



## Cataplexy in a patient treated for prolactinoma: Case report

### Katapleksija kod bolesnice sa prolaktinomom

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#### Abstract

**Introduction.** Isolated cataplexy, without the presence of narcolepsy, is a relatively rare condition, and can be regarded as attacks of motor inhibition with loss of muscle tone and areflexia. The diagnosis of cataplexy relies on the clinical presentation and medical history and it is rarely confirmed by video-polygraph. We here described a female patient treated for prolactinoma who developed isolated cataplexy. **Case report.** A 53-year-old female treated with bromocriptine for a macroprolactinoma presented with sudden episodes of weakness and toneless legs leading to falls and injuries on several occasions. Cardiovascular evaluation was completely normal. Psychiatric evaluation showed no psychotic phenomenology or suicidal ideas. Pituitary imaging showed empty sella with a remnant sellar mass with infra- and parasellar extension. Neurological examination revealed mild obstructive sleep hypopnea/apnea. Electroencephalographic monitoring during sleep and awakening did not show appearance of epi potentials. HLA haplotyping was positive for HLA-DR3,16;DR51;DQ1 allele, confirming a diagnosis of isolated cataplexy. Treatment included tricyclic antidepressants and reduction of bromocriptine dosage with resolution of cataplexy. **Conclusion.** We reported the first case of isolated cataplexy most probably associated with dopamine agonist treatment for prolactinoma.

#### Key words:

prolactinoma; pituitary neoplasms; cataplexy; comorbidity; diagnosis; magnetic resonance imaging; genetics, medical; treatment outcome.

#### Apstrakt

**Uvod.** Izolovana katapleksija bez prisustva narkolepsije relativno je retko stanje i može se smatrati napadom motorne inhibicije sa gubitkom mišićnog tonusa i arefleksijom. Dijagnoza katapleksije se oslanja na kliničku prezentaciju i medicinsku dokumentaciju i retko se potvrđuje video-poligrafom. Opisali smo bolesnicu tretiranu zbog prolaktinoma koja je razvila izolovanu katapleksiju. **Prikaz bolesnika.** Kod bolesnice stare 53 godine lečene bromokriptinom zbog makroprolaktinoma ispoljile su se iznenadne, nagle epizode slabosti i nedostatak mišićne snage u nogama, koji su doveli do padova i povreda u nekoliko navrata. Kardiovaskularna evaluacija bila je potpuno normalna. Psihijatrijska procena je pokazala da bolesnica nije imala psihotičnu fenomenologiju ni samoubilačke ideje. Snimci hipofize pokazali su prazno tursko sedlo (*empty sella*) sa ostatkom selarne mase sa infra i paraselarnim širenjem. Neurološki pregled pokazao je blagu opstruktivnu hipopneju/apneju u snu. Elektroencefalogramski nadzor u toku sna i buđenja nije pokazao epi potencijale. HLA halotipizacija bila je pozitivna za HLA-DR3,16, DR51, DK1 alele, potvrđujući dijagnozu izolovane katapleksije. Terapija sa uključenjem tricikličnih antidepresiva i smanjenjem doze bromokriptina dovela je do rezolucije katapleksije. **Zaključak.** Prikazan je prvi slučaj izolovane katapleksije koji je najverovatnije povezan sa terapijom prolaktinoma dopaminskim agonistom.

#### Ključne reči:

prolaktinom; hipofiza, neoplazme; katapleksija; komorbiditet; dijagnoza; magnetna rezonanca, snimanje; genetika, medicinska; lečenje, ishod.

## Introduction

Narcolepsy, cataplexy, and emotions constitute a special triad. Cataplexy and sleep paralysis can be regarded as attacks of motor inhibition with loss of muscle tone and areflexia. The diagnosis of cataplexy is thus based on the medical history and on clinical observations and it is rarely confirmed by video-polygraph<sup>1</sup>. Cataplexy is defined as a transition phase from wakefulness directly into an atonic state as seen in rapid eye movement (REM) sleep, that is triggered by emotional stimuli. Supportive therapy includes medication with REM suppressing properties.

