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MANIA ASSOCIATED WITH CABERGOLINE: A BRAZILIAN CASE REPORT

Mariana de Freitas Castro Marques

Tatiana Yumi Bando
https://orcid.org/0000-0002-9563-4799

Gabriela Yumi Hosogi Senaha
https://lattes.cnpq.br/7285423308755065

Márcio Krakauer
http://lattes.cnpq.br/3248830797446243

Cíntia de Azevedo-Marques Périco
https://orcid.org/0000-0002-2664-5101

Abstract: Introduction: Cabergoline is a highly effective dopamine agonist agent to reduce prolactin levels. It has adverse side effects such as cardiovascular, gastrointestinal, and neuropsychiatric common to other drugs of the same category. However, in international literature, there are few reports of patients that develop a mania episode. This case is possibly the first of mania induced by cabergoline reported in Brazilian medical literature. **Case Report:** Patient, N.M.G.F., was identified with high prolactin levels and, after an investigation, a pituitary microadenoma was diagnosed. The medical conduct prescribed was Cabergoline 0.25 mg twice a week (as reported in the medical record). After 24 days of treatment, the patient's wife reported a relevant behavioral change, consistent with a manic episode. Due to that, Cabergoline was suspended and Lithium Carbonate was administered. The clinical condition evolved with symptom improvement. **Discussion:** There are few facts that support the association of Cabergoline administration with developing symptoms of mania. The correlating of mania and brain dopaminergic pathways are recognized and Cabergoline, which is a dopaminergic agonist can stimulate these pathways. Besides that, the patient did not have a familiar or personal record of mania and did not use any other medication that could cause these conditions. Lastly, as the patient showed this symptom 3 weeks after the first administration of the medication and got better rapidly as well after he stopped taking the pills and started using Lithium Carbonate. For this reason, we can ratify the diagnostic hypotheses. To summarize, the behavioral change must be observed and questioned by Cabergoline users. Even though it is a very safe and effective medication to reduce prolactin levels, it could induce psychiatric side effects associated with it.

Keywords: Cabergoline, Mania, Microadenoma, Behavioral Change.

INTRODUCTION

Cabergoline, is a medication used for hyperprolactinemic disorders (such as pituitary adenomas), Parkinson's disease and restless legs syndrome (Willis-Ekbom disease). The drug is a dopaminergic agonist derived from ergot, that acts by direct stimulation of D2 dopaminergic receptors of the lactotrophic pituitary gland, thus inhibiting prolactin secretion for a long time after oral administration.[1]

Its adverse reactions are like other dopaminergic agonists including cardiovascular, gastrointestinal and neuropsychiatric effects. It is known that this drug can cause psychiatric disorders such as depression, drowsiness, anorexia, anxiety, insomnia, distractibility, hallucination, irritation, psychosis.[2] However, reports of mania are scarce in medical literature and this is might be the first Brazilian case.

In this case report, a rare correlation between Cabergoline and mania will be discussed, showing the importance of using this medicine sparingly and with fresh eyes so that this kind of diagnosis can be made more briefly by the professionals who use it.

CASE REPORT

N. M. G. F., male, 69 years old, white, born in São Paulo, College degree, a retired lawyer, married and without religion. He has smoked an average of 8 to 10 cigarettes a day for 50 years. No family history of psychiatric disorders but with a personal history of general anxiety disorder. He has used Escitalopram 10mg daily for 3 months and, irregularly, Salmeterol and inhaled Fluticasone.

