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Master thesis

Identifying neuropsychological dysfunctions of Myotonic Dystrophy Type 2 in everyday clinical practice

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Prologue

This thesis is an outcome of hard, long-term work that was established with the contribution of high profile academicians and researchers. From the very beginning of deciding the subject -and later the title- with my supervisor, until the moment of writing these lines after the completion of our research and analyses, it was a thoroughly fascinating and edifying experience. It also marks the end of my postgraduate studies, in regards to M. Sc. level, a fact that makes it even more significant scientifically and also, emotionally.

I would like to specially mention a few contributors. Firstly, my supervisor Dr. Zalonis, who accepted me as his postgraduate student in order to carry through with this project. His knowledge, advice, instructions including his positive thinking and clemency aided and motivated me to the full. Secondly, my collaborator Dr. Christidi, whose contribution was of paramount importance from the very beginning. She was utterly supportive, giving me the chance to learn from her knowledge and experiences about the research conduction, the clinical neuropsychological assessment, the statistical analyses, even the proper way to write a scientific article. Thirdly, Dr. Potagas who was also on my side in crucial, personal, situations offering heartfeltly his aid and support. Fourthly, the scientific team behind this project, especially Dr. Papadimas, who contributed in many ways in order to conduct this research. Finally, my Professors who taught me about the multidimensional field of Clinical Neuropsychology and Cognitive Neuroscience. Words are powerless to express my gratitude to all above.

I wish this conclusion would become a very significant step for my academic, research and clinical future as a Clinical Neuropsychologist.

Table of Contents

Abstract

Introduction: Myotonic Dystrophies (MD) are autosomal predominantly transferred multidimensional disorders that affect, besides all other, the brain. In contrast to MD Type 1 (MD1) in which cognitive impairments are often reported, the neuropsychological profile of MD Type 2 (MD2) is still insufficiently studied. The use of a single and short neuropsychological scale, capable of covering distinct cognitive domains, is considered to be of paramount importance in regards to disorders, like MD, that are followed by motor disabilities and/or intense physical fatigue. The aim of our study is the identification of neuropsychological dysfunction in Greek MD2 patients via a single yet multidomain cognitive screening scale that can be also administered in patients with mild or more severe upper limbs disabilities, such as the ones that might be observed in the course of MD2.

Materials and Methods: The group of participants consisted of 11 patients, who were genetically diagnosed with MD2, and 26 healthy controls (HC) with similar demographic characteristics. All participants were administered the Edinburgh Cognitive and Behavioral ALS Screening (ECAS) scale, which includes subtests of executive functions, verbal fluency, episodic memory, language and visuospatial functions. We used ECAS total score as a measure of general cognitive status, as well as subscores for each cognitive domain. We assessed ECAS internal consistency (Cronbach's a) and furthered examined the differences between patients and HC.

Results: We found a satisfactory measure of internal consistency (Cronbach's a = 0.71) regarding ECAS. Based on normal values for ECAS, 73% of MD2 patients showed general cognitive impairment, which was also confirmed by the significantly reduced performance in the total score of ECAS ($p < 0.001$). Moreover, significant differences were highlighted in executive functions ($p < 0.001$), verbal fluency ($p = 0.015$) and memory ($p = 0.015$).

Conclusions: The ECAS scale seems to be a reliable, multifaceted tool in examining MD2-related cognitive impairment in everyday clinical practice and enables the identification of dysfunction in distinct cognitive domains in Greek MD2 patients (i.e. executive functions, verbal fluency and memory).

Keywords: Myotonic Dystrophy, Cognitive Impairment, Everyday Clinical Practice

Introduction

Myotonic Dystrophy (MD) is considered to be the most common form of muscular dystrophy in adults (Harley et al., 1992). It is a multisystem autosomal dominant disorder, considered to be long-term and it profoundly has a genetical basis. MD affects the muscle and other types of the human tissue, including the nervous tissue. Common symptoms include muscle weakness, myotonia, early cataracts emergence, cardiac arrhythmia and cognitive changes (Udd & Krahe, 2012).