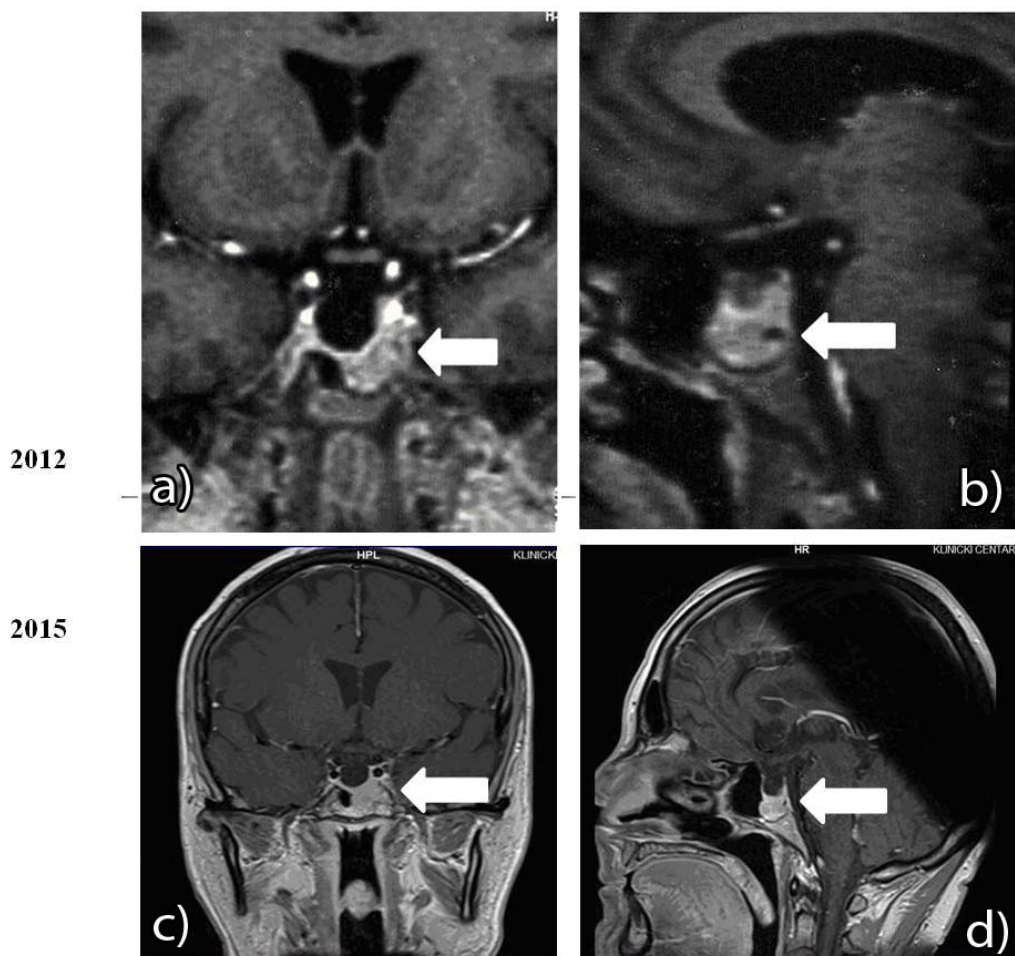
Isolated cataplexy should always be considered in the differential diagnosis of a patient with drop attacks. Drop attacks are characterized by spontaneous falls followed by quick recovery<sup>2</sup> as is observed in patients with syncope, associated with transient loss of consciousness. In some patients falls may also result from seizures.

Here, we describe for the first time, a patient with macroprolactinoma and drop attacks that was diagnosed as isolated cataplexy, that completely resolved with antidepressant treatment and with reduction of the dose of bromocriptine.

## Case report

A 53-year-old female patient presented with sudden attacks characterized by complete loss of muscle tone with subsequently collaps and injuring herself on several occasions. Occasionally, the attacks were precipitated and triggered by emotional shock such as surprise, excitement or laughing. These events occurred without visual, olfactory or sensory auras, and without motor signs of epilepsy symptoms. She had been treated for macroprolactinoma with dopamine agonists (bromocriptine) for 2 years in a daily dosage of 15 mg. Prolactin levels at the time of diagnosis were high (6,498 mU/L; reference range 151.5–757.5 mU/L). Pituitary imaging showed empty sella configuration but with expansive parasellar mass and infrasellar propagation (Figure 1). While on treatment, prolactin was only mildly elevated (1,102/998/776 mU/L).

