THE IMPACT OF MYOTONIC DYSTROPHY ON THE BRAIN AND SLEEP

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Review

Abstract

Myotonic dystrophy type 1 is a multisystemic neurological disorder with a CTG trinucleotide repeat expansion in the 3'UTR of the *DMPK* gene. One of the manifestations with a severe impact on daily life is the dysfunction of the central nervous system (CNS), such as excessive daytime sleepiness (EDS), which can lead to cognitive problems. In this review, we try to gain more profound knowledge on the cause of the cognitive impairment in individuals with myotonic dystrophy type 1 and its relationship with EDS. Previous research has shown that individuals with this disorder have atrophy in both white and grey matter, contributing to a decrease in the volume of the brain. These changes in brain structure seem to influence EDS. As it has been shown that sequestering of muscleblind-like proteins affects splicing, it is thought that changes in downstream proteins might be the cause of the CNS defects. Brain structures that are mainly affected in EDS are the brainstem regions involved in the sleep-wake cycle. Next to this, a correlation has been found between atrophy of the corpus callosum and EDS. These disturbances could lead to alteration of the sleep-wake system and rapid eye movement sleep dysregulation. Thus, evidence suggests that the proposed mechanism causing EDS is related to primary disturbances in CNS.

KEYWORDS: Myotonic dystrophy, excessive daytime sleepiness, CNS

Myotonic dystrophy type 1 (DM1) is a dominant, autosomal inherited disease caused by a progressive cytosine-thymine-guanine (CTG) trinucleotide repeat expansion in the 3' untranslated region (UTR) of the *DMPK* gene, located on chromosome 19q13.3 [1]. The *DMPK* gene codes for myotonic dystrophy protein kinase (DMPK), which is expressed in muscle, heart, and brain cells, among other tissue types [1]. DM1 is, therefore, classified as a multisystemic neurological disease. It is the most common muscular disorder, with an estimated prevalence of 1:8,000 [1]. The clinical manifestations are widely variable and include dysfunctions in the central nervous system (CNS), such as hypersomnia, apathy, visuospatial abnormalities, working memory deficits, and excessive daytime sleepiness (EDS) [1-3]. Next to these, symptoms include muscle atrophy and myotonia, cataracts, gastrointestinal manifestations, cardiac abnormalities, and endocrine system-related manifestations, such as diabetes, thyroid dysfunction, and hypogonadism (Figure 1).

Due to the enormous negative impact on the lives of individuals with DM1, dysfunction of the CNS has become of considerable interest within the field of medical research. Recent studies provided initial experimental evidence that several brain areas are affected and suggested damaged proteins causing neuronal defects [4, 5]. Several cognitive dysfunctions have been associated with DM1, including defects in the memory of the patients. However, a condition that also severely affects the lifestyle of individuals with DM1 is EDS [6]. This dysfunction is present in up to 80% of the patients, and effective treatment is not yet available [7]. Sleep-related disordered breathing in individuals with DM1 has previously been thought to be associated with EDS. However, it has been shown that even if the sleep-related disordered breathing is treated well, the EDS persists and must, thus, have a different underlying mechanism. Therefore, researchers started an investigation at a structural and molecular level in the brain as the underlying cause(s) for the EDS could possibly be located there [7].

Patients with EDS have a high desire to sleep, which is only slightly improved through sleeping [6]. Their sleepiness, however, increases with rest, and patients tend to take daytime naps easily. Yet, these naps seem to be unrefreshing without associated dream content [6]. Additionally, the quality of life is decreased through the with EDS-occurring low energy, further contributing to a decrease in memory, concentration, and motivation [6]. Patients have difficulty staying awake after meals and might fall asleep at work [7]. EDS has a high impact on the quality of life of individuals with DM1; thus, a deeper insight into the mechanism is to improve the life of patients.

