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Coexistence of Myotonic Dystrophy and Normal Pressure Hydrocephaly: Causative or Incidental?

Myotonik Distrofi ve Normal Basınçlı Hidrosefali Birlikteliği: Nedensel mi Rastlantısal mı?

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Summary

Objective: Myotonic dystrophy type 1 (DM1) is the most common adult muscular dystrophy involving not only the striated muscle but also multiple systems including central nervous system, and resulting from a gene mutation with autosomal dominant inheritance causing trinucleotid repeats. Neuroimaging findings in patients with DM1 are ventricular enlargement, hyperintensity of white matter at the posterior-superior trigone (HWMPST), hyperostosis frontalis interna and thinning of corpus callosum. Although ventriculomegaly is reportedly the most common finding, DM1 in association with normal pressure hydrocephalus (NPH) has been reported in anecdotal case reports. The aim of this study is to investigate the frequency of ventriculomegaly and also clinical diagnosis of NPH in patients with DM1 in a retrospective case series.

Material and Method: Neuroimaging (mostly cranial MRI) findings in 20 patients (9 women; mean age: 38.25 years±10.26[range: 18-60]; mean disease duration: 18.9 years±10.5 [5-43]) with DM1 diagnosed with clinical and electromyographic findings are examined retrospectively.

Results: The available neuroimaging data came from MRI scans in 19 cases and CT scans in the remaining case. Ventriculomegaly as decided by increased ventriculocerebral index (VCI) was evident in only two patients who were siblings, one of whom also had the classical NPH clinical triad. After a ventriculoperitoneal shunt his urinary incontinence and gait difficulty had improved.

Discussion: The increase in the serum levels of MDA, TOS, and TAS in ICH patients may demonstrate that there is an increase in oxidative stress and this supports the fact that that oxidative stress may play a significant role in the pathogenesis of the ICH. However, the increase of these parameters was not found to be associated with hematoma volume and GCS in patients with ICH. *(Turkish Journal of Neurology 2013; 19:56-9)*

Key Words: Myotonic dystrophy type 1, neuroimaging, ventriculomegaly, normal pressure hydrocephaly

Özet

Amaç: Myotonik distrofi tip 1 (DM1), yalnız çizgili kasları değil aynı zamanda santral sinir sistemini de içeren birden fazla sistemi etkileyen, trinükleotid tekrarlarının neden olduğu otozomal dominant geçişli gen mutasyonu sonucu en sık görülen erişkin tip müsküler distrofidir. DM1 tanılı hastalarda yapılan nörogörüntüleme bulguları ventriküler genişleme, posterior-superior trigonda beyaz cevher hiperintensiteleri (HWMPST), frontal kemikte kalınlaşma ve korpus kallosumda incelmedir. Ventrikülomegalinin en sık bildirilen bulgu olmasına rağmen, DM1 ve normal basınçlı hidrosefali (NBH) birlikteliği olan az sayıda olgu sunumları vardır. Bu çalışmanın amacı DM1 tanılı retrospektif olgu serisinde ventrikülomegali sıklığını ve aynı zamanda NBH klinik sunumunu araştırmaktır.

Gereç ve Yöntem: Klinik ve elektromyografik bulguları ile DM1 tanısı alan 20 hastada (9 kadın; ortalama yaş: 38,25±10,26 [aralık: 18-60]; ortalama hastalık süresi: 18,9 yıl±10,5 [aralık: 5-43]) nörogörüntüleme (sıklıkla beyin MRG) bulguları retrospektif olarak incelendi.

Bulgular: 19 hastanın MRG'si, kalan bir hastanın ise BT'si değerlendirildi. Artmış ventrikülöserebral indeks (VCI) ile hesaplanan ventrikülomegali yalnızca aynı zamanda kardeş olan iki hastada saptandı. Kardeşlerden birinde klasik NBH klinik tablosu vardı. Ventrikülöperitoneal şant sonrası hastanın üriner inkontinansı ve yürüme güçlüğü düzeldi.

