

Degenerative pontine lesions in patients with familial narcolepsy

Zmiany zwyrodnieniowe w moście u chorych na narkolepsję rodzinną

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Abstract

Background and purpose: Narcolepsy is characterized by chronic excessive daytime sleepiness with episodic sleep attacks. There are several associated symptoms of narcolepsy: cataplexy (bilateral muscle weakness without loss of consciousness provoked by an emotional trigger, e.g. laughter), sleep paralysis and hypnagogic-hypnopompic hallucinations. Most cases are sporadic; familial narcolepsy contributes to only 1–5% of all cases. While most cases of narcolepsy are idiopathic and are not associated with clinical or radiographic evidence of brain pathology, symptomatic or secondary narcolepsy may occur occasionally in association with lesions caused by tumours, demyelination or strokes of the diencephalon, midbrain, and pons. There are some examples of non-specific brainstem lesions found in magnetic resonance imaging (MRI) in patients with idiopathic narcolepsy.

Material and methods: The authors present eleven patients from a five-generation family with many members who suffer from episodic excessive daytime sleepiness. Narcolepsy was diagnosed in 9 patients. Sleepiness was frequently associated with cataplexy, hypnagogic-hypnopompic hallucinations and sleep paralysis. Improvement in their clinical state was observed during the treatment with modafinil. All probands had MRI of the brain, routine blood tests, EEG, polysomnography, examination of the level of hypocretin in cerebrospinal fluid and evaluation by means of Epworth and Stanford Sleepiness Scales.

Streszczenie

Wstęp i cel pracy: Narkolepsja charakteryzuje się długotrwałym występowaniem senności z napadami zasypiania w ciągu dnia. Występuje kilka objawów towarzyszących narkolepsji: katapleksja (obustronne osłabienie napięcia mięśniowego prowokowane czynnikami emocjonalnymi bez towarzyszących zaburzeń świadomości), porażenia oraz halucynacje przysenne. Większość przypadków narkolepsji to przypadki sporadyczne, narkolepsja rodzinna występuje rzadko, jedynie u 1–5% wszystkich chorych. Narkolepsja jest głównie chorobą idiopatyczną, nie wiąże się z występowaniem zmian radiologicznych w mózgu. Tylko sporadycznie obserwuje się przypadki objawowej narkolepsji spowodowanej zmianami w śródmózgowiu, pniu mózgu lub w moście. W piśmiennictwie istnieją opisy przypadków chorych na narkolepsję sporadyczną, u których stwierdzono występowanie niespecyficznych zmian w pniu mózgu w badaniu za pomocą rezonansu magnetycznego (RM).

Material i metody: W pracy przedstawiono opis 11 osób z napadami wzmożonej senności w ciągu dnia, pochodzących z sześciopokoleniowej rodziny, w której stwierdzono liczne przypadki narkolepsji. Napadom senności u niektórych z badanych towarzyszyły incydenty katapleksji oraz porażenia śródsenne i omamy przysenne. Znaczne zmniejszenie napadów senności w ciągu dnia odnotowano po leczeniu modafinilem. Wszyscy badani oceniani byli za pomocą Skali Senności Epworth, Stanfordzkiej Skali Katapleksji, mieli wykonane badania rutynowe krwi, EEG, polisomnografię, badanie pły-

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Results: In 9 patients with narcolepsy, decreased thickness of the substantia nigra was found and in six of them degenerative lesions in the pontine substantia nigra were also noticed.

Conclusions: The significance of these changes remains unclear. No data have been published until now concerning the presence of any brain lesions in patients with familial narcolepsy.

Key words: familial narcolepsy, magnetic resonance imaging, pontine substantia nigra.

Introduction

Narcolepsy is a chronic central nervous system disorder that is characterized by periods of irresistible excessive daytime sleepiness (EDS). Cataplexy, hypnagogic hallucinations, sleep paralysis and disturbed nocturnal sleep are frequently associated with narcolepsy and may be found in various combinations [1].

