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Case Report

Cataplexy as a side effect of modafinil in a patient without narcolepsy

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ARTICLE INFO

Article history:

Received 18 July 2013

Accepted 10 March 2014

Available online 19 August 2014

Keywords:

Narcolepsy

Modafinil

Cataplexy

Sleep Obstructive Apnea Syndrome

Side effect

ABSTRACT

Narcolepsy is a disease in which there is diurnal excessive sleepiness with sleep attacks and a prevalence in the general population of 1/4000 individuals. Classically, it is characterized by cataplexy, sleep paralysis, hypnagogic hallucinations and fragmented sleep. The use of modafinil in the treatment of narcolepsy is the first option of treatment for diurnal excessive sleepiness.

Although considered a safe drug for use in patients with narcolepsy, being utilized for more than 20 years, modafinil possesses a series of side effects, some of them still not fully researched or described.

Side effects such as headache, nausea, anxiety, insomnia, lumbago, diarrhea, dyspepsia, rhinitis and vertigo are the most frequent. However, the clinical follow-up of patients under treatment with modafinil must be intensive and the side effects ought to be noted and evaluated. The under-response to treatment or the unexpected side effects must always be directed to differential diagnostics.

The objective of this article is to describe an unexpected side effect of the use of modafinil in a patient with incorrect diagnosis of narcolepsy.

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*Support: AFIP & FAPESP – CEPID 98/14303-3.

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Peer review under responsibility of Brazilian Association of Sleep.

1. Introduction

Narcolepsy is a chronic disease in which there is excessive sleepiness (ES) with sleep attacks and with a prevalence of 1/4000 individuals in the general population. It is classically characterized by ES, cataplexy (loss of muscle tonus), sleep paralysis (body immobility during the transition awake/sleep cycle), hypnagogic hallucinations (dreams during the awake/sleep transition cycle) and fragmented sleep [1,2].

Narcolepsy may be mono-symptomatic (only ES) or oligo-symptomatic (ES and cataplexy). The degree of ES is variable and the attacks of cataplexy might involve several muscle groups being triggered by emotions [1,3].

The use of modafinil in the treatment of narcolepsy is a first option for the treatment of diurnal excessive sleepiness (DES) in patients with narcolepsy. Modafinil shows several advantages when compared with the other stimulants due to smaller cardiovascular alterations and smaller risk of addiction [4]. Modafinil is a stimulant, of the non-amphetamine type, with agonist action upon the hypocretin-1 system, besides blocking the dopamine and norepinephrine transport [4].

Other indications of modafinil are for the treatment of idiopathic hypersomnia or even for residual somnolence in patients with Sleep Obstructive Apnea Syndrome (SOAS). However, there are no studies on the safety and side effects in these groups of patients [5].

Although being considered a safe drug for use in patients with narcolepsy, already being utilized for more than 20 years, modafinil presents a series of possible side effects, some of them still not fully studied and described [4].

The objective of this article is to describe an unusual side effect of the use of modafinil in a patient misdiagnosed with narcolepsy.

2. Clinical case

A 58-year-old male patient searched for medical treatment 3 years ago, with an anamnestic case characterized by diurnal excessive sleepiness with progressive worsening. This was associated with sound snoring and apneas, as perceived by his partner. He did not have parasomnia, previous somnolence, cataplexy or any other sleep disorder. The patient did not show family or personal history of any neurological degenerative diseases and the neurological exam was completely normal. As co-morbidities the patient demonstrated overweight (IMC=29), systemic arterial hypertension and dyslipidemia.

At the beginning of the investigation (performed in other medical facilities), a polysonogram was performed with inadequate protocol and its result led to a false negative diagnosis for SOAS. As per this negative result and the intense patient symptomatology (Epworth index of 18 at the time), we began the modafinil treatment with 100 mg/day with a diagnostic hypothesis of idiopathic hyper-somnolence or even narcolepsy. The patient developed loss of muscle tonus with a consequent fall in situations of happiness or sadness, without loss of consciousness and with a maximum duration of 2 min after beginning this medication, thus

characterizing a case of cataplexy. Due to the presence of this symptom and owing to the little improvement upon the sleepiness symptom, the drug dosage was increased to 200 mg/day of modafinil, with additional worsening of the clinical picture. The patient demonstrated during this period an average of 12 episodes of cataplexy per day with intense social impairment. After 3 months of treatment with modafinil, the drug was discontinued with prompt resolution of the cataplexy.

Polysonogram performed posteriorly with adequate protocol resulted in a severe case of SOAS. Basal polysonogram presented an index of respiratory disorder of 39.4 events/h and exam's minimal saturation of 64%. The test of multiple latencies of sleep (MLST) confirmed the hyper-sleepiness (average latency was 1.2 min for sleep) and did not demonstrate the presence of REM sleep in any of the opportunities.

We initiated a treatment with CPAP (titrated in laboratory with a pressure of 7 cmH₂O) with clinically marked improvement and resolution of the excessive sleepiness.

3. Discussion

The diagnosis of SOAS is much more frequent than that of narcolepsy. We estimate that it may be over 30% in terms of prevalence of SOAS in the general population and that the one for narcolepsy is around only 0.02% [6]. However, DES is a common factor among these 2 disorders. Some clinical characteristics, such as the presence of cataplexy, age of onset of symptoms, hallucinations and sleep paralysis, do help us diagnose narcolepsy. Moreover, complementary exams such as full night sonogram, MLST, dosage of the allele HLA-DQB1*0602 and the level of hypocretin-1 also help us in differential diagnosing [1].

A well-done polysonogram within the recommended Brazilian Association of Sleep's criteria gives us the diagnosis of SOAS [7]. However, the association of the 2 diseases may happen and the initial treatment of SOAS is thus mandatory for posterior evaluation of the signs and symptoms of narcolepsy. In this described case, the patient was not initially and adequately investigated. The false-negative polysonogram and the absence of MLST were the main factors leading to the mischaracterization of a narcolepsy case.

Narcolepsy with cataplexy is generally treated with drugs that produce an increase in awareness and with antidepressants that control cataplexy [1]. Modafinil has been the drug of first choice in narcolepsy and idiopathic hypersomnia [4]. Other indications for the use of this drug are treatment of sleepiness and fatigue related to neurological and psychiatric diseases, attention deficit, sleep control in night workers and residual sleepiness in SOAS being treated with CPAP [5].

Although safe, the use of modafinil for the clinical treatment of ES in patients with narcolepsy must always be preceded by a very careful and complete clinical and complementary evaluation for the definition of the diagnostic and therapeutic indication. The clinical follow-up of these patients during the use of modafinil must be intensive and the side effects must be closely scrutinized [8].

The little treatment response or unexpected side effects must always point to possible differential diagnosis. In this

case, the absence of the use of some substances such as tricyclic antidepressants might have led to cataplexy, besides the association with another sleep disorder, which is always a possibility to be kept in mind [9-11].

The patient did not present any clinical characteristic suggestive of narcolepsy, did not show the allele HLA-DQB1*0602 and improved completely regarding the cataplexy episodes after modafinil withdrawal.

The abovementioned case show us a probable and unusual side effect of the use of modafinil, with worsening of cataplexy, in a patient with diagnosis of SOAS erroneously misinterpreted as a case of narcolepsy [12,13]. This case strengthens the need of a complementary and correct investigation, aimed at the clinical suspicion, besides the revision of the original diagnosis when the treatment does not lead to improvement or even worsens the symptoms.

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