

**Introduction**

Neuromuscular diseases present a wide variety of clinical manifestations, but their effects on the cognitive function spectrum are still poorly understood. In contrast to the studies on how altered executive functions in mental disorders such as anxiety, depression and bipolar disorder can affect motor performance, the mechanisms by which essentially motor dysfunctions can affect cognitive performance still remain poorly understood. Although it is known that neuromuscular diseases mainly affect the motor functioning of the patient, the cognitive effects of these conditions can be significant. This can occur from molecular defects that significantly affect neuromotor functioning but also participate in the functioning of neural networks involved in cognitive processes, leading to dysfunctions of executive, behavioral and psychosocial functions. For example, mutations in the dystrophin protein gene, responsible for the Duchenne Muscular Dystrophy (DMD) phenotype, concurrently affect the stability and function of muscle fibers and central nervous system (CNS) function. However, the complex nature of neuromuscular diseases and the different effects on cognition make it difficult to understand the neuropsychological process.

Three large, heterogeneous groups of neuromuscular diseases have been implicated in cognitive alterations. i) Motor Neuron Diseases, neurological disorders that affect the neurons that control voluntary motor activity. ii) Muscular dystrophies, represented mainly by dystrophinopathies, diseases caused by hereditary defects in the dystrophin protein gene. iii) Mitochondrial disorders, which are caused by mutations in cytoplasmic or nuclear mitochondrial DNA, which alter the structure and mitochondria function. Often neuromuscular disease comes from an already known molecular disorder that is also associated with changes in brain function and cognition, such as mitochondrial myopathies. In other cases, neuromuscular disorders also have cognitive deficits, but without a well-defined molecular alteration such as Amyotrophic Lateral Sclerosis (ALS). In this context, the present review aims to highlight the neurofunctional and cognitive alterations in the main congenital neuromuscular disorders.

**Materials and Methods**

The systematic review was conducted in line with the PRISMA statement. A computer-based literature search was conducted in two main databases: ISI Web of Science and PubMed (2003-present) were initially performed in October 2017 using relevant search terms: (e.g. [Cognitive Impairment and Neuromuscular Diseases] [Motor Neuron Diseases and Cognitive Impairment] [Cognitive Impairment and Dystrophinopathies] [Cognitive Impairment and Mitochondrial Disorders]). Abstracts were examined for references to the research question and if the study appeared relevant, then the full text was retrieved. As selection criteria: (a) Experimental studies, case reports and reviews written in English; (b) Without restriction of publication dates of the paper (c) Magnetic Resonance Imaging (MRI) scans, assessments with cognitive and functional scales applied to neuromuscular diseases, and cognitive tasks healthy individuals and/or individuals with neuromuscular diseases (e.g. children, young adults, middle-aged and elderly). In addition, experimental studies using rats were considered.

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**Abstract**

Neuromuscular diseases are multifactorial pathologies characterized by extensive muscle fiber damage that leads to the activation of satellite cells and to the exhaustion of their pool, with consequent impairment of neurobiological aspects, such as cognition and motor control. To review the knowledge and obtain a broad view of the cognitive impairment on Neuromuscular Diseases. Cognitive impairment in neuromuscular disease was explored; a literature search up to October 2017 was conducted, including experimental studies, case reports and reviews written in English. Keywords included Cognitive Impairment, Neuromuscular Diseases, Motor Neuron Diseases, Dystrophinopathies and Mitochondrial Disorders. Several cognitive evaluation scales, neuroimaging scans, genetic analysis and laboratory applications in neuromuscular diseases, especially when it comes to the Motor Neuron Diseases, Dystrophinopathies and Mitochondrial Disorders. In addition, organisms model using rats in the genetic analysis and laboratory applications to verify the cognitive and neuromuscular impacts. Several studies indicate that congenital molecular alterations in neuromuscular diseases promote cognitive dysfunctions. Understanding these mechanisms may in the future guide the proper management of the patient, evaluation, establishment of prognosis, choice of treatment and development of innovative interventions such as gene therapy.
analyze the papers results and answer the hypothesis of the present research.

**Study selection and data extraction**

Three reviewers (M.O, S.T and V.M) independently read the titles and/or abstracts of the identified papers and eliminated irrelevant studies. Studies considered eligible for inclusion were read in full and their suitability for inclusion was determined independently by three reviewers (M.O, S.T and V.M). Disagreements were managed by consensus. However, if this was not successful, consensus was sought by a fourth reviewer (M.R.G.F.). Data were extracted based on study design and setting. Some authors were contacted to provide supplementary information when insufficient data were provided in the study. The authors of three studies were contacted for further information having read their titles and abstracts. Two replied; since it bases the review of literature fulfilled the inclusion criteria.

**Study selection**

Studies were included if they met the following inclusion criteria. Initially, retrieved papers from each database were compared to remove duplicate records. Papers were then screened for eligibility based on their title and abstract and, once they were elicited, the full text publication was reviewed.

In summary: Study design: Case reports, original papers and reviews designs were included.

Population: Study population composed of healthy individuals and/or individuals with neuromuscular diseases (e.g., children, young adults, middle-aged and elderly). In addition, experimental studies with rats were included.