Therefore, in this article, we will review existing literature to gain in-depth knowledge on the causes of cognitive impairment in DM1

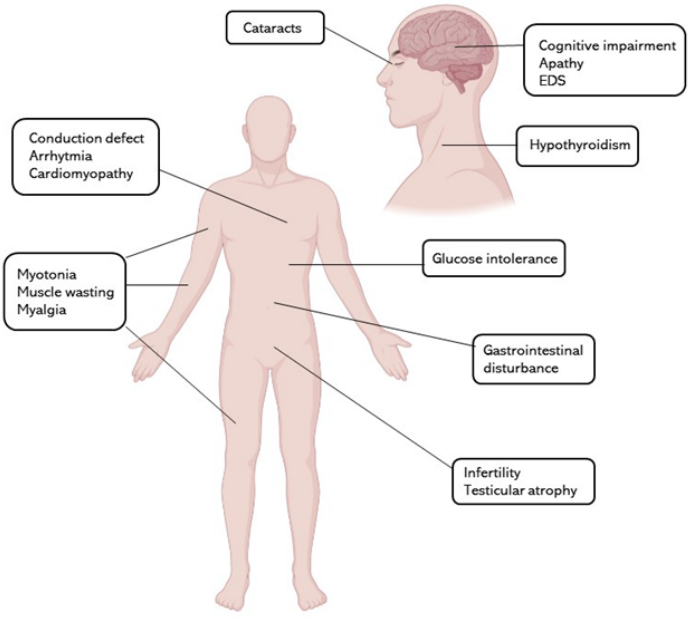

Figure 1: *Symptoms related to myotonic dystrophy type 1 (Takeda, S. et al., 2016). EDS = excessive daytime sleepiness*

and its relationship with excessive daytime sleepiness. This will hopefully lead to a better understanding of this area in the disease.

Pathophysiology

As previously mentioned, the CTG repeat is expanded in DM1 patients [1]. Healthy individuals have between 5-37 CTG triplets in the *DMPK* gene, whereas DM1-affected individuals carry repeat expansions with a length of 50 to over 1,000s of CTG triplets [8]. The length of this expansion correlates with the severity of the disease and the earlier onset of symptoms in life. However, this correlation is not proven for the severity of EDS [9]. In individuals with a repeat number above 38, the repeat can undergo a somatic expansion, which is the largest in brain and muscle cells but also takes place in the germline cells, where it leads to genetic anticipation. In other cells in the body, like the blood cells, the CTG expansion accumulates at a lower rate, suggesting that the expansion rate is tissue-specific [10]. This expansion over a patient's lifetime leads to the increase of severity of most features of the disease [11]. The main mechanism thought to be responsible for the somatic expansion takes place during DNA repair [12]. The long repeat expansions can form hairpin structures that are recognised by DNA polymerase II during replication. A random hairpin formation can also lead to the recruitment of the mismatch repair proteins MSH2 and MSH3 [12]. These proteins cut the DNA strand at the loops. If the strands then slip, gaps are formed that are subsequently filled with more repeats, causing the increased number of CTG triplets [12].

Molecular mechanisms

In the brain, there are several ways in which the elongated repeat can affect the protein its function. The primary mechanism underlying the dysfunction of several proteins is thought to be caused by the in hairpin folded RNA repeat that cannot leave the nucleus [3]. These formed foci then bind other essential RNA-binding proteins needed for splicing and/or transcription [3]. These proteins can, therefore, not execute their function anymore, leading to defective proteins [3].

The RNA binding protein muscleblind-like (MBNL) 2 is sequestered by the repeat expansion, leading to a loss of function of this protein. The loss of MBNL2 leads to a change in alternative polyadenylation regulation [13]. It also affects the splicing of other proteins, which is thought to cause the CNS defects, including changes in rapid eye movement (REM) sleep [14]. Proteins that are affected by the missing splicing proteins include tau, NMDA receptor 1, and the amyloid precursor protein [15, 16]. Tau is responsible for the stabilisation of microtubules, and, if defected, it can form neurofibrillary tangles instead, which are aggregates of hyperphosphorylated tau [15]. Aggregates are found in the limbic system, brainstem, hippocampus, entorhinal cortex, and temporal cortical areas of DM1 patients [17]. NMDA receptor 1 is needed for long-term potentiation in the hippocampus [16].

