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Impulse Control Disorders in Patients with Prolactinoma on Cabergoline in Basrah

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Abstract

Background: Prolactinoma is the most common pituitary tumor in Basrah. Impulse control disorders (ICDs) were reportedly associated with cabergoline use for patients treated for prolactinoma. The study aimed to assess the prevalence of ICDs in cabergoline treated patients with prolactinoma versus healthy matched control.

Methods: A cross-sectional case-control study including 30 cabergoline treated patients with prolactinoma and 30 healthy matched control at Faiha Specialized Diabetes, Endocrine and Metabolism Center in Basrah, southern Iraq from January 2023 to May 2023. Questionnaire for ICDs in Parkinson's disease was used as a screening tool and then positively screened patients were evaluated using validated criteria accordingly to diagnose impulse control disorders.

Results: ICDs was diagnosed in 9 (30%) cabergoline treated patients with prolactinoma versus 2 (6.7%) in control, (P 0.02). The most frequent ICDs types were hypersexuality and binge eating while no patient reported pathological gambling. Three patients reported multiple types of ICDs. The patients' socio-demographic characteristics, prolactinoma duration and size, and cabergoline dose did not correlate significantly with ICDs diagnosis.

Conclusions: treatment with cabergoline is associated with development of ICDs and the clinicians should be aware of this disabling side effect to detect it early and treat it properly.

Categories: Endocrinology/Diabetes/Metabolism, Psychiatry
Keywords: compulsive eating, hypersexual disorder, impulse control disorders, cabergoline, prolactinoma

Introduction

About 40% to 50% of all pituitary adenomas are prolactinomas, which are a significant contributor to hypogonadism and infertility [1, 2] and the mass effect with loss of visual fields being the most concerning symptom [3]. Pituitary adenomas are the major pituitary disorders in Basrah and about 26.9% of these are prolactinomas [4].

Cabergoline is currently first line for treatment of prolactinoma with starting dose of 0·25-0·5 mg per week [5], which is much lower than that used in patients with Parkinson disease(up to 3 mg once daily) [6]. Cabergoline has a very long duration of action. Once or twice weekly dosing is typically sufficient for controlling pathological hyperprolactinemia [7] and studies have shown that cabergoline is superior to other Dopamine agonists(DA) in terms of efficacy in reducing tumor size and prolactin level [8] .Cabergoline exerts its effect through activation of D2 and D3 receptors. Activation of D3 receptors in brain maybe responsible for development of abnormal behaviors in patients developing ICDs as shown by J. E. Ahlskog in 2011 [9]. Interest in impulse control disorders (ICDs) is on the rise, particularly in Parkinson's disease patients receiving dopamine replacement medication and this suspicion was raised by JA Molina in 2000 when he noticed pathological gambling among patients receiving D.A. therapy for Parkinson disease [10].

ICDs include pathological gambling, compulsive shopping, excessive eating, and hypersexuality. According to a recent study, ICDs are linked to conditions including fibromyalgia, progressive supranuclear palsy, multiple system atrophy, restless legs syndrome, and multiple system atrophy that are also treated with dopaminergic medicines (dopamine agonists) [11].

ICDs are defined by excessive and/or hazardous desires and behaviors that seriously affect social and occupational functioning as well as generate legal and financial issues [12].

Studies involving large population and indeed randomized control trials for incidence of ICDs in patients on

cabergoline for prolactinoma are lacking and this issue is largely underestimated due to lack of awareness and specially in our society due to social limitations.

The study aimed to assess the prevalence of ICDs in cabergoline treated patients with prolactinoma versus healthy matched control.

Materials And Methods

This is a cross-sectional case-control study was carried out at Faiha Specialized Diabetes, Endocrine, and Metabolism Center (FDEMC) in Basrah, southern Iraq from January to May 2023.

Inclusion criteria were in the form of patients diagnosed with prolactinoma and on cabergoline treatment for at least six months. Further age, gender, and body mass index (BMI) matched control were included for comparison.

