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Letter to the Editor

Treatment complexities in psychosis associated with cabergoline treatment in patients having pituitary prolactinomas

1. Introduction

Cabergoline, a D_2 agonist, is the first line agent for management for prolactinomas. (Melmed et al., 2011) There have been a few reports of psychosis and mania associated with its use (Chang et al., 2008; Bilal and Ching, 2012; Harris et al., 2012; Burback, 2015; Ozturk, 2016; Rovera et al., 2016; Sanchez et al., 2016; Yuksel, 2016; Mohapatra and Nayak, 2017; Pérez-Esparza et al., 2017). Antipsychotics (D_2 antagonists) are usually the mainstay of treatment for psychosis and mania, but in such cases, their use becomes complicated because of the mutually contradicting mechanism with cabergoline. Here we present two patients having micro-prolactinomas, who developed psychotic and mood symptoms after treatment with cabergoline. We further discuss the principles of their management.

2. Case reports

A 37-year-old lady consulted her gynecologist for menstrual irregularities and galactorrhoea. Investigations revealed elevated serum prolactin (401 ng/mL), negative urine pregnancy test and pituitary microadenoma (5 × 6 mm) on brain MRI. Cabergoline 0.25 mg twice a week was prescribed with which galactorrhoea improved and prolactin reduced to 10 ng/mL. After eight months of continued treatment, she started having depressive symptoms- persistent sadness, low energy, anhedonia, reduced interaction, insomnia, decreased appetite and reduced personal hygiene- without any apparent stressors. Three weeks later she also developed auditory hallucinations (second person) and some delusions like suspecting her husband of having an extramarital relationship with her sister, believing that her brother has been replaced by an impersonator, and that police have installed cameras in her home to keep her under vigilance. She never had any psychiatric problems in the past, had a well-adjusted pre-morbid personality, and never used substances. There was no history of psychiatric problems in her family. Her psychiatrist prescribed her risperidone (2–6 mg/day) and sertraline (100 mg/day), though cabergoline was continued. With continued treatment, some depressive and psychotic symptoms improved over three months, but delusion of misidentification against her brother persisted. Galactorrhoea and hyperprolactinemia (201 ng/mL) reappeared, considering which Risperidone was discontinued for a few days, which led to a flare up of psychiatric symptoms. Moreover, she started having intermittent periods of irritability, anger, rapid speech, loud volume, elevated self-esteem, and verbal and physical aggression, lasting a few days. Considering the possibility of bipolar disorder, sertraline was stopped and valproate (750 mg/day) started, but the symptom control was still poor. Subsequently, in consultation with endocrinology and neurosurgery, both cabergoline and risperidone were stopped, and the patient was observed in an inpatient setting. Valproate was continued due to severe mood symptoms. Within two weeks, galactorrhoea reduced and psychotic symptoms resolved completely. Mood symptoms improved in a month and full functionality was achieved. At the time of discharge, prolactin levels were 12 ng/mL and prolactinoma did not change in size. At 3-month follow-up, there were no active psychiatric symptoms, and gradual reduction of valproate was started. Prolactin levels were 15 ng/mL and the size of prolactinoma was constant. At 6-month follow-up, the patient was off medicines and maintaining well.