Changes in the brain structure

Imaging studies have shown pathological abnormalities of the CNS in DM1 patients [18-37]. Among others, the calculated brain parenchymal fraction showed that there was global brain atrophy in DM1 patients (Figure 2) [20, 21, 38]. In adult DM1, brain atrophy progresses with age, whereas in juvenile DM1, atrophy is present in early childhood [39]. Additionally, some studies have shown a dilatation of the Virchow-robin spaces (extensions of the subarachnoid space) [20, 22, 23]. This dilatation is mainly shown in young DM1 patients [24]. On top of that, voxel-based morphometry and MRI studies found a decrease in the grey matter volume in all cortical lobes, the basal ganglia, and the cerebellum [5, 39, 40].

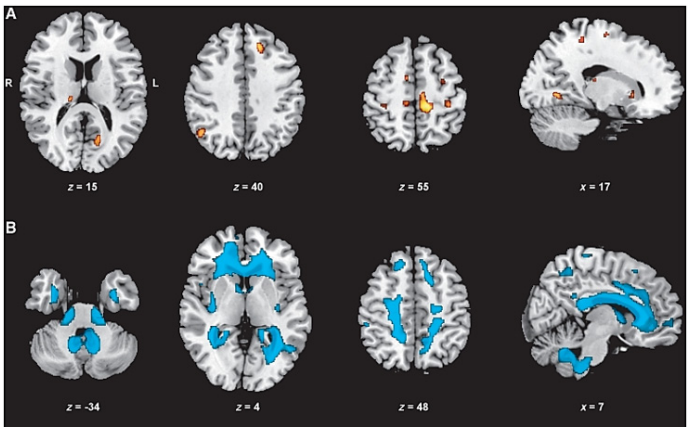

Figure 2: *The neuroimaging of the brain of DM1 patients with VBM. The top row displays areas of gray matter decrease in DM1 patients compared with controls. The bottom row displays areas of white matter decrease in DM1 patients compared with controls (Minnerop et al., 2011).*

However, damage to the white matter tract was much more dominant than the effect of DM1 on the grey matter tract [5]. In these MRI and voxel-based morphometry studies, white matter hyperintensities were mainly found at the level of the frontal and temporal lobe [5, 38-40]. Caso *et al*. found that white matter hyperintensities were associated with memory, executive, reasoning, and visuospatial impairments [22]. Several studies also suggest that the extent of the white matter intensities is related to cognitive deficits in DM1 patients [26, 28-30, 41, 42]. However, other studies do not confirm this relationship [33, 43, 44].

The damage of these white matter tracts affects the association fibres (axons that connect regions within one hemisphere), the commissural fibres (axons that connect the hemispheres), mainly the corpus callosum, and the projection fibres in the brainstem (in both in- and external capsules) [5, 33, 37]. Brain atrophy and white matter involvement will progress over time in DM1 patients [45]. Furthermore, the strength and the local efficiency of the white matter networks is lower in DM1 patients compared to unaffected controls, although the number of connections is not aberrant [36]. A proposed mechanism by Dorst *et al.* regarding CNS symptoms is that they are associated with these above described structural alterations in the white matter network [36]. With transcranial sonography, studies can measure the echogenicity of the brainstem raphe, mesencephalon, substantia nigra, and third ventricle [5]. A hypoechogenicity of the brainstem raphe was seen in DM1 patients. This hypoechogenicity was also significantly associated with excessive daytime sleepiness in DM patients [35]. Most studies show no correlation between the neuropathological changes and the length of the CTG repeat [5].

Effects of DM1 on EDS

Some studies have been performed to investigate the cause of EDS [20, 46-50]. However, its pathogenicity still remains unclear. As a consequence, research began to focus on the different processes that are involved in primary CNS disturbances in DM1 [5]. It is hypothesised that these disturbances could lead to alterations of the sleep-wake system and REM sleep dysregulation [5].

MRI studies were conducted to investigate these disturbances. Cabada *et al.* showed an association between EDS and a decrease of the volume in the right ventral diencephalon and right pallidum [20]. Additionally, damage to the brainstem regions that control sleep was found to be a possible cause of EDS [39]. A correlation between EDS and corpus callosum atrophy has also been seen [46].

However, how these changes in brain structure cause and influence EDS is still unclear. Besides changes in the brain structure, some other mechanisms have been proposed to be involved in the primary CNS disturbances related to DM1 [6, 7]. A disruption of the pulsatile secretion of cortisol and growth hormone and increased cytokine levels were found to be involved in EDS [49, 50].

