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Nocturnal myoclonus syndrome (periodic movements in sleep) related to central dopamine D2-receptor alteration

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Abstract The nocturnal myoclonus syndrome (NMS) consists of stereotyped, repetitive jerks of the lower limbs that occur during sleep or wakefulness. NMS is often related with restless-legs syndrome (RLS) and can cause severe sleep disturbances and daytime sleepiness. The efficacy of dopamine agonists in the treatment points to a dopaminergic dysfunction in NMS. We investigated the central dopamine D2-receptor occupancy with [^{123}I] labeled (S)-2-hydroxy-3-iodo-6-methoxy-([1-ethyl-2-pyrrolidinyl]methyl) benzamide (IBZM) (a highly selective CNS D2 dopamine receptor ligand) ([^{123}I]IBZM) and single photon emission tomography (SPET) in 20 patients with NMS and in 10 healthy controls. In most of the patients with NMS there was a lower [^{123}I]IBZM binding in the striatal structures compared to controls. The results indicate that NMS is related to a decrease of central D2-receptor occupancy.

Key words Nocturnal myoclonus syndrome (NMS) · Restless-legs syndrome (RLS) · [^{123}I]IBZM · SPET · Dopamine

Introduction

The nocturnal myoclonus syndrome (NMS) regularly occurs during sleep and consists of a rhythmically dorsal extension of the big toe and/or foot. In some cases it can be extended to a flexion of the leg at the knee and hip, in rare occasions also combined with a flexion of the forearms (for an overview, see [17]). The NMS is often associated with short micro-arousals (for a definition, see [16]) or awakenings and may cause severe sleep disturbances. Prevalence increases with age and affects up to 45% of subjects aged 65 years or older [2]. The therapy response to dopamine agonists [4, 19] and the worsening of NMS by pimozide, a dopamine antagonist [1] and by gamma hydroxybutyrate, a blocker of dopamine release [10, 13] supports the hypothesis of an underlying decreased dopaminergic activity in the central nervous system (CNS). High levels of free dopamine and homovanillic acid (HVA) in the cerebrospinal fluid of a patient with NMS [9] indicate no decrease in biosynthesis but suggest an impaired sensitivity or a loss of postsynaptic dopamine receptors. Supporting this point of view, we recently found in in-vivo investigations using the highly selective CNS D2 dopamine receptor ligand [^{123}I] labeled (S)-2-hydroxy-3-iodo-6-methoxy-([1-ethyl-2-pyrrolidinyl]methyl) benzamide (IBZM) and single photon emission tomography (SPET) a reduced central dopamine D2-receptor occupancy in patients with NMS [15]. However, the interpretation of these preliminary data was limited by the small number and age difference of the controls ($n = 4$) and patients ($n = 12$). For further validation, we enlarged our patient and control group and now present the data of 20 patients and 10 controls, which confirm our preliminary results.

Methods

Twenty patients (6 women, 14 men, mean age 57.9 years) and 10 healthy control subjects (4 women, 6 men, mean age 42 years) were examined. Informed consent was obtained. The study was approved by the ethics committee of the medical faculty of our university and by the Federal Health Institute ("Institut für Strahlenhygiene des Bundesgesundheitsamtes"). Of the patients, 14 suffered from NMS combined with restless-legs syndrome (RLS) and 6 from NMS alone. All patients (except one, who has had a transnasal exstirpation of a chromophobe pituitary adenoma 7 years ago, and two others who suffered from fi-

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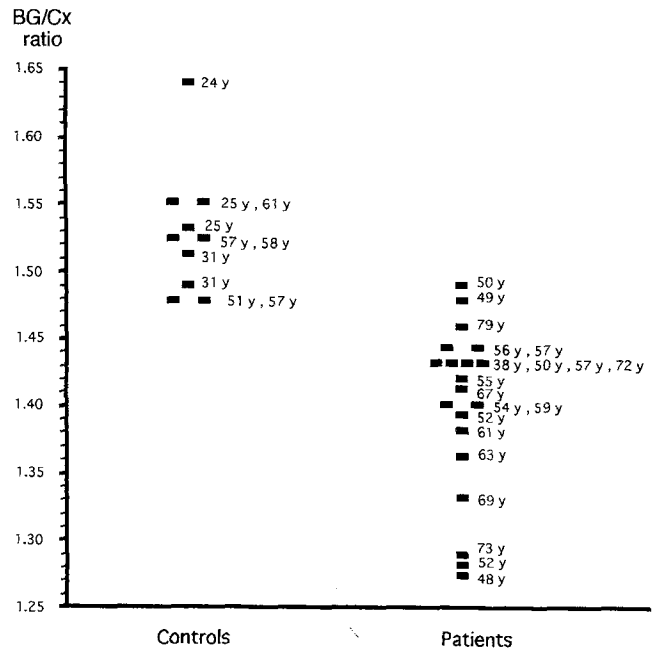

Fig. 1 Distribution of BG/Cx ratios of the 20 patients, (mean BG/Cx = 1.40) with NMS and the 10 controls, (mean BG/Cx = 1.53)

bromyalgia syndrome for several years) were healthy according to history and results of neurological examination, cCT scans, EEG and EMG examination of the lower limbs. Blood and urine biochemistry revealed no abnormalities. Patients and controls were free from drugs interfering with the central dopaminergic system. The all-night polysomnographic recording (PSG) (including EMG of ant. tibialis muscles) and staging were done according to the standard criteria [11] for two consecutive nights.

