REVIEW

Neuropsychiatric and metabolic aspects of dopaminergic therapy: perspectives from an endocrinologist and a psychiatrist

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Abstract

The dopaminergic treatment represents the primary treatment in prolactinomas, which are the most common pituitary adenomas and account for about 40% of all pituitary tumours with an annual incidence of six to ten cases per million population. The dopaminergic treatment includes ergot and non-ergot derivatives with high affinity for the dopamine receptors D1 or/and D2. Through the activation of the dopaminergic pathway on pituitary lactotrophs, the dopamine agonists inhibit the prolactin synthesis and secretion, therefore normalizing the prolactin levels and restoring eugonadism, but they also lead to tumour shrinkage. Treatment with dopamine agonists has been associated – apart from the common side effects such as gastrointestinal symptoms, dizziness and hypotension – with neuropsychiatric side effects such as impulse control disorders (e.g. pathological gambling, compulsive shopping, hypersexuality and binge eating) and also with behavioral changes from low mood, irritability and verbal aggressiveness up to psychotic and manic symptoms and paranoid delusions not only in patients with prolactinomas but also in patients with Parkinson's disease and restless leg syndrome. They usually have de novo onset after initiation of the dopaminergic treatment and have been mainly reported in patients with Parkinson's disease, who are being treated with higher doses of dopamine agonists. Moreover, dopamine and prolactin seem to play an essential role in the metabolic pathway. Patients with hyperprolactinemia tend to have increased body weight and an altered metabolic profile with hyperinsulinemia and increased prevalence of diabetes mellitus in comparison to healthy individuals and patients with non-functioning pituitary adenomas. Treatment with dopamine agonists in these patients in short-term studies seems to lead to weight loss and amelioration of the metabolic changes. Together these observations provide evidence that dopamine and prolactin have a crucial role both in the regard and metabolic system, findings that merit further investigation in long-term studies.

Introduction

Case report

To emphasize the possible role of dopamine agonists in the development of impulse control disorders that could be potentially devastating for the patient's life, we report a case of a giant-prolactinoma in a young male adult that developed severe pathological gambling under dopamine agonists. Informed consent for publication has been obtained from the patient after full explanation of the

purpose and nature of all procedures used. The patient presented initially with tinnitus at the age of 19 years. The magnetic resonance imaging revealed a large, invasive pituitary tumor with a diameter of $60 \times 60 \times 65$ mm with an intracranial frontal part and perifocal oedema of the white matter. The diagnosis of the prolactinoma was based on an enormous highly prolactin value of 10,000 ng/mL (normal range up to 25 ng/mL). The laboratory results at baseline revealed a pituitary insufficiency of the gonadotropic, thyreotropic and corticotropic axis, although stimulation tests were not performed at diagnosis due to the risk of bleeding or necrosis. Adequate hormonal substitution with testosterone, thyroid hormones and hydrocortisone was initiated. As first-line treatment, the patient received bromocriptine. The first psychiatric symptoms that were depressed mood and gambling tendencies were reported in February 1998, shortly after the diagnosis of prolactinoma and the beginning of bromocriptine treatment. Under 40 mg of bromocriptine neither imaging nor laboratory improvement could be documented so that quinagolide was initiated. Under quinagolide, the tumor shrank and prolactin fell. After at least two years of treatment with dopamine agonists (bromocriptine and quinagolide) and under ongoing quinagolide treatment, at the age of 21 years, the patient was admitted for the first time in a psychiatric clinic due to pathological gambling. He had started playing with gaming machines and in online casinos, gave up his studies and lost about 5000 Euro in one day. He used the credit cards of his father and used to play – even if he won – until all the money he had was gone. He was sentenced to a prison sentence of 1½ years and later on to another sentence of 5½ years due to fraud and other criminal acts in order to collect money. In that time, he accumulated private debts of about 200,000 Euro. Remarkably, there was no family history of impulsive or affective behavior or further psychiatric diseases. The patient did not abuse alcohol or other illegal drugs or medications. The psychiatric treatment at this time included behavior therapy initially in the outpatient unit and later on systemic psychotherapy in the psychiatric ward without medical treatment. Quinagolide was applied for a total of about two years (03.09.1998–01.03.1999; 24.06.1999–03.12.2001) with interruptions and in combination with cabergoline (02.10.1998–07.10.1999; 03.12.2001-ongoing). Interestingly, the psychiatric symptoms were similar under all dopamine agonists administered with the ICD codes including pathological gambling (F63), borderline personality disorder (F60.3) and major depressive disorder (F33.1) remaining stable over the years. Since 2010 and up to 2012, the patient

was under cabergoline and citalopram, and after 2012, the psychiatric medication was stopped. Today, sixteen years after the diagnosis of prolactinoma, the patient is biochemically well controlled under a weekly dose of 4 mg cabergoline and stable without psychiatric medication.