The pathophysiology of human narcolepsy is still poorly understood. Predisposition to narcolepsy involves both environmental and genetic factors. First-degree relatives of narcoleptic subjects have 10-40 times higher risk for narcolepsy compared with the general population [2]. The observation that narcolepsy is associated with human leukocyte antigens (HLA)-DR2 was the first indication of an aetiological source. More than 85% of Caucasian and Japanese patients with narcolepsy-cataplexy syndrome have a specific HLA haplotype that includes HLA-DR1501 (formerly called DR15 or DR2) and HLA-DQB1-0602 (formerly DQ1 or DQ6) [3]. In the African-American population the DQB1*0602 allele is present among narcoleptic probands; however, the DRB1*15 allele is found in 75% of cases [4,5]. Genetic factors other than HLA are also likely to be involved. In a canine model of narcolepsy, the disorder is transmitted as a non-major histocompatibility complex (non-MHC) single autosomal recessive trait with full penetrance [6]. The association of HLA subtypes with narcolepsy raises the question of whether narcolepsy is an autoimmune disease. The existence of twins discordant for narcolepsy suggests that non-genetic, environmental factors may play a critical role in the development of narcolepsy.

Brain lesions in the upper brainstem and in the region of the third ventricle may precipitate narcolepsy [7]. Some observations indicate that narcolepsy is associated with the degeneration of posterolateral hypo-

thalamic neurons containing the neuropeptide hypocretin and abnormal neurotransmitter functioning and impaired immune modulation [8]. Recently selective loss of hypocretin immunoreactivity has been reported in the hypothalamus of humans [9].

Wyniki: U wszystkich 9 chorych z narkolepsją stwierdzono zwężenie warstwy zbitej istoty czarnej, u 6 chorych ponadto występowanie zmian zwyrodnieniowych w substancji czarnej pnia mózgu.

Wnioski: Znaczenie opisywanych zmian degeneracyjnych pozostaje niejasne. Dotychczas nie odnotowywano takich zmian u chorych na narkolepsję rodzinną.

Słowa kluczowe: narkolepsja rodzinna, rezonans magnetyczny, substancja czarna pnia mózgu.

thalamic neurons containing the neuropeptide hypocretin and abnormal neurotransmitter functioning and impaired immune modulation [8]. Recently selective loss of hypocretin immunoreactivity has been reported in the hypothalamus of humans [9].

Histopathological studies have revealed that narcolepsy is caused by a loss of hypocretin (Hcrt) neurons [10]. Hypocretin-1 (Hcrt-1) and hypocretin-2 (Hcrt-2) (also called orexin-A and orexin-B, respectively) are newly discovered neuropeptides that are deficient in narcolepsy and in primary hypersomnia. Dysfunction of the hypothalamic hypocretin system plays an important role in the pathophysiology of narcolepsy; normal hypocretin level, however, does not exclude the diagnosis of narcolepsy [11].

While most cases of narcolepsy are idiopathic and are not associated with clinical or radiographic evidence of brain pathology, symptomatic or secondary narcolepsy may occur occasionally in association with lesions (caused by tumours, demyelination or strokes) of the diencephalon, midbrain, and pons [12]. On the other hand, there are some examples of non-specific brainstem lesions found in magnetic resonance imaging (MRI) of patients with idiopathic narcolepsy [13]. The significance of these changes remains unclear. No data have been published until now concerning the presence of brain lesions in patients with familial narcolepsy. We observed nine relatives with familial narcolepsy, and six of them had degenerative lesions in the pontine substantia nigra in routine MRI.

Material and methods

The material consisted of 11 closely related patients from a six-generation family that remains under the