Exclusion criteria: treatment course less than six months, patients with history of previous psychiatric disorders, patient on other types of treatment with adverse psychiatric effects, patents with known organ dysfunction impairing adequate mental function and patients with mental handicap.

Impulse control disorders diagnosis:

All cases and controls were screened first using the validated questionnaire for ICDs in Parkinson's disease (QUIP). This questionnaire is composed of four parts and is the same previously used for studies of ICDs in Parkinson disease and restless leg syndrome and its validity was studied in 2009 [13].The screening was done by asking the QUIP questions by direct interview. To avoid gender bias, questions regarding sexual activity in female patients were asked by a female doctor. For those who screened positive by QUIP, a second evaluation using the Diagnostic and Statistical Manual of Mental Disorders (DSM) questionnaires to confirm the diagnosis of ICDs according to valid criteria for each type of ICD. Patients who positively screened for hypersexual disorder will be evaluated with Proposed criteria for Hypersexual Disorder according to DSM V [14]. Those who screened positive for compulsive eating also will be evaluated using DSM V criteria application [15].

Compulsive buying disorder was diagnosed according to proposed diagnostic criteria from 2021 Delphi consensus study after screening positive by QUIP [16].No patient screened positive for pathological gambling mostly due to unavailability of gambling in our society. Other domains (repeated cleaning, door closing) were diagnosed also using DSM V criteria.

The included patients consented to the study by a written forum. The study was approved based on the ethical standards of the FDEMC Research Committee and ethical approval was given (ref #12/23/23).

Statistical analysis:

The statistical package for social sciences version 26 was used for data analysis with the p value < 0.05 being significant. The quantitative and qualitative variables were summarized as mean ± standard deviation and numbers (%) respectively. The correlations between qualitative variables were done using the Chi Square test and Fisher Exact test. While the correlations between qualitative and quantitative variable were done using the independent student t test.

Results

The cases and control groups were matched regarding sociodemographic characteristics as shown in Table *1*. The patient with prolactinoma on cabergoline for a mean duration of 2.9 ± 2.3 years and current cabergoline dose of 0.6 ± 0.3 mg. seventeen patients had macroadenoma on presentation, mean prolactin were 1120.4 ± 600.7 ng/ml and 68.9 ± 76.8 ng/ml at presentation and currently respectively.

Variable	Prolactinoma (30) Mean ± SD or N (%)	Control (30) Mean ± SD or N (%)	P value
Age (years)	37.0 ± 11.8	33.2 ± 10.6	0.2
Age at diagnosis (years)	34.1 ± 11.6		
BMI (kg/m2)	32.4 ± 6.3	30.3 ± 2.9	0.1
Men	14 (46.7)	18 (60.0)	0.3
Women	16 (53.3)	12 (40.0)	
Marital status			
Married	26 (86.7)	23 (76.7)	0.2
Unmarried	3 (10)	7 (23.3)	
Divorced	1 (3.3)	0	
Occupation			
Employed	7 (23.3)	10 (33.3)	0.4
Unemployed	23 (76.7)	20 (66.7)	
Education			
Primary	13 (43.4)	8 (26.7)	0.4
Secondary	7 (23.3)	10 (33.3)	
College	10 (33.3)	12 (40)	
Microadenoma	13 (43.3)		
Macroadenoma	17 (56.7)		
Duration of treatment (years)	2.9 ± 2.3		
Baseline PRL (ng/ml) Normal (male 4-23 ng/mL and female 4-30 ng/mL)	1120.4 ± 600.7		
Current PRL (ng/ml)	68.9 ± 76.8		
Cabergoline dose (mg) per week			
Maximum	0.8 ± 0.4		
Current	0.6 ± 0.3		

TABLE 1: General characteristics of the study population (N = 60)

Abbreviations: SD, standard deviation; N, number; BMI, body mass index; PRL, prolactin; mg, milligram.