These findings and observations regarding our patient posed the following questions: what is the incidence of neuropsychiatric side effects to be seen under dopamine agonists and what are the predisposing factors for developing this kind of side effects?

Approval of the local ethical committee was not required for this study as clinical study in human subjects was not conducted.

The psychiatrist's perspective: neuropsychiatric aspects of the dopaminergic treatment

Apart from the common side effects of the dopaminergic treatment including gastrointestinal symptoms, hypotension and dizziness, an increased frequency of impulse control disorders (ICDs) has been widely reported, mainly in a subset of patients with Parkinson's disease (PD) and restless legs syndrome (RLS) that are being treated with dopamine agonists (DAs) in much higher doses (1). More specifically, these neuropsychiatric side effects include pathological gambling, hypersexuality, compulsive shopping and binge eating (2, 3, 4, 5). These symptoms are generally characterized by the maladaptive nature of the preoccupations and the inability of the subject to control these urges, and they mainly have a de novo onset after the initiation of the DA on the basis of a negative psychiatric history. Whereas the overall lifetime prevalence of pathological gambling under DAs has been reported to be from 3.4 up to 6.1% (6) in Parkinson's disease patients under DAs – significantly increased beyond that of the general population – the overall prevalence of at least one ICDs – including not only gambling but also compulsive buying, compulsive sexual behavior or binge eating – was as high as 17.1% under DAs in the study of Weintraub and coworkers with patients under DAs showing a 2- to 3.5-fold increased risk of developing an ICD (7). Furthermore, a retrospective analysis of 267 PD patients documented new-onset compulsive gambling or hypersexuality in nearly every fifth patient (18.4%) in the group of subjects taking therapeutic doses of dopamine agonists (defined as ≥2 mg of pramipexole or 6 mg of ropinirole daily) (8). Apart from the dosage, male gender, younger age and being unmarried have been identified as

risk factors for developing an ICD, both in the general population and in PD patients (7). All symptoms and signs abated with discontinuation of agonist therapy or dose reduction.

Similar side effects such as pathological gambling, compulsive shopping and hypersexuality have also been described in patients with restless leg syndrome treated with DAs, but the prevalence is less clearly established (9). In a prospective case-control study, the prevalence of ICDs in patients under modest doses of dopaminergic agents was as high as 17% (10).

In patients with prolactinomas, these rare central side effects have not been systematically investigated. Even if the doses of DAs used in these instances are considerably smaller (5–10 times) than those used to treat PD or RLS, distinct dopaminergic personality patterns have been already described. The largest study up to now by Bancos and coworkers was a case-control study (including a postal survey, review of medical electronic records and telephone interviews) comparing patients with prolactinomas with ongoing or past dopaminergic treatment and patients with non-functioning pituitary adenomas (NFPA) without history of dopaminergic treatment. The total prevalence of ICDs was significantly higher in patients with prolactinomas (24.6%-referring to the prevalence of one or more ICD) compared to the NFPA group (17.14%) or the general population of Sao Paulo, Brazil (8.4%) (11) with predominantly increased rate of hypersexuality. Males with prolactinomas treated with DAs showed a 9.9 higher risk than their counterparts with NFPA to develop an ICD, whereas female sex, age, type, dose and duration of treatment were no risk factors (12).

Apart from the aforementioned case-control study of Bancos and coworkers, there are six case reports and three case series that describe dopamine agonist-induced pathological gambling and hypersexuality in patients with prolactinomas, resulting in a number of 18 patients that developed hypersexuality and pathological gambling under DAs (13, 14, 15, 16, 17, 18, 19, 20). Interestingly, all patients had no psychiatric history and developed the symptoms after initiation of the dopamine agonist treatment. The dose of DAs was variable and symptoms were present regardless of the type of DAs as cabergoline, bromocriptine and quinagolide were implicated as treatment options.

De Sousa and coworkers suggested the term 'dopa-testotoxicosis' to refer to this distinct drug toxicity (18) as the phenomenon of a possible synergy between reward dopaminergic pathway stimulation by dopamine agonists and rapid restoration of the eugonadal state after prolonged hypogonadism. The occurrences of these ICDs may possibly be due to overstimulation of mesolimbic dopamine receptors in the central dopaminergic reward system (1), but the factors that predispose for the development of these central side effects of a systematically administered drug are unknown. Gender seems to play a significant role with men being at a higher risk (18). Up to now, there are three female patients reported in the literature with hypersexuality under DAs (12). Another case of a female patient that developed hypersexuality under DAs was to be seen in terms of psychosis (21). The possible role of restoration of hypogonadism either pharmacological through testosterone substitution or physiological should be discussed, as patients with prolactinomas suffer from hypogonadism and its symptoms, including diminished libido and erectile dysfunction. The restoration of the hypogonadism, reflecting the state of relative testosterone excess, could potentially contribute to the development of hypersexuality.