On the more molecular level, a defect in the synthesis of the neuropeptide Orexin-A/Hypocretin-1 is known to be involved in narcolepsy, which symptoms also include EDS. Therefore, it was investigated if this might also be a cause for EDS in DM1 patients [47]. A significantly lower level of Hypocretin-1 in DM1 patients was found compared to idiopathic hypersomnia patients that are considered normal Hypocretin-1 levels in the cerebrospinal fluid ($p<0.001$) [47]. However, a more recent study could no longer show this significant difference ($p<0.001$), meaning that Hypocretin-1 might influence EDS in patients but that it is not the primary cause [48].

Solutions for EDS in DM1 patients have not yet been found. Besides the treatment for muscle-related causes of sleepiness, which include breathing difficulty, there are only a few medications that treat other possible causes for the EDS. Modafinil is used to treat excessive somnolence in DM1 patients [51, 52]. The exact mechanism of Modafinil is not clear yet but is thought to act through various neurotransmitters, especially in the hypothalamus [53]. Apart from Modafinil, there seem to be no major treatment methods for EDS.

Conclusion

Based on the available literature summarised in this article, we found that in DM1 a multitude of brain areas are affected and show atrophy [5, 20, 23, 24, 35, 38-40]. The cause of this atrophy is not clear, but on the molecular level, sequestering of MBNL by the elongated repeat could be one of its causes [13]. For EDS in individuals with DM1, the proposed mechanisms are related to primary disturbances in the CNS, especially in the brainstem [5]. It is suggested that these could lead to modification of the sleep-wake systems and REM sleep dysregulation [6, 7]. Further research needs to be done on the brain-related cause of EDS in DM1 patients to gain a more profound knowledge of the potential mechanism. This could enhance adequate patient management regarding DM1 and EDS, lead to better treatment possibilities, and improve the patients' quality of life.