Intervention: Neurobiological interventions were defined as any intervention aimed at evaluating the neuromuscular diseases - Motor Neuron Diseases, Dystrophinopathies and Mitochondrial Disorders.

Screening: Genetic analysis in vivo and post-mortem; MRI scans, mobile transcutaneous sensor for tissue blood gas tensions, ALS Functional Rating Scale, Reye Oestriehl Complex Figure Test, Premorbid Full-Scale IQ, Wechsler Test of Adult Reading, Pyramid and Palm Trees Test, Boston Naming Test, Rey-Osterrieth Complex Figure, Reverse Digit Span subtest, Oral Trail Making Test, Edinburgh Cognitive, Behavioural ALS Screen (ECAS), Griffiths scale, Child Behavior Check List (CBCL), Youth Self Report (YSR), Strength and Difficulties Questionnaire (SDQ), Mini Mental State Examination (MMSE), Addenbrooke’s Cognitive Examination-Revised (ACE-R), California Verbal Learning Test (CVLT), Stroop Color and Word Test (SCWT).

**Outcome**

The primary outcome measure was the potential ability to accurately assess neuromuscular diseases and their implications for cognitive impairment through screening: Genetic analysis, MRI scans, mobile transcutaneous sensor for tissue blood gas tensions and cognitive Scales. Papers were assessed for eligibility based on title and abstract; 80 were classified as meeting eligibility criteria. The next stage of the winnowing process involved full-text screening of the potentially relevant papers; Eventually, 63 studies were included in the review.

**Results**

Seventeen experimental studies and 30 case reports with cognitive scales and neuromuscular assessment using scales, as well as genetic studies and neuroimaging studies with MRI, 16 review papers about neuromuscular diseases. This study demonstrated that the neuromuscular diseases are multifactorial pathologies characterized by extensive muscle fiber damage that leads to the activation of satellite cells and to the exhaustion of their pool, with consequent impairment of the regenerative process.

The prospective population-based study of cognitive impairment in neuromuscular diseases

The majority of neuromuscular diseases patients presented with features consistent with executive dysfunction, and have shorter survival time. This last finding, in turn, suggests that studies reliant on prevalent cases are likely to underestimate the incidence of these frontotemporal syndromes. In patients without dementia, we observed an overrepresentation of executive dysfunction. The incidence of executive impairment in this cohort was higher using the screening criteria. The cognitive evaluation and cognitive tasks demand heavily on multiple frontostriatal circuits leading to sensitivity in detecting any disturbance of neural circuits established for cognitive and motor demands.

In this present study, neuromuscular diseases patients showed generally a moderate muscular impairment, impaired cognitive performance over a broad range of functions, including frontal, visuospatial, naming and memory abilities and working memory abnormalities. The degree of cognitive impairment in patients with neuromuscular diseases is greatly variable, and significant cognitive impairment is observed only in some patients. Symptoms such as depression and anxiety as well as deficits of visuospatial abilities, executive functions, and naming have been frequently reported. Several MRI studies have shown that neuromuscular diseases patients have generally more deficiencies of neural connections in the frontal, parietal and temporal regions; and these dysfunctions increase with the progression of the disease.

**Discussion**

**Motor neuron diseases and cognitive impairment**

Motor Neuron Disease (MND) is a degenerative disease caused by motor neuron degeneration, whether inferior or superior. Amyotrophic Lateral Sclerosis (ALS), the most well-known form of MND, is a devastating severe disease that simultaneously affects the lower motor neuron (LMN) and upper motor neuron (UMN).9,10 Descriptions in the literature have been linking, for more than a century, emotional liability with bulbar-onset ALS. After pathological and genetic discoveries, over the years, the overlap of frontotemporal dementia (FTD) and MND was strengthened.9,10 Data from recent studies show that more than 50% of ALS patients at some point in the disease course, will develop a phenotypic picture of cognitive or behavioural impairment, and about 13% will exhibit concomitant behavioural-variant frontotemporal dementia (b-FTD).10,16 Patients who present cognitive or behavioural changes, that do not fulfil all the formal criteria for FTD, can be grouped into three different categories: ALS with behavioural impairment; ALS with executive dysfunction; and ALS non-executive dysfunction.10,17,18

Frontotemporal dysfunction, when present, is strongly linked to lower survival in patients with ALS. In addition, regardless of the age of onset, delayed diagnosis, baseline severity, education and respiratory status, the presence of executive dysfunction is a factor and risk for a worse prognosis.10,16

Unless FTD is advanced enough to cause significant frontal and temporal lobe atrophy, neuroimaging is rarely useful in diagnosing cognitive and behavioural deficits in ALS. Studies of neural networks have been increasingly used for the analysis of frontotemporal dysfunction in ALS. In studies with resting state functional MRI, it has been observed three main dysfunctional networks in ALS: the salience network, the...
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presence of minipolymyoclonus. It is a striking feature in Kennedy's Disease (KD). KD is an X-linked recessive pathology that affects men specifically. It is characterized by degeneration of the bulbospinal muscular atrophy or the adult-onset form, and fasciculation of limbs and bulbar musculature. The repeat expansion of C9orf72 results in dipeptide repeat proteins (DPRs), which form inclusions in the nervous system (CNS). Finally, it induces the mislocalization and aggregation of TAR DNA-binding protein 43 (TDP-43). It is estimated that in the European population, 50 to 70% of patients with familial frontotemporal dementia-motor neuron disease and 15 to 20% with apparent sporadic familial frontotemporal dementia-motor neuron disease, exhibit the expansion of the C9orf72 gene. The penetrance of C9orf72 gene expansion has not yet been determined, but it seems unlikely to be a complete penetrance.