ICDs were diagnosed in nine patients within case group (30%) and only two patients were diagnosed with ICDs within control group, (P 0.02). as shown in Figure *1*.

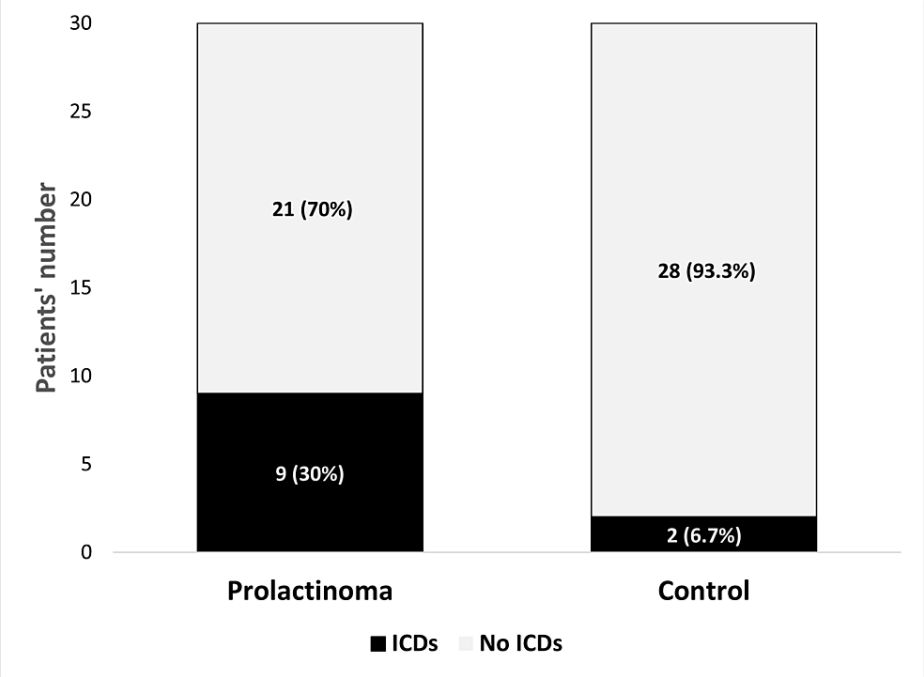

FIGURE 1: Prevalence of ICDs among patients with prolactinoma versus control

Odd ratio and 95% confidence interval, 6 (1.1-30.7), P = 0.02 by Chi Square test. Abbreviation: ICDs, impulse control disorders.

Figure-2 shows the frequencies of different types of ICDs in the case group. Four patients had hypersexuality (men only affected), four patients had compulsive eating, two patients had compulsive shopping, two patients had repeated cleaning, and one patient had repeated door closing. Three patients had ICDs with multiple ICDs types.

