents and adults. Researchers [32] currently suggest that the anomalies in the brain's development concern atypical connectivity patterns (or even disconnection), associated with a local overconnectivity, mainly in the posterior cerebral areas, and an interhemispheric and antero-posterior underconnectivity, which would entail deficits in integrative cognitive functions such as language and executive functions.

Due to the small number of studies providing insight on the brain's functioning of childhood DM1, the comparison with the ASD population remains limited. Although WM anomalies have been noticed in the two populations, the characterization of cerebral maturation process in DM1 children has yet to be identified.

Discussion and perspectives

The aim of the current review was to address the question of comorbidity between DM1 and ASD, two pathologies with very heterogeneous symptoms (Table 2).

Insert Table 2

So far, only Ekström *et al.* [7] report a prevalence of ASD in the DM1 child population superior to that found in the general population (respectively 36% vs 1%). The frequency of

ID in Ekström's population may constitute a partial explanation of these results; it seems that, the more severe the global cognitive deficiencies, the closer subjects are to ASD. In all studies, there is a 34% prevalence of ASD (19/56) in the congenital form of DM1, and 5,3% (4/75) in the childhood onset-form. The DM1 subjects described by Ekström *et al.* could in fact display a form of “passive” autism [13] characterized by a lesser initiation of interaction, but adapted responses to the requests from adults.

It is important to consider that in neurodevelopmental disorders, the emergence of a specific phenotype depends not only on genetic factors, but also on the interaction of the subject with his/her environment. The passive disposition, the hypotonia and the relative facial inexpressiveness of DM1 patients are often interpreted as indifference to other people. These subjects' difficulties in social interactions and in communication may also be linked to environmental aspects, such as a paucity of early interpersonal experiences, one of the parents suffering from the disease too.

Deficiencies in the field of executive functions are a common point, as are impairments in the field of social cognition for ASD subjects and probably for DM1 subjects as well (as is suggested by studies on adult subjects, and by the high frequency of alexithymia in children). The causal link between executive functions and theory of mind has been extensively demonstrated in healthy subjects or in the case of early pathologies [33].

The question of the comorbidity of these two pathologies remains open although future studies would have to consider changes introduced in DSM-5 to define ASD [34]. We wonder whether DSM-5 diagnosis of “Social (pragmatic) Communication Disorder” (SCD) would fit better those patients with childhood DM1 showing social withdrawal [5], difficulties in peer relationships [23], communication disorder [35] and emotional recognition impairment [36]. Individuals with SCD cannot evidence restricted interests, repetitive behaviors,

insistence on sameness, or sensory abnormalities [37] but they present persistent difficulties in the social use of verbal and nonverbal communication (as manifested by deficits in using communication for social purposes, making inferences, understanding of nonliteral or ambiguous meaning of language) and will have also hampered abilities to assess the emotional and mental states of others as well as their one [38].

The presence of ID among the populations under study necessarily produces a bias in the results of the evaluation of the autistic symptoms as established in diagnostic manuals. Future researches comparing the neuropsychological profiles (with IQ as a covariate), notably in the fields of social cognition and executive functions (domains in which weakness or deficit have been identified for both pathologies), as well as the behavioral and the sensory processing profiles of age- and gender-matched subgroups, would allow a deeper more nuanced picture of both similarities and differences between DM1 and ASD or SCD. It would also provide insights into underlying psychological and neurobiological aspects and leads to elaborate adapted therapeutic programs.

The treatment of DM1 subjects frequently focuses separately on the neuromuscular or cognitive/psychiatric impairments. Identifying the neuropsychological and psychiatric symptoms specific to the childhood-onset form of the disease and characterizing their impact on quality of life with sensitive instrument (e.g., ccDMHI – Congenital and Childhood Myotonic Dystrophy Health Indexes) [39] would be a fundamental step to guide professionals better. An idea could be, among others, to pay particular attention to early cognitive, developmental and socio-emotional symptoms (visual contact, joint attention, pretend play, emotional regulation, pragmatic language and fine motor skills development, *etc.*) even before characteristic neuromuscular signs have appeared.