supervision of the Department of Neurology, Military Medical Institute, Warsaw, Poland. Nine persons with previously recognized familial narcolepsy and two with idiopathic hypersomnia were re-evaluated. Nine other persons with formerly diagnosed idiopathic hypersomnia did not agree to take part in the study. Comprehensive family history was reassessed. Narcolepsy and idiopathic hypersomnia definitions proposed by the International Classification of Sleep Disorders (ICSD) (2001) were used [14]. Narcolepsy was defined as the presence of EDS with either unequivocal cataplexy or presence of at least two sleep-onset REM periods on a multiple sleep latency test (MSLT) [15]. Idiopathic hypersomnia was defined as the presence of EDS with frequent daily sleep episodes occurring for more than 6 months, with onset before age 25 and after other sleep disorders had been excluded. Narcolepsy was regarded as mild when there was mild sleepiness or rare cataplexy (less than once per week); moderate when there was moderate sleepiness or infrequent cataplexy (less than daily); and severe when there was severe sleepiness or severe cataplexy (occurring daily). To confirm the diagnosis and to exclude symptomatic cases, all patients underwent a complete general physical and neurological examination. Sleepiness was evaluated with the Epworth Sleepiness Scale (ESS). Common stroke risk factors (hypertension, ischaemic heart disease, atrial fibrillation, obesity, diabetes, smoking, hypercholesterolaemia) were recorded. Well-controlled hypertension was defined with a mean level of serial blood pressure of < 140/90 mm Hg. Carotid arteries Doppler ultrasound and transthoracic echocardiography were performed in all cases. Blood and cerebrospinal fluid were taken for biochemical and hypocretin analysis. All patients underwent overnight polysomnography, MSLT and MRI of the brain. The control group consisted of 10 healthy subjects matched with patients according to age (mean 42 years, range 23-65 years) and sex (5 males, 5 females). Each control subject had brain MRI performed. The MRI study was performed at the Radiological Department on General Electric 1.5 T SIGNA Horizon LX ECHO SPEED PLUS scanners. The examination included the following sequences: SE, T1-weighted axial and transverse scans (5-mm layers), FLAIR, PD and FSE T2-weighted transverse (2-mm layers, distance between layers of 1 mm) and frontal scans (5 mm layers). Special attention was paid to examination of the dopaminergic system. The mean bilateral thickness of the substantia nigra was assessed in every patient.

Results

The mean (range) age in the familial narcolepsy group was 38 (5-78) years; 6 were women. The mean age in persons with idiopathic hypersomnia was 58 (54-61) years; all were men. All probands were Caucasian. The youngest patient with narcolepsy was 5 years old and fell asleep during play in kindergarten. In the case of the oldest, 78-year-old patient, the symptoms of cataplexy dominated and caused several limb fractures. Six of 9 patients with narcolepsy had symptoms of cataplexy, 2 experienced sleep paralysis and all adults (excluding the 5-year-old child) had hypnagogic hallucinations. The mean duration (range) of the disease in the familial narcolepsy group was 23 (2-61) years. Any patients had been previously treated with stimulants (modafinil, methylphenidate). All subjects suffering from cataplexy were taking imipramine. No significant abnormalities in physical or neurological examination were found among analyzed probands. Results of routine haematological, serum and cerebrospinal fluid chemistry tests as well as carotid ultrasound, echo- and electrocardiography examinations were normal. The hypocretin levels assessed in cerebrospinal fluid in all patients were normal. Any of the patients suffered from diabetes or hypercholesterolaemia. Five patients (3 with familial narcolepsy and 2 with idiopathic hypersomnia) had well-controlled hypertension. Three patients (1 with familial narcolepsy and 2 with idiopathic hypersomnia) had obesity. Only 2 patients with narcolepsy had positive results of polysomnography. MRI of 6 patients with diagnosed narcolepsy and in 1 with idiopathic hypersomnia showed similar, bilateral, symmetric hyperintensities in T2-weighted images, probably reflecting degenerative changes in the pontine substantia nigra. No degenerative lesions were observed in the control group. In all familial narcolepsy patients, a symmetric, bilateral decrease of substantia nigra thickness was noticed (mean 2.61 ± 1 mm, range 1.4-3.1 mm) as compared with the control group (3.5 ± 1 mm, range 3-4.0 mm). No other MRI abnormalities, including cerebral white matter lesions or sub- and cortical infarcts have been detected in studied patients and controls. Figure 1 presents examples of MRI scans showing narrowing of the substantia nigra in 2 familial narcolepsy patients and degenerative lesions in 1 adult with familial narcolepsy. Baseline characteristics of the study group are presented in Table 1. Figure 2 shows the genealogical pedigree of the studied family.

