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CASE REPORT

Narcolepsy with cataplexy and Parkinson's disease

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Abstract

We present the case of an 86 year old female, in whom narcolepsy with cataplexy (NC) manifested at 52 years of age. She was treated by an amphetamine-like drug phenmetrazine and tricyclic antidepressants for more than 10 years. Hypokinetic-rigid syndrome manifested at 83 years of age and Parkinson´s disease (PD) was diagnosed. Detailed examination at the age of 86 confirmed the previous diagnosis of NC and the diagnosis of PD. Severe periodic limb movements in sleep, severe sleep apnea, REM sleep behavior disorder and restless legs syndrome, which are frequently comorbid in NC and PD, were revealed. The patient's somnolence worsened, apparently accentuated by pramipexole treatment, as changing therapy to levodopa led to a reduction of sleepiness.

INTRODUCTION

Narcolepsy with cataplexy (NC) is a chronic neurological disease with a prevalence of approximately 0.045% in North America and Europe (Ohayon *et al.* 2002). The manifestations of NC are excessive daytime sleepiness and cataplexy, and roughly half of patients experience hypnagogic hallucinations and sleep paralysis. Additionally, most patients have fragmented nighttime sleep. Dysregulation of REM sleep is typical, with sleep onset REM periods (SOREMp) occurring within the first 15 minutes of sleep, at day and at night (Dauvilliers *et al.* 2007). Pathologic basis of the disease is a deficiency of neurons in the lateral hypothalamus that produce hypocretin (orexin) (Thannickal *et al.* 2009). The HLA DQB1*06:02 allele is present in nearly 100% of cases (Mignot *et al.* 1997). NC is very likely a T-cell-mediated autoimmune disease similar to other HLA-associated diseases such as type 1 diabetes or celiac disease, with its onset triggered by an external stimulus such as streptococcal infection or vaccination against H1N1 influenza (Partinen *et al.* 2014). NC may manifest suddenly at any time during life, with incidence peaking at 15 years of age and a second peak at 35 years of age (Dauvilliers *et al.* 2001). Commonly, there is a long latency between symptomatic onset and diagnosis in narcolepsy (Carter *et al.* 2014), and it is believed that some patients remain undiagnosed even in developed countries. The intensity of the cardinal manifestations of NC, somnolence and cataplexy, usually remain stable throughout life but may also decrease slightly with age (Nevsimalova *et al.* 2013, Sonka *et al.* 1991).

Parkinson´s disease (PD) is a chronic, progressive neurodegenerative disease characterized clinically by presence of akinesia together with rigidity,

resting tremor and/or postural instability, with an estimated prevalence of approximately 0.3% of the population in industrialized countries, affecting roughly 1% of people over 60 years of age (de Lau & Breteler 2006). PD arises due to the gradual deposition of alpha-synuclein protein in neurons presumably advancing from the medulla oblongata to the cortex, with motor impairment due to involvement of the substantia nigra pars compacta (Braak *et al.* 2006). The accumulation of inclusion bodies and subsequent neuronal degeneration affects not only the dopaminergic system, but other neurotransmitter systems such as cholinergic and hypocretinergic as well as other parts of central and peripheral nervous system. Thus, manifestations are not only motor but also include cognitive impairment, depression, anxiety, behavioral disorders, hyposmia, color vision impairment, autonomic dysfunction, somnolence and impaired atonia in REM sleep (Postuma *et al.* 2009).

A patient was referred to our clinic twice over a period of 30 years with differing symptoms. At the first evaluation the patient was diagnosed with NC. At the second evaluation patient was diagnosed with PD and the original diagnosis of NC was confirmed. Considering the rarity of the simultaneous occurrence of these two diseases, we present the following case.

CASE REPORT

The patient was a Caucasian female patient of Czech heritage, and at the time of the second examination in 2013 was 86 years old. The family history was negative with regard to sleep disorders as well as neurodegenerative disease. No history of smoking or alcohol abuse was reported. The patient had a history of Scheuermann disease. At 55 years of age, the patient underwent hysterectomy due to uterine fibroids, and at 68 years of age underwent cholecystectomy due to lithiasis. From 85 years of age the patient has been treated for mild hypothyroidism. At 73 years of age the patient suffered a myocardial infarction and currently has mild dilated cardiomyopathy and mild dyspnea (NYHA II). The patient further suffers from chronic bronchitis and at 80 years of age had interlobar pleuritis. At 84 years of age a tumor was detected in the colon; the patient has not undergone surgery and the only clinical manifestation of tumor is persistent, progressive weight loss (Body Mass Index 21.3 in year 2013). The patient's mood has not declined (Beck Depression Inventory – 5 in year 2013).