During a preoperative evaluation for varicocele correction, the following exams were solicited:

Exam	Result	Reference Value
FSH	9.8 mUl/ml	Up to 10mUl/ml
LH	6,7 mUl/ml	Up to 9 mUl/ml
Total Testosterone	322,97 ng/dL	240 to 816 ng/dL
Bioavailable Testosterone	116,83 ng/dL	84,1 to 269,9 ng/dL
TSH	1,019 mUl/mL	0,45 to 4,5 mUl/L
Free T4	1,30 ng/dL	0,6 to 1,3 ng/dL
Prolactin	81,63 ng/mL	24 ng/mL

In view of these results, an endocrinological evaluation was requested at which a progressive weaning from Escitalopram was started, due to the possible diagnosis of drug induced hyperprolactinemia. Under strict supervision, the dose was reduced to 5mg / day for two weeks. As there was no change in behavioral progress, the withdrawal of Escitalopram progressed with the alternation of drug administration. 15 days after the antidepressant weaning was completed, a new dosage of the prolactin level was performed and maintained at 79.2 ng / mL. Therefore, a sella turcica computed tomography was indicated.

The report revealed a nodular formation in the pituitary gland with a lower degree of enhancement with 5mm right side and contact with the medial wall of the cavernous sinus.

With this diagnosis of pituitary microadenoma, the decision to start a drug treatment with Cabergoline at a dosage of 0.25mg twice a week was made. Twenty-four days after the first dose,there were changes in patient behavior such as: irritability, impulsiveness for tobacco, binge eating, verbiage, disconnected and accelerated thoughts, reduced need for sleep and increased libido.

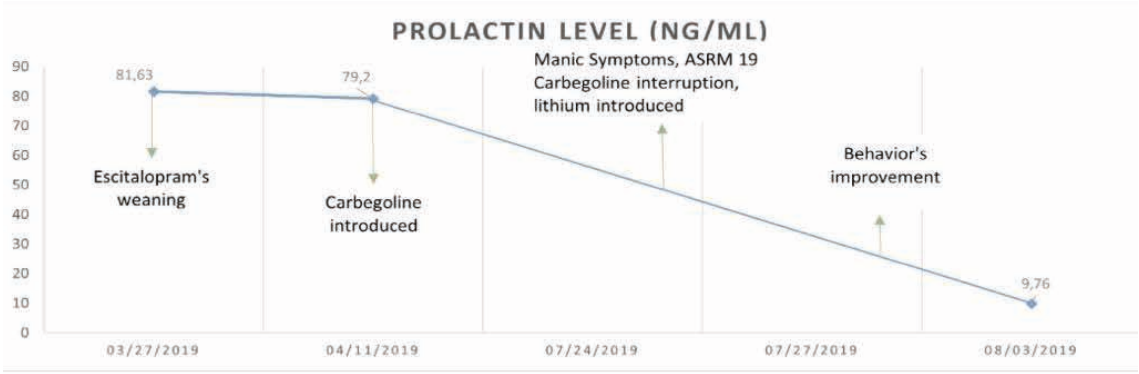
In view of the complaints, the Altman Mania Scale (EACA-M or, in English, CARS-M), was administered by a psychiatrist. The value obtained from the test, resulted in 19, indicating the presence of moderate mania.[3]

Due to the medical condition, the administration of carbonate of Lithium 1200 mg / day was chosen, the use of Cabergoline was interrupted and new tests were done. Three days after the new medication was prescribed, his wife reported by phone, some behavioral improvement.

In personal attendance, three weeks after the changes of his behavior, N.M. G. F. brings the exams that were performed during the Cabergoline break and with the use of Lithium carbonate, showing the following results: 9.76 ng / mL prolactin (15 days without Cabergoline) and 0.71 mmol / L litemia (reference value in therapeutic levels: 0.6 to 1.2 mmol / L). However, ten days before the appointment, he paused the use of lithium carbonate and restarted the use of Cabergoline on his own.

During the face-to-face consultation, he highlighted his appreciation for the advances in medicine, answered questions in English spontaneously, recognized an improvement in his general condition and recovery of your masculinity, demonstrating a behavioral change after the reintroduction of the dopaminergic agonist in question. Amid this, the EACA-M test was reapplied, and its sum resulted in 15, indicating, therefore, the presence of mild mania. 3 At that moment, N. M. G. F. refused to reintroduce lithium carbonate because he claimed to be well without taking this medicine.