Although C9orf72 is the most frequent genetic cause of frontotemporal dementia-motor neuron disease, other gene mutations (VCP, SQSTM1, OPTN and UBQLN2) have already been linked to this pathology, but they are rare causes.

Another MND with cognitive impairment is the bulbospinal muscular atrophy or Kennedy's Disease (KD). KD is an X-linked recessive pathology that affects men and is caused by the repetition of the CAG trinucleotide in exon 1 of the androgen receptor gene, slowly progressive, with adult-onset. It is characterized by degeneration of LMN that leads to atrophy, weakness, and fasciculation of limbs and bulbar musculature. A striking feature in KD is the presence of minipolymyoclonus. It is required more than 38 repeats to consider the CAG repeat size correlates inversely with disease onset, but not with disease progression or severity. Systemic

<table>
<thead>
<tr>
<th>Author</th>
<th>Protocol</th>
<th>Results</th>
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<tr>
<td>Balcin et al., 2017</td>
<td>Case report: Mutations in GMPPB gene in patients with early-onset disease ranging from severe congenital muscular dystrophies to limb-girdle muscular dystrophy (LGMD) with mental retardation.</td>
<td>The results of the two cases with LGMD that underwent clinical, histopathological and genetic studies. In both cases, we found identical compound heterozygous GMPPB mutations c.79G&gt;C p.D27H and c.859C&gt;T p.R287W, leading to a glycospiric defect of alpha-dystroglycan. The onset of muscle weakness was 30-40 years and the progression rate mild to moderate. No cognitive or behavior symptoms were noted. Two were mental retardation severe and 30% in the full scale IQ, with a greater impairment of severe in the verbal IQ and mild in the performance IQ. The mean FSIQ in the patient was more than one SD below the mean (83.50) with a greater impairment of verbal IQ and mild in the nonverbal IQ. The mean FSIQ in the patient was more than one SD below the mean (83.50) with a greater impairment of verbal IQ and mild in the nonverbal IQ.</td>
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<td>Mereu et al., 1999</td>
<td>Group: Twenty-two children with merosin-positive or merosin-deficient congenital muscular dystrophy. Evaluation: FMRI and Wechsler Intelligence Scale.</td>
<td>Twelve were merosin-positive and ten merosin-deficient. The full scale IQ in the remaining 21 ranged from 51 to 134, the verbal IQ ranged from 78 to 136 and the performance from 51 to 136. Of the twelve children with normal merosin one had a mild delay (IQ&lt;75) and two were borderline (IQ 75-95). While the children with normal merosin IQ, the verbal IQ (1.5) and the performance IQ were within normal limits.</td>
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<td>Colonbro et al., 2017</td>
<td>Group: 10 boys with DMD (aged 2-12 years). Evaluation: Child Behavior and Difficulties Questionnaire (SDQ) and Strength of Will Assessment for Attention (SOWA).</td>
<td>The mean FSIQ in DMD patients was more than one SD below the mean (80.38), with a greater impairment of verbal IQ (84.31) and mild in the nonverbal IQ. The mean FSIQ in the patient was more than one SD below the mean (83.50) with a greater impairment of verbal IQ and mild in the nonverbal IQ.</td>
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<td>Ueda et al., 2016</td>
<td>Group: Fifteen patients with DMD (mean age = 30.4 years, age range = 19–44 years). Evaluation: WechslerAdult Intelligence Scale III (WAIS-III), the Clinical Assessment of Attention (CATT) and the Clinical Memory Assessment (CMA).</td>
<td>The mean FSIQ in DMD patients was more than one SD below the mean (80.38), with a greater impairment of verbal IQ (84.31) and mild in the nonverbal IQ. The mean FSIQ in the patient was more than one SD below the mean (83.50) with a greater impairment of verbal IQ and mild in the nonverbal IQ.</td>
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<td>Fu et al., 2016</td>
<td>Group: 12 patients [age 9.14±2.52 years] with a diagnosis of DMD, and 14 healthy volunteers [age 9.39±2.99 years]. Evaluation: Wechsler intelligence of CC and the full intelligence quotient (FIQ).</td>
<td>Compared with the 14 subjects in the normal control group, no significant difference between the groups was observed in terms of FIQ.</td>
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<tr>
<td>Ueda et al., 2016</td>
<td>Group: 416 patients with DMD. Evaluation: Muscular Impairment Rating Scale, including small-pool polymerase chain reaction (PCR), EMG examination, MRI scans of EDNM.</td>
<td>A significant worsening over time was observed for verbal memory, visual attention, and processing speed.</td>
</tr>
<tr>
<td>Bartolini et al., 2017</td>
<td>Group: 13 patients with DMD. Evaluation: Genetic analysis for C9orf72 triplet repeat expansions including small pool polyadenylic chain reaction (PCR), EMG examination, MRI scans of EDNM.</td>
<td>Results of MRI and cognitive tests in DM1 patients showed reduced cerebral metabolic rate for glucose, reduced GM volume, and increased WM abnormalities in DM1 patients.</td>
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symptoms are also found in KD. The most common non-neurological manifestation is gynecomasia. In addition, reduced motor activity due to testicular atrophy, oligo/azoospermia, erectile dysfunction and reduced libido may be present. Cognitive impairment may be found in KD. Guidetti et al. have observed in their patients a predominant impairment in long-term memory and selective attention. Kessler et al. observed clinical characteristics of frontal lobe dysfunction with disinhibition, impaired executive functions and reduced affective modulation.