There are two types of MD, i.e. MD type 1 (MD1) and MD type 2 (MD2), which are related to different clinical features and pathophysiology (Meola, Biasini, Valaperta, Costa & Cardani, 2017). MD1 is caused by expansion of a CTG triplet repeat in the 3' untranslated region of MD protein kinase gene (DMPK) on chromosome 19q13.3, while MD2 is caused by expansion of a CCTG tetranucleotide repeat in the first intron of the nucleic acidbinding protein (CNBP) gene on chromosome 3q21. MD2 is more rare compared to MD1 and refers to approximately 1:8000 births. Its complexity is due to the unpredicted onset of the symptoms which also vary among patients. Another factor of great importance is that the clinicians experience difficulties in successfully -and on time- diagnose MD2 because of unfamiliarity or inexperience with that specific disorder (Meola et al., 2017).

Although MD1 has been deeply examined with regards to CNS dysfunction and patients' cognitive profile, this is not the case for MD2 (Peric et al., 2016). With regards to MD1, cognitive deficits seem to be slightly different based on symptoms onset; specifically, when MD1 diagnosis is made on birth, the patients appear to experience mental retardation, while on childhood they appear to show learning disabilities, attention deficit/hyperactivity disorder, autistic behavior, lack of interest-inhibition, and visuospatial impairment. If the onset is in early adulthood, then they possibly show dysexecutive syndrome, visuospatial deficits, verbal and visual memory difficulties, whereas when the onset is at a later stage (late adulthood), then the difficulties refer mainly to memory function (Bajrami et al., 2016; Baldanzi et al., 2016; Cabada et al., 2017; Gaul et al., 2006; Meola et al., 2003; Modoni et al., 2008; Peric et al., 2016; Zalonis et al., 2010).

On the other hand, in MD2 the scientific and clinical knowledge seems to be unclear so far, with minimal and vague information. Few available studies indicate dysexecutive syndrome, episodic memory difficulties and visuospatial difficulties (Meola et al., 2003; Meola & Sansone, 1996; Peric et al., 2016). A more recent study

combining neuropsychological measures and neuroimaging techniques (Peric et al., 2017) compared patients with MD1 and MD2 and found that the greatest difficulties of the MD2 patients referred to information processing speed, the ability to alternate between two sets of cognitive stimuli, naming and verbal episodic memory. In addition, these MD2-related neuropsychological findings were in accordance with the neuroimaging findings regarding hypometabolism of prefrontal and frontotemporal regions, insula, basal ganglia and thalamus.

Considering the above-mentioned points and the lack of evidence for cognitive functions in Greek patients with MD2, the aim of the present study is to characterize MD2-related neuropsychological dysfunctions in everyday clinical practice via the use of a short though multidimensional cognitive assessment; an assessment that is capable of evaluating and providing clinicians with both a total cognitive score as well as subscores for distinct cognitive domains.

Materials and Methods

Participants

Over a 10-month period, we recruited and included genetically confirmed MD2 adult patients, who have visited the specialized outpatient clinic for muscular disorders of the A' Department of Neurology of Aeginition Hospital. All patients were given a clinical examination and diagnosis confirmation by experienced neurologists and clinical data regarding disease duration and muscle strength (MRC score) were recorded for all patients. A group of healthy volunteers with similar demographic characteristics was also included as a healthy control (HC) group. Inclusion criteria were: age < 76 years old; Greek as native language; education > 3 years. Exclusion criteria were: neurological diseases (other than MD for patients); major psychiatric disorders (e.g. major depression; schizophrenia); organic disorders; alcohol and/or substance abuse; developmental/cognitive disabilities; somatosensory deficits.

Psychometric Measures

The neuropsychological assessment was conducted using the Edinburgh Cognitive and Behavioral Amyotrophic Lateral Sclerosis Screen (ECAS) scale (Abrahams, Newton, Niven, Foley & Bak, 2014; Kourtesis, 2018) that enables a brief

yet multidimensional assessment of the following cognitive domains: language (naming, spelling); verbal fluency (under two phonemic efficiency conditions); executive functions (working memory, social cognition, inhibition); memory (immediate recall, delayed recall, retention); visuospatial functions (simple and composite visuospatial organization and planning).

