Neurologist-in-training

The aim of this section is to prepare the neurologist-in-training for the FMH examination, to confront her or him with specific problems of everyday neurological practice, and to give him or her updates on recent controversies in clinical neurology.

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A 40-year-old midwife with diagnosed migraine, asthma and chronic iron deficiency since the age of 18 complained about tiredness, sleepiness and serious problems in concentrating for a period of about one year. The problems began about one month after a swine flu vaccination and later also presented as involuntary sleep lapses when travelling by train or while driving. She also noticed an exaggerated physical exhaustion and occasional sudden bouts of weakness in the knees. Sleepiness was most prominent after night shifts when driving home from work, and she attributed her problems to the shift work that she did as a midwife in addition to household work. In parallel to her sleepiness, she noticed an increase in appetite and a weight gain of 10 kg within one year.

Her father and a sister had been diagnosed with depression and a brother has reported similar symptoms. The family doctor found an Epworth Score of 15, no abnormal signs in the physical examination and normal values in laboratory investigations. The iron status was corrected by intravenous iron substitution, but this measure did not change the complaints.

MCQ

1. *At this stage, what would be your primary diagnostic suspicion?*

A Drop attacks and hypersomnia of cerebrovascular aetiology
B Non-Organic Hypersomnia due to depression
C Narcolepsy cataplexy syndrome
D Familial Hyperekplexia
E Idiopathic hypersomnia with long sleep duration

Specific questioning revealed emotional stimuli such as laughing as the main cause of the sudden bouts of weakness in the knees with preserved consciousness, which is suggestive of cataplexy. Cataplexy, when only mild, would primarily affect the jaw, face or neck muscles and spread to the lower body parts when more severe. She also reported occasional sleep-paralysis before falling asleep. No hallucinations were reported but vivid and sometimes terrifying dreams were reported. Night sleep was often disturbed by several periods of wakefulness but daytime sleepiness was not related to bad nights. Sleepiness was not a problem when getting up in the morning but often started just 2 hours after getting up. Daytime naps had a restorative effect on sleepiness lasting for a few hours and when no naps were possible automatic behaviour could develop.

At this stage, narcolepsy-cataplexy was certainly the primary suspected diagnosis.

2. *Which element is rare (1–2%) in narcolepsy-cataplexy?*

A A positive family history for narcolepsy-cataplexy
B Relatively well rested when getting up in the morning and restorative daytime naps
C Disturbed night sleep of normal duration
D Weight gain at onset of disease
E Predominant affection of cranial muscles in milder cataplexy

3. *Which of the investigations below has the most specific diagnostic value for narcolepsy-cataplexy today?*

A Genetic testing
B Human leukocyte antigen (HLA) testing
C Hypocretin in the cerebral spinal fluid (CSF)
D Multiple Sleep Latency test (MSLT)
E Polysomnography

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The Epworth score is most valuable to separate tiredness or fatigue from excessive daytime sleepiness (EDS) [1] and often scores >14 in narcolepsy. EDS in narcolepsy may start just 2 hours after awakening and also presents in active situations while working or eating. Sleep drunkenness immediately after awakening has been reported by 50% of patients [2]. Daytime napping of only 10 to 20 minutes can often restore wakefulness for a period of a few hours. Sleep onset at night is quick and night sleep may be normal in

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quality and duration at the onset of the disease or superficial and disturbed in the later course, but not particularly deep. Sleep drunkenness in connection with a more continuous sleepiness during the whole day without the restorative effect of naps is suggestive of "Idiopathic Hypersomnia" or "Non-Organic Hypersomnia", both being important differential diagnoses [3]. In the absence of cataplexy, other REM phenomena such as sleep paralysis or hypnagogic hallucinations can support the diagnosis of mono-symptomatic narcolepsy but are only reported by ~60% of patients.

Cataplexy is a bilateral sudden loss of muscle tone provoked by emotions, most often laughing. Weakness in the face or neck muscles is more specific for clear cut cataplexy than the often reported weakness in the knees, which also occurs in healthy persons (pseudo-cataplexy).

The more frequent sporadic form of narcolepsy is probably due to an auto-immune process starting in genetically predisposed subjects because of a hitherto unknown external factor – a still unproven hypothesis [4]. A specific gene for narcolepsy has not been found yet. The genetic predisposition is characterised by the presence of the human leukocyte antigen (HLA) allele DQB1*0602 in >90% of narcolepsy-cataplexy cases and in ~40% of the mono-symptomatic form of narcolepsy which is still somewhat greater compared to the normal population (~24%). The subsequent autoimmune process destroys the hypocretin-producing cells in the lateral hypothalamus and explains the absence of hypocretin in the CSF in ~90% of narcolepsy-cataplexy cases [5]. The weight gain observed in many narcolepsy patients is considered to be a consequence of hypocretin loss, since the same neurotransmitter, also known under the name "Orexin", plays a role in food intake.

In mono-symptomatic narcolepsy, hypocretin is normal in the great majority (>70%) of patients, and diagnostically is not helpful here. Hypocretin is most helpful in case of doubtful or atypical cataplexy.

The external factor suspected to trigger the autoimmune process is largely unknown. Infections, particularly streptococcus infections, and vaccinations, but also head trauma and psychic stress reactions have been suspected. A causal relationship with the swine flu vaccination is actually disputed because of a rise of the incidence of narcolepsy in adolescents in Finland and Sweden, which could not be confirmed in other countries until now. Regular updates can be found under http://vaesco.net and www.ema.europa.eu.