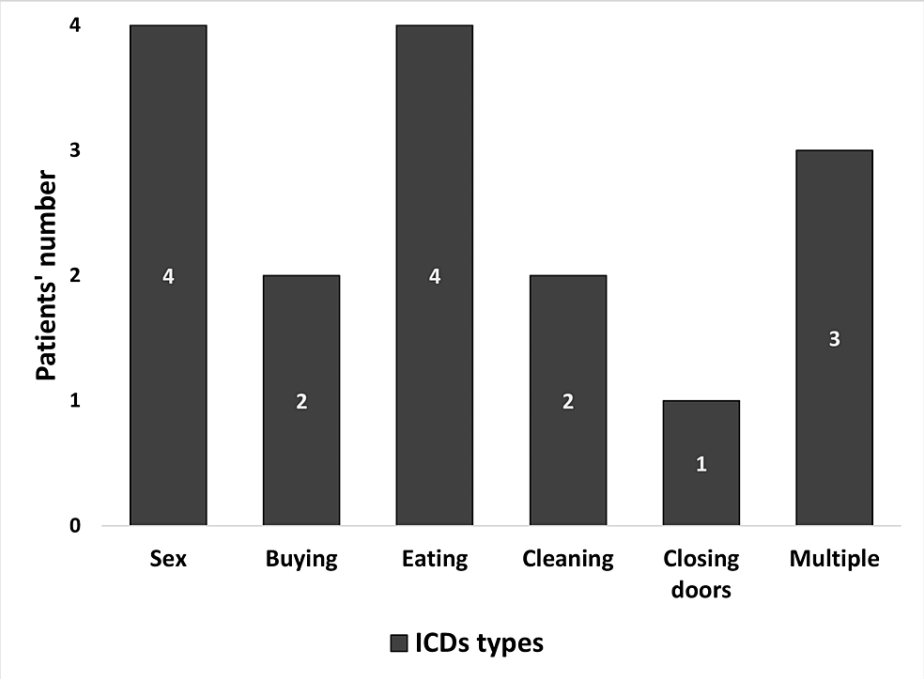

FIGURE 2: Frequencies of different impulse control disorder types.

Abbreviation: ICDs, impulse control disorders.

The patients' socio-demographic characteristics, prolactinoma duration and adenoma size, and cabergoline dose did not correlate significantly with ICDs diagnosis. However, the patients with prolactinoma affected by ICDs had higher maximum cabergoline doses during their treatment course, (1.0 ± 0.5 mg versus 0.6 ± 0.2 mg), but with no statistical difference. As shown in Table *2*.

Variable	ICDs (9) Mean ± SD or N (%)	No ICDs (21) Mean ± SD or N (%)	P value £
Age (years)	34.7 ± 9.3	38.0 ± 12.2	0.4
Age at diagnosis (years)	32.1 ± 9.9	35.0 ± 12.4	0.5
BMI (kg/m2)	32.3 ± 7.5	32.4 ± 5.9	0.9
Men	5 (35.7)	9 (64.3)	0.6 α
Women	4 (25)	12 (75)	
Marital status			
Married	7 (26.9)	19 (73.1)	0.4 α
Unmarried	2 (66.7)	1 (33.3)	
Divorced	0	1 (100)	
Occupation			
Employed	1 (14.3)	6 (85.7)	0.3
Unemployed	8 (34.8)	15 (65.2)	
Education			
Primary	5 (38.5)	8 (61.5)	0.7 α
Secondary	2 (28.6)	5 (71.4)	
College	2 (20)	8 (80)	
Microadenoma	4 (30.8)	9 (69.2)	0.6 α
Macroadenoma	5 (29.4)	12 (70.6)	
Duration of treatment (years)	2.7 ± 1.8	2.9 ± 2.6	0.7
Baseline PRL (ng/ml)	309.6 ± 171.9	717.2 ± 1312.6	0.3 μ
Current PRL (ng/ml) (male 4-23 ng/mL and female 4-30 ng/mL)	88.7 ± 74.6	60.4 ± 78.0	0.3 μ
Cabergoline dose (mg) per week			
Maximum	1.0 ± 0.5	0.6 ± 0.2	0.07
Current	0.8 ± 0.5	0.5 ± 0.2	0.2

TABLE 2: Variables' effects on ICDs among patients with prolactinoma.

£ Chi Square P value.

αFisher Exact P value.

μIndependent student t test P value.

Abbreviations: SD, standard deviation; N, number; BMI, body mass index; PRL, prolactin; mg, milligram.

Discussion

This is the first study assessing the prevalence of ICDs in patient taking cabergoline for treatment of prolactinoma in Iraq, which showed a prevalence of ICDs in 30% of cabergoline treated prolactinoma patients. Most common type of ICDs were compulsive buying and hypersexuality, while no cases of gambling were detected, and this is due to prohibition of gambling in Iraq. Interestingly some of the patients reported symptoms of extreme nervousness, irritability and being easily provoked shortly after starting cabergoline therapy. This suggests that some types of ICDs may not be detected by QUIP or there may be early symptoms not meeting criteria for diagnosis of ICDs. De Sousa et al. in 2020 suggested addition

of other types of impulsive activities like excessive caffeine intake or exercise and video games and this is consistent with our finding [17].

