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Case Report

Cabergoline Induced Pathological Gambling in an Adolescent with Prolactinoma

Tercan U et al. Cabergoline Induced Pathological Gambling

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What is already known on this topic?
Dopamine agonists are known to be associated with the development of impulse control disorders, such as pathological gambling, particularly in adult populations..Pathological gambling has been reported as a rare side effect of dopamine agonist in adolescent group.

What this study adds?
This is the first documented case of cabergoline-induced pathological gambling in an adolescent patient being treated for prolactinoma. This case highlights the need for careful psychiatric monitoring of patients, especially those undergoing treatment with dopamine agonists. Early identification and intervention may be critical in preventing and managing such impulse control disorders.

Abstract
Prolactinomas are the most common hormone-secreting pituitary adenomas in adolescents. Dopamine agonists (DA) are used as first-line medical treatment. DAs are associated with an array of physical side effects; however, impulse control disorders (ICDs), such as pathological gambling (PG), have also been reported in adults. A 15.7-year-old male with no psychiatric history was referred for headache and elevated prolactin (PRL) levels. He was diagnosed with PRL-secreting pituitary macroadenoma After initiating DA therapy with cabergoline (CBG), normalization of PRL levels and a considerable decrease in tumor size were observed. Central hypothyroidism and adrenal insufficiency present at the time of diagnosis were resolved. CBG dose was adjusted according to the test results over time. However, after two and a half years of therapy (while using 1.5 mg CBG per week), the patient developed PG, incurring debts and affecting familial relationships. Upon reducing the CBG dosage, PG symptoms ceased. This is the first case report of an adolescent with a prolactin-secreting macroadenoma who developed PG as a side effect of CBG treatment. This case highlights the need for careful monitoring of psychiatric symptoms in pediatric patients with prolactinoma on DAs.
Keywords: adolescent, cabergoline, dopamine agonist, pathological gambling, prolactinoma

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Introduction
Prolactinomas are the most prevalent hormone-secreting pituitary adenomas in adolescents (1,2). For prolactinomas, medical therapy, typically with dopamine agonists (DA), such as bromocriptine (BRC) or cabergoline (CBG), is the first-line treatment (2,3). DAs are generally well tolerated but can be associated with an array of side effects, which predominantly manifest during the initial phase of therapy. Gastrointestinal disturbances are the most frequent adverse events. Neurologically, patients might have headache, dizziness, dyskinesia, and confusion (4). The side effects of DAs may also include psychiatric complications such as depression, anxiety, insomnia, hallucinations, and mania. Although impulse control disorders (ICDs) have been associated with the treatment of Parkinson's disease (PD), they have also been described in pituitary adenoma patients treated with DAs (5). ICDs are psychiatric disorders characterized by difficulty in regulating emotions and behaviors, ranging from mild issues like punding to more serious conditions such as pathological gambling and hypersexuality, which can negatively impact personal and social well-being (6). ICDs, including pathological gambling (PG), share a biological background with other addictive disorders. PG is considered a behavioral ICD, where the individual is unable to resist urges to gamble (7).
Here, we report the case of an adolescent boy with a macroadenoma secreting prolactin, who developed PG as a side effect of cabergoline treatment. To the best of our knowledge, this is the first documented cabergoline-induced gambling disorder among adolescents within the current literature. Moreover, this emphasizes the importance of careful monitoring and management of DA-induced side effects.