The patient has suffered from somnolence from 52 years of age and cataplexy from 55 years of age. The onset of symptoms was not associated with any event. At 55 years of age the patient was clinically examined at our department. At this time SOREMp was detected using a single nap afternoon sleep study (Roth *et al.* 1986), and narcolepsy with cataplexy was diagnosed. The patient was subsequently treated with the central stimulant phenmetrazine (synthetic compound similar to amphetamine), as well as with the tricyclic antidepressant imipramine and later clomipramine (Sonka *et al.* 2014). At approximately 68 years of age, when already retired, the patient stopped taking medication against somnolence and cataplexy as the symptoms without medication became weaker and did not bother her.

Parkinsonian syndrome with symmetric rigidity and akinesia in the upper extremities and mild gait difficulty with instability was diagnosed when the patient was 83 years of age. The patient's symptoms improved after initiating pramipexole 0.7 mg bid. At that time, the patient reported the reoccurrence of hypersomnia and frequent falls. Frequent daytime sleep attacks of variable duration with refreshing effect were reported. Somnolence was present at rest as well as during social activities. The Epworth sleepiness scale (ESS) score was 14 while hospitalized. The patient reported falls, mostly backwards, which were not triggered by emotion or associated with decreased muscle tone; they were sometimes preceded by presyncopal feeling, but mostly were related to gait instability.

The patient did not report any other symptoms that would indicate cataplexy in recent years, nor did the patient report hypnagogic hallucinations or sleep paralysis. Nighttime sleep from 22:30 to 8:00 was reported to be somewhat intermittent, without snoring. At night the patient had numerous lively, rather pleasant dreams with sleep talking. The patient awakened in the middle of a dream, which she remembered. She awoke several times with minor injuries after falling from bed. The patient was refreshed after nighttime sleep. In the period before initiating antiparkinsonian therapy the patient had manifestations of restless legs syndrome (RLS) several times per week, which were moderately intense and compelled her to arise and walk.

Clinical examination (year 2013)

The patient presented with parkinsonian syndrome with mild hypophonia and hypomimia, slightly asymmetric bradykinesia and rigidity of the upper and lower extremities with left-sided predominance, stooped posture, shuffling gait with infrequent freezing, without recovery on the pull test. Tremor was not present. She scored 28 points on the motor subscore of the Unified Parkinson Disease Rating Scale (UPDRS-III). In addition to parkinsonian syndrome, mild psychomotor slowing, mild cognitive dysfunction (Mini-Mental State Exam score 26) and polyneuropathy were present.

Night polysomnography showed a sleep latency of 2 minutes and REM sleep latency of 1 minute. Sleep was extremely fragmented by frequent periodic limb movements (PLM); the average number of PLM per one hour was 122, and by severe sleep apnea and hypopnoea (apnoe-hypopnoe index 43, oxygen desaturation index 38) including periods of Cheyne-Stokes respiration. Sleep respiratory events were mostly obstructive. Sleep efficiency was 65%. In REM sleep, insufficient

atonia and frequent gestures, facial movements, voiceless articulation and incomprehensible speech were observed.

The Multiple Sleep Latency Test (MSLT) performed the next day confirmed narcolepsy. The average sleep latency was 0.2 minutes and 2 SOREMp occurred within five tests. REM sleep without atonia and dream-enacting behavior also occurred within REM sleep periods during the MSLT.

HLA haplotype DQB1*06:02 was detected.

Brain magnetic resonance imaging (MRI) showed cortical and subcortical atrophy of intermediate severity, hyperintense lesions of presumed vascular origin on T2-weighted images located in the periventricular and deep white matter. Calcifications were present in the *globus pallidus* according to computed tomography (CT).

Clinical diagnosis and therapy

During hospitalization in 2013 (age 86 years) the original diagnosis of NC was confirmed according to International classification of sleep disorders 2nd edition (American Academy of Sleep Medicine 2005) and REM sleep behavior disorder (RBD), obstructive sleep apnea, periodic limb movements in sleep (PLMS) associated with RLS (not currently present, likely due to antiparkinsonian therapy) were additionally identified. According to clinical findings and history of responsiveness to dopaminergic therapy the diagnosis of PD was confirmed. Falls in the recent history were considered a manifestation of postural instability due to PD with a possible contribution of sensory ataxia due to mild polyneuropathy, rather than cataplexy.

PD treatment was switched because of marked sleepiness coinciding with the initiation of pramipexole treatment; pramipexole was replaced with 250/50 mg levodopa/carbidopa ¾ tablet three times daily (562.5 mg levodopa, i.e., higher equivalent dose). After agreement with the patient and her family, treatment for sleep apnea was not initiated. Further examination did not reveal any other potential cause of polyneuropathy other than colon tumor. At the follow-up examination 2 weeks later, the patient and her family reported a significant reduction in sleepiness (ESS 11) and subjective improvement of movements and gait stability leading to marked reduction of falls. Objective improvement of hypokinesia was reflected in a slightly decreased UPDRS III score of 25.

In the following two years the patient continued to gradually lose weight, but the neurological status remained practically unchanged.

DISCUSSION

Coincident NC and PD

To the best of our knowledge, we present the sixth documented case of combined NC and PD. Two subjects have been reported by the Barcelona group (Gaig *et al.* 2010), one subject by the Swiss Italian group (Economou *et al.* 2012) and two at the University of California San Francisco (Christine *et al.* 2012). Symptoms of NC preceded symptoms of PD for many years in all reported patients.