Cognitive impairment of muscular dystrophies: dystroglycanopathies

Congenital muscular dystrophies (CMDs) are clinically and genetically heterogeneous inherited disorders that compass muscle weakness typically manifested at birth or in infancy. The spectrum ranges from severe floppy infant syndrome to moderate motor delay and mild or moderate limb-girdle involvement during childhood, compatible with survival into adult life and relatively good quality of life. Besides muscle compromise, white matter and structural abnormalities of the brain, seizures, cognitive impairment, and eye abnormalities may occur depending on the genetic cause. Mutations occur in genes encoding structural proteins of the extracellular matrix, glycosylation enzymes, and proteins of the endoplasmic reticulum (ER) and nuclear envelope. However, just in 25-50% of CMD-affected subjects, mutations can be identified, suggesting that there are additional genes to be acknowledged. On the other hand, it is frequently unfeasible to establish a one-to-one relationship between a given gene and a defined phenotype. For example, mutations in the FKRP (Fukutin-related protein) gene may lead to manifestations extended from the severe Walker-Warburg (WW) syndrome to the late adult-onset limb-girdle muscular dystrophy (LGMD). The genetic defects might not only interfere with the translated sequence, but also with the posttranslational processing, as described with α-dystroglycan, a major extracellular matrix receptor on muscle.

The term dystroglycanopathies encompass the mutation in the dystroglycan gene (DAG1) itself or mutations in genes encoding glycosyltransferases of alpha-dystroglycan (α-DG), which are necessary to allow α-DG binding to laminin. In brain, dystroglycan is expressed in astrocytic end feet abutting the glia limitans and the intracerebral vasculature, in photoreceptor cells of the retina, and in major neurons and glia in the developing CNS. Cases of milder course of the disease seem to be related to a less severe and remaining glycosylation of α-DG. In the more severe end of the clinical spectrum, there are brain and eye abnormalities, as illustrated by: Fukuyama congenital muscular dystrophy (FCMD), muscle-eye-brain (MEB) disease and WWS, examples of a continuum in increasing of severity. The typical CNS involvement among dystroglycanopathies includes various degrees of lissencephaly type II (also known as cobblestone complex), pachygria, neuronal heterotopias, ponto cerebellar hypoplasia, and cerebellar cysts.

Merosin-deficient congenital muscular dystrophy also referred to as MDC1A, is caused by mutations in the LAMA2 gene, which encodes the α2 subunit of laminin (merosin). Patients manifest severe muscular weakness and atrophy, diffuse contractures, inability to walk and facial dysmorphosis. Ventilatory is needed within the first 10 years for most patients. Since laminin-α2 chain is localized to the basal lamina of all cerebral blood vessels, the lack of α2 may lead to a disruption of the blood-brain barrier (BBB), increased water content, and a resulting abnormal white matter signal intensity (WM). The typical abnormal signal in WM seen in T2-weighted MRI (T2 MRI) spares the compacted fibre tracts such as the corpus callosum (CC). The cognitive functions are not impaired if the WM changes are isolated. Nevertheless, it has been reported a child with cortical dysplasia and severe mental retardation, and a series of children who in addition to the typical findings had cerebellar hypoplasia and a lower performance IQ.

Duchenne muscular dystrophy (DMD) is one of the most common genetic disorders, affecting about 1:3000 boys. It is an X-linked dystrophy caused by genetic mutations disrupting the protein dystrophin (DYS), another core protein of dystrophin-glycoprotein Complex (DGC), as DG. DMD is characterized by progressive muscle degeneration and non-progressive cognitive deficits. DYS also plays an important role in the architectural organization of the CNS. It is involved in the organization of GABA-A receptors, once is normally expressed at the postsynaptic membrane in inhibitory synapses of structures related to cognition and emotional behaviour, such as hippocampus, amygdala, cerebellum and sensory cortices.