Case Report
A 15.7-year-old male presented with a complaint of headache and was referred to pediatric endocrinology due to a markedly elevated PRL level of 462 ng/mL (N: 4.04-15.2). The patient was previously healthy and his medical history was unremarkable, with no psychiatric history. He was born at term, with a birth weight of 4380 g, from healthy parents with a nonconsanguineous marriage. At presentation, his body weight was 88 kg (-0.81 standard deviation score (SDS)), height was 178 cm (1.88 SDS), and body mass index (BMI) was 27.9 kg/m2 (1.62 SDS). His blood pressure was within the normal limits, and neither galactorrhea nor gynecomastia was detected. Testicular volumes were 15 mL/15 mL and pubic hair was compatible with Tanner stage 5. His systemic physical examination results were otherwise normal.
Hormonal evaluation revealed a markedly elevated PRL level of 539.9 ng/mL (N: 4.04-15.2). Growth hormone and gonadotropin levels were within normal limits. Free T4 level was below the lower limits and retest-confirmed central hypothyroidism. As the patient's baseline cortisol level was low, a low-dose (1 µg) ACTH test was performed, and peak cortisol was found to be inadequate at 10.9 µg/dL (N >18 µg/dL). The hormonal profiles of the patients at the time of diagnosis are shown in Table 1. Magnetic resonance imaging (MRI) revealed a pituitary adenoma, 19 × 14 × 13 mm in diameter, extending into the suprasellar cistern with peripheral and thin septal enhancements. This finding was

consistent with a cystic degenerated adenoma with hemorrhagic leveling, and the optic chiasm was slightly elevated. The infundibular stalk was deviated to the left side, and a 14 × 10 × 10 mm cystic lesion was found in the pineal gland. Visual field examination at the time of diagnosis was normal. Thyroid hormone and hydrocortisone therapies were commenced for central hypothyroidism and central adrenal insufficiency. For hyperprolactinemia, CBG treatment with a dosage of 0.5 mg three days/week was initiated. Echocardiography findings before CBG therapy were normal.

After three months, his headaches regressed. Serum PRL level was 1.93 ng/mL, which was below the normal range. and control MRI revealed a 40% reduction in the size of the macroadenoma. Subsequently, the CBG dose was gradually reduced to 0.75 mg per week, and the PRL level normalized to 5.92 ng/mL The maintenance dose was adjusted according to the test results over the years. Ten months after the onset of hydrocortisone therapy, it was discontinued because of an adequate peak cortisol response in a low-dose ACTH test (off-therapy for 24 h). There was no longer need for LT4 treatment as well. Subsequent medication-free evaluations showed that thyroid function test results were within normal limits.

Two and a half years after the initiation of treatment, at 18.2 years, the CBG dosage was 1.5 mg per week. According to his parents' statement, although he had no gambling history before, the patient's change in behavior was dramatic, having been gambling on the Internet for 4 months. He gambled on most days, lost 60.000 Turkish liras (3900 Euro), and incurred increased debts due to gambling. This behavior resulted in significant financial losses and deteriorated family relationships. There was no impulsive or affective behavior or other psychiatric diseases in his family history. In his laboratory evaluation, the PRL level was 14.9 ng/mL, baseline cortisol level was 12.4 µg/dL, IGF-1 was 262.3 ng/mL, LH level 4.87 IU/L, FSH level was 6.38 IU/L, total testosterone was 3.5 ng/ml, all within the normal range. He was referred to a psychiatry clinic and diagnosed with PG secondary to CBG treatment. The diagnosis was based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for non-substance addictive disorders and supported by a clinical interview. Gambling behavior started after initiating CBG, persisted during treatment, and resolved after dose reduction, suggesting a direct link to the medication. Other impulsive control disorders, including hypersexuality, were investigated but not identified. Because it was thought to be the triggering factor for his PG, the CBG dosage was reduced to 0.5 mg per week. Three months after dose reduction, the patient's gambling issues ceased. At the last visit, the patient had no complaints. His PRL level was 20 ng/mL. Serum PRL levels and CBG dosage over time is shown in **Figure 1**. The control pituitary MRI showed regression in adenoma size compared with the previous MRI. The visual field examination and echocardiography results were normal. CBG was continued at a dose of 0.25 mg twice a week. The patient has now been transferred to adult care. He continued to take his medications and attended regular check-ups.

