



ARAŞTIRMA / RESEARCH

Relationship between pulmonary and cognitive functions in myotonic dystrophy type 1: a preliminary study

Myotonik distrofi tip 1'de pulmoner ve kognitif fonksiyonların ilişkisi: bir ön çalışma

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Abstract

Purpose: We aim to evaluate the correlation of neurocognitive findings with pulmonary functions in Myotonic dystrophy type 1 (DM1).

Materials and Methods: This is an observational prospective (between 2013-2015 years) cross-sectional single center study at Neurology and Chest clinics of Cukurova University. Mini mental state examination, forward and backward digit span, verbal fluency (semantic and lexical), clock drawing, verbal and visual memory, pulmonary function tests, arterial blood gas samples were performed to DM1 patients and control group. The presence of correlation between neurocognitive tests and pulmonary function, arterial blood gas samples were researched in DM1.

Results: There were significant differences between DM1 (10 male, 14 female) and control group (12 male, 9 female) on verbal fluency, clock drawing, forward and backward digit span tests. There was a positive correlation ($p<0.05$) between verbal fluency and respiratory function tests (total lung capacity) in DM1.

Conclusion: In the present study; we encountered a positive correlation between total lung capacity and verbal fluency in DM1. Pulmonary function tests and neurocognitive assessment should be performed concomitantly in DM1 patients. This provides early detection and treatment of cognitive impairment and loss of pulmonary functions.

Key words: Myotonic dystrophy, pulmonary function, cognitive function

Öz

Amaç: Bu çalışmada myotonik distrofi tip 1 (DM1) olgularında kognitif bulgular ile pulmoner fonksiyonların ilişkisinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Bu çalışma 2013-2015 yılları arasında Çukurova Üniversitesi Nöroloji ve Göğüs Hastalıkları kliniklerinde prospektif olarak yapılmıştır. DM1 olguları ve sağlıklı kontrol grubunda minimental durum testi, sayı menzili testi, sözel akıcılık (semantik ve leksikal), saat çizme testi, sözel ve görsel bellek testleri, solunum fonksiyon testi, arteriel kan gazı değerlendirilmiştir. Çalışma grupları arasında kognitif testler ile pulmoner fonksiyonlar arası ilişki incelenmiştir.

Bulgular: DM1 (10 erkek,14 kadın) ve kontrol grubu (12 erkek, 9 kadın) arasında sözel akıcılık, saat çizme testi, sayı menzili testlerinde anlamlı farklılık saptanmıştır. Ayrıca DM1 olgularında total akciğer kapasitesi ve sözel akıcılık arasında pozitif korelasyon gözlenmiştir ($p<0.05$).

Sonuç: Bu çalışmada DM1 olgularında total akciğer kapasitesi ve sözel akıcılık arasında pozitif korelasyon gözlenmiştir. DM1 olgularında pulmoner ve kognitif fonksiyonların korele olması, bu fonksiyonların birlikte değerlendirilmesi gerekliliğini ortaya çıkarmaktadır. Böylece erken tanı ve tedavi mümkün olacaktır

Anahtar kelimeler: Myotonik distrofi, pulmoner fonksiyon, kognitif fonksiyon

INTRODUCTION

Myotonic dystrophy type 1 (DM1) is a multisystem disorder and could affect to muscle, endocrine organs, lens, heart, and brain. DM1 is primarily

noted as a neurological disease characterised by myotonia and muscle weakness. And also excessive daytime sleepiness, the loss of executive functions and visuospatial ability could be observed in DM1¹. Neuropsychological studies has shown especially executive functions on frontal lobe has been

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deteriorated at DM1². While on imaging studies with magnetic resonance imaging (MRI) brain atrophy is detected at particularly anterior temporal lobe³, on brain positron emission tomography (PET) studies hypometabolism was observed on frontal and temporal lobes^{4,5}. Also intraneural neurofibrillary tangles and tau protein accumulation in DM1 were same as frontotemporal dementia on pathological studies⁶. Although there was no correlation between cognitive functions and radiological, pathological and genetic studies^{1,7,8}, in a few studies there was a correlation between cognitive deficits and loss of muscle strength or cardiac arrhythmia^{3,9,10}. Hypoxemia can be seen due to respiratory failure in DM1¹¹. In literature it was shown that attention, abstraction, configuration, executive functions, learning and memory impairment could be seen due to long-term hypoxemia¹². Although since now neurocognitive tests and neuroimaging findings have been evaluated in DM1 studies, the relationship with pulmonary functions has not been evaluated. In the study we aim to evaluate the correlation of neurocognitive findings with pulmonary functions in DM1.