After a new guidance with the caregiver, the drug was reintroduced, following the guidelines of the psychiatrist. In the first week, a lithium carbonate tablet was administered every twelve hours and in the next weeks, two tablets every 12 hours, aiming to reach a daily dosage of 1200mg. In addition, laboratory tests were conducted to control renal function and lithium level. In eight months after starting the treatment for Mania, the patient is more stable and his behavior is the same he presented before using Cabergoline.



DISCUSSION

Although there are 5 case reports in literature, in our knowledge this is the first Brazilian episode of mania induced by cabergoline related. It is a rare side effect of this class of medication, but when present it can be a serious adverse event, consequently, all physicians should be aware of this effect for an adequate management of the case.

Cabergoline is a long- acting and selective ergot-derivative dopamine receptor agonist. His main action is to inhibit the activity on prolactin secretion from lactotrophs of the anterior pituitary.[1]

There are two types of dopamine receptors, D1-like and D2-like receptors.[1] Cabergoline binds to D2 receptors. This receptor is responsible for encoding two molecularly distinct isoforms, the short form of D2 (D2S) and the long form of D2 (D2L). Cabergoline acts mainly by stimulating the D2S present in the lactotroph cells.[2] When the dopamine agonist is bound to that receptor, it stimulates the G protein Giα- linked to D2S- inducing an Adenylyl cyclase inhibition consequently there is a decrease of AMPc molecules in the system and blocks IP3- dependent release of intracellular Ca^{2+}.[3]

Once the concentration of AMPc drops, the release of prolactin by the lactotroph cell ceases.[4]

N. M. G. F was diagnosed with Prolactin-secreting pituitary microadenoma in the pituitary gland. In these cases, cabergoline acts decreasing serum prolactin levels but also inducing tumor destruction.[5]

It is well known that dopamine agonists can cause psychiatric adverse side effects such as depression, anorexia, anxiety, somnolence, insomnia,hallucinations, nightmares, psychosis and mania.[6] Impulsive disorders, such as pathological gambling, increased libido and hypersexuality and depressed mood have been described in patients treated with agonists of the dopamine including cabergoline [7,8,9] , moreover there are few studies associating this medication with the development of mania.[6, 10, 11, 12, 13]

The first case of Mania induced by bromocriptine, a non-selective ergot-derivative dopamine receptor, which binds to D1 and D2 receptors [6, 14], was described in 1978.[15,]Nowadays, we know that the side effects described above are common in patients in use of bromocriptine and the incidences of those are less than one to three percent.[6]

The scale used to assess Mania symptoms were the "Clinician-Administered Rating Scale for Mania" (CARS-M) that is a instrument to measure whether a patient has or has not signs of mania,[16] which evaluates patients for symptoms of mania on a scale of 0- 26 or more. Officially translated into Portuguese in 2003, this test is considered an instrument with precise psychometric properties for the assessment of the mania state. Another scale

used is the Young Mania Rating Scale (YMRS). [17] This one was developed in 1978 based on the authors clinical experience conjoint with a review. Considering it and other aspects of YMRS, i.e. the arbitrary selection of some items to have higher scores than others, it has flaws. [17]

While the CARS-M is a test that fulfills all the prerequisites that are considered mandatory nowadays in order to create a new valid scale [17], such as the use of the content validation instrument recognized by the scientific community known as SADS.[18] Moreover, the results obtain in CARS-M scale were evaluated by Intraclass Correlation Coefficient (ICC) which is considered to be the best measurement standard for psychometric quality. [17]

Therefore the test to measure the maniac symptoms of the patient is as adequate as other scales used in the clinical practice.

At first, N. M. G. F. CARS-M score was 19 indicating moderate mania. In this context, the patient was reported with changes in his behavior such as irritability, impulsiveness for tobacco, binge eating, verbiage, disconnected and accelerated thoughts, reduced need for sleep and increased libido.

The second time CARS-M was applied the score was 15 indicating mild mania. At this moment, the patient had spontaneously restarted the use of Cabergoline after clinical improvement with lithium carbonate.