Sonuç: Bu retrospektif analiz, erişkin DM1'de ventrikülomegalinin sık görülen nörogörüntüleme bulgusu olduğu görüşünü desteklemedi. Tercihan anormal nörogörüntüleme bulguları ile trinükleotid tekrar sayısının muhtemel ilişkisinin de cevaplanacağı genetik verilerin de dahil olduğu tarzda tasarlanan bir prospektif çalışma, erişkin DM1 ile ventrikülomegalinin nedensel bir ilişkisi olup olmadığı ve zaten kendisi bir engellilik nedeni olan bu hastalığın ileri dönemlerini daha da komplike edebilecek, oysa kier kentanındığında geri dönüşlü olabilen NBH'nin ventrikülomegalinin klinik sunumu olup olmadığı sorusuna cevap verebilir. *(Türk Nöroloji Dergisi 2013; 19:56-9)*

Anahtar Kelimeler: Myotonik distrofi tip I, nörogörüntüleme, ventrikülomegali, normal basınçlı hidrosefali

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Introduction

Myotonic dystrophy type 1 (DM1; OMIM 160900) is the most common form of autosomal dominant inherited adult onset muscular dystrophy characterized with an increase of the cytosine-thymine-guanine (CTG) trinucleotide repetition in the 3' untranslated region (3'-UTR) of the dystrophia myotonica-protein kinase (DMPK) gene (OMIM 605377) encoded in the 13.32 locus on the long arm of the 19. chromosome. Clinical picture is polymorphic and presents with myotonia, amyotrophy, cataracts, endocrine disorders, cardiac myopathy, as well as central nervous system findings of varying severity. While mental retardation is seen in congenital cases, behavioural disorders including obsessive compulsive disorder, schizotypal personality disorder, lack of empathy and cognitive loss are seen in the adult form (1,2). There is no general consensus on whether cognitive loss is permanent or progressive, and it is usually seen in executive functions, as impairment of visual – spatial abilities, slowing in information processing and attention and memory impairment (3,4,5,6,7,8).

Neuroimaging investigations performed in patients diagnosed with DM1 have shown hiperostosis frontalis interna, thinning in the corpus callosum, cortical atrophy, hyperintensity in the white matter and dilation in the ventricles (9,10,11). Although an increase in the incidence of ventriculomegaly is seen in DM1 patients, there are few case reports in the literature for coexistence of DM1 and clinical picture of normal pressure hydrocephaly (NPH) characterized with urinary incontinence, gait disorder and cognitive loss (12, 13,14,15,16,17,18). As we diagnosed NPH in a patient under follow-up for DM1 in our clinic, we reviewed retrospectively the imaging findings of patients who were diagnosed with DM1 and who had a cranial imaging performed for another reason.

Material and Method

Patients: Hospital records of 35 patients diagnosed with DM1 via neurologic examination and electromyography were reviewed at the Akdeniz University Medical School Hospital, Neuromuscular Diseases Outpatient Clinic. A total of 20 (11 male, 9 female) patients were enrolled in the study. Demographic information are presented in Table 1. The remaining 15 subjects were excluded from the study for reasons including not having a cranial imaging study, history of one or more disease or risk factor such as hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, coronary artery and peripheral vascular disease, pre-existing cerebral infarction, transient ischemic attack and vascular dementia that could cause white matter changes. Patients with a congenital DM1 diagnosis and patients whose cranial magnetic resonance imaging (MRI) was taken during diagnosis were not included in the study because of probable distinct etiopathogenesis of neuroimaging findings and the possibility of correlation of disease duration in adult DM1, respectively.

MRI scans: When patients were retrospectively reviewed, all, except one, were seen to have had brain MRIs taken at the Akdeniz University Medical School Radiology department, because they were under long term follow-up at our clinic. Routine brain MRI scans are performed with a 1.5 Tesla Philips, Intera device using a standard head coil. As long as a specific sequence is not requested routine MRI scans are taken with sagittal T1 (repetition time (RT) 495 msec, echo time (ET) 12 msec, slice thickness (ST) 5 mm), transverse T2 weighted TSE (RT 4663 msec, ET 100 msec, ST 5 mm, TSE factor 15) sequences and transverse FLAIR sequences (RT 6000 msec, ET 1000 msec, TI 2000 msec, ST 5 mm). All of the sequences were present in the MRI scans of 19 of the patients. Brain MRI scans were assessed by evaluating white matter lesions, ventriculocephalic index (VCI), hyperintensities of white matter in the posterior-superior trigon (HWMPST), corpus callosum thickness, cortical atrophy and frontal bone thickness measurements.