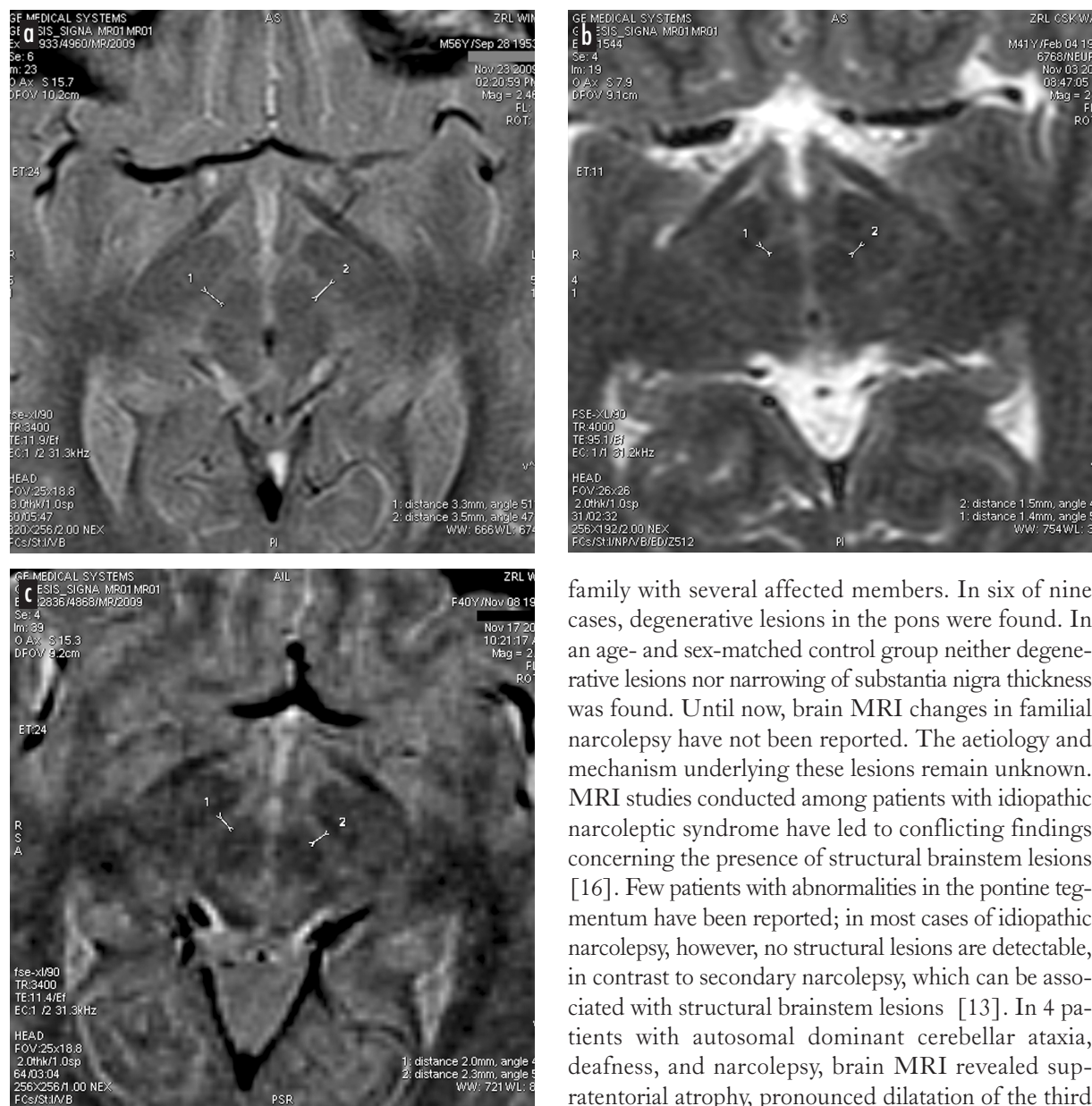


Fig. 1. MRI scans performed at the level of the substantia nigra (SN): a) PD-weighted image in transverse plane obtained in a 56-year-old male from the control group, showing normal SN thickness (left 3.5 mm; right 3.3 mm); b) T2-weighted scan in transverse plane obtained in a 41-year-old male with familial narcolepsy, showing bilateral decrease of SN thickness (left 1.5 mm; right 1.4 mm); c) PD-weighted image in transverse plain obtained in a 40-year-old female with familial narcolepsy, showing bilateral narrowing of SN (left 2.3 mm; right 2 mm) as well as hyperintense, degenerative lesions in SN