ECAS has been originally created for use on patients with amyotrophic lateral sclerosis (ALS), assessing those functions that are typically affected in ALS and frontotemporal dementia (executive and language domains, verbal fluency, behavior) in addition to cognitive functions that are more typically affected in other dementias (including memory and visuospatial functions). Likewise, ECAS was also used in order to detect cognitive impairments in Parkinsonian syndromes (Foley et al., 2018). The brief behavioral evaluation of patients' behavioral changes is conducted based on questions addressed to patients' caregivers/informants. ECAS scale can be administered in an oral or writing way, thus enabling patients' examination in clinical practice irrespectively of the presence of any motor difficulties affecting upper extremities or oral expression (Abrahams et al., 2014). The ECAS scale, besides the fact that it permits us to assess specific cognitive fields with their specific subfields leading to subscores on each one of them, it has also the advantage of deriving a general score based on all the above-mentioned subscores which acts as a general indicator of patient's cognitive status. Therefore, the clinician collects information for each cognitive domain separately and, also, a general score that could be used as a point of reference for the patients who are assessed at baseline, should they get re-assessed later on their therapy.

Given that ECAS was created for another clinical population, we have also used other standardized neuropsychological tests in order to check ECAS constructive validity for use in MD2 patients. In particular, attention/inhibitory control (i.e. executive-related process) was evaluated using the Stroop Neuropsychological Screening Test (SNST; Trenerry, Crosson, DeBoe & Leber, 1989; Zalonis et al., 2008); visuospatial organization and visual memory was evaluated using the Rey-Osterrieth Complex Figure Test (RCFT; Meyers & Meyers, 1955); semantic memory was evaluated using the Information subtest of the Wechsler Adult Intelligence Scale (WAIS) (Weschler, 1939; Kokkevi, Repapi, Adamou & Stefanis, 1979). In addition, these specific neuropsychological tests were chosen based on current literature in MD

and correlation analysis was assumed to demonstrate the existence or absence of any correlations with the ECAS respective cognitive domains.

Participants mood state was evaluated using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983; Michopoulos et al., 2007) whereas patients' daily sleepiness, which is considered to be one of the usual symptoms especially in MD1 (Zalonis et al., 2010), was examined using the Epworth Speepiness Scale (Johns, 1991; Tsara, Serasli, Amfilochiou, Constantinidis & Christaki, 2004).

Statistical Analysis

Continuous variables are presented as mean (standard deviation; SD), whereas categorical variables are presented as absolute frequencies. Assumptions for normality (skewness; kurtosis; Q-Q plots; Kolmogorov-Smirnov test) were initially examined and then parametric or non-parametric analyses were used. Comparison between MD2 patients and HC on demographic characteristics was made using t-test (age, education) and chi-square (gender) test. Psychometric properties of the ECAS scale in MD2 patients were examined considering internal consistency (i.e. Cronbach's a) and constructive validity. For the latter, Pearson's r was employed to examine correlations between the cognitive domains of ECAS (language, verbal fluency, executive functions, memory, visuospatial functions) and other neuropsychological tests (SNST, RCFT copy, RCFT recall, WAIS Information,) in order to examine the fulfillment of the psychometric properties. Comparisons between MD2 patients and healthy controls on the ECAS total scores, as well as in the five core ECAS domains (i.e. language; verbal fluency; executive functions; memory; visuospatial functions) were performed using two-tailed independent samples t-test or Mann-Whitney U test. In addition to group-based analysis, we used the available normative values for ECAS scale (Kourtesis et al., under review), considered a cut-off score of 2 standard deviations and estimated the percentage of the patients who were categorized with preserved or impaired performance on total score and separate cognitive domains. Finally, correlation analysis (Pearson's r) was used to demonstrate possible correlations between ECAS total score (i.e. general indicator of cognitive functions) and patients' clinical characteristics (i.e. symptoms duration in years); muscle strength based on the Medical Research Council (MRC) score; depression and anxiety symptoms based on HADS and sleepiness based on the ESS. The statistical significance was set at $p <$

0.05 without further correction for multiple comparisons due to the small sample size of our study. For the same reason, effect size was calculated for between-group differences with the following convention (Cohen, 1988): large effect size: 0.20; medium effect size: 0.50; small effect size: 0.80. All analyses were conducted using JASP computer software, 0.8.6 version (JASP Team, 2018).

