COMORBIDITY OF STRUCTURAL EPILEPSY AND MULTIPLE SCLEROSIS: MRI, ^{18F}FDG PET/CT AND EEG INVESTIGATIONS

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ABSTRACT

There is accumulating evidence of a mutual relationship between multiple sclerosis and structural epilepsy. Comorbidity of these severe neurological disorders is reported in numerous recent publications in the available foreign literature. Modern diagnostic tools include comprehensive neurological examinations as well as computed tomography, electroencephalography and ^{18F}FDG positron emission tomography. In this paper we report the case of a female patient with multiple sclerosis and structural epilepsy who was admitted to the clinic due to weakness of left limbs, difficulty in walking, and blurred vision in the left eye. The neurological examination showed small horizontal nystagmus, left-sided hemianopia, quadrihyperreflexia, non-sustained clonus of both feet, left-sided latent hemiparesis, paresthesia in the left limbs. Electroencephalography (EEG) revealed paroxysmal activity on the left side, MRI indicated evidence of cerebrospinal MS with activity . ^{18F}FDG PET scans were normal. Based on the literature data and our own case report we could draw the conclusion that as epileptic seizures in MS patients may occur due to inflammatory plaques of demyelination it could be suggested that there exists a correlation between MS and structural epilepsy.

Keywords: *multiple sclerosis, structural epilepsy, diagnosis, MRI, ^{18F}FDG PET/CT, EEG*

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INTRODUCTION

Evidence exists that some symptoms of multiple sclerosis (MS) which are due to plaques of demyelination in the affected brain areas may be similar to those of structural epilepsy. Recently, essential contemporary viewpoints in the field of epileptic seizures in patients with MS have been summarized (1).

It has been suggested that cortical and subcortical demyelination and inflammation could explain the increased frequency of seizures in MS (12).

The ^{18F}FDG-PET/CT co-registration for localization diagnosis of epileptogenic brain lesions in 21 patients with structural epilepsy reveals a larger zone of hypometabolism than the anatomical image of the corresponding brain lesion in 11 cases (2). Computed tomography (CT) shows a larger epileptogenic region in four cases.

MS patients with seizures have a significantly higher number of cortical and juxtacortical lesions on T2-weighted/fluid attenuation inversion recovery magnetic resonance imaging than MS patients without epilepsy (15).

CASE REPORT

A 24-year-old woman with MS was hospitalized in January, 2014 in the First Multiprofile Clinic of Neurology at St. Marina University Hospital of Varna, on the occasion of weakness of left limbs, difficulty in walking, and blurred vision in the left eye. She reported that she had a 'twist' on the left eye and double vision about four to five years before. Brain magnetic resonance imaging (MRI) in 2008 demonstrated optic neuritis. In 2011, she complained of vision loss in the right eye. In July, 2013, she reported numbness in the left limbs and blurred vision in the left eye. MRI indicated evidence of cerebrospinal MS with activity (Fig.1). The findings of ^{18F}FDG PET were normal (Fig.2). From November, 2013 to January, 2014, she experienced two seizures with incontinence during sleep. In November, 2013, electroencephalography (EEG) revealed paroxysmal activity on the left side. Small horizontal nystagmus, left-sided hemianopia, quadrihyperreflexia, non-sustained clonus of both feet, left-sided latent hemiparesis, paresthesia in the left limbs were found on neurological examination. Laboratory examinations remained within reference limits. In January, 2014, EEG identified diffusely scattered sharp and theta waves.

DISCUSSION

The investigation of 23 relapsing remitting MS patients with epileptic seizures by advanced multimodal 3T MRI reveals that the regions most affected by grey matter lesions are the hippocampus (in 14.2%), the lateral temporal lobe (in 13.5%), the cingulate (in 100%) and the insula (in 8.4% of the cases) (5). There are more alterations of diffusion metrics and cortical thinning in several regions of temporal