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References

1. Meola, G. & Cardani, R. Myotonic dystrophies: An update on clinical aspects, genetic, pathology, and molecular pathomechanisms. *Biochimica et biophysica acta* **1852**, 594-606 (2015).
2. Pelargonio, G., *et al.* Myotonic dystrophy and the heart. *Heart (British Cardiac Society)* **88**, 665-670 (2002).
3. De León, M.B. & Cisneros, B. Myotonic dystrophy 1 in the nervous system: from the clinic to molecular mechanisms. *Journal of neuroscience research* **86**, 18-26 (2008).
4. Lee, K.-Y., *et al.* Deprivation of Muscleblind-Like Proteins Causes Deficits in Cortical Neuron Distribution and Morphological Changes in Dendritic Spines and Postsynaptic Densities. *Frontiers in Neuroanatomy* **13**(2019).
5. Minnerop, M., *et al.* Current Progress in CNS Imaging of Myotonic Dystrophy. *Front Neurol* **9**, 646-646 (2018).
6. Laberge, L., *et al.* Daytime sleepiness and myotonic dystrophy. *Current neurology and neuroscience reports* **13**, 340 (2013).
7. Dauvilliers, Y.A. & Laberge, L. Myotonic dystrophy type 1, daytime sleepiness and REM sleep dysregulation. *Sleep medicine reviews* **16**, 539-545 (2012).
8. Souidi, A., *et al.* Dissecting Pathogenetic Mechanisms and Therapeutic Strategies in Drosophila Models of Myotonic Dystrophy Type 1. *Int J Mol Sci* **19**, 4104 (2018).
9. Laberge, L., *et al.* Sleep complaints in patients with myotonic dystrophy. *Journal of sleep research* **13**, 95-100 (2004).
10. Thornton, C.A., *et al.* Myotonic dystrophy patients have larger CTG expansions in skeletal muscle than in leukocytes. *Ann Neurol* **35**, 104-107 (1994).
11. Yum, K., *et al.* Myotonic dystrophy: disease repeat range, penetrance, age of onset, and relationship between repeat size and phenotypes. *Curr Opin Genet Dev* **44**, 30-37 (2017).
12. Mcmurray, C.T. Mechanisms of trinucleotide repeat instability during human development. *Nature reviews. Genetics* **11**, 786-799 (2010).
13. Goodwin, M., *et al.* MBNL Sequestration by Toxic RNAs and RNA Misprocessing in the Myotonic Dystrophy Brain. *Cell Rep* **12**, 1159-1168 (2015).
14. Charizanis, K., *et al.* Muscleblind-like 2-mediated alternative splicing in the developing brain and dysregulation in myotonic dystrophy. *Neuron* **75**, 437-450 (2012).
15. Wang, Y., *et al.* Tau exons 2 and 10, which are misregulated in neurodegenerative diseases, are partly regulated by silencers which bind a SRp30c.SRp55 complex that either recruits or antagonizes htra2beta1. *The Journal of biological chemistry* **280**, 14230-14239 (2005).
16. Jiang, H., *et al.* Myotonic dystrophy type 1 is associated with nuclear foci of mutant RNA, sequestration of muscleblind proteins and deregulated alternative splicing in neurons. *Human molecular genetics* **13**, 3079-3088 (2004).
17. Itoh, K., *et al.* Neuropathology does not Correlate with Regional Differences in the Extent of Expansion of CTG Repeats in the Brain with Myotonic Dystrophy Type 1. *Acta Histochem Cytochem* **43**, 149-156 (2010).
18. Baldanzi, S., *et al.* Relationship between neuropsychological impairment and grey and white matter changes in adult-onset myotonic dystrophy type 1. *Neuroimage Clin* **12**, 190-197 (2016).
19. Minnerop, M., *et al.* Current Progress in CNS Imaging of Myotonic Dystrophy. *Front Neurol* **9**, 646 (2018).
20. Cabada, T., *et al.* Brain Involvement in Myotonic Dystrophy Type 1: A Morphometric and Diffusion Tensor Imaging Study with Neuropsychological Correlation. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists* **32**, 401-412 (2017).
21. Kassubek, J., *et al.* Quantification of brain atrophy in patients with myotonic dystrophy and proximal myotonic myopathy: a controlled 3-dimensional magnetic resonance imaging study. *Neurosci Lett* **348**, 73-76 (2003).
22. Caso, F., *et al.* Cognitive impairment in myotonic dystrophy type 1 is associated with white matter damage. *PLoS One* **9**, e104697 (2014).
23. Di Costanzo, A., *et al.* Dilated Virchow-Robin spaces in myotonic dystrophy: frequency, extent and significance. *Eur Neurol* **46**, 131-139 (2001).
24. Schneider-Gold, C., *et al.* Cortical and Subcortical Grey and White Matter Atrophy in Myotonic Dystrophies Type 1 and 2 Is Associated with Cognitive Impairment, Depression and Daytime Sleepiness. *PLoS One* **10**, e0130352 (2015).