However, as patients seem to react to DAs also with other ICDs such as gambling or binge eating that do not seem to be related with the sexual hormones, further possible pathophysiological mechanisms that contribute to this phenomenon should be discussed such as the ability of the medication to pass the blood-brain barrier, the physical barrier of the central nervous system, formed by endothelial cells and astrocytic expansions that restrict the penetration of specific molecules into the brain. This ability has been proven to be actively controlled by transporter molecules such as the P-glycoprotein (P-gp), encoded by the *ABCB1* gene (or alternatively multidrug resistance gene – *MDR1*), located on chromosome 7 (22), that transports substrates – among them cabergoline – back into the blood circulation, thus protecting the central nervous system from harmful substances. Specific genetic polymorphisms seem to correlate with different levels of the P-gp activity, leading to an increased or diminished function of this transporter molecule. At the moment, there is only one study conducted by our group, examining the hypothesis of the genetic predisposition for the development of central side effects, that revealed increased central common side effects such as fatigue, dizziness and sleep disorders under cabergoline in individuals with specific *ABCB1* polymorphisms, but no correlation with the rare neuropsychiatric side effects could be established (23). Whether the central side effects of cabergoline also depend from polymorphisms of the dopamine 2 receptor (*DRD2*) gene or the density or function of the D2 receptor is yet not known.

Furthermore, psychosis – not being included in the classical ICDs – seems to be a well-known side effect under DAs. Other psychotic symptoms such as hallucinations and illusions are also associated with the dopaminergic treatment. Several reports have described an induction of psychosis by most of the common dopamine agonists such as pergolide and bromocriptine in patients with PD, with dementia being a risk factor (24). In patients with prolactinomas, several case reports describing behavioral changes from low mood, irritability and verbal aggressiveness up to psychotic and manic symptoms and paranoid delusions have been published (25, 26, 27, 28). This phenomenon seems to be more frequent in patients with previous personal or familial history of mental illness with DAs triggering the development of the psychiatric illness. However, also previously healthy individuals seem to be affected (27). As psychosis is being treated with dopamine-receptor blockers (that in patients with prolactinomas may result in elevated serum prolactin, tumor growth or further uncontrolled hyperprolactinemia-related symptoms), clinicians are being confronted with the dilemma of treating patients while having to deal with severe possible side effects. According to the available literature, treatment options contain a discontinuation of the DA and/or adding clozapine for its low effect on prolactin and growth of the prolactinoma (26). Other approaches suggest administering aripiprazole, as it is a partial dopamine agonist especially at low doses and seems to reduce prolactin levels in patients with and without hyperprolactinemia (27, 29) whereas other studies propose quetiapine (30) or the combination of clozapine and quinagolide (31). The underlying mechanism of triggering psychosis or mania seems to be the stimulation of mesocortical and mesolimbic D2 and D3 receptors by the DAs (32, 33) whereas (ICDs) may also be mediated by D3 receptors.

As also in our case of the male patient, ICDs can have devastating consequences in these patients' and their families' lives, including relationship discord, financial consequences, job loss and illegal activities possibly leading to imprisonment. Taking into account these consequences, awareness of these rare but distinct ICDs from not only the treating physician but also the patient should lead to considerations of cessation of DA on time and alternative treatment options such as pituitary surgery. Due to the highly personal nature of the symptoms, patients may be reluctant to report them and therefore we consider these side effects as underreported, whereas De Sousa and coworkers suggested screening with at least one simple questionnaire within six months of commencing DA therapy (18). The management and pathophysiological background of these side effects merits further investigation in longitudinal, prospective studies.

The endocrinologist's perspective: metabolic aspects

Hyperprolactinemia seems to be associated with a high prevalence of obesity, insulin resistance and low-grade inflammation (34) – independently of the body mass index (BMI) – (35) and patients with prolactinomas tend to have increased body weight in comparison to healthy individuals (36) but also to patients with non-functioning pituitary adenomas (NFPA) (37).

Dopaminergic treatment in prolactinomas seems to induce weight loss and lead to amelioration of other metabolic parameters such as lipid profile and insulin resistance in some patients (37, 38, 39) not only by normalizing prolactin or by mechanisms related to the pharmacological side effects (35, 40). As only data from few retrospective studies are available and as weight loss seems to take more than 6 and 12 months, improvement of metabolic parameters seems to occur in advance (35,40, 41, 42).