Discussion

PG is a relatively rare side effect of DAs, which are the mainstay in the management of prolactin-secreting pituitary adenomas. In this case report, we focused on a significant instance of gambling addiction linked to the use of CBG in managing prolactinomas that manifest during childhood.

Currently, two drugs, CBG and BRC, have been approved by the Food and Drug Administration for the treatment of hyperprolactinemia, pergolide and quinagolide, and have been less frequently used or no longer available (8). CBG is preferred in clinical practice for its efficacy at low weekly doses (0.25–0.5 mg), which is generally well-tolerated. The goal of DA therapy is to reduce PRL levels and shrink adenomas, with dosages adjusted according to the severity of the condition and patient's response to treatment. This involves tapering off or discontinuing DAs after normalization of serum PRL levels and adenoma resolution, typically after a minimum of two years of therapy (9). ICDs are a group of psychiatric conditions defined by the DSM-5, and are characterized by significant challenges in regulating emotions and behaviors (10). These disorders manifest as actions that may infringe upon the rights of others or bring individuals into serious conflict with societal norms and authority figures. The clinical presentation of ICDs has a wide range, from less severe forms such as punding to more hazardous behaviors. such as PG and hypersexuality, which can pose considerable risks to personal and social well-being (6). Reports have indicated high prevalence rates of ICD ranging from 6% to 24% (11,12). Although effective in controlling PRL levels, there is an emerging concern regarding the onset of ICDs in patients undergoing DA therapy. Even if the doses of DAs used in these instances are considerably 5–10 times lower than those used to treat PD or restless leg syndrome, distinct dopaminergic personality patterns have been described (13-16). In adults treated with DAs for prolactinoma, the prevalence of ICD ranges between 8% and 61% (17-20). Our patient was an adolescent boy who developed PG as a side effect of the CBG treatment. In some case reports, the gender of individuals who developed PG as a result of cabergoline use was male (13-15). Males seem to have an increased risk of developing pathological hypersexuality and gambling, whereas females are more likely to exhibit compulsive eating and shopping behaviors in the general population (21).

In most reported studies, neither the DA dose (17-20,22) nor duration of therapy (17,19,23) were found to be associated with the occurrence of ICDs. In prolactinomas, the correlation between DA dosage and the emergence of ICDs is unclear. While Bancos et al. (17) observed that DA dosage did not play a significant role in ICD development, Barake et al. (23) observed an association between higher doses of CBG and increased impulsivity. In another study, even though patients with ICDs were on higher maintenance doses of CBG, the difference was not statistically significant (18). Also, several case reports in adult patients with prolactinomas have indicated that ICDs can become apparent even with low dosages of DAs (13,14,24). Our patient exhibited signs of PG while using 1.5 mg of CBG per week, and this dosage was not considered high.

Gambling disorder is an addiction in which individuals engage in problematic gambling. The DSM-5 outlines that those affected by PG are driven to bet increasingly larger amounts of money to achieve the desired excitement and have repeatedly failed to control their gambling (24). ICDs and addictive disorders share similar brain processes, which implies that they might benefit from comparable treatment strategies. PG is categorized as an addiction due to its compulsive aspects, reflecting a shift in the most recent editions of diagnostic manuals, such as DSM-5 and ICD-11, where PG is classified as an addictive disorder rather than an ICD (6,24). The tendency for gambling may increase with the use of dopamine-related drugs because of the potential overstimulation of dopamine-dependent reward and reinforcement circuits in the brain (25). The use of DAs in the treatment of hyperprolactinemia is based on their effects on dopamine receptor isoforms, specifically D2 and D3. D2 receptors are key to inhibiting PRL release from the pituitary gland. D3 is highly expressed within the limbic system, ventral striatum, frontal cortex and thalamus (8). The mesocorticolimbic pathway, which begins in the ventral tegmental area and connects the limbic system and the frontal cortex, is thought to be involved in the development of DA-induced ICDs (28). The induction of ICDs is believed to be due to the activation of D3 dopamine receptors in the mesocorticolimbic pathway (8).