25. Abe, K., *et al.* Involvement of the central nervous system in myotonic dystrophy. *J Neurol Sci* **127**, 179-185 (1994).
26. Bachmann, G., *et al.* The clinical and genetic correlates of MRI findings in myotonic dystrophy. *Neuroradiology* **38**, 629-635 (1996).
27. Huber, S.J., *et al.* Magnetic resonance imaging and clinical correlates of intellectual impairment in myotonic dystrophy. *Arch Neurol* **46**, 536-540 (1989).
28. Kuo, H.C., *et al.* Correlation among subcortical white matter lesions, intelligence and CTG repeat expansion in classic myotonic dystrophy type 1. *Acta neurologica Scandinavica* **117**, 101-107 (2008).
29. Romeo, V., *et al.* Brain involvement in myotonic dystrophies: neuroimaging and neuropsychological comparative study in DM1 and DM2. *Journal of neurology* **257**, 1246-1255 (2010).
30. Weber, Y.G., *et al.* Comparative analysis of brain structure, metabolism, and cognition in myotonic dystrophy 1 and 2. *Neurology* **74**, 1108-1117 (2010).
31. Ota, M., *et al.* Relationship between diffusion tensor imaging and brain morphology in patients with myotonic dystrophy. *Neurosci Lett* **407**, 234-239 (2006).
32. Di Costanzo, A., *et al.* Brain MRI features of congenital- and adult-form myotonic dystrophy type 1: case-control study. *Neuromuscul Disord* **12**, 476-483 (2002).
33. Fukuda, H., *et al.* Diffusion tensor imaging of cerebral white matter in patients with myotonic dystrophy. *Acta radiologica (Stockholm, Sweden : 1987)* **46**, 104-109 (2005).
34. Conforti, R., *et al.* Brain MRI abnormalities in the adult form of myotonic dystrophy type 1: A longitudinal case series study. *Neuroradiol J* **29**, 36-45 (2016).
35. Krogias, C., *et al.* Evaluation of CNS involvement in myotonic dystrophy type 1 and type 2 by transcranial sonography. *Journal of neurology* **262**, 365-374 (2015).
36. Van Dorst, M., *et al.* Structural white matter networks in myotonic dystrophy type 1. *Neuroimage Clin* **21**, 101615 (2019).
37. Minnerop, M., *et al.* The brain in myotonic dystrophy 1 and 2: evidence for a predominant white matter disease. *Brain* **134**, 3530-3546 (2011).
38. Baldanzi, S., *et al.* Relationship between neuropsychological impairment and grey and white matter changes in adult-onset myotonic dystrophy type 1. *NeuroImage: Clinical* **12**, 190-197 (2016).
39. Caso, F., *et al.* Cognitive impairment in myotonic dystrophy type 1 is associated with white matter damage. *PLoS One* **9**, e104697-e104697 (2014).
40. Okkersen, K., *et al.* Brain imaging in myotonic dystrophy type 1: A systematic review. *Neurology* **89**, 960-969 (2017).
41. Abe, K., *et al.* Involvement of the central nervous system in myotonic dystrophy. *Journal of the neurological sciences* **127**, 179-185 (1994).
42. Huber, S.J., *et al.* Magnetic Resonance Imaging and Clinical Correlates of Intellectual Impairment in Myotonic Dystrophy. *Archives of Neurology* **46**, 536-540 (1989).
43. Ota, M., *et al.* Relationship between diffusion tensor imaging and brain morphology in patients with myotonic dystrophy. *Neurosci Lett* **407**, 234-239 (2006).
44. Di Costanzo, A., *et al.* Brain MRI features of congenital- and adult-form myotonic dystrophy type 1: case-control study. *Neuromuscular disorders : NMD* **12**, 476-483 (2002).
45. Conforti, R., *et al.* Brain MRI abnormalities in the adult form of myotonic dystrophy type 1: A longitudinal case series study. *Neuroradiol J* **29**, 36-45 (2016).
46. Giubilei, F., *et al.* Excessive daytime sleepiness in myotonic dystrophy. *Journal of the neurological sciences* **164**, 60-63 (1999).
47. Martínez-Rodríguez, J.E., *et al.* Decreased hypocretin-1 (Orexin-A) levels in the cerebrospinal fluid of patients with myotonic dystrophy and excessive daytime sleepiness. *Sleep* **26**, 287-290 (2003).
48. Omori, Y., *et al.* Orexin/hypocretin levels in the cerebrospinal fluid and characteristics of patients with myotonic dystrophy type 1 with excessive daytime sleepiness. *Neuropsychiatric disease and treatment* **14**, 451-457 (2018).
49. Johansson, A., *et al.* Abnormal cytokine and adrenocortical hormone regulation in myotonic dystrophy. *J Clin Endocrinol Metab* **85**, 3169-3176 (2000).
50. Culebras, A., *et al.* Absence of sleep-related growth hormone elevations in myotonic dystrophy. *Neurology* **27**, 165-167 (1977).
51. Macdonald, J.R., *et al.* Modafinil reduces excessive somnolence and enhances mood in patients with myotonic dystrophy. *Neurology* **59**, 1876-1880 (2002).
52. Talbot, K., *et al.* Reduction in excess daytime sleepiness by modafinil in patients with myotonic dystrophy. *Neuromuscular disorders : NMD* **13**, 357-364 (2003).
53. Easow Mathew, M., *et al.* Modafinil for excessive daytime sleepiness. *Cochrane Database Syst Rev* **2017**, CD010843 (2017).