MATERIALS AND METHODS

This is an observational prospective cross-sectional single center study at Neurology and Chest clinics. Patients with DM1, diagnosed clinically, electrophysiologically and genetically, who admitted to outpatient clinic of neurology department between 2013-2015 years has been included in the study. And also healthy controls with similar age, gender, education in respect with DM1 patients were included to study.

Patients with using drugs (antiepileptic, antipsychotic, antidepressant), obstructive sleep apnea syndrome, psychiatric disease, stroke, diabetes mellitus, hypertension, mental retardation, diagnosed as dementia according to DSM-IV, mini mental state examination test (MMSE) <24 and Epworth Sleepiness Scale test ≥ 9 , the finger flexor muscle strength <+3/5, pathologies in brain MRI which may affect cognition, who were unable to perform pulmonary function tests and neurocognitive tests were excluded from study.

All of DM1 patients' brain MRI, complete blood count, liver, kidney and thyroid function tests,

vitamin B12 and folate levels were recorded. MMSE¹³, forward and backward digit span¹⁴, verbal fluency (semantic and lexical fluency)¹⁵, clock drawing¹⁵, verbal and visual memory¹⁶ tests were performed by a neurologist experienced in neurocognitive tests. An also pulmonary function test and arterial blood gases were performed.

After cognitive data of DM1 and control group were compared. The presence of correlation between neurocognitive tests and pulmonary function, arterial blood gas samples (ABG) in DM1 were researched. Approval was received from the ethics committee on School of Medicine, Cukurova University (Approval no: 06.06.2013/20/2), and written informed consent was obtained from all subjects.

Statistical analysis

All analyses were performed using SPSS 20 statistical software package (IBM SPSS Statistics). Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and minimum-maximum where appropriate. For comparison of continuous variables measured at basal and control visit, paired samples t-test or Wilcoxon Signed Rank test was used depending on whether the statistical hypotheses were fulfilled or not. To evaluate the correlations between basal measurements, Pearson Correlation Coefficient or Spearman Rank Correlation Coefficient was used depending on whether the statistical hypotheses were fulfilled or not. The statistical level of significance for all tests was considered to be 0.05.

RESULTS

Although 30 DM1 patients were admitted to in the study, 6 DM1 patients were excluded from study due to unable to perform pulmonary function tests and neurocognitive tests. Finally; 24 DM1 (10 male, 14 female) and 21 healthy controls (12 male, 9 female) were included in the study. No significant differences were found in demographic data between these two groups ($p > 0.05$) (Table 1). The duration of DM1 was 7.5 ± 6.74 (1-23) years. The results of brain MRI, complete blood count, liver, kidney and thyroid function tests, vitamin B12 and folate levels were normal.

Table 1. Comparisons of data between DM1 and control groups

| | DM1 (n:20) | Control (n:21) | p |
|----------------------|--------------------|--------------------|---------|
| Age (years) | 36.95±6.75 (25-51) | 33.43±6.77 (19-50) | 0.73 |
| Gender (Male/Female) | 10/10 | 12/9 | 0.85 |
| Education (years) | 7.15±3.37 (5-15) | 9.00±3.67 (5-15) | 0.26 |
| MMSE | 29.33±1.00 (26-30) | 29.10±1.37 (24-30) | 0.27 |
| Forward | 5.33±1.43 (2-7) | 6.19±1.12 (4-7) | 0.03* |
| Backward | 3.05 ± 1.04 (0-4) | 4.43±0.97 (3-6) | <0.001* |
| SF | 14.00±5.19 (1-23) | 16.86±3.86 (10-25) | 0.04* |
| LF | 8.04±4.60 (1-16) | 12.29±4.70 (0-21) | 0.004* |
| CD | 8.05±1.86 (4-10) | 9.76±1.09 (5-10) | 0.001* |
| Verbal M(FR) | 3.61±1.53 (0-5) | 3.48±1.56 (0-5) | 0.71 |
| Verbal M(CR) | 4.67±1.02 (1-5) | 4.57±0.97 (1-5) | 0.37 |
| Visual M(FR) | 2.57±0.38 (2-3) | 2.82±01 (2-3) | 0.65 |

DM1: Myotonic dystrophy, MMSE: Mini mental state examination, Forward: Forward Digit Span, Backward: Backward Digit Span, SF: Semantic Fluency, LF: Lexical Fluency, CD: Clock Drawing, Verbal M(FR): Verbal Memory (Free Recall), Verbal M(CR): Verbal Memory (Recall With Clue), Visual M(FR): Visual Memory (Free Recall)

On forward-backward digit span, semantic-lexical fluency and clock drawing tests were found significant differences between DM1 and control group ($p < 0.05$) (Table 1). Clock drawing test was negatively correlated with the duration of disease ($p: 0.045$, $r: -0.432$). Also there was a positive

correlation between total lung capacity and semantic fluency ($p: 0.006$, $r: 0.639$), lexical fluency ($p: 0.039$, $r: 0.504$). No correlation was found between neurocognitive tests and arterial blood gases. The results of pulmonary function tests and arterial blood gases in DM1 were presented on Table 2.