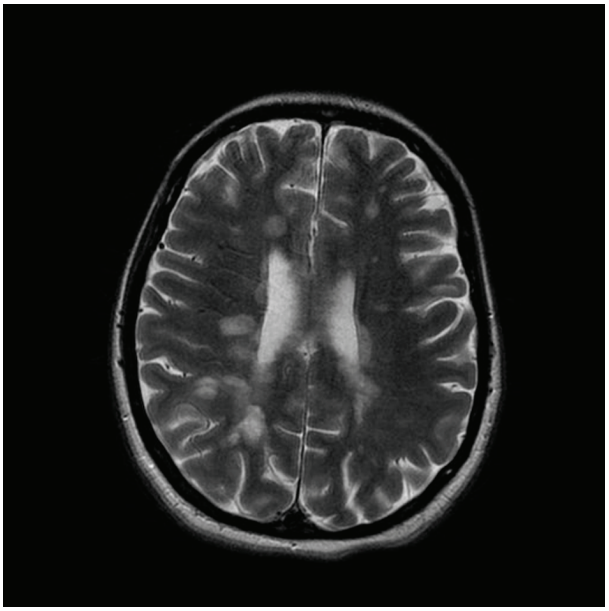

Fig. 1. MRI findings in line with MS

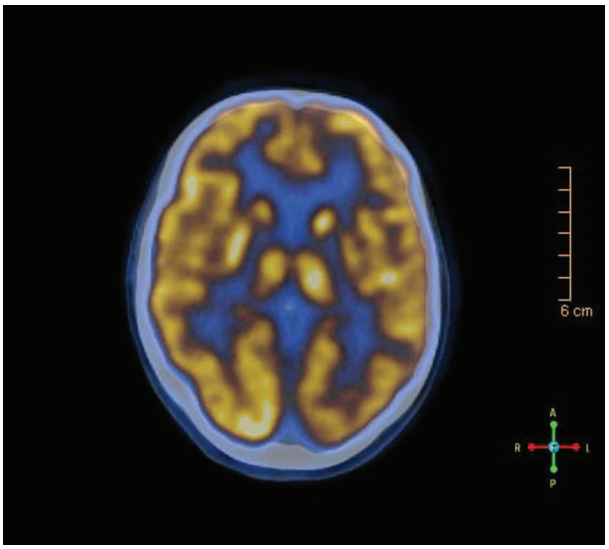

Fig. 2. Normal FDG-PET/CT

lobe, in insular cortex and in cingulate gyrus of these patients than in 23 disease duration-matched MS patients without epilepsy ($p<0.05$ for all comparisons).

In a three-year longitudinal study, the comparison between 32 relapsing-remitting MS patients with epilepsy and 60 matched patients without epilepsy reveals that at baseline, cortical lesions are observed in 84.38% of the cases in the first group and in 43.33% of the cases in the second group ($p<0.001$) (4). The number and total volume of these lesions are higher (10.2±8.9 versus 4.5±2.4; $p<0.001$ and 2.0±1.3

versus 0.7±0.8 cm^3; p<0.001, respectively) among the MS patients with epilepsy. Global cortical thickness is, however, lower in this group (2.12±0.19 versus 2.35±0.14 mm; p<0.001). After three years, these patients present with a higher accumulation of new cortical lesions (3.4±3.2 versus 1.2±1.1; p<0.001) and with a faster reduction of the grey matter fraction (p=0.022).

The systematic analysis of 32 population-based studies searched in *PubMed*, *EMBASE*, *Web of Knowledge*, and *Scopus* databases, as well as in conference proceedings reference lists indicates that the incidence rate of seizure disorders among MS patients is 2.28% while the prevalence rate is 3.09% (14).

The analysis of two datasets of linked statistical hospital admission records reveals that the relative risk for admission for epilepsy following an admission for MS is significantly high - at 4.1 in the Oxford Record Linkage Study area (1963-1998) and at 3.3 - in all England (1999-2011) (3). The relative risk for a first recorded admission for epilepsy ≥10 years after the first recorded admission for MS is 4.7 and 3.9, respectively. The relative risk for the converse-MS following hospitalization for epilepsy is 2.5 and 1.9, respectively. One possible explanation is that a MS lesion acts as a focus of an epileptic seizure.

In a retrospective population-based study between April, 2003 and July, 2010 in Iran, there is epilepsy in 81 out of 3522 MS patients (in 2.29% of the cases) (11). Epilepsy has occurred within a mean duration of 5.6±5.4 years after MS in 64 cases (in 79.01%), a at MS onset as the presenting symptom in five cases (in 6.17%) and by a mean duration of 4.3±4.3 years prior to MS onset in 12 patients (in 14.81% of the cases). The results from the same study display that early-onset MS defined as the first presentation of symptoms before the age of 16 years is diagnosed in 117 patients, 19 males and 98 females, with a mean age at onset of 14.2±2.0 years (range: 7-16 years) (10). Among them, ten patients have experienced at least two epileptic seizures, providing a crude prevalence rate of 8.55%. This value is significantly greater (p<0.001) than that of the non-early-onset MS cohort.