Discussion

We observed a high incidence of neurodegenerative changes and narrowing of the substantia nigra in persons with familial narcolepsy who were from a large

family with several affected members. In six of nine cases, degenerative lesions in the pons were found. In an age- and sex-matched control group neither degenerative lesions nor narrowing of substantia nigra thickness was found. Until now, brain MRI changes in familial narcolepsy have not been reported. The aetiology and mechanism underlying these lesions remain unknown. MRI studies conducted among patients with idiopathic narcoleptic syndrome have led to conflicting findings concerning the presence of structural brainstem lesions [16]. Few patients with abnormalities in the pontine tegmentum have been reported; in most cases of idiopathic narcolepsy, however, no structural lesions are detectable, in contrast to secondary narcolepsy, which can be associated with structural brainstem lesions [13]. In 4 patients with autosomal dominant cerebellar ataxia, deafness, and narcolepsy, brain MRI revealed supratentorial atrophy, pronounced dilatation of the third ventricle, low intensity of T2 signal in the basal ganglia, and periventricular high-signal rims [17,18]. In the present analysis, no association between severity of narcoleptic syndrome, disease duration and presence of MRI lesions has been observed. No correlation between pontine abnormalities and concomitant cataplexy or hypnagogic hallucinations and with atherosclerosis risk factors has been noted. Based on the association of narcolepsy with HLA, it may be inferred that neurodegenerative lesions might be caused by an auto-immunological or inflammatory process [19]. The significance of these lesions is unclear, but their location

Table 1. Baseline characteristics of studied patients with familial narcolepsy

No./Sex	Age	Epworth Sleepiness Scale score	Degenerative lesions in substantia nigra in MRI	Polysomnography	Hypocretin level in CSF	Diagnosis according to ICSD criteria
1/F	36	17	yes	+	normal	narcolepsy
2/F	30	14	yes	-	normal	narcolepsy
3/F	68	12	yes	-	normal	narcolepsy
4/M	5		yes	-	normal	narcolepsy
5/M	41	8	no	-	normal	suspected narcolepsy
6/M	54	7	yes	-	normal	hypersomnia during daytime
7/M	61	12	no	-	normal	hypersomnia during daytime
8/M	16	9	no	-	normal	suspected narcolepsy
9/F	51	19	yes	+	normal	narcolepsy
10/F	16	16	no	-	normal	narcolepsy
11/F	78	9	yes	-	normal	narcolepsy

M – male, F – female, MRI – magnetic resonance imaging, CSF – cerebrospinal fluid, ICSD – International Classification of Sleep Disorders

corresponded to the pontine rostral oral reticular formation, which is the suggested location of the neuronal network generating REM sleep.

Numerous studies concerning the basic mechanisms of sleep regulation have led to consideration of the role of several neurotransmitter or neuromodulator systems, including noradrenergic, serotonergic, cholinergic, adenosinergic, histaminergic, hypocretin and also dopaminergic systems [20]. The association of narcolepsy with deficiency of a specific neurotransmitter, hypocretin, is reminiscent of the association between

Parkinson disease (PD) and dopamine. The substantia nigra as a part of the dopaminergic system is involved in development of PD. PD and PD-like conditions have often diverse presentations of disturbed sleep and can be classified by their predominance during nighttime, daytime, or both times of day. Night-time disturbances represent the absence of normal REM atonia or REM sleep behaviour disorder. The prevalence of these symptoms ranges from 74% to 98% in patients with PD and may predate any classic signs of parkinsonism, by more than a decade, although many