Acknowledgments

This paper was supported by a grant (16716) of the AFM (Association Française contre les Myopathies)

Accepted Manuscript

Références

1. Brook JD, McCurrach ME, Harley HG, Buckler AJ, Church D, Aburatano H et al. Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3' end of a transcript encoding a protein kinase family member. *Cell* 1992; 69(2): 385.
2. Harley HG, Rundle SA, MacMillan JC, Myring J, Brook JD, Crow S, et al. Size of the unstable CTG repeat sequence in relation to phenotype and parental transmission in myotonic dystrophy. *Am J Hum Genet.* 1993;52(6):1164–74.
3. De Antonio M, Dogan C, Hamroun D, Mati M, Zerrouki S, Eymard B et al. Unravelling the myotonic dystrophy type 1 clinical spectrum: a systematic registry-based study with implications for disease classification. *Rev Neurol* 2016; 172:572-80.
4. Meola G, Sansone V, Perani D, Scarone S, Cappa S, Dragoni C, et al. Executive dysfunction and avoidant personality trait in myotonic dystrophy type 1 (DM-1) and in proximal myotonic myopathy (PROMM/DM-2). *Neuromuscul Disord* 2003;13(10):813–21.
5. Douniol M, Jacquette A, Cohen D, Bodeau N, Rachidi L, Angeard N, et al. Psychiatric and cognitive phenotype of childhood myotonic dystrophy type 1. *Dev Med Child Neurol* 2012;54(10):905–11.
6. Steyaert J, Umans S, Willekens D, Legius E, Pijckels E, Die-Smulders C, et al. A study of the cognitive and psychological profile in 16 children with congenital or juvenile myotonic dystrophy. *Clin Genet* 1997;52(3):135–41.
7. Ekström A-B, 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* 2008;147B(6):918–26.
8. 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(4):317–27.
9. Echenne B, Rideau A, Roubertie A, Sébire G, Rivier F, Lemieux B. Myotonic dystrophy type I in childhood. *Eur J Paediatr Neurol* 2008;12(3):210–23.
10. Yoshimura I, Sasaki A, Akimoto H, Yoshimura N. [A case of congenital myotonic dystrophy with infantile autism]. *No To Hattatsu* 1989;21(4):379–84.
11. Vig S, Jedrysek E. Autistic features in young children with significant cognitive impairment: autism or mental retardation? *J Autism Dev Disord* 1999;29(3):235–48.
12. Kim SH, Lord C. Combining information from multiple sources for the diagnosis of autism spectrum disorders for toddlers and young preschoolers from 12 to 47 months of age: Combining information for the diagnosis of ASD for toddlers and young preschoolers. *J Child Psychol Psychiatry* 2012;53(2):143–51.
13. Douniol M, Jacquette A, Guilé J-M, Tanguy M-L, Angeard N, Héron D, et al. Psychiatric and cognitive phenotype in children and adolescents with myotonic dystrophy. *Eur Child Adolesc Psychiatry* 2009;18(12):705–15.