A 29-year-old lady consulted her physician for amenorrhea, hirsutism and headache. Investigations showed elevated serum prolactin (169 ng/mL), negative urine pregnancy test and pituitary microadenoma (2 × 3 mm) on brain MRI. Mild bitemporal visual field constriction was found on examination, despite no obvious mass effects of the prolactinoma. No other cause of visual field defect could be found despite thorough ophthalmologic evaluation. Cabergoline 0.5 mg once a week was prescribed, with which her symptoms improved, though visual field abnormality persisted. After four months of continued treatment, she abruptly developed incessant crying, agitation, anger outbursts, suicidal ideas, insomnia and decreased appetite after the sudden unexpected death of her boyfriend. She never had any psychiatric problems in the past, had a well-adjusted pre-morbid personality, and never used substances. Family history was significant only for a single episode of depression in her uncle. She was brought to the hospital emergency one week after the onset of symptoms. She was agitated and banging her head against the wall, and was in denial of her boyfriend's death. Injection lorazepam (2 mg) was administered to prevent self-harm. Subsequently, in an inpatient setting escitalopram (5–10 mg/day) was started considering suicidality and complicated grief. Cabergoline was continued during this time. Interviews over the next week revealed that the denial of her boyfriend's death was fixed and held with conviction even when pictures of his pyre and death certificate were shown. She believed that he had been kidnapped by his parents and was kept hostage in some middle-eastern country. She was making plans to quit her job to find him. Considering this delusion, olanzapine 10 mg/day was started. No improvement was seen even after three weeks, instead she gained weight and headache recurred. Moreover, she developed hypomanic symptoms- euphoria, increased talkativeness, intrusiveness, increased energy and decreased need for sleep. At this time, escitalopram was stopped (for the possibility of an antidepressant induced hypomanic switch) and olanzapine continued, but even after two weeks, hypomania persisted, and delusion continued unabated. Subsequently, in consultation with neurosurgery and endocrinology, both cabergoline and olanzapine were stopped. Over the next three weeks, mood symptoms resolved completely. The delusional denial of boyfriend's death persisted, but her explanations became less morbid. She now felt that he was not kidnapped or taken to middle-east, rather he has gone back to his hometown. Moreover, she dropped the plan of leaving her job and searching him. Nevertheless, aripiprazole 5 mg was

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Table 1
Published reports of psychosis or mania associated with cabergoline.

Author		Patient profile (age/gender)	Pre-existing psychiatric condition	Family history of psychiatric disorder	Indication for cabergoline	New onset psychiatric symptoms	Time taken for onset after starting cabergoline	Time taken for improvement after stopping cabergoline	Psychiatric treatment provided
Bilal and Ching, 2012		44/F	Depression	Attempted suicide in father Completed suicide in uncle	Prolactinoma (size not mentioned)	Psychosis	3 months	48 h	No
Burback, 2015		32/F	No	Depression, bipolar disorder and alcohol dependence (relations not mentioned)	Micro-prolactinoma	Mania with psychotic features	6 months	6 days	Aripiprazole
Chang et al., 2008	1	32/F	Schizophrenia	**	Hyper-prolactinemia	Aggravation of psychosis	6 h	1 week	Amisulpiride (continued in same dose as given prior to aggravation)
	2	44/F	Schizophrenia	**	Hyper-prolactinemia	Aggravation of psychosis	After 1st dose of twice a week regimen (duration not mentioned)	1 week	Risperidone (continued in same dose as given prior to aggravation)
Harris et al. (2012)		45/F	No	Schizophrenia in father Schizophrenia and completed suicide in aunt	Hyper-prolactinemia	Mania	8 months	9 days	Valproate and Quetiapine
Mohapatra and Nayak (2017)		25/F	No	Absent	Micro-prolactinoma	Mania	6 months	10 days	Lithium
Ozturk (2016)		24/F	No	**	Idiopathic hyper-prolactinemia	Psychosis	3–4 weeks	1 week	No
Pérez-Esparza et al., 2017		31/F	No	Absent	Macro-prolactinoma	Psychosis	2 days	Cabergoline was not stopped	Clozapine
Rovera et al. (2016)		34/F	Bipolar disorder type-I	Bipolar in mother Depression in aunt Pathological gambling in two brothers and one uncle	Micro-prolactinoma	Mania with psychotic features	1 month	1 month	Valproate and Aripiprazole (earlier Haloperidol and Asenapine were given, which were not tolerated)
Sanchez et al. (2016)		50/F	Past history of depression	**	Micro-prolactinoma	Psychosis	6 weeks	5 days	Aripiprazole (Risperidone was discontinued once prolactinoma was found)
Yuksel (2016)		26/F	No	**	Polycystic ovarian syndrome	Mania with psychotic features	2 days	3 weeks	Olanzapine and Carbamazepine (replaced with Lithium due to poor tolerability)

** Not reported.