Although dystrophin expression in brain is only one-tenth of that found in muscle, brain tissue exhibits much greater variability in the protein products from the dystrophin gene. It includes the full-length protein, Dp427, and shorter proteins being Dp71 the main product expressed in the brain. Dp71 is found around perivascular astrocyte end feet, which suggests its role in BBB function and possible in the possible access of peripheral inflammatory molecules into the brain. In the CNS, Dp427 is only found in neurons, and only within specific regions of the brain such as the hippocampus, amygdala, cerebellar Purkinje cells, and neocortex. The interaction of Dp47 with DGC would be important for the formation and maintenance of new synaptic connections.

The lack of dystrophin in mdx mice) seems to alter neuron proliferation, survival and/or differentiation and perturb neuronal migration (The density of CA1 pyramidal neurons was reduced by ~34% in the anterodorsal hippocampus, although quantitative reductions varied along the hippocampal antero-posterior axis. In their hippocampus were identified cytokines, which are also chronically elevated in peripheral tissue and plasma of patients with DMD. Key proinflammatory cytokines such as IL-1, TNF-α, and IL-6 exert neuro-modulatory effects on the hippocampus and have been linked to altered capacities for learning and the formation of memories. Hence, there may be a neuroimmune contribution in the CNS disturb of dystrophin-deficient patients.

In mice, the loss of DYS leaded to enhanced unconditioned fears, anxiety and deficits in fear conditioning and memories, suggesting the role of the protein in the functioning of the neuronal circuit of fear. The absence of dystrophin resulted in a significant elevation of [Ca2+]i and [Na+]i in intact adult cortical and especially hippocampal pyramidal neurons of mice, as well as an increase in ROS production, and cell death. This ion dyshomoeostasis was related to a spatial learning deficit.

In humans, the lack of this protein might also lead to neurobehavioral disorders, including attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders, and obsessive-compulsive disorder. In the context, Colombo et al. reported a non-progressive lower IQ in DMD boys compared to controls. Boys may present specific learning disabilities such as dyslexia and impaired executive functions, namely problem solving, inhibition and working memory. In addition, Astre et al. demonstrated that 15 patients with DMD (age range = 19–44 years) demonstrated impairment in the ability to sequentially process auditory and visual information and attention. A controlled study of diffusion tensor imaging (DTI) involving 15 boys with DMD showed significantly lower fractional anisotropy (FA) values in the spleni-
A recent study assessing 47 Italian boys with DMD found that 14.89% of the boys had a diagnosis of ASD. Full Scale Intelligence Quotient (FSIQ) <70 were registered in 36.2% of them, with a greater impairment of verbal than other performance components. Distal DMD mutations were implicated to more severe cognitive deficit, as reported by previous studies. Similar results were found in a longitudinal study following 41 preschool DMD boys until school age. It was confirmed a correlation between neurodevelopmental assessments and later cognitive scales and on both evaluation the overall results were better when the mutation was upstream in the exon 44 without affecting Dp140 expression. Distal mutations are associated with loss of cerebral dystrophin isoforms, which are more expressed in the cerebellum and limbic system. It is worth to remember that literature supports the cerebellar contribution even to aspects of social emotional and regulatory behaviour.

Mutations in the DYS gene are also responsible for causing Becker muscular dystrophy (BMD). However, in BMD there is a production of partially functional dystrophin. Patients typically remain ambulatory at least until age 15 and commonly well into adult life. Cognitive impairment and neurobehavioral comorbidities are also not as common or severe in BMD compared with DMD.

Myotonic dystrophies (DM) are autosomal dominant multisystemic disorders that affect also the brain. Myotonic dystrophy type 1 (DM1) is caused by a CTG trinucleotide repeat expansion in the non-coding region of the dystrophiamyotonia-protein kinase (DMPK) gene, resulting in alternative splicing of pre-messenger RNAs for various proteins, including the TAU and NMDA. Cognitive deficits have been observed in 24-75% of DM1 patients and it depends on the age at onset of the disease. Congenital patients tend to have mental retardation, while those with onset in the childhood have learning disabilities due to lower IQ, the ADHD, autistic behaviour, visuospatial impairment, lack of interest and inhibition. Adult onset is related to the dysexecutive syndrome and visuospatial deficit, while verbal functions and memory seem to be age dependent. Late-onset DM1 patients were reported to have predominantly age-dependent memory deficit.

Lower IQs seems to be correlated with longer expansions, mainly related to maternal inheritance and age of onset of symptoms although it does not represent a more severe neuromuscular impairment. Neuropsychological analysis of 101 DM1 patients (childhood, juvenile, adult, and late-onset) registered normal general intellectual level. Visuospatial impairment was the main cognitive defect with prevalence of 75-86% among different phenotypes. Executive dysfunction was the second most common cognitive impairment, affecting 60-79% of the sample. Adult DM1 subjects with older age and longer duration of disease were more susceptible to memory and language defects. Late onset was associated with the affection of multiple cognitive domains including the highest prevalence of memory impairment (more than 80%). Among 46 DM2 patients, it was showed that even one-third of them had completely normal neuropsychological findings. Visuospatial and executive dysfunctions were also the most prevalent in DM2, but less common than in DM1.