Results

Brain MRI scans were evaluated for 19 of the patients enrolled in the study, while 1 patient only had a computed tomography (CT) scan. None of the cases except the index case and his sibling had a VCI of 41%. Four patients were found to have white matter lesions, two patients HWMPST, 2 patients corpus callosum atrophy, 6 patients cortical atrophy and 5 patients frontal bone thickening (Table 2). Index case was a 51-year old university graduate, right hand dominant male patient who had been under follow-up for 22 years with a diagnosis of DM1. For the last three months he had been complaining of "urge" incontinence, pollachiuria and difficulty of walking that caused falls and memory defects. Neurological examination revealed bilateral atrophic masseter muscles and typical triangular facial appearance and labial dysarthria. He was conscious, with full orientation and cooperation, normal tongue examination; examination of cranial nerves was normal except for bilateral ptosis and facial paresis. Deep tendon reflexes were hypoactive and there were no pathologic reflexes. Motor examination revealed slight loss of strength in neck flexion and distal muscles of both lower and upper extremities. Mental state examination showed attention deficit, impairment of executive functions and non-limbic type memory disorder where recognition was protected. VCI of 0.50 and clinical findings helped confirm the diagnosis of NPH. Following a procedure of draining lumbar puncture, the patient's urinary complaints improved clearly and his gait improved partially. Although there was no clear change in his cognitive complaints on examination, the patient reported that he felt more lively. Later, a ventriculoperitoneal shunt was inserted

Table 1. Demographic information of 20 DM1 patients enrolled in the study

Sex (F/M)	9/11
Age, mean±SD (range)	38.25±10.26 (18-60)
Disease Duration Level (years), mean±SD (range)	18.9±10.5 (5-43)
CPK Level, mean±SD (range)	266.11±159.15 (88-631)

Table 2. Abnormal findings in retrospectively reviewed cranial MRIs of DM1 patients

Brain MRI Findings	Number of Patients
Hyperintensity in White Matter	4
HWMPST	2
Corpus Callosum Atrophy	2
Cortical Atrophy	6
Frontal Hyperostosis	5

*VCI: Ventriculocephalic index, † HWMPST: Hyperintensity in white matter in the posterior-superior trigon

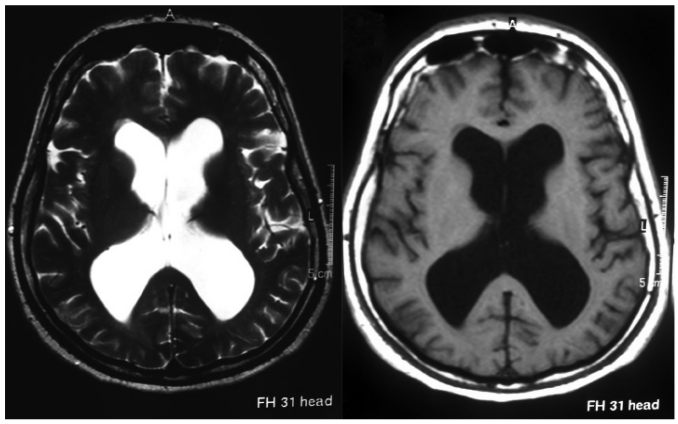

Image 1: Index case – dilation in lateral ventricles in T1 and T2 weighted MRI transverse sequences. Ventriculocephalic index: 50%

and his post-operative sphincter control improved markedly, and his difficulty of walking and forgetfulness improved partially. The 67-year old brother of this patient could not be clinically evaluated but his VCI was found to be 46% in the CT scan review.

Discussion

We reviewed the presence of ventriculomegaly in cranial MRI scans of patients under follow-up with a DM1 diagnosis in our clinic and planned to evaluate the clinical findings of patients whose VCI was above 41%. However, none of the patients, except the index patient and his sibling, had a VCI of above 41%. As we could not reach the brother of the patient who had NPH and marked and partial improvements in his urinary problems and gait disorder and cognitive complaints, respectively, we could not examine him, but when we reviewed his CT scan we found that his VCI was 46%.

In addition to these clinical findings of the central nervous system, microcephaly and especially pronounced thickening in the frontal bone, white matter lesions, atrophy and dilation in the ventricles, decrease in the cerebral glucose metabolism, hypoperfusion in the frontotemporoparietal cortex and decrease in the cerebral blood flow have been reported in functional imaging investigations (6,19,20,21,22,23,24). Although the presence of MRI findings are considerably accepted in DM1 patients, they may be controversial due to some investigators claiming white matter changes to be nonspecific and MRI findings to be accepted within normal limits (22,24). Cranial MRI findings in adult type DM1 patients including cerebral atrophy, white matter changes and thinning in the corpus callosum have been shown to be strongly related with the duration of the disease (25). Ota et al. have shown positive correlation between number of CTG repeats and loss of brain volume (26). Based on these results, the reason of varying results in the imaging findings in DM1 patients may be different disease durations or progression rates in enrolled patients or difference of expressivity of the mutation, especially related with the number of repeats.