Although a correlation has been observed between DA therapy and PG, the development of PG symptoms can occur at different stages of DA therapy. Notably, these patients had no prior psychiatric history, and the symptoms occurred independent of the type of medication administered; that is BRC and CBG (13,14,18,27). However, data on this side effect in childhood are limited. In a case report by Thondam et al. (27), a 14-year-old girl with prolactinoma commenced BRC therapy, and two years after the initiation of therapy, she developed symptoms of PG. In contrast, a 19-year-old young adult developed gambling behavior shortly after beginning BRC for a giant prolactinoma (16). Another report described a 19-year-old boy who presented with signs of increased sexual behavior concurrently with the initiation of treatment with 4 mg CBG per week (28). In our case report, the manifestation of PG occurred two and half years after the initiation of cabergoline therapy, when the patient was on a dose regimen of 1.5 mg per week. This observation is consistent with the existing literature and suggests that the onset of PG is not influenced by the dosage or initial timing of the treatment. In addition, our case report contributes to the literature as the first documented instance of PG developing in an adolescent undergoing treatment for prolactinoma with CBG, thereby expanding the understanding of such occurrences in this age group.

Currently, there are no published guidelines for the management of ICDs in patients with hyperprolactinemia receiving DA therapy. Studies have indicated that reducing the dose or cessation of DA therapy might be beneficial for those who develop ICDs (13,14,18,27). Owing to the side effects of DA therapy, it may be necessary to reduce the dose or discontinue the therapy. Patients with hyperprolactinemia who develop ICDs should be withdrawn from DA therapy or, at least, undergo DA dose reduction, as well as being considered for psychiatric consultation and cognitive behavioral therapy. It is also important to evaluate preexisting psychiatric disorders before prescribing DAs and to carefully follow up patients who are prone to or have a history of psychiatric disorders (5,25). Before considering cessation, a reduction in DA dosage should be attempted, as it could improve symptoms in certain patients. Switching between different DAs is generally not recommended, as it could lead to different ICDs, exemplified by a patient who developed compulsive gambling and eating when switching from BRC to CBG (15). Considering the current literature, we adopted a dose reduction strategy for our patient, who exhibited PG as a side effect of CBG therapy. Three months after the reduction in medication dose, the symptoms disappeared.

Conclusion

In conclusion, to our knowledge, this is the first case of PG reported in an adolescent patient with macroadenoma who was receiving CBG treatment. Our case report demonstrates that ICDs are an important complication of dopaminergic therapy in patients with prolactinomas. Here, we aimed to emphasize the careful monitoring of psychiatric symptoms in patients treated with DAs for prolactinomas, especially in the pediatric and adolescent age groups. It has been suggested that every patient who is prescribed DA, along with their family, should be informed about the possible side effects. This was done to ensure early recognition and prevent the development of severe financial and social issues. The occurrence of PG in this patient, without a prior psychiatric history, emphasizes the potential for DA-induced PG, irrespective of the DA dosage and duration of treatment.

Statements

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Statement of Ethics

This study was conducted in compliance with the terms of the Helsinki II Declaration and written informed consent was obtained from the parents on behalf of the children. In our country, this type of clinical study does not require Institutional Review Board/Institutional Ethics Committee approval to publish the results.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

U.T., E.S., and M.Y.. managed the patient and gathered clinical data. UT , ADK and M.Y. drafted the manuscript. M.O. and O.N.E. provided expert input on psychiatric evaluation and management. F.B., S.P. and F.D. revised the manuscript. All authors approved the final version of the manuscript.

Data Availability Statement

All data are presented in the manuscript. Further enquiries can be directed to the corresponding author.