14. Angeard N, Gargiulo M, Jacquette A, Radvanyi H, Eymard B, Héron D. Cognitive profile in childhood myotonic dystrophy type 1: Is there a global impairment? *Neuromuscul Disord*. 2007;17(6):451–8.
15. Angeard N, Jacquette A, Gargiulo M, Radvanyi H, Moutier S, Eymard B, et al. A new window on neurocognitive dysfunction in the childhood form of myotonic dystrophy type 1 (DM1). *Neuromuscul Disord* 2011;21(7):468–76.
16. Kobayakawa M, Tsuruya N, Kawamura M. Theory of mind impairment in adult-onset myotonic dystrophy type 1. *Neurosci Res*. 2012;72(4):341–6.
17. Winblad S, Hellström P, Lindberg C, Hansen S. Facial emotion recognition in myotonic dystrophy type 1 correlates with CTG repeat expansion. *J Neurol Neurosurg Psychiatr* 2006;77(2):219–23.
18. Boucher J, Bowler DM, editors. *Memory in autism*. Cambridge, UK ; New York: Cambridge University Press; 2008.
19. Baron-Cohen S. Theory of mind and autism: A review. *International review of research in mental retardation: Autism* (vol. 23). Glidden, Laraine Masters (Ed); pp. 169-184; San Diego, CA, US: Academic Press; 2001.
20. Jones CR, Pickles A, Falcaro M, Marsden AJ, Happé F, Scott SK, Charman T. A multimodal approach to emotion recognition ability in autism spectrum disorders. *J Child Psychol Psychiatry* 2011;52(3): 275-85.
21. Hill EL. Executive dysfunction in autism. *Trends Cogn Sci* 2004;8(1):26-32.
22. Meola G. Myotonic dystrophy is not only a disease affecting the muscles, it is also a CNS disorder. *Eur J Neurol* 2014;21(2):183-4
23. Gourdon G, Meola G. Myotonic dystrophies: State of the art of new therapeutic development for the CNS. *Front Cell Neurosci* 2017; 11:1-14.
24. Bosco G, Diamanti S, Meola G, Angeard N, Bassez G, Ekström AB, et al. Workshop report: consensus on biomarkers of cerebral involvement in myotonic dystrophy, 2-3 December 2014, Milan, Italy. *Neuromuscul Disord* 2015; 25:813-23.
25. Peric S, Mandic-Stojmenovic G, Ilic V, Kovacevic M, Parojcic A, Dobricic V et al. Clusters of cognitive impairment among different forms of myotonic dystrophies. *Eur J Neurol*;23:550.
26. Okkersen K, Buskes M, Groenewoud J, Kessels R, Knoop H, van Engelen B, Raaphorst J. The cognitive profile of myotonic dystrophy type 1: A systematic review and meta-analysis. *Cortex* 2017;95:143-55.
27. Amiet C, Gourfinkel-An I, Bouzamondo A, Tordjman S, Baulac M, Lechat P et al. Epilepsy in autism is associated with mental retardation and gender: evidence from a meta-analysis. *Biological Psychiatry* 2008; 64: 577-582.
28. Okkersen K, Monckton D, Darren G., Tuladhar N, Raaphorst J, van Engelen B. Brain imaging in myotonic dystrophy type 1. A systematic review. *Neurol* 2017;89:960-69.

29. Wozniak JR, Mueller BA, Ward EE, Lim KO, Day JW. White matter abnormalities and neurocognitive correlates in children and adolescents with myotonic dystrophy type 1: A diffusion tensor imaging study. *Neuromuscul Disord* 2011;21(2):89–96.
30. Amaral DG, Schumann CM, Nordahl CW. Neuroanatomy of autism. *Trends in Neurosci* 2008;31(3):137–45.
31. Wolff JJ, Gu H, Gerig G, Ellison JT, Styner M, Gouttard S, et al. Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. *Am J Psychiatry* 2012;169(6):589–600.
32. Geschwind DH, Levitt P. Autism spectrum disorders: developmental disconnection syndromes. *Curr Opin Neurobiol* 2007;17(1):103–11.
33. Calderon J, Bonnet D, Courtin C, Concordet S, Plumet M-H, Angeard N. Executive function and theory of mind in school-aged children after neonatal corrective cardiac surgery for transposition of the great arteries: Executive Function and Theory of Mind in Children with TGA. *Dev Med Child Neurol* 2010;52(12):1139–44.
34. Xavier J, Bursztein C, Stiskin M, Cohen D. Autism spectrum disorders: A historical synthesis and multidimensional assessment toward a tailored therapeutic program. *Research in Autism Spectrum Disorder* 2015; 18: 21–33.
35. Johnson N, Ekström AN, Campbell C, Hung M, Adams H, Chen W et al. Parent-reported multi-national study of the impact of congenital and childhood onset myotonic dystrophy. *Dev Med Child Neurol* 2016; 58: 698–70.
36. Angeard N, Huerta E, Chaby L, Jacquette A, Cohen D, Gargiulo M, Servais L, Eymard B, Héron D. Emotional recognition in the childhood form of Myotonic Dystrophy type I (DM1). 10th edition of the International Myotonic Dystrophy Consortium Meeting (IDMC10). 2015 8-12 June, Paris, France.
37. Swineford L, Thurm A, Baird G, Wetherby A, Swedo S. Social (pragmatic) communication disorder: a research review of this new DSM-5 diagnostic category. *Journal of Neurodevelopmental disorders* 2014;6:41.
38. Brukner-Wertman Y, Laor N, Golan O, Social (Pragmatic) Communication Disorder and Its Relation to the Autism Spectrum: Dilemmas Arising From the DSM-5 Classification. *J Autism Dev Disord* 2016; 46:2821–29.
39. Johnson N, Luebke E, Eastwood E, Chin N, Moxley R, Heatwole C. Identifying high impact symptoms and issues in congenital and juvenile myotonic dystrophy, *Neurol* 2012;78:P05.186