The most recent study of Pala and coworkers (43) conducted in nineteen patients with prolactinomas showed that they presented with increased level of fasting plasma glucose, higher levels of leptin without a significant difference in adiponectin levels as compared to age-, gender- and BMI-matched healthy controls. There was a significant decrease of body weight and BMI after 3 months and a decrease of waist circumference, waist-to-hip ratio, total body fat, plasma glucose and leptin levels after 6 months of continuous treatment.

In a retrospective study conducted from our group in 44 prolactinoma patients, we examined whether the prevalence of *TAQ1A*, a polymorphism considered as a gene marker for the *DRD2* linked to altered brain dopaminergic activity due to reduced receptor binding and lower density of the dopamine 2 receptor, could be associated with a different metabolic profile and reduced weight loss response under DAs. In our cohort, we observed that continuous 2-year dopaminergic treatment leads to a significant mean weight loss regardless of the Taq1a status (44).

Delibasi and coworkers (45) attempted to investigate, whether this observed body weight gain and the consequent weight loss in patients with prolactinomas could be attributed to ghrelin. Both patients with

prolactinomas newly diagnosed and under ongoing cabergoline treatment but also healthy subjects were included. The study revealed no significant difference in terms of the ghrelin levels between these three groups suggesting that ghrelin levels have no significant effect on weight gain and could not explain increased obesity prevalence in prolactinoma.

Different studies not only in hyperprolactinemic patients but also in other patients' settings have addressed the metabolic impact of dopaminergic treatment. In diabetic patients, it could be shown that bromocriptine – as monotherapy or in conjunction with the available treatments for type 2 diabetes mellitus (metformin, sulfonylureas, thiazolidinediones and insulin) – can lower fasting glucose levels, postprandial glucose, HbA1c and potentially decrease cardiovascular events in this population so that in 2009 bromocriptine was approved by the Food and Drug Administration (FDA) as a treatment for type 2 diabetes mellitus (46). Cabergoline, a more specific central dopamine agonist, has been shown in one study to have significant effects in lowering HbA1c, fasting plasma glucose and postprandial glucose in diabetic patients; however, further studies in these patients are lacking (47).

Studies in obese normoprolactinemic individuals suggest that bromocriptine administration promotes significant weight and body fat loss (8), whereas cabergoline administration seems to improve glucose tolerance independent of weight loss or prolactin reduction (41, 48).

The exact mechanism of this phenomenon remains unclear. Dopamine in hibernating animals seems to be involved in changes seen in adipose tissue and insulin sensitivity, limiting resource utilization, a condition that seems to be similar to the obese state to survive hibernation (46). Animal models, including genetically obese ob/ob mice, have decreased hypothalamic dopamine and dopamine agonist administration decreases hepatic gluconeogenesis and lipid generation, promoting an insulin sensitivity state (49, 50). As the reduction of prolactin levels did not directly correlate with changes in serum leptin levels and BMI, changes in prolactin levels do not seem to be the predominant determinant of changes in body weight (51). The dose of DAs does not seem to play a significant role as in general, patients with prolactinomas are being treated with relatively low doses of DAs and weight loss has been documented even under a low dose of cabergoline (38). An alternative mechanism could be the increase of the central dopaminergic tone through the dopaminergic stimulation leading to weight loss by mechanisms additionally to reducing hyperprolactinemia (51), a plausible hypothesis on the basis of the altered dopaminergic function experienced from these patients already documented (52, 53).

The role of the peripheral dopamine and its implications in weight loss should also be discussed. *In vitro* studies showed that human adipocytes express functional dopamine receptors, suggesting a regulatory function of peripheral dopamine in the adipose tissue (54). Furthermore, other receptors of the adipocytes such as the adrenergic receptor seem to interfere with dopamine agonists (55). Further prospective studies need to be conducted to address the important question of the metabolic impact of DAs.

Conclusion

The dopaminergic treatment in prolactinomas and also in Parkinson's disease and restless legs syndrome is associated with the development of neuropsychiatric side effects such as impulse control disorders (e.g. pathological gambling, compulsive shopping, hypersexuality and binge eating) with a varying prevalence in different studies and different patient groups up to 24.6%. Risk factors seem to be the dosage of dopamine agonist, male gender, younger age and being unmarried. Given the potentially devastating consequences of these side effects, further prospective studies are needed for a better understanding of the frequency of these behaviors and improvement of their medical management.

Moreover, dopamine and prolactin seem to play an essential role in the metabolic pathway. Patients with hyperprolactinemia tend to have an altered metabolic profile with hyperinsulinemia, increased body weight and increased prevalence of diabetes mellitus in comparison to healthy individuals and patients with non-functioning pituitary adenomas. Treatment with dopamine agonists in these patients in short-term studies seems to lead to weight loss and amelioration of the metabolic changes.

Together these observations provide evidence that dopamine and prolactin have a crucial role both in the regard and metabolic system, findings that merit further investigation in long-term studies.

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