Results

Demographics and Clinical Data

Our group consisted of 11 MD2 patients (5 males / 6 females) and 26 HC (11 males / 15 females). Demographic characteristics of both groups as well as patients' clinical characteristics are presented in Table 1. The groups did not differ with regards to age, gender distribution and education ($p > 0.05$, ns).

Table 1. Demographic characteristics of MD2 patients and HC and clinical characteristics of MD2 patients

	MD2 Patients	HC
Age (yrs)	61.7 ± 11.0	58.7 ± 9.1
Gender (M / F)	5 / 6	11 / 15
Education (yrs)	9.4 ± 3.9	11.4 ± 3.1
Disease duration (yrs)	14.7 ± 9.1	-
MRC	38.4 ± 2.9	-

Note. MD 2 = myotonic dystrophy type 2; HC = healthy controls; yrs = years; M / F = male / female; MRC = Medical Research Counseling scale. Our groups did not differ in age, gender distribution and education ($p > 0.05$, ns).

Psychometric Properties of ECAS

In order to implement our research plan using the ECAS scale, we examined its psychometric properties. This search on MD2 patients pointed out a satisfactory level of internal consistency, Cronbach's a = 0.711.

Table 2 shows the correlation between ECAS subdomains and standardized neuropsychological tests (SNST; RCFT copy; RCFT recall; WAIS Information). The ECAS language domain was associated with SNST ($r = 0.87$; $p = 0.001$), RCFT recall ($r = 0.75$; $p = 0.008$) and WAIS Information ($r = 0.70$; $p = 0.017$). The ECAS verbal

fluency domain was correlated with SNST (r = 0.70; p = 0.023), while the ECAS executive functions domain was correlated with SNST (r = 0.64; p = 0.045). The ECAS memory domain was associated with RCFT recall (r = 0.76; p = 0.007) and WAIS Information (r = 0.75; p = 0.005). Lastly, the ECAS visuospatial functions domain demonstrated no correlation with any of the neuropsychological tests.

Table 2. Correlation analysis between ECAS subdomains and other standardized neuropsychological measures

ECAS subdomains	**Neuropsychological Tests**			
	SNST	**RCFT copy**	**RCFT recall**	**WAIS Information**
Language	r = 0.87; p = 0.001	-	r = 0.75; p = 0.008	r = 0.70; p = 0.017
Verbal Fluency	r = 0.70; p = 0.023	-	-	-
Executive Functions	r = 0.64; p = 0.045	-	-	-
Memory	-	-	r = 0.76; p = 0.007	r = 0.75; p = 0.005
Visuospatial Functions	-	-	-	-

Note. ECAS = Edinburgh Cognitive and Behavioral Amyotrophic Lateral Sclerosis Scale; SNST = Stroop Neuropsychological Screening Test; RCFT = Rey-Osterrieth Complex Figure Test; WAIS = Wechsler Adult Intelligence Scale.

Cognitive performance in ECAS: between-group differences

Based on the available normative data (Kourtesis, 2018), we have estimated the total number (in percentage) of the patients who scored lower than 2 SDs. In particular, 73% of the patients fell with the impaired range of performance in ECAS total score, 55% in executive functions, 45% in verbal fluency, 27% in memory, 18% in visuospatial functions and 9% in language.

The between-groups comparison demonstrated significant differences in ECAS total score and subdomains (Table 3). The greatest difference was found on the ECAS total score ($p < 0.001$; $|d| = 1.49$). With regards to subdomains, we found significant differences in verbal fluency ($p = 0.015$; $|d| = 0.92$), executive functions ($p < 0.001$; $|d| = 1.32$) and memory ($p = 0.015$; $|d| = 0.92$), while there were no

significant differences in language ($p = 0.145$; $|d| = 0.54$) and visuospatial functions ($p = 0.106$; $|d| = 0.60$).