Escitalopram is a selective serotonin reuptake inhibitor (SSRI). Its indication is mainly for the treatment of depression and generalized anxiety disorder,[19] which the patient presented. The SSRI acts in the presynaptic neuron by binding to the sodium-dependent serotonin transporter protein (SERT). When the SSRI binds to the SERT they inhibit the reuptake of serotonin, hence increases serotonin levels in the synaptic cleft.[20] Serotonin or 5-hydroxytryptamine (5-HTT) is responsible for many human behavioral processes: mood, perception, memory, anger, aggression, fear, stress response, appetite, addiction, and sexuality,[21] thus it could be responsible for the manic symptoms in the patient. About this, a confounding factor was the possibility of escitalopram causing mania symptoms, but considering that the weaning off was properly executed and that these symptoms began after the escitalopram was discontinued, this possibility was removed.

As many SSRIs have adverse effects so does escitalopram, even if its toxicity is lower than older antidepressants.[22] The most common side effects are insomnia or somnolence, sexual disfunction (mostly decreased libido, anorgasmia, and ejaculatory delay), nausea, increased sweating, and fatigue.[23] This antidepressant can also cause SSRI-induced syndrome of inappropriate antidiuretic hormone secretion (SSRI-induced SIADH) responsible for hyponatremia, mostly in elder people.[24] Low levels of sodium results in anorexia, nausea, vomiting, fatigue, and headache. It can also lead to more severe conditions such as altered mental status (present in the patient as the disconnected and accelerated thoughts), seizures, and even coma.[24,25] Another possible side effect is serotonin syndrome which mostly occurs in patients who use high-dose SRRI, overdose or take more than one serotonergic drug.[26] This syndrome symptoms are autonomic instability related: tachycardia, hypertension, dizziness, diaphoresis, flushing, mydriasis, increases temperature, nausea, vomiting, diarrhea, mental status change (ie agitation, delirium, hallucinations, somnolence, coma).[26]

Another side effect of SSRIs is serotonin overactivity which is defined as serum prolactin high levels.[27] The mechanisms of SSRI-induced hyperprolactinemia is yet to be clarified, but some authors suggest that it is associated with serotonin indirect effect

through serotonin receptors and serotonin-GABA-dopamine interaction.[28] Other authors based on the physiology defends that as an inhibitory neurotransmitter, serotonin increases prolactin secretion by decreasing the activity of tuberoinfundibular dopaminergic system.[29] Thus the hyperprolactinemia reported in this case could have been induced by escitalopram, hence the decision to wean and discontinue escitalopram.

Currently, there is little information about the pathophysiology of mania, however its symptoms are possibly associated with an inefficiency in the transmission of information in brain dopaminergic circuits.[30] In addition, studies indicate that a reduction in frontal cortex activity occurs including prefrontal and orbitofrontal cortex and the increase in the basal thalamocortical ganglion circuit activity.

There is evidence that there is some change in the areas of the limbic and paralimbic systems.[31-33] The role of dopamine in the pathophysiology of mania is supported by a series of evidences. First, the dopamine precursor (L-Dopa) and amphetamines, which promote their release and inhibit their absorption, precipitate mania in patients with bipolar disorder.[34,35] From another perspective, dopaminergic antagonists effectively treat mania.

In evidence based medicine, case reports are in the bottom layer of the hierarchy of evidence. Still, it has a major role in the progress of medical science and education. Despite the highlight of the unusual, which is a critical point regarding case reports, the reported novelties have a key point in the future management of unknown conditions. [36]

CONCLUSION

Cabergoline is a safe and effective medicine to reduce the rates of prolactin, however relevant psychiatric adverse effects can be induced. Prior and during observation during the use of the medicine of the possible symptoms is essential to differentiate them from a secondary craze for Cabergoline.

Finally, it is worth mentioning that in our PubMed survey there are 5 reports of cases that correlate Cabergoline with induction of mania. With that, it can be said that this clinical case represents the first report in the Brazilian medical literature and the respect of an adult man who evolved into a mania associated with the use of Cabergoline.

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