Impulse Control Disorder in a Patient with Invasive Prolactinoma on Dopamine agonist Therapy: A Case Report

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Abstract

Prolactinomas constitutes a major bulk of pituitary adenomas. All symptomatic prolactinomas require dopamine agonist (DA) therapy. Impulse control disorders (ICD) or pathological behaviours are rare adverse events described with use of DA. Herein we are describing a male patient with pathological gambling and doctor shopping following use of bromocriptine and higher dose of cabergoline. The pathological behaviour disappeared after debulking surgery, reduction in cabergoline dose and several sessions of counselling. Physicians prescribing DA should be aware of this potential adverse event. This should be emphasized to the patient and family members before starting DA and physician should be inquisitive for eliciting pathological behaviour on follow up.

Keywords: prolactinomas; Impulse control disorder; cabergoline dopamine agonists

Introduction

Prolactinomas constitutes 40% of all pituitary adenomas, amongst them 5-10% are macro adenoma and rest 80% micro adenomas [1]. All macroadenomas and all symptomatic microadenoma requires treatment with dopamine agonists (DA) [1]. The most important adverse events described with use of DA include nausea, dizziness and postural hypotension. Neuropsychiatric adverse events commonly described include hallucinations, mania and depression [2-6]. There are occasional reports of impulse control disorder (ICD) with use of DA in patients with prolactinomas [2-9]. These case reports have evaluated association of ICD and DA mostly among adults and one case report reported the similar association in an adolescent [7,9]. One case control study examined the association of ICD with smaller dose of DA used for prolactinomas. FDA has recorded 25 ICD cases on 10 years of DA use indicating its rarity/ill recognition.

The most important risk factor for development of ICD with DA is use of higher dose. DA are first line treatment modalities in prolactinoma cases, but the usual dose is 40 times less than the dose used in neurodegenerative disorders [2]. Therefore ICD is expected to be low. The paucity of data available on this issue in patients with prolactinomas could also be because of under recognition.

ICD is characterized by broad range of disorders which are repetitive and gives pleasure and not associated with guilt but are usually outside the societal norms. The spectrum of ICD includes pathological gambling, Trichotillomania, intermittent explosive disorder, kleptomania and pyromania.

The pathogenesis of ICD is believed to be either dose related as more often it is found in neurodegenerative diseases in which higher dose of the drug is used. Rarely it could be idiosyncratic. Dopamine acts as a neurotransmitter in the central reward and risk taking behaviour manifestation areas. The prevalence of ICD in neurodegenerative disorder amongst which the most well studied being Parkinson’s is 17-39% in cross sectional data[6-11].

Here we are reporting a case who presented with pathological gambling, doctor shopping and several cases of financial irregularities while receiving DA.

Case Report

A 52-year-old male, a former insurance officer presented with history of ptosis of right eye. Exploration of history revealed that at the age of 37 in March 2000 he consulted a local doctor with complaints of loss of libido, erectile dysfunction and headache of 3 months duration. These were associated with decreased vision in both eyes. CEMR sella revealed a 4.2x3.6x2.9 cm sellar mass with bilateral parasellar extension (figure). He was euthyroid and had a border line glucocorticoid reserve (240 nmol/L). Prolactin level (PRL) of 700 ng/ml and in dilution 5200 ng/ml. The serum testosterone was 8 nmol/L. (N-9.8-27.8).

He was started on bromocriptine (BEC) 2.5 mg three times a day. A follow up MRI done at 3rd month down the line revealed tumor of 3.6x2.2 cm. His serum PRL was 1233 ng/ml. At this point of time patient started doing doctor shopping and indulged in gambling with a lot of financial loss. Till date he underwent 72 brain/pituitary imaging and consulted more than 20 doctors/institutes. He was subjected to stereotactic radio surgery (46Gy) in May 2003 and was advised to continue BEC. Additionally he was advised to take testosterone which he never took.

The follow up MRI in November 2003 showed tumor of 4.2x3.6x2.9 cm, and he was still hypogonadal and there was radiation induced changes, thinned out optic chiasma and infundibular stalk which was iso-intense on T1 and hyper-intense on T2 weighed image.

In September 2003 he went to Mayo Clinic Rochester, Minnesota, USA to fulfil his quest of doctor shopping where he was explained that he has to continue the same treatment as advised by his doctor friends in India. From 2003-2009 he continued taking BEC 7.5 mg/day. During those periods he was so much indulged in gambling that he lost 4 crore rupees, sold ancestral property, gold and jewellery of wife and a car. After that he started withdrawing from accounts of people who had invested money in an insurance company where he was working.
He was also involved in various job scams to get more money. Whenever he used to stop BEC the indulgence in gambling used to decrease. Prior to the diagnosis of prolactinoma, he never had any history of gambling.

In March 2009 repeat MRI revealed 3.4x6.8x2.85 cm sellar para sellar mass and his serum PRL was 5200 ng/ml. At this point of time he was started on cabergoline 0.5mg twice weekly and BEC was stopped. He continued cabergoline irregularly till August 2017. At that time he was convicted by the court in a cheque bounce and several financial fraud cases and was sentenced imprisonment of 6 months duration. In December 2017 he was referred to our hospital for evaluation of vomiting, headache and recent onset ptosis of right eye (Figure 1).

After discussing the pros and cons of various treatment strategies patient opted for surgery. He underwent endoscopic transnasal trans sphenoidal tumor resection in late Dec. 2017 which was uneventful.