The evaluation of 255 patients with MS from the United Kingdom MS Tissue Bank demonstrates seizures in 37 cases, i. e. 14.51% lifetime incidence rate (17). In them, death and wheelchair use occur earlier and in 59% of the cases, seizures develop 15 years after the disease onset. Epilepsy is associated with type 1 grey matter lesions which underlie a loss of inhibitory interneurons in cortical layers IV and VI as well as with reduced cortical thickness in the middle temporal gyrus.

The investigation of MS patients living in the County of Vestfold, Norway, during the period between 1963 and 2003 demonstrates that the portion of the cases with epileptic seizures increases from 2.9% in 1963 up to 7.4% in 2003 (13).

The retrospective review of the records of MS patients between 2009 and 2012 at Pontificia Universidad Católica of Chile's Multiple Sclerosis Center shows that ten out of 310 patients (3.23% of the cases) have epilepsy (20). These patients are younger (aged 32 versus 40 years; p=0.04) and have an earlier onset of MS symptoms (at the age of 25 versus 32 years; p=0.02) when compared to the patients without epilepsy. In four patients, seizures are the first MS symptom. The most frequent seizure type is partial secondary generalized (in six patients). MRI shows cortical lesions in all the cases. Along with the progressive brain atrophy, these lesions could, probably, be the pathophysiological mechanism underlying the association between epilepsy and MS.

Among 2300 patients with definite MS, there are 36 with epileptic seizures while among 146 pediatric cases, ≤16 years of age, there are eight with seizures (9). Prevalence rate of epileptic seizures is 1.5% in definite MS patients, 1.3% in adult-onset and 5.5% in pediatric MS patients. Mean annual relapse rate (p≤0.001), mean expanded disability status scale score (p=0.04) and the ratio of patients with pediatric onset (p=0.01) are higher in MS patients with seizures.

Among 63 MS Japanese patients, there are four cases with epileptic seizures (6.35%) at a mean age of 32.5 years (16). MS onset age of patients with seizures is significantly younger than that without seizures by 13.1 years. The patients show brain lesions on MRI.

Eight out of 93 Chinese relapsing-remitting MS patients (8.60% of the cases) have epileptic seizures (7). The seizure type is focal onset in all of them as six patients have secondarily generalized seizures. On EEG, only one patient has focal epileptiform dis-

charges. The frequency of seizures is significantly higher in patients with recurrent seizures than in those with acute-MS-related ones in whom there are diffuse or extensive lesions.

The role of the comprehensive clinical, MRI and ^{18F}FDG PET examinations for the diagnosis of a rare case of glioblastoma multiforme, multiple sclerosis and epilepsy was emphasized (8).

The analysis of the authors' own experience and of 25 scientific papers demonstrates that 1.95% of MS patients experience seizures at any time during life (19). There are three groups of patients experiencing seizures before MS diagnosis: i) in 25 or 7.3% of the cases, seizure is the initial presentation of MS; ii) in 27 or 7.9% of the cases, seizures appear with other signs and symptoms of MS, and iii) in 68 or 20% of the cases, seizures occur years or an unknown period of time before MS onset. The higher prevalence rate of seizures among MS patients than that in the general population indicates a relationship between these diseases.

The median age at occurrence of the first epileptic seizure in 67 MS patients in whom epileptic seizure could be explained by MS only is 33 years (6). Epilepsy is the initial clinical MS manifestation in seven patients. Some 62 patients (92.54%) present with only one or a few seizures, and 18 patients (26.87% of the cases) present with at least one episode of status epilepticus that is fatal in two patients.

There is a positive association between the presence of epilepsy in MS patients and the abnormalities of brainstem auditory and upper short latency somatosensory evoked potentials (18). Thus, brainstem lesions may be the cause of epileptogenicity in MS.

Based on the literature data and our own case report we could draw the conclusion that as epileptic seizures in MS patients may occur due to inflammatory plaques of demyelination it could be suggested that there exists a correlation between MS and structural epilepsy.

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