The SPET acquisition was started 90 min after the intravenous administration of 185 MBq [^{123}I]IBZM and was performed with a rotating gamma camera (Picker International, Cleveland, Ohio, USA) connected to a computer system (Picker Odyssey). A series of 64 images were collected at 6° increments for 30 s each into a 64 × 64 pixel matrix. The tomographic image reconstruction and the adjustment of regions of interest (ROIs) was done as has been previously described [15]. The ratios of "specific" radioligand binding to striatal dopamine D2-receptors (BG/Cx) were expressed as mean and the data obtained were compared by the non-parametric Wilcoxon rank-sum test.

Differences were regarded significant with $P < 0.01$.

Results

The PSGs of the 10 controls showed no sign of NMS. The SPETs of the controls showed "hot spots" within the striatal structures and a low tracer uptake in the surrounding brain. The mean BG/Cx ratio of the 10 control subjects was 1.53 ± 0.05. In contrast, the PSG of the 20 patients revealed in most of the patients a severe sleep disturbance with frequent arousals and stage shifts caused by the NMS (data not given in detail). The SPETs of the patients showed a lower contrast between striatal structures and the surrounding brain, except for the 2 patients with the fibromyalgia syndrome. The mean BG/Cx ratio was 1.40 ± 0.06 and significantly lower compared to the control group ($P = 0.0001$; Fig. 1).

Discussion

The results obtained here, indicate that a reduced D2 dopamine receptor occupancy in striatal structures is related to the presence of NMS. In comparison to our previously published results [15], we observed a normal D2-receptor occupancy in 2 patients of this enlarged sample. In the case of these two patients, the coexsistence of a fibromyalgia syndrome, which is often associated with depression [6], could have influenced the dopaminergic system and might have affected the expression of movements [14]. However, in comparison to the enlarged control group, we found in the SPETs of the patient group a significantly lower mean "specific" [^{123}I]IBZM binding to central dopamine D2-receptors.

The decrease of the receptor occupation did not show a linear correlation with the intensity of the NMS symptomatology. However, the lowest tracer binding was found in the most sleep disturbed patients. Since D2 dopamine receptor density is reported to decrease with increasing age [20], the age difference between controls and patient group has to be taken into account. However, as pointed out elsewhere [15], our semiquantitative approach should "counteract" this effect. In addition, as Fig. 1 shows, an age-associated trend could not be replicated within each group. Therefore, we regard this effect as negligible concerning our results.

Theoretically, these changes in receptor occupancy could be influenced by alterations in the density or sensitivity of dopamine receptors or could result from an in-vivo competition of exogenous or endogenous ligand with the radioligand as demonstrated in animal experiments with dopamine receptor ligands [7]. The worsening of NMS by dopamine D2-receptor antagonists [1] seems to indicate a reduction or functional inactivity of dopamine receptor binding sites in NMS. There is, however, no reason for an in-vivo competition with exogenous ligands in our patients, because both the patients and the controls were free from drugs interfering with the central dopaminergic system. Whether there are high levels of a potential endogenous ligand remains hypothetical. However, if elevated endogenous dopamine would act as a competitor, the therapeutic efficacy of L-dopa in NMS would be paradoxical. Based on these considerations, we believe that the altered receptor occupancy in NMS can not be attributed to artifacts. Since receptor changes are mostly those of density and not of sensitivity, the results indicate that a reduced dopamine receptor density is related to NMS. Our results can explain the increasing prevalence of NMS with age [2], since the reduction of D2-receptors with age [20] may lower the threshold for development of NMS symptomatology.

Dopamine plays a role in sleep/wake regulation [3], and we found the lowest receptor binding in the most sleep-disturbed patients, so that these changes in dopamine receptor occupancy could possibly reflect the sleep disturbance.

Since NMS is also a "movement disorder", findings of a reduced D2-receptor binding in SPET investigations in Huntington's chorea [5], Tourette's syndrome [12], Parkinson's syndrome and Wilson's disease [18] are of interest, especially since Lugaresi described the occurrence of NMS in Huntington's chorea [8].

Chronic treatment of NMS with dopamine agonists could result in changes in D2-receptor density. Recently, we reported an increase in central dopamine receptor occupancy in a 58-year-old patient with NMS after 3 months of successful dopamine replacement therapy [17]. Further longitudinal investigations under different treatment conditions are planned to elucidate the underlying physiology of the NMS. [^{123}I]IBZM SPET imaging provides an available and useful tool for these longitudinal in-vivo studies.

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