Symptoms common to NC and PD

Sleepiness is the key symptom of narcolepsy with and without cataplexy. Sleepiness in PD has been reported for a number of years, noted to be a manifestation of PD itself and demonstrated to be present even in the absence of dopaminergic replacement (Arnulf *et al.* 2002, Roth *et al.* 2003). It is usually aggravated by dopamine replacement therapy, especially by dopamine agonists (Frucht *et al.* 1999). In NC and PD, sleepiness is considered independent of other conditions that disturb night sleep such as sleep apnea and PLM in sleep. Narcolepsy subjects present multiple SOREMp within MSLT, however this feature may be absent (Sonka *et al.* 2014). PD patients may show SOREMp even on daytime naps (Monaca *et al.* 2006, Roth *et al.* 2003, Bliwise *et al.* 2013), particularly in advanced forms of PD (Wienecke *et al.* 2012), although not all studies have confirmed this (Buskova *et al.* 2011). In the present case, increased sleepiness during the last period was likely accentuated by pramipexole treatment.

Nighttime sleep is impaired in NC and PD, even in the absence of any disturbing conditions such as sleep apnea and PLM in sleep. Nighttime sleep in patients with PD and NC is commonly accompanied by PLM, which in both diseases is considered a comorbidity rather than a separate nosological unit (American Academy of Sleep Medicine 2005). However, PLM is also an optional symptom of RLS (American Academy of Sleep Medicine 2005), which was diagnosed in our patient. RLS in NC is increasingly described (Plazzi *et al.* 2010), concurrent PD and RLS has been described, and some work suggests that severe RLS may be considered an early stage of PD (Wong *et al.* 2014). Another common manifestation of NC and PD is RBD. RBD in narcolepsy occurs in approximately one third of patients, in all age groups (Nevsimalova *et al.* 2013). In PD, the incidence of RBD increases with patient age and disease duration (Sixel-Doring *et al.* 2011, Wienecke *et al.* 2012), however RBD may also precede the development of motor manifestations (Schenck *et al.* 1996). The presence of RBD in PD patients indicates a greater likelihood of further non-motor manifestations (Neikrug *et al.* 2014) and an increased likelihood of developing cognitive impairment (Anang *et al.* 2014). A similar association with other manifestations and comorbidities has not been reported in RBD associated with NC. RBD was mentioned in both Barcelona cases (Gaig *et al.* 2010) and was diagnosed in our patient as well. Pramipexole may have had a favorable influence on the intensity of RBD (Schmidt *et al.* 2006), however, RBD did not worsen after the discontinuation of pramipexole in our patient.

The appearance of sleep-related manifestations in NC and PD suggests that late-onset narcolepsy in PD patients may remain unrecognized. Distinguishing PD with extreme sleepiness from narcolepsy without cataplexy is difficult. This has yet to be designated as either somnolence due to PD (Rye *et al.* 1999), or as narcolepsy secondary to PD, even in case of low levels of hypocretin in the cerebrospinal fluid (Maeda *et al.* 2006, Wakai & Kanbayashi 2011). Recently, the high occurrence of symptoms suspected of NC (Ullanlinna Narcolepsy Scale ≥14 and ESS ≥11) has been observed in 9.3% of the PD subjects. Ullanlinna Narcolepsy Scale ≥14 and ESS ≥11 were associated with RBD, all types of hallucinations, daytime sleepiness, fatigue, insomnia, and intense dreaming (Ylikoski *et al.* 2015) documenting close relationship between NC and PD.

Common neuropathophysiological elements of NC and PD

NC is characterized by the depletion of the neuropeptide hypocretin due to selective loss of hypocretin neurons in hypothalamus (Mignot *et al.* 2002). Daytime sleepiness in PD may be due to lower hypocretin transmission despite the fact that evidence both in support of (Drouot *et al.* 2003, Thannickal *et al.* 2007, Fronczek *et al.* 2008) and against (Baumann *et al.* 2005) this hypothesis has been presented in the literature. The pathophysiology of RBD in NC and PD appears to differ.

Amphetamine therapy may also play a role in coincident narcolepsy and PD since amphetamines can damage dopaminergic axons and PD patients reportedly have a higher rate of amphetamine use than controls (Garwood *et al.* 2006). Not surprisingly, since amphetamine and amphetamine-like drugs were the only central stimulants available in the 20th century, all previously reported cases of coincident NC and PD, as well as the presented case, were treated by these compounds. However, it is a case only of six patients in total. In conclusion, there is no compelling evidence that long-term amphetamine treatment increases the risk of developing PD.

CONCLUSION

The present case with a typical history of NC with PD appearing later in life illustrates common manifestations related to sleep in these two diseases. Similar cases have been only rarely reported in the literature and we believe that co-occurrence of NC and PD in our patient is a co-incidence rather than a reflection of common pathophysiology.

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