In 2019 a multicenter study detected prevalence of 17%, with hypersexuality being the most common type occurring mostly in males as in our study [18]. Another study founded a prevalence of 25.8% in cabergoline treated group as compared to 15% in non-cabergoline treated group and this did not reach statistical significance but compared to our study the prevalence of ICDs in control group was much higher [19]. A comparable results with 24.8% in patient versus 17.1% in control group but non-significant [20]. Overall, there is a large variation in prevalence of ICDs in different studies (ranging from 0 to 60 %) [21] This large difference may suggest social and economic factors affecting occurrence and even the type of ICDs [22]. Another explanation attributed to the fact that most studies use self-administered questionnaire or online questionnaire and not direct survey by the doctors themselves. On the other hand, some studies used different methods for diagnosing ICDs and different types of questionnaires.

There are studies suggesting that genetics may affect the susceptibility to ICDs in patients on cabergoline; for example a study found the prevalence of DRD3 p.Ser9Gly (rs6280) CT genotype in Indian patients with parkinsonism is a risk factor for developing ICDs [23]. Other study found polymorphism of number of genes may increase the incidence of ICDs in Cabergoline treated prolactinoma significantly [24].

In general effect of gender on prevalence of ICDs was not significant but hypersexuality occurred only in men and this may be attributed to society norms in addition to reporting bias by female patients despite using female doctor to evaluate the patients. This was the same as reported by a study in USA in 2019, as most of hypersexuality occurred in male patients [17]. Effect of other variables like dose or duration of treatment on prevalence of ICDs were not significant but the dose of cabergoline was numerically higher in cases versus controls. De Sousa et al had found the resolution of symptoms after cabergoline dose reduction [25]: and this gives the idea of developing ICDs is dose dependent. On the other hand, since the dose used for treatment of prolactinoma is very low as compared to Parkinson disease, ICDs were still seen in patients treated with cabergoline for both diseases.

So, what to do if ICDs occur? This may be one of most important question to answer after raising this association. There are several options in this regard. Sometimes ICDs could resolve spontaneously but this may leads to severe social consequences [26]. Reducing to lowest possible dose may be an option since it was effective in some case reports [11, 27]. Furthermore, sertraline was effective for treatment of ICDs, so using Selective serotonin reuptake inhibitors may be an option [27]. Surgical management of prolactinoma could be an option for patient with severe symptoms [28].

Despite being based on small sample size these results clearly raise the question of clinician's awareness about occurrence of ICDs in patients treated with cabergoline and the need for further large cohort studies regarding. This study had number of limitations: first it a single center study with small sample size, thus a larger and multicenter cohort study would be advisable to assess this relationship between cabergoline and ICDs. Second, due to the population norms and prohibitions, it was difficult to interview females especially regarding hypersexuality despite being done by female doctors. Third, patients in our society prefer not to consult psychiatrists for mental disorders due to shyness and this may lead affect the exact prevalence of ICDs in patients having previously undiagnosed mental disorder.

Conclusions

ICDs were prevalent in 30% of patients with prolactinoma on cabergoline treatment. The most frequent ICDs types were hypersexuality and binge eating, and some patients reported multiple types of ICDs. The patients' socio-demographic characteristics, prolactinoma duration and size, and cabergoline dose did not correlate significantly with ICDs diagnosis. Clinicians should be aware of this significant side effect and detect it early and to prevent its negative impacts. Further larger studies are recommended to detect cofounders and to detect other behavioral side effects not included in QUIP.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Ethical committee of Faiha Specialized Diabetes, Endocrine, and Metabolism Center issued approval ref #12/23/23. The included patients consented to the study by a written forum. The study was approved based on the ethical standards of the FDEMC Research Committee and ethical approval was given (ref #12/23/23). **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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