The medical history included acute myocardial infarction, hypertension, probable cerebrovascular accident and urinary incontinence after total hysterectomy (performed 30 years ago for uterus myomatosis). In addition, she had suffered from depression. Her family history was negative for any psychiatric or neurologic illnesses, including narcolepsy and cataplexy.



**Fig. 1 – Magnetic resonance imaging (MRI) of sellar region shows empty sella configuration but with expansive parasellar mass and infrasellar propagation at the time of diagnosis [a – coronal (frontal), b – sagittal view] and with a slight regression of the changes 3 years later (c – frontal, d – sagittal view).**

At the admission, blood pressure and glycaemia levels were normal. In addition, an extensive evaluation of blood count, biochemistry and electrocardiograph (ECG) were all normal. Basal hormonal analyses were within normal range except for elevated prolactin levels.

During hospitalization, an attack was observed, characterized by collapse as a result of a sudden loss of tone in both lower extremities, resulting in a fall on the floor without losing consciousness. Blood pressure and glucose were normal without vegetative symptoms like sweating and bradycardia. Because a diagnosis of syncope was suspected she was referred for cardiological evaluation, which turned out to be completely normal (including ECG, 24-hour arterial blood pressure monitoring and 24-hour ECG monitoring). Due to prolonged mild depression which became symptomatic few months after the first attack, she was referred to the psychiatrist who concluded that she was not suicidal and advised an expectative approach and treatment with tricyclic anti-depressants. There was no history of insomnia or parasomnia.

Neurological examination confirmed attacks with sudden loss of muscle tone that could be regarded as cataplexy. Additional investigations like electroencephalography (EEG) and carotid ultrasonography were all normal. HLA standardization haplotyping was confirmatory for cataplexy (HLA-DR3,16; DR 51; DQ 1) but negative for narcolepsy (HLA-DQB1 and DQA1 negative). Since cataplexy is often associated with narcolepsy, polysomnography (PSG) was also performed revealing mild obstructive hypopnea/apnea during sleep with dissociation of the architecture and continuity of sleep. The described phenomenology was responsible for temporary patient's somnolence. Also, EEG monitoring during sleep and awakening did not reveal any epi potentials.

Treatment was initiated with tricyclic antidepressants that rapidly reduced the attacks which after few weeks completely disappeared. Thereafter, the dose of bromocriptine was also reduced. During follow-up, she has been free of any attacks since 2012.

## Discussion

To the best of our knowledge, this is the first report of isolated cataplexy in a patient with prolactinoma. This is intriguing because both dopamine and serotonin are proposed to play a key role in the pathophysiology of narcolepsy and cataplexy<sup>3</sup>, and dopamine agonists and serotonin-reuptake inhibitors are frequently prescribed.

Cataplexy and sleep paralysis can be regarded as attacks of motor inhibition with loss of muscle tone and areflexia, triggered by strong emotions and typically occurring while laughing or joking<sup>1</sup>. Cataplexy, originating from the Greek word *kataplexis* (down-stroke), is considered the main symptom of the narcolepsy syndrome according to the International Classification of Sleep Disorders-2<sup>4</sup>. Isolated cataplexy without narcolepsy is associated with specific genetic predisposition<sup>5</sup>.

Cataplexy is characterized by attacks that may last from a few seconds to several minutes that can be prolonged by

emotional stimuli (e.g. by reiteration of the trigger, interventions of helpers)<sup>2,6</sup>. Long-lasting attacks may evolve into a REM sleep episode, but in rare cases, attacks of cataplexy may occur in tightly packed clusters or be almost continuous, a condition known as "status cataplecticus". This condition may appear at the onset of the disease or may be provoked by antidepressant withdrawal.

Drop attacks are defined as spontaneous falls followed by quick recovery, consequently, syncope and seizures should be excluded. The patient should firstly be clinically screened for cardiovascular causes like orthostatic hypotension, aortic stenosis, and arrhythmias. Since seizures might be the manifestation of epilepsy, brain imaging and EEG should also be performed. In the majority of patients recurrent falls occur without affecting consciousness, and no underlying cause of the drop attacks is found<sup>2,7</sup>.

Cataplexy and sleep paralysis occur only in relation to REM sleep periods, and it may be that they derive from the *nucleus locus coeruleus*. Although cataplexy can result in a complete and often dramatic loss of postural muscle tone with complete paralysis and collapse, the loss of tone in the majority of cases is partial affecting only some muscles<sup>8</sup>. In accordance, the attacks in our patient were provoked by emotional stimuli, such as laughing<sup>4</sup>.