At the time of discharge his serum prolactin was 2 ng/ml. He was discharged on testosterone, hydrocortisone and thyroid hormone replacements. The histopathology revealed a dense fibrosis with inflammatory cell infiltrates. At 3 months of follow up his prolactin increased to 217 ng/ml. He was restarted on 0.25 mg of cabergoline weekly once and sent to psychiatrist for behavioural therapy and counselling. With this he completely stopped gambling and doctor shopping. After discussing his case with the concerned legal advisor and giving a security bond of 3 lacs, he was exonerated from the charges. At six months of follow-up repeat CEMR sella revealed small right parasellar residue (figure 3).

**Discussion**

Intracranial tumors are known to cause a wide variety of behavioural issues with associated burden due to direct involvement or blood flow changes in the adjacent structures, complications of medical, surgical and radiation therapies [13-15]. Pituitary adenomas mostly present with visual complaints and mostly do not have such explicit abnormal behaviour [16] neither because of tumor compressing surrounding structures nor because of drugs. The domain of ICD includes pathological gambling, hypersexuality, compulsive shopping, binge eating, punding (compulsive fascination with the performance of repetitive mechanical tasks) in that chronological order. They can have catastrophic effects on marital life, job, put financial constraints and rarely jail sentence. The cause and effect relationship is established by drug challenge, withdrawal and rechallenge. In a retrospective disproportionality analysis the association of ICD was strongest for DA pramipexole and ropinirole which acts on D3 receptor [5-9]. In neurodegenerative disorder association of ICD has been found with use of D2 agonist as well dopamine enhancers [5].

ICD (pathologic behaviour) is under recognised in 50% of cases due to lack of awareness amongst physician and sometimes patient themselves hesitate to report or minimize it. They are more common in middle aged male. The patient with family history of Obsessive Compulsive Disorder, Bipolar Affective Disorder, alcohol and drug abuse, addictions impulsive behaviour are more predisposed to develop ICDs [9]. Patients with prolactinoma are 9.9 times more predisposed to develop ICDs as compare to NFPA patients with same dose of cabergoline [10,11]. This unusual complication is more often found in macroadeninoma patients as compared to microprolactinomas probably because of the higher dose used in macroadenomas. Rarely they can occur as a consequence of brain tumor, traumatic brain injury, aneurysm rupture and drugs.

Therefore dopaminergic drugs should be dispatched with black box and information regarding ICD in the package insert. Physicians should be proactive in identifying this condition to avoid disaster as happened in our case. In one series of Parkinsonism patient the prevalence of pathological gambling was 5% with cabergoline therapy [17]. On the contrary only 2 cases of pathological gambling has been documented in patients with prolactinoma [18,19]. Cabergoline related ICD can occur with very low dose and ergot and nonergot DA have equal propensity.
Our patient never received other hormone supplementation/replacement to cast doubt in the cause and effect relationship. If adverse events are not collected systematically individual case report may not prove cause and effect or apophenia [5]. In our case there must be underlying hidden personality trait which was precipitated by D2A. ICD in our patient was more with bromocriptine and higher dose of cabergoline, but it disappeared with lower dose of cabergoline given post debulking. So if the disease was brought on by the tumor it is hard to ascertain which caused more symptom relief. However the casual association of cabergoline with ICD has been reported in previous cases as all and none phenomena [1].

As the patient had recent evidence of invasion and poor response despite 9 years of DA therapy and SRT he was considered for debulking surgery and the dose of DA was reduced.Temozolomide was not considered because of potential adverse events.

Interpretation of symptoms and cause and effect relationship in our patient is strong for that of DA. But, further case control studies with longitudinal follow-up consisting of normal age matched controls, microprolactinoma patients who are not on treatment and non functioning pituitary adenoma patients with and without DA may answer the cause and effect relationship. Timely recognition is essential to avoid psychosocial repercussion as happened in this case.

The ICD in this patient was in form of pathological gambling and probably doctor shopping. The other components could not be elicited even with careful probing. The ICD was more often when he was on BEC than cabergoline and there was waxing and waning course on stoppage and reintroduction of DA which was never realised by the patient. We presume that doctor shopping and repeated MRI’s of brain/pituitary were part of spectrum of the same disease. After psychiatry review and review of the case by few of the authorities in this field and due to presence of predominantly rightparasellar disease with recent onset ptosis, previous history of SRT surgical debulking was justified. As per our expectation the post operative prolactin came down to 2 ng/ml but there was a rebound increase on follow-up for which D2A was continued at a dose of 0.25 mg weekly once.

The increased D2 and D3 receptor agonism releases brake on brain mechanisms that normally inhibits risky behaviour while simultaneously increasing reward seeking behaviour by augmenting mesolimbic dopaminergic system [5]. Previously, Martinkova et al had described two out of twenty cases that were treated with surgery, radiotherapy and low dose D2A bromocriptine. The first case of D2A associated ICD in pituitary adenoma was reported by Davjeeta in 2007 in a female who was receiving 25 mg/week of cabergoline after one year of therapy [18]. So it can happen as an all or none phenomenon but this was not found in our patient. The occurrence of ICD with lower dose of DA could be due to up-regulation of p-glycoprotein transporter which is responsible for increase permeability of DA through blood brain barrier [20].

The ICDs can cause psychosocial, occupational, family hazards and sometimes catastrophic effect on job and finance as happened in our case. So, before prescribing D2A to patients, care takers, family members should be explained regarding the potential for developing ICD on follow up. The doctor should also enquire regarding various ICDs on follow up.

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References