A longitudinal neuropsychological assessment among 115 DM1 – only adult phenotypes disclosed that executive functions (Stroop color-word, fluency tests and WAIS-R for digit symbol coding and block design), language (fluency and Boston Naming Test), and visual memory (Rey Complex Figure Test) were the most impaired cognitive functions at baseline. However, they did not significantly decline through the time, in opposition to verbal memory, processing speed, and visual attention, which, actually, also imply the requirement of some specific executive functions (i.e. processing speed itself, mental flexibility, and selection and maintaining of accurate strategies). The FSIQ and the visual construction also remained stable. The adult phenotype performed more poorly than the late-onset phenotype on most of the tests, both at baseline and follow-up. Nevertheless, the rate of decline was higher in the late-onset than in the adult phenotype. The level of progression in most of the cognitive performances correlated with age and disease duration but not with the CTG repeats, educational level nor muscular impairment. These findings are consistent with the hypothesis that DM1 could be considered as a progeroid disease (an accelerated and increased ageing process).

A comparative study involving nine DM1 patients and age matched healthy controls using T1-weighted and DTI disclosed changes in cortical thickness and WM in the widely distributed network of the frontal, temporoparietal, medial parietal, and sensorimotor areas. CTG repeats were negatively correlated to thickness in the right medial orbitofrontal cortex, left middle temporal, supramarginal, and the lateral occipital cortex and to the WM integrity in the left entorhinal, anterior corona radiate, orbitofrontal, and lateral occipital areas. This study revealed higher occurrence of WM than cortical abnormalities. This finding together with the correlation between WM lesion severity and disease duration suggests that DM1 represents a slow demyelinating process, which eventually progresses to axonopathy. Moreover, the decreased integrity of connectivity, as well as cortical pathology, was located mostly in the ventral side connecting the fronto-temporal cortex. These findings may be relevant to the behavioural symptoms, including dysexecutive syndrome, apathy, and depression. In that study, diffusion metrics were also affected in the external capsule, which might be related to decrease verbal fluency resulting from impairment in semantic processing.

Mitochondrial disorders and cognitive impairment

Mitochondrial diseases (mtD) are those caused by mutations in mitochondrial DNA (mtDNA) and/or nuclear DNA (nDNA) genes due to the dual genetic control (mtDNA and nDNA) of the respiratory chain (RC), the complexity of intergenomic signalling and its functional consequences. The mutation rate for mtDNA is much higher than that for nuclear DNA, especially for deletions. The diagnosis of mtD is challenging since the clinical picture is varied and can occur at almost any stage of life, often with involvement of unusual combination of organs. Systems/organs most frequently clinically or subclinically affected in mtD are the peripheral nervous system (PNS), the central nervous system (CNS), endocrine glands, heart, ears, eyes, gastrointestinal tract, liver, kidneys, bone marrow, and dermis. The second most frequently affected system is the CNS. Common CNS findings are fluctuating encephalopathy, seizures, migraine, stroke-like episodes, ataxia, spasticity and cognitive decline through dementia. The cognitive decline among manifestations of CNS is increasingly recognized and diagnosed, it is essential to guide the optimal management of these patients.

Mitochondrial syndromes associated with cognitive impairment due to mtDNA mutations include mitochondrial encephalopathy, lactic acidosi and stroke-like episodes (MELAS) syndrome, myoclonus epilepsy with ragged-red fibres
(MERRF) syndrome, maternally inherited diabetes and deafness (MIDD), mitochondrial chronic progressive external ophthalmoplegia (CPEO), Kearns-Sayre syndrome (KSS) and neuropathy, ataxia and retinitis pigmentos (NARP) syndrome. The assessment of cognitive functions in these patients is made through a neuropsychological test, and the domains impaired were abstract reasoning, verbal memory, visual memory, language, executive or constructive functions, calculation, attention or visuospatial functions. Cognitive functions and intellectual abilities may decline from initially focal cognitive impairment to lastly dementia. In addition, the investigation proposed to detect mitochondrial dementia is based on imaging studies, including MRI, PET, SPECT or MR-spectroscopy, cerebrospinal fluid (CSF) investigations or electroencephalography.

The mitochondrial disorders are a genetically heterogeneous group and variable phenotype, therefore we select the most frequent mitochondrial diseases with cognitive impairment to approach:

MELAS - mitochondrial encephalopathy, lactic acidosis and stroke-like syndrome is typified by characteristic neurological manifestations including seizures, encephalopathy, and stroke-like episodes, and other secondary manifestations just like short stature, cognitive impairment, migraines, depression, cardiomyopathy, cardiac conduction defects and diabetes mellitus. The patients suffer from cognitive dysfunction of nuclear pathogenesis. Emmanuele et al. present a study exploring a possible link between cognitive dysfunction and hippocampal expression of calbindin D 28KD (CB), a high-affinity calcium-binding protein, in four MELAS patients, using post mortem hippocampal tissues. Reduction in CB expression is associated with aging and with neurodegenerative disorders. They found a reduction in CB expression in these patients and postulated that the reduced CB expression may play a role in the cognitive abnormalities in MELAS.