The treatment of cataplexy includes norepinephrine and serotonin reuptake inhibitors (tricyclic antidepressants such as amitriptyline) or agents that stimulate the presynaptic release of norepinephrine (amphetamines). Fluoxetine and venlafaxine have also been given to the patients. Sodium oxybutyrate, the sodium salt of  $\gamma$ -hydroxybutyrate (GHB) and a metabolite of gamma amino butyric acid (GABA), was approved in 2002 by the Food and Drug Administration (FDA) for special treatment of cataplexy in patients with narcolepsy. Reduction of cataplectic attacks may be explained with binding specifically to GABA<sub>B</sub> and GHB receptors, but the exact mechanisms still remain to be elucidated<sup>2</sup>.

It was also shown that obstructive sleep apnea prevalence in patients with prolactinoma, which was found in a very mild form in our patient, is similar to that in the obese subjects and did not change after treatment<sup>9</sup>.

Our patient was treated with the dopamine agonist bromocriptine for prolactinoma. It is tempting to speculate that the treatment with a dopamine agonist might have facilitated the manifestation of cataplexy in our patient. In accordance, in a canine model of narcolepsy, the systemic administration of D(2)-dopaminergic agonists increased the frequency of cataplexies<sup>10</sup>. Even more, Burgess et al.<sup>11</sup> showed that a D1 receptor mechanism can suppress sleep attacks and a D2 receptor mechanism can regulate cataplexy. In our patient, the attacks rapidly resolved with antidepressant treatment and she remained free of recurrence with additional reduction of the dose of bromocriptine with stable prolactin concentrations in the high-normal range.

## Conclusion

Isolated cataplexy in patients treated for prolactinoma has not been previously reported. The observations in our patient

strengthen the observed effects of dopamine agonists on cataplexy in animal models, and merit further investigations on the

role of dopamine agonists in genetically predisposed patients for cataplexy, especially in the presence of depression.

#### R E F E R E N C E S

1. *Krahn LE*. Reevaluating spells initially identified as cataplexy. *Sleep Med* 2005; 6(6): 537–42.
2. *Egel RT, Lee A, Bump T, Javois A*. Isolated cataplexy in the differential diagnosis of drop attacks: A case of successful clinical diagnosis and treatment. *Case Rep Neurol Med* 2012; 2012: 757586.
3. *Gonda CR, Lundt LP*. Mechanism of action of narcolepsy medications. *CNS Spectr* 2014; 19 Suppl 1: 25–33; quiz 25–7, 34.
4. *American Academy of Sleep Medicine*. International Classification of Sleep Disorders: Diagnostic and Coding Manual. 2nd ed. Wetchester, USA: American Academy of Sleep Medicine; 2005.
5. *Hartse KM, Zorick FJ, Sicklesteel JM, Roth T*. Isolated cataplexy: A familial study. *Henry Ford Hosp Med J* 1988; 36(1): 24–7.
6. *Vertugno R, D'Angelo R, Moghadam KK, Vandi S, Franceschini C, Mignot E*, et al. Behavioural and neurophysiological correlates of human cataplexy: A video-polygraphic study. *Clin Neurophysiol* 2010; 121(2): 153–62.
7. *Meissner I, Wiebers DO, Swanson JW, O'Fallon WM*. The natural history of drop attacks. *Neurology* 1986; 36(8): 1029–34.
8. *Plazzi G, Parmeggiani A, Mignot E, Lin L, Scano MC, Posar A*, et al. Narcolepsy-cataplexy associated with precocious puberty. *Neurology* 2006; 66(10): 1577–9.
9. *Barbosa FR, Silva CM, Lima GA, Warszawski L, Domingues RC, Dominic M*, et al. Prevalence of obstructive sleep apnea in patients with prolactinoma before and after treatment with dopamine agonists. *Pituitary* 2014; 17(5): 441–9.
10. *Eguibar JR, Cortés Mdel C, Lara-Lozano M*. Presynaptic dopaminergic agonists increased gripping-generated immobility episodes in the myelin-mutant taiep rat. *Neurosci Lett* 2010; 483(3): 189–92.
11. *Burgess CR, Tse G, Gillis L, Peever JH*. Dopaminergic regulation of sleep and cataplexy in a murine model of narcolepsy. *Sleep* 2010; 33(10): 1295–304.

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