The etiology and pathology of the changes in the brain are not clearly understood. Although there are pathologic changes including ventricular dilation, neuronal heterotopia and periventricular leucomalacia in the congenital form, normal gross anatomic and microscopic findings were reported in the post-mortem examinations of some cases where ventriculomegaly was found in ante-mortem CT scans (27). This interesting result was explained by investigators as ante-mortem hypoxic ischemic damage preventing the visualization of gross anatomical ventriculomegaly by causing intracellular edema, or decrease in the myelin concentration in the dyed field of the preparation causing the microscopic image to seem near normal due to dehidration (27).

The neuropathology in the adult form is characterized with pachygyria, neuronal heterotypia, intracytoplasmic inclusion bodies and neurofibrillar tangles (28,29,30,31). In two studies focusing on lobar white matter lesions, myelin loss where axons were relatively protected, increased interfascicular spaces, cellular infiltrates, findings of active destruction of the myelin sheath and presence of fatty granular cells were shown (10,32). When neuropathology and imaging findings were evaluated together, symmetric white matter changes with a tendency of confluence, progressing ventricular dilation, the correlation of the severity of white matter lesions and disease duration all support a slowly progressing demyelinating process (33). The ventriculomegaly and white matter changes seen in both congenital and adult forms of DM1 are thought to arise from different causes. Absence of a correlation with age in the congenital form and reporting no progression in follow-up studies suggest these findings to be a developmental impairment. On the other hand, the findings in the adult form show a strong correlation with disease duration; therefore degenerative changes can be said to be predominant (12).

When findings of neuroimaging studies performed with DM1 patients are evaluated, dilation in ventricles is found in approximately 40% of cases (10,16,18,34,35). Refsum et al. first found ventricular dilation in 5 of 10 patients in a study performed with pneumoencephalography and kept the patients under long term follow-up; as disease duration increased ventricular dilation was found to progress. However, this progression was not seen in disease periods shorder than 30 months (35). In another series opposing this, it was reported that when 10 of 20 DM1 patients were compared with the control group, ventricular dilation was seen, but there was no correlation between this finding and disease duration or severity (11). Current opinion, albeit controversial, is that changes in the adult form of DM1 are correlated with disease duration. Ventricular dilation and white matter changes in DM1 are associated with cognitive loss (14,36).

Although ventriculomegaly is commonly reported in patients diagnosed with DM1, there are few case reports of a clinical picture of NPH. The first clinical report of classic triad of NPH was in 1985 in a patient followed with a diagnosis of DM1 (18). Three years after this, late onset NPH was reported in two siblings diagnosed with DM1 and NPH was suggested to be a late complication (16). Following a long hiatus, another case was reported with co-existence of DM1-NPH, that had been under follow-up for 10 years post-treatment (17). This case was confirmed by measuring the intracranial pressure (ICP) and the improvement in clinical findings following ventriculoperitoneal shunt has been stable during the 10-year follow-up. This case is noteworthy for both the confirmation of diagnosis by ICP measurement and the long-term follow-up. NPH is a clinical picture characterized by impairment of the reabsorption of the cerebrospinal fluid due to the obliteration of arachnoid villi. Impairment of the reabsorption of the cerebrospinal fluid causes ventriculomegaly. Development of NPH in DM1 may be explained by diffuse cellular membrane defect caused by genetic anomaly (16). Complex membrane

protuberances are needed for the absorption of the cerebrospinal fluid; therefore, diffuse cellular membrane defect impairs absorption and communicating hydrocephalus develops. Delavallée et al. explain that DM1-NPH co-existence may have been escaped observation due to the facts that DM1 patients die at a young age or NPH symptoms may be perceived as normal in elderly patients (17). Cases presented for DM1-NPH co-existence are above the age of 50, as was our case, who was 61 years old when NPH was clinically described. The criticism we got following this case presentation argued that this co-existence was mainly incidental. Longitudinal follow-up studies evaluating DM1 patients for NPH with clinical and neuroimaging findings may or may not support such hypotheses. Clinical findings of NPH will clearly worsen the quality of life of DM1 patients; on the other hand, early diagnosis is important because clinical signs may be partly irreversible with treatment. Close follow-up of central nervous system involvement of DM1 patients throughout follow-up is important to increase quality of life and to identify treatable secondary causes.

We did not observe that VCI was above 41% in DM1 patients enrolled in this cross sectional retrospective study, although disease duration was longer than 30 months. Although this negative result in our study with a non-negligible patient population seems to oppose a causal relationship between DM1 and NPH, the mean disease duration may not be long enough to identify these late complications. A prospective study performed by detecting CTG repeat numbers to reveal whether there is a relationship between VCI and CTG repeat numbers may provide a more definite answer to the question of whether NPH is causal or incidental or co-existing in DM1.

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