MERRF – Myoclonus Epilepsy associated with Ragged-Red Fibers had as diagnostic criteria typical manifestations of the disease such as myoclonus, generalized epilepsy, cerebellar ataxia and ragged-red fibres on muscle biopsy. Other multisystemic alterations can be found as: deafness, exercise intolerance, peripheral neuropathy, abnormal cardiac conduction, dementia, among others. Kaufmann et al. studied 91 individuals from 34 families with MELAS and the A3242G point mutation and 15 individuals from two families with MEERF and the A8344G mutation. The patients were divided into groups (asymptomatic, oligosymptomatic and symptomatic), and submitted to neurologic examination, neuropsychological testing and spectral resonances. The study showed that the MELAS probands had higher ventricular lactate estimates on spectral resonances than the MEERF probands, and the MELAS probands had lower scores on formal neuropsychological testing than MEERF probands. In this way the authors correlated high levels of ventricular lactate, the brain spectroscopic signature of MELAS are associated with more severe neurologic impairment. The study also evidenced that the 15 patients with MEERF had score for degree of impairment on neurologic examination lower than MELAS patients and that worsening of neuropsychological functions was independent of the severity of clinical manifestations.

Kearns-Sayre syndrome (KSS) presents that classic triad: pigmentary retinopathy, chronic progressive external ophthalmoplegia and heart block, beyond features like cerebellar ataxia. Chronic Progressive External Ophthalmoplegia (CPEO) is a mitochondrial myopathy with slowly progressive, often symmetric blepharoptosis and limitation of ocular motility in all directions of gaze. Bosbach et al. performed a study with 22 patients with CPEO or KSS included screening for mitochondrial DNA (mtDNA) point mutations (3243/8344) and mtDNA deletions. All patients underwent a neuropsychological test battery. The neuropsychological testing did not reveal signs that would suggest general intellectual decline or dementia, but provided evidence of specific focal neuropsychological deficits, suggesting particular impairment of visuospatial perception associated to parieto-occipital lobes and executive deficits associated to the prefrontal cortex.

Autosomal CPEO presents with similar manifestations as mitochondrial CPEO but is due to mutations in the twinkle, POLG1 or ANT1 genes. Simoncini et al. reported a case of a woman with ANT1 related adPEO and dementia. The patient started to report disorders of short-term memory, and the neuropsychological evaluation showed a mild impairment of verbal memory and the attentive functions, magnetic resonance of brain revealed widespread moderate cortical atrophy, and magnetic resonance spectroscopy of brain disclosed mild elevation of lactate in the posterior interhemispheric region and in ventricular region. However, studies are needed to assess the prevalence of central neurological manifestations in ANT1 mitochondrial disease.

Leigh syndrome also referred to as subacute necrotizing encephalomyelopathy is a
### Table 3: Summary of studies investigating the impact of cognitive deficit in Motor Neuron Diseases.