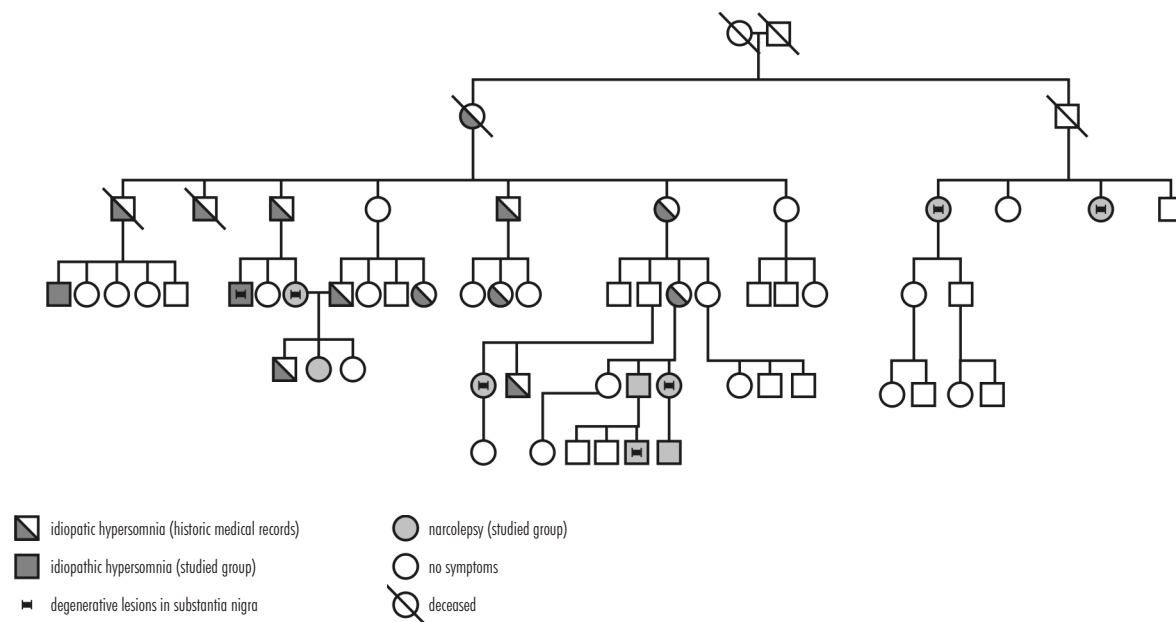


Fig. 2. Six-generation pedigree displaying affected members of the family

(but not all) parkinsonian patients may show such behaviours intermittently throughout the course of their disease [21]. All those symptoms are also characteristic for narcolepsy, suggesting that these diseases may in part have a common cause. Massive loss of Hcrt neurons and hypothalamic melanin concentrating hormone (MCH) neurons in PD has been reported. The loss of Hcrt and MCH neurons is significantly correlated with the clinical stage of PD, not disease duration, whereas the loss of neuromelanin cells is significantly correlated only with disease duration [22].

Some findings provide evidence for the effectiveness of intranasal orexin-A in alleviating cognitive deficits produced by loss of sleep [23]. Hypocretin-containing cells are located exclusively in the lateral and posterior hypothalamus, with widespread projections of the nerve fibres into the olfactory bulb, cerebral cortex, thalamus, hypothalamus, and brainstem. Recent work indicates that the hypocretin and MCH cells were lost throughout the anterior to posterior extent of their hypothalamic distributions in PD [24]. Hypocretin neurons in the lateral hypothalamus and adjacent perifornical area innervate midbrain dopamine neurons that induce locomotor activity [25]. Dysfunction of the orexin modulation of dopaminergic neurons in the ventral tegmental area in narcolepsy may be important in triggering attacks of cataplexy. Cataplexy is one element of narcolepsy that is absent in PD. However, the presence of cataplexy is not necessary for the diagnosis of narcolepsy [12]. The degeneration of the nigrostriatal system characterizing PD may either potentiate or ameliorate the deficits caused by Hcrt cell loss. Degenerative changes in Hcrt cells in the hypothalamus were correlated with disease progression in the substantia nigra [26]. The threshold level of Hcrt cell loss for the onset of symptoms in narcolepsy has not been determined.

Some studies in which CSF hypocretin levels in PD were assessed have yielded contradictory results with frequently abnormally low levels, but within the normal range in some patients as well [27]. In narcolepsy, the level was low more often, but in familial narcolepsy it may be within the normal range [28]. Hcrt deficiency is highly associated with narcolepsy with cataplexy (89.5%) and is found in 95.7% of patients with narcolepsy-cataplexy who are HLA DQB1*0602-positive. The relationship between Hcrt-1 levels and narcolepsy without cataplexy or the DQB1*0602 allele is less clear [29]. In analyzed cases, we did not find abnormalities of Hcrt levels in CSF; normal Hcrt levels,

however, are frequently found in narcoleptic families. In SPECT examination of narcoleptic patients, elevation of D2-receptor binding was found that correlated with the frequency of cataplectic and sleep attacks, which proved the involvement of the striatal D1 and D2 dopaminergic neurotransmitter system in the pathophysiology of the narcoleptic syndrome [30].

Conclusions

1. This study is the first to show high incidence of MRI lesions in the substantia nigra in patients with familial narcolepsy.
2. Further investigations are necessary to explain the relationship between pathophysiology of familial narcolepsy and neurodegenerative lesions in the substantia nigra.

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Disclosure

Authors report no conflict of interest.

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