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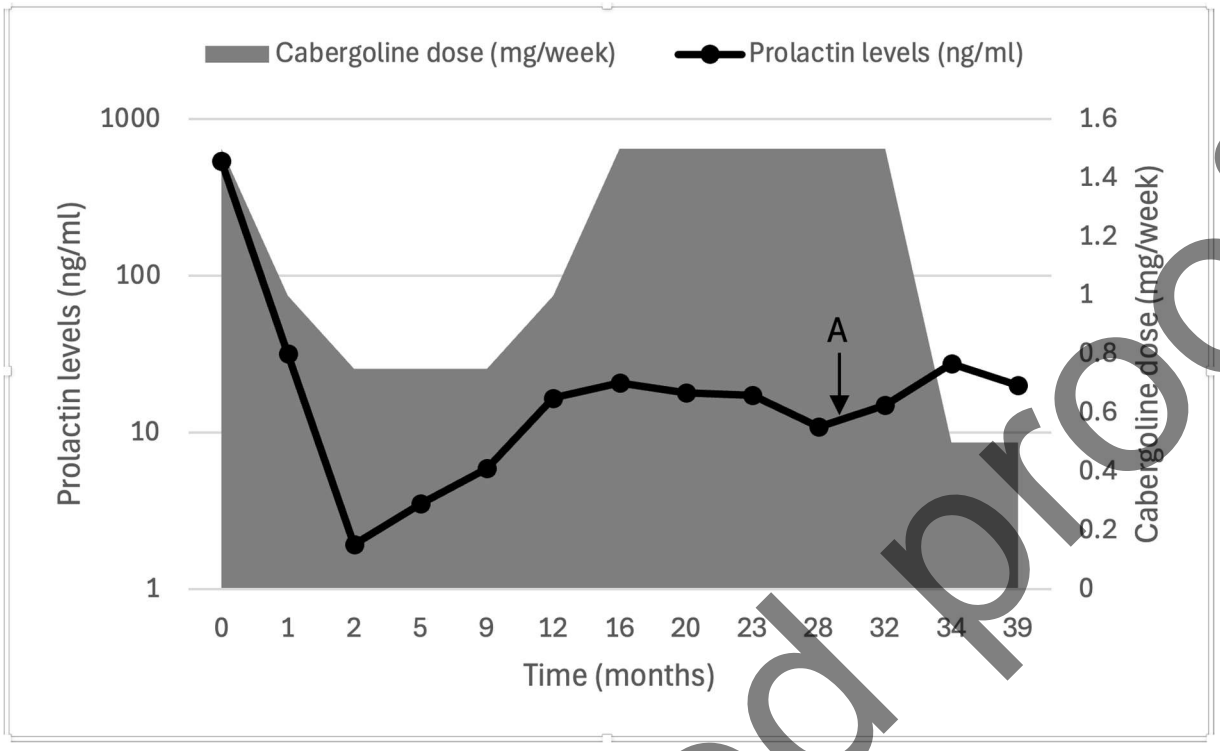
Table 1. Hormonal profile of the patient at the time of diagnosis

Test	Result	Normal range
Prolactin (ng/mL)	539.9	4.04-15.2
FSH (IU/L)	5.79	1.5-12.4
LH (IU/L)	5.4	1.7-8.6
Total testosterone (ng/mL)	3.05	2-6.2
TSH (µIU/mL)	2.04	0.53-3.59
Free T4 (pmol/L)	9.6	12-20.6
Free T3 (pmol/L)	6.88	3.5-7.7
IGF-1 (ng/mL)	365	211-512
IGFBP3 (µg/mL)	9.53	3.4-9.5
Growth hormone (ng/mL)	0.38	0.077-10.6
Cortisol (08:00 am) (ug/dL)	3.06	3-21
ACTH (pg/mL)	30	7.2-63.3

FSH: follicle stimulating hormone, LH: luteinizing hormone, TSH: thyroid stimulating hormone, IGF-1: insulin like growth factor-1, IGFBP3: insulin like growth factor binding protein 3, ACTH: adrenocorticotropic hormone.

Figure 1: Serum prolactin levels and cabergoline dosage over time.



Arrow 'A': Onset of symptoms of pathological gambling disorder.