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<tr>
<th>Author</th>
<th>Study Design</th>
<th>Participants</th>
<th>Evaluation Tools</th>
<th>Results</th>
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<td>Phukan et al., 2012</td>
<td>Case-control study: Group 1, 160 ALS patients and 110 controls.</td>
<td></td>
<td>Interviews: Collect the demographic and clinical data. Performed: Full Scale Q, Wechsler Test of Adult Reading, and Pyramid and Palm Trees Test. Mobile transcutaneous sensor for arterial blood gas tensions.</td>
<td>13.8% of patients fulfilled the Rebr family criteria for frontotemporal dementia. In addition, 34.1% of patients showed evidence of cognitive impairment without executive dysfunction, and no cognitive abnormalities were detected in almost half the cohort (46.9%). Blood gases were documented, and none of the patients had evidence of hypoxemia.</td>
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<tr>
<td>Elamin et al., 2013</td>
<td>Case-control study: Group 2, 138 ALS patients and 110 controls.</td>
<td></td>
<td>Executive Impairment was associated with higher rate of disability or death and higher rates of motor functional decline, particularly in patients who were cognitively impaired at baseline. Cognitive impairment was associated with remaining cognitive and motor impairment.</td>
<td>Executive impairment was associated with higher rate of disability or death and faster rates of motor functional decline, particularly in patients who were cognitively impaired at baseline. Cognitive impairment was associated with remaining cognitive and motor impairment.</td>
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<td>Trojsi et al., 2015</td>
<td>Case-control study: Group 3, 30 right-handed ALS patients.</td>
<td></td>
<td>Magnetic resonance imaging. ALS functional rating scale.</td>
<td>No difference between patients and control group for demographic variables. Disease duration did not differ between the ALS and bvFTD groups. Both cohorts of patients showed a mild stage of disease: mean score of ALSFRS-R was 22.</td>
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<td>Hu et al., 2013</td>
<td>Case-control study: Group 4, 37 ALS patients and 43 controls.</td>
<td></td>
<td>ALS Functional Rating Scale, Reverse Digit Span subtest, Oral Trail Making Test.</td>
<td>The ALS-FTD was highly sensitive (90%) and specific (85%) for ALS-Dementia. (P &lt;0.05). ALS-D patients had shorter overall survival, primarily due to the poor survival among ALS-DFT patients with AL S-DFT.</td>
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<td>Woolley et al., 2010</td>
<td>Case-control study: Group 5, 112 ALS patients.</td>
<td></td>
<td>ALS Cognitive Behavioral Screen.</td>
<td>The results demonstrated that mean cognitive scores differed between ALS and normal controls with 100% accuracy. Normal controls could be distinguished from those with ALS significantly better in the AL S cohort compared to controls (P &lt;0.0001), and redefined ALS-FTD with 90% specificity and 80% specificity.</td>
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<td>Raaphorst et al., 2016</td>
<td>Case-control study: Group 6, 435 samples. 20 (41%) cases of familial ALS and 19 (5%) cases of apparently sporadic ALS had the C9orf72 repeat expansion.</td>
<td></td>
<td>The Frontal Systems Behavior Scale (FrSBe).</td>
<td>The results demonstrated that mean cognitive scores differed between ALS and normal controls with 100% accuracy. Normal controls could be distinguished from those with ALS significantly better in the ALS cohort compared to controls (P &lt;0.0001), and redefined ALS-FTD with 90% specificity and 80% specificity.</td>
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<td>Abrahams et al., 2014</td>
<td>Case-control study: Group 7, 33 males, 15 females.</td>
<td></td>
<td>Edinburgh Cognitive and Behavioural ALS Screen (ECAS).</td>
<td>The most prevalent deficit occurred in language functions (35%) followed by executive functions and fluency (23% each).</td>
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<td>Burrell et al., 2016</td>
<td>Case-control study: Group 8, 30 family members.</td>
<td></td>
<td>Detailed longitudinal clinical, neurocognitive, and behavioral data, MRI and survival data have been gathered on this cohort, and DNA has been paired for linkage analysis.</td>
<td>Detailed longitudinal clinical, neurocognitive, and behavioral data, MRI and survival data have been gathered on this cohort, and DNA has been paired for linkage analysis.</td>
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</table>
Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive disorder in which the patients suffer from gastrointestinal dysmotility, cachexia, ptosis, external ophthalmoplegia, myopathy, and polyneuropathy. MNGIE also includes leukoencephalopathy. Carod-Artal et al. reported a case of a Brazilian man with MNGIE who had poor weight gain, muscular atrophy, and chronic diarrhea since childhood. He presents episodic gastric pain, recurrent nausea and vomiting, muscle aching and cramps, and had signs of memory impairment. On neuropsychological examination, patient scored 28/30 on MMSE. Working memory scores were 14/25 and 7/25 on immediate recall, and 6/25 and 1/25 on long-term recall. The patient could repeat seven digits in direct order and only four digits in reverse sequence. Verbal learning was involved (7/15 words).

The treatment of mitochondrial dementia includes general measures and specific therapy, which encompass: physiotherapy and physical exercise below the maximal individual limit; dietary measures; avoidance of mental and physical stress, alcohol, nicotine and infections; supplementation of respiratory chain components such as coenzyme Q. Various studies have reported a positive effect of coenzyme Q in mitochondrial dementia; administration of artificial electron acceptors, such as vitamin C or K; administration of metabolites or cofactors like carnitine. Overall, cognitive decline in mitochondrial dementia needs to be included in the differentials of dementia.

**Conclusions**

The literature about cognition in neuromuscular diseases is still scarce, but studies converge on the influence of these disorders on mental processes (see Tables 1-3 for a summary on previous studies). Congenital disorders are common to neuromuscular function and brain function impaired. Considering that severe neuromuscular conditions such as DMD and ALS have shown a marked improvement in prognosis in the last decades, the search for the improvement of patients’ quality of life has become increasingly important, which can be compromised by the primary and secondary cognitive effects of the evolution of the disease. More work should be done to better evaluate cognitive deficits in patients with neuromuscular disorders, in order to improve the patient’s relationship with the medical staff, the family, and society and improve the patient’s quality of life. In addition, knowing the evolution of the cognitive symptoms of each disease is important for proper management of the patient, evaluation of survival, establishment of prognosis and choice of appropriate therapeutic intervention.

**References**

27. Kessler H, Prudlo J, Kraft S, Supprian T.
22. Raaphorst J, Beeldman E, Schmand B,
14. Congenital Muscular Dystrophies and
11. Dementia of frontal lobe type in
10. of a large family. Clin Neurophysiol
7. Macular findings in Spectral Domain
6. Optical Coherence Tomography and
5. OCT Angiography in a patient with
3. Optical Coherence Tomography and
2. when should MERRF (myoclonus
1. Mitochondrial Myopathy Associated with
0. with neurological impairment in
-20.05.
16. Consensus criteria for the diagnosis of
15. Amyotrophic lateral sclerosis. Amyotroph
13. Cognitive and clinical characteristics of
12. amyotrophic lateral scele-
11. a population-based cohort study. Lancet
10. 119x46]
9. Elamin M, Bede P, et al. Cognitive and clinical characteristics of patients with amyotrophic lateral scele-
8. Cognitive and clinical characteristics of patients with amyotrophic lateral scele-
2. Non-commercial use only