The familial form of narcolepsy cataplexy is rare [6]. Only ~1–2% of diagnosed cases with narcolepsy-cataplexy report affected relatives. In this rare form, HLA is positive in 50%.

Additional investigations

HLA was positive for DQB1*602. Actigraphy in a week without night shifts showed a regular sleep–wake schedule and a nocturnal inactivity period (presumably representing sleep) of 8 hours on average, excluding sleep insufficiency syndrome and irregular sleep–wake rhythm. Polysomnography revealed a low sleep efficiency of 80% and excluded sleep apnoea syndrome and periodic leg movements in sleep (PLMS). The multiple sleep latency showed a mean sleep latency of 2.8 minutes and REM sleep in three of five trials, fulfilling the criteria of "Sleep Onset REM" (SOREM). In the maintenance of wakefulness test (MWT), the patient had a mean latency of 7.5 minutes, raising concerns about her ability to drive.

According to the international diagnostic criteria [3], narcolepsy-cataplexy can be diagnosed by confirming clear cut cataplexy in the patient's history in addition to EDS. In case of atypical or doubtful cataplexy, as well as to diagnose mono-symptomatic narcolepsy, a short sleep latency of <8 minutes and 2 or more SOREMs need to be found in the MSLT. Most importantly, the diagnosis can still not be confirmed unless an irregular sleep schedule or other causes of EDS, such as depression, are ruled out. Therefore, we recommend actigraphy for 7 to 14 days preceding the MSLT and a psychiatric consultation if appropriate.

Hypocretin analysis was not performed because typical cataplexy was sufficient to make a diagnosis of narcolepsy-cataplexy.

MCQ

4. How would you treat this narcoleptic patient who is much disturbed by EDS, cataplexy and disturbed nocturnal sleep?

A Methylphenidate (Ritalin®) during the day and a benzodiazepine at night
B Gamma-Hydroxy-Butyrate (GHB, Xyrem®) at night and Modafinil (Modasomil®) during the day
C Antidepressant with activating effects such as Clomipramine (Anafranil®), Bupropion (Wellbutrin®) or Reboxetin (Edronax®) during the day and a sedative antidepressant such as Mirtazapine (Remeron®) or Trimipramine (Surmontil®) at night
D Coffee, Guarana and other over-the-counter compounds, eventually combined with Etilefrin (Effortil®)
E Dextroamphetamine (Dexedrin®) or Methamphetamine in combination with antidepressants such as Clomipramine (Anafranil®)

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The treatment of narcolepsy-cataplexy is still symptomatic, until a better understanding of the pathogenesis allows a treatment of the causes. In cases when the diagnosis is made within the initial 6 months, some experts propose an early treatment with intravenous immune globulines (IVIG), but others do not.

The first choice treatment in narcolepsy-cataplexy patients suffering from all major complaints (EDS, cataplexy and disturbed sleep) is a combination of Modafinil or Methylphenidate against EDS, and GHB against cataplexy and disturbed night sleep [7]. In cases when GHB is not effective or not tolerated, activating antidepressants can be combined with stimulants. Despite the limited experience with new antidepressants in treating cataplexy, side effects may be less frequent with Reboxetin or Bupropion compared to the well-known Clomipramine.

In Switzerland, the initial prescription of Modafinil in narcolepsy-cataplexy is formally accepted, although insurance firms often, but incorrectly, require a previous treatment trial with the cheaper Methylphenidate. Scientific evidence about the effects and side effects is better established in Modafinil than it is in Methylphenidate. Patients should be informed about the most frequent side effects in both, such as headache or an increase of pre-existing migraine headache, nervousness, tremors and development of arterial hypertension. A relative contraindication exists in patients with cardiovascular or psychiatric disorders.

Xyrem® must initially be prescribed by a neurologist. Dosages between 2.25 and 9 g (not mg!) per day can be used. A gradual increase of dose is recommended according to its effects and possible side effects reported in control-visits or telephone consultations every 3 months. This drug, which is taken like a hypnotic at bedtime and a second time 3 hours later, is not compatible with alcohol and other sedating drugs. The effect on disturbed night sleep is observed as soon as the effective dose is reached, while its positive effects on cataplexy can gradually increase over months. Side effects are most often due to its sedative effect lasting a few hours after intake. Somnambulism, enuresis and confusion also can occur as consequences of the elevated arousal threshold and elderly patients might be at risk for falls if they have to get up within this period.

Obviously, whilst the efficient therapy is not established, the patient is advised not to drive. We should however be aware that the risk of an accident due to sleepiness (Sekundenschlaf) is not only dependent on the severity of sleepiness, but also on the subject's ability to perceive his or her sleepiness early and react accordingly. Scientific studies have shown a higher incidence of sleepiness-induced accidents in untreated narcolepsy compared to the average incidence in a general population [8], but not when compared to other sub-populations such as healthy young males. Moreover, the overall accident risk in narcolepsy (all types of accidents included) is not necessarily increased in comparison to the general population. In treated narcoleptics, the accident risk is most probably not increased compared to the acceptable range of risk within our society.

In patients who have already reported accidents whilst driving due to sleepiness, subjective judgment may be impaired and we recommend an MWT under optimal therapy, also assessing subjective sleepiness signalling [9].

Answers to MCQ

1: C; 2: A; 3: C; 4: B

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