Table 3. Cognitive performance in ECAS scale and between-group differences

ECAS scores	MD2 Patients	HC	p-value	Effect size |d|
Total score	88.45 ± 17.22	106.73 ± 9.64	$p < 0.001$	$\|d\| = 1.49$
Language	23.36 ± 2.50	24.65 ± 2.37	$p = 0.145$	$\|d\| = 0.54$
Verbal fluency	13.82 ± 5.55	17.77 ± 3.68	$p = 0.015$	$\|d\| = 0.92$
Executive functions	27.82 ± 7.77	36.12 ± 5.62	$p < 0.001$	$\|d\| = 1.32$
Memory	12.64 ± 6.50	16.77 ± 3.36	$p = 0.015$	$\|d\| = 0.92$
Visuospatial functions	10.82 ± 1.40	11.42 ± 0.81	$p = 0.106$	$\|d\| = 0.60$

Note. ECAS = Edinburgh Cognitive and Behavioral Amyotrophic Lateral Sclerosis Scale; MD 2 = myotonic dystrophy type 2; HC = healthy controls. Cohen's |d| values are interpreted as: $|d| = 0.20$ small effect size; $|d| = 0.50$ medium effect size; $|d| = 0.80$ large effect size.

Following the aforementioned statistically significant differences between patients and HC on specific subdomain, we also examined between-group differences in specific tests of fluency, executive functions and memory. MD2 patients scored significantly worse than HC alteration ($p = 0.03$; $|d| = 0.39$) and social cognition ($p = 0.002$; $|d| = 1.20$) of the executive functions domain, in immediate ($p = 0.007$; $|d| = 1.03$) and delayed story recall ($p = 0.033$; $|d| = 0.80$) of memory domain and, lastly, in one of the two phonemical verbal fluency tasks ($p = 0.004$; $|d| = 0.56$) of verbal fluency domain.

MD2 cognitive performance and clinical parameters: within-group correlation analysis

We did not find any significant correlation ($p > 0.05$, ns) between ECAS total score and the following variables: disease duration, MRC, HADS, ESS.

Discussion

Our study sought to evaluate the usefulness of a short yet multidomain cognitive screening scale (i.e. ECAS scale) in MD2 everyday clinical practice. In order to achieve our aim, we examined the psychometric properties of ECAS and used it afterwards for the between-groups comparisons between MD2 patients and HC, providing preliminary strong evidence over the usefulness of the ECAS scale in detecting cognitive impairment in MD2 patients in everyday clinical practice.

The ECAS scale fulfilled the psychometric properties in order to be used in the identification of neuropsychological dysfunctions of MD2 patients. Specifically, it was found a satisfactory internal consistency score, although ECAS hasn't been originally created for MD2 clinical population, thus it was expected to show a lower score. Overall, Cronbach's a should be > 0.70 in order to be reassured for the internal consistency of a scale (Houser, 2008). The other crucial psychometric property refers to constructive validity, which was examined via the comparison (existence or absence of correlation) of ECAS subscales with other standardized neuropsychological tests. Firstly, ECAS executive functions domain is correlated with SNST which is also a measure of executive functions (Garrard, Martin, Giunti & Cipolotti, 2008; Higginson et al., 2003; Kravariti, Dixon, Frith, Murray & McGuire, 2005; Zalonis et al., 2008) and, in fact, it shows great specificity value in regards to MD1 patients (Zalonis et al., 2008). Secondly, ECAS verbal fluency domain is correlated with SNST, as both of them are characterized by their executive components (Ross et al., 2007). Thirdly, ECAS memory domain is correlated with RCFT Recall (visual memory) and WAIS Information (semantic memory); though, it is crucial to highlight that the memory domain includes the aforementioned as its components (Papanicolaou, 2005), thus ECAS memory underlines the same theoretical and practical approach. Fourthly, ECAS visuospatial domain doesn't show any correlations with RCFT recall; that absence of differences is possibly attributed to the use of neuropsychological tests with low executive features, since previous studies in both MD1 and MD2 administered RCFT (Modoni, 2008; Peric, 2016), which requires also executive planning of the figure during its copy (Shin, Park, Park, Seol & Kwon, 2006). Eventually, these properties enabled us to use the ECAS scale in Greek MD2 patients that have never been examined so far.