Table 1. Comorbidity of ASD in DM1 subjects according to the phenotype and the IQ

References	DM1 Phenotype	IQ	ASD (%)
Douniol (2012)	Congenital (n=0)	--	--
	Childhood (n=28)	M=73.6 [56-91]	0%
Ekstrom (2008)	Congenital (n=37)	20-34 (30%)	48% (18/37) With 1 Asperger)
		35-49 (46%)	
		50-59 (13.5%)	
		70-84 (8%)	
		IQ>85 (2.5%)	
	Childhood (n=18)	35-49 (50%) 50-59 (39%) 70-84 (5.5%) IQ>85 (5.5%)	16% (3/18)
Echenne (2008)	Congenital (n=17)	M=53.6 [40-69]	5% (1/17)
	Childhood (n=15)	M= 60 [47-85]	0%
Steyaert (1997)	Congenital (n=2)	M=68 [62-73]	0%
	Childhood (n=14)	M=94 [63-95]	7% (1/14)

M: mean IQ

Table 2 –Social/communication, cognitive functioning profiles and brain abnormalities in subjects with the childhood-onset form of DM1 or ASD

	DM1	ASD
Social Communication	<p>Social interaction impairment, no initiation of interaction but contingent responses, passivity, social withdrawal.</p> <p>No self-injurious behavior Few restricted, repetitive and stereotyped behavior</p>	<p>Social interaction deficit, no initiation of interaction, no response contingency, passivity, social withdrawal.</p> <p>Self-injurious behavior (variability) Limited interest and activities, stereotyped behavior</p>
Language	Speech and late language acquisition related to ID	<p>Absence of language (echolalia), delayed acquisition or sophisticated language Pragmatic language deficits.</p>
Cognitive Functioning	<p>Heterogeneous spectrum (from mild ID to borderline or normal IQ).</p> <p>Cognitive discrepancy with higher VCI than POI Visual constructive and visual spatial information encoding impairments Executive functions deficits (cognitive flexibility and verbal working memory).</p> <p>Alexythimia</p>	<p>Heterogeneous spectrum (from severe ID to high level IQ)</p> <p>Cognitive discrepancy with higher POI than VCI Good visual spatial search and visuoconstructive abilities</p> <p>Executive functions deficits (cognitive flexibility, inhibitory control, planning and working memory). Social cognition deficits (social information processing, ToM or emotion regulation).</p>
Brain / Neuro	<p>Widespread WM abnormalities. Significant correlations between diffuse connectivity abnormalities and global IQ, cognitive flexibility and verbal working memory</p> <p>Hypotonia</p> <p>Motor coordination disorder</p> <p>No comorbidity with epilepsy</p>	<p>White and grey matter abnormalities. Atypical connectivity pattern (local overconnectivity mainly in posterior areas and antero-posterior underconnectivity).</p> <p>Hypotonia (variability) Atypical sensory processing Motor coordination disorder (variability) Comorbidity with epilepsy</p>

ID: Intellectual Disability, VCI: Verbal Comprehension Index, POI: Perceptive Organization Index, ToM: Theory of Mind, WM: White Matter