Table 2. Pulmonary function test and arterial blood gas values in myotonic dystrophy patients

| Pulmonary function test values | | Arterial blood gas values | |
|--------------------------------|-----------------------|---------------------------|--------------------------|
| FEV1 | 71.00±21.47 (22-115) | ph | 7.38±0.03 (7.35-7.46) |
| FVC | 73.50±22.12 (21-123) | SO2 | 94.46±3.18 (90.50-98.40) |
| FEV1/FVC | 82.02±6.29 (62-97) | PO2 | 80.53±17.30 (50-112) |
| RV | 102.2±42.21 (10-161) | PCO2 | 37.83±8.66 (27.2±54.2) |
| TLC | 80.53±17.30 (50-112) | CHCO3 | 22.02±4.19 (16.90±29.50) |
| RV/TLC | 134.86±45.22 (66-233) | BE | 3.4±18.16 (-6.60-47.80) |

FEV1: Forced expiratory volume in the first second, FVC: Forced vital capacity FEV1/FVC: Forced vital capacity ratio, RV: Residual volume, TLC: Total lung capacity, ph: Power of hydrogen, SO2: Arterial oxygen saturation, PO2: Pressure of oxygen, PCO2: Pressure of carbon dioxide, CHCO3: Bicarbonate concentration, BE: Blood base excess

DISCUSSION

DM1 is a neurological muscular disease. Awareness for DM1 is low among neurologists. Patients generally misdiagnosed as muscular dystrophy, myasthenia gravis, and mitochondrial cytopathies in clinical practice. Clinician, even if correctly recognizes the disease, may not know the problems in spectrum of the disease (such as cataract, diabetes mellitus, cholelithiasis, polyneuropathy, cognitive dysfunction) and can't properly manage the disease course. Most of the clinicians, usually, do not assess the cognitive functions in DM1 patients. Thus, there are a few studies of cognitive assessment and DM1 in the literature^{2,3,7-10}. Previously done several neuropsychological studies have shown that particularly executive functions had been

deteriorated among DM1 patients^{2,3,7-10}. Similarly, in our study, it is observed that there is lower performance in "forward-backward digit span, semantic-lexical fluency, and drawing clock" tests assessing executive functions among DM1 patients, and also we found the clock drawing test was negatively correlated with the duration of disease. Forward - backward digit span, semantic - lexical fluency and drawing clock tests can evaluate influenced attention, executive functions, abstraction, configuration, and visiospatial abilities^{18,19}. When the results of these tests are taken in consideration, it is found that frontotemporal area functions were significantly influenced among DM1 patients, same as previous studies²⁰⁻²². Rubinsztein et. al has shown that memory was influenced in early stages of the disease course, rather than executive

functions²³, however, in our study, tests of verbal and memory functions were not found different in control group contrarily.

The presence of hypercapnia in DM1 patients is more prevalent than Duchenne muscular dystrophy in literature. This is possibly due to loss of neuronal injury rather than loss of respiratory muscle²⁴. And also it is known that DM1 causes a significant loss in tidal volume by influencing respiratory muscles, and ultimately respiratory failure^{25,26}. Hypoxemic status due to chronic hypoventilation in DM1 patients may cause cognitive impairment^{24,27}. Since chronic hypoxemia can deteriorate cognitive functions we can speculate that hypoxemia in DM1 may deteriorate cognitive functions, also²⁸. Therefore, we evaluated the correlation between neurocognitive tests and respiratory function tests in DM1 cases. We observed a positive correlation between semantic (p: 0.006, r:0.639) - lexical (p: 0.039, r:0.504) fluency and total lung capacity. However, no similar correlation was observed by comparison of neurocognitive tests and arterial blood gas.

Arterial blood gas samples were obtained and evaluated in daily routine practice, and we were unable to collect arterial blood gas samples at nightlong. Since sleep disturbance is more prevalent among DM1 patients²⁹, we should be able to detect nightly hypoxemic conditions, which may affect mental conditions. That's why, we were unable to correlate day-time arterial blood gas samples with cognitive functions, but only total lung capacity in pulmonary function tests was found diminished, which may reflect the deterioration of cognitive functions.

In the present study; although there is no apparent loss parenchymal lesions in brain, we encountered cognitive loss in DM1. Also a positive correlation between total lung capacity and semantic-lexical fluency. When a patient with DM1 is evaluated initially, pulmonary function tests and neurocognitive assessment should be performed concomitantly and they have to be repeated in 6-month-visits. This provides early detection of cognitive impairment and loss of pulmonary functions. In this way we can provide a better survival and quality of life of DM1 patients.

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