A significant proportion of our MD2 patients demonstrated general cognitive impairment in ECAS total score. Actually, it is nearly 3 out of 4 patients (73%) who showed general cognitive dysfunctions. The greatest impairment along with significant differences with the healthy participants appeared in the following distinct cognitive domains: executive functions, verbal fluency, memory. Firstly, with regards to executive functions, MD2 patients showed difficulties in alteration ability and social cognition. Secondly, in the cognitive domain of verbal fluency, our patients appeared to struggle to deal with the one of the two phonemical verbal fluency tasks. Lastly, their memory was negatively influenced by the MD disorder, as shown at immediate and delayed story recall tasks.

As far as our results are concerned, our findings in distinct cognitive domains and tests are congruent to the majority of the neuropsychological literature. Among other researchers, Meola et al. (1996, 2003) and Peric et al. (2015) indicated dysexecutive syndrome, episodic memory difficulties and visuospatial difficulties. In our research we did indicate executive dysfunction, as well as verbal episodic memory impairment. The absence of differences in visuospatial functions, though, is possibly attributed to the use of neuropsychological tests with low executive features, as it is mentioned above.

In addition, our results highlight for the first time the existence of social cognition impairment with respect to MD2 patients. Previous research on MD1 patients has clearly observed (Kobayakawa, Tsuruya & Kawamura, 2012; Kobayakawa, 2016) or provided evidence (Zalonis et al., 2010) for social cognition dysfunction. Social cognitive dysfunction in MD1 patients could be an outcome of the brain abnormalities affecting patients' emotional and theory of mind abilities (Kobayakawa, 2016). Our research indicates, possibly, a similar dysfunction in MD2 patients.

Another point of paramount importance is the fact that our results correspond with recent neuroimaging findings (Peric et al., 2017). In particular, Peric and colleagues have combined neuropsychological measures with neuroimaging techniques of positron emission tomography. The neuropsychological findings were in accordance with ours, especially in regards to executive functions and verbal episodic memory tasks. They also observed significant hypometabolism in prefrontal and frontrotemporal regions, insula, basal ganglia and thalamus, which were in line with their patients' cognitive profile and provide further evidence for our findings.

Although, social cognition wasn't examined in that research, frontotemporal regions which are considered to be profoundly associated with it (Seeley et al., 2007) are also mentioned. That is another point of interest that should be included in future research.

The most important limitation of this study refers to its small sample size of MD2 patients. Based on the aforementioned, i. e. lack of clinicians' experience and difficulty in successfully diagnose it or differentiate it from MD1, the successful MD2 recruitment is characterized by its high difficulty factor; though, that is not the case only for our study as similar ones have also a small group of MD2 patients (Meola et al., 2003; Peric et al., 2017). Knowledge, experience and useful/efficient neuropsychological tools, like ECAS, should be considered. Based on our findings, it is important for future studies to examine visuospatial functions using neuropsychological tests that do not tap onto complicated executive demands, such as the ROCFT that also requires executive planning during the figure copy. Moreover, social cognition dysfunction in MD2, which is firstly described in our study, needs to be thoroughly examined in larger sample sizes with more similar or other social cognition measurements. Lastly, future endeavors should include neuroimaging techniques in order to correlate patients' brain structure and function with cognitive performance (which is part of one of our ongoing projects) and enable the longitudinal follow-up of MD2 patients to further characterize the progression of general and/or specific cognitive dysfunction.

In conclusion, the present short yet multidomained cognitive screening scale (i.e. ECAS scale) is a reliable, valid and useful neuropsychological tool in order to assess the neuropsychological profile of adult MD2 patients in everyday clinical practice. It identifies cognitive impairment in MD2 patients in regards to executive functions, including social cognition, verbal fluency and verbal episodic memory. The available ECAS total score as well as separate scores in distinct cognitive domains should be considered as a point of reference and an assessment basis for MD2 patients in their routine clinical evaluation.

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