

# NEUROPSYCHIATRIC MANIFESTATIONS OF IDIOPATHIC HYPERPROLACTINEMIA, DIAGNOSTIC AND THERAPEUTIC CHALLENGES: A CASE REPORT

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## INTRODUCTION

Despite vast advances in the field of neuro-psychopharmacology, approximately 20-30% of the patients with depression fail to respond to the first-line antidepressants (Bennabi et al. 2019). Predictors and prognostic factors of unresponsiveness include comorbidities such as anxiety disorder, substance abuse, personality disorders, chronic medical illness, and organic diseases (Bennabi et al. 2019). Among the organic diseases, the abnormalities in the endocrine system are frequently reported in patients with treatment-resistant depression (TRD) (Duval et al. 2005, Ransing et al. 2016). The TRD treatment guidelines recommend the systematic measurement of endocrine parameters such as thyroid hormones, cortisol, parathyroid hormone, calcium, insulin, and glucose (Bennabi et al. 2019, Duval et al. 2005).

Serum prolactin (PRL) is one of the most versatile, adaptive hormone; which has a crucial role in stress response, during pregnancy, and lactation (Duval et al. 2005). Published case reports suggest the possible role of serum prolactin in anxiety, depression among non-pregnant women and men (Korali et al. 2003). However, most of the researchers have not reported any differences in the prevalence of depression among patients with hyperprolactinemia than in the healthy controls (Reavley et al. 1997). This may be the reason for the non-consideration of serum prolactin level estimation in patients with TRD. We report a case of TRD secondary to idiopathic hyperprolactinemia in a non-pregnant woman who was later treated successfully with dopamine receptor agonists.

## CASE REPORT

Mrs. ABC, a 35-year-old female, referred by a general practitioner (GP), with a history of non-responsive headache for 24 months. On detailed clinical evaluation, the headache has an insidious onset, continuous, present throughout the day, progressive in nature, located more in the occipital-frontal region, was not associated with nausea, vomiting, and blurring of vision. The symptoms minimally responded to the previous medications (de-

tails of which were unavailable). During the same period, she also developed sadness of mood, impulsivity, decreased appetite, sleep disturbance, and loss of interest in pleasurable activities for five months. Though she received medications, no response was reported.

Further, on examining the patient, she was found to have decreased psychomotor activity, reduced speech, and depressed affect. A clinical diagnosis of Severe Depressive episode without psychotic symptoms was made and she was treated with a combination of Escitalopram 10 mg and Lorazepam 1 mg. After 1 month of treatment, in view of non-responsiveness, the dose of escitalopram was increased to 20 mg and 1 mg of lorazepam was continued. Olanzapine 2.5mg was added as an augmenting agent after 45 days. Despite the dose titration, the depressive symptoms were persistent and along with which the patient now reported of heavy and prolonged uterine bleeding (menorrhagia).

On assessment at this juncture, she had reduced facial expressions, a blank stare, reduced talk, and slow bodily movements, which were considered as extrapyramidal symptoms (EPS), possibly secondary to the antipsychotic drug. Therefore, she was further evaluated for the possible endocrine abnormalities in view of atypical symptoms of menorrhagia, galactorrhoea, and EPS at a low dose (Table 1).

Most of the investigations were within normal limits, except the serum prolactin value of 3131 ng/ml which was exceptionally high. The serum prolactin test was subsequently repeated, to find yet another high value of 2896 ng/ml. These extremely high prolactin values raised a clinical suspicion of a possible prolactin-secreting macro-adenoma (? probably Giant) which could explain the chronic, non-responsive headache which could have been due to the pressure symptoms. To confirm our diagnosis, the patient was further evaluated. Optic nerve examination was found to be normal with no signs of raised intracranial pressure. Quite surprisingly, the Magnetic Resonance Imaging (MRI) revealed a normal-sized pituitary gland. Concurrently, the patient scored 37 and 46 on HAM-D and MADRS rating scales respectively, suggestive of severe depression.

**Table 1.** Laboratory Investigations in the Index Case

Laboratory Investigations	Baseline	6 weeks after initiation of treatment	Normal Range
Serum Prolactin (microIU/ml)	3131	12.45	4.8-23.3
	Repeated after 1 week (2343)		
FSH [mIU/ml (Luteal phase)]	5.4	2.59	0.2-17.2
LH [mIU/ml (Luteal phase)]	10.4	6.10	0.6-16.3
Serum cortisol (microgram/ml)		10.47	6.2-19.4
T3 (ng/ml)	97.66	142.2	70-204
T4 (microgram/ml)	8.08	8.33	5.1-14.1
TSH (microgram/ml)	1.18	1.75	0.45-4.5
HAM-D	37	6	0-7
MADRS	46	4	0-6
ESRS	6	1	<3
Y-BOCS	24	7	<8

*Abbreviations:* HAMD-D: Hamilton rating scale for depression; MADRS: Montgomery-Åsberg Depression Rating Scale; ESRS: Extrapyramidal Symptom Rating Scale; Y-BOCS: Yale-Brown Obsessive Compulsive Scale

Subsequently, based on clinical history, laboratory investigations, and neuroimaging, a diagnosis of Idiopathic Hyperprolactinemia was contemplated. After a thorough discussion of this academically challenging case with a multidisciplinary team (Psychiatrist, neurosurgeon, physician, gynecologist, ophthalmologist, and radiologist), the anti-depressant and antipsychotic were tapered gradually and stopped. Instead, she was started on a dopamine receptor agonist Bromocriptine 2.5 mg once a day and was closely monitored by the psychiatry team in view of the possible worsening of depressive symptoms and the emergence of obsessive-compulsive symptoms. After 4 to 6 weeks of treatment with bromocriptine, Mrs. ABC reported significant improvement in headache and depressive symptoms. The serum prolactin levels when repeated, were found to have reverted to the normal range. HAM-D and MADRS scale scores on follow up (after 6 weeks) were found to be 6 and 7 respectively. The extrapyramidal rating scale score was 1. She remains symptom-free for nearly 8 months to date.

## DISCUSSION

Firstly, in the current case scenario, non-responsive headache and sleep disturbances were the core symptoms. However, in the light of a middle-aged woman presenting with typical depressive symptoms without any major signs and symptoms of an organic or medical illness, a probable diagnosis of a severe episode of depression without psychotic symptoms was considered (Malhi & Mann 2018). Published literature suggests that the prevalence of primary headache among the patients with MDD is about 40-50% and often responsive to the first line of anti-depressants. Therefore, Escitalopram and lorazepam were prescribed to treat these symptoms (Benasi et al. 2018). Despite increasing the dosage of escitalopram to 20 mg and the addition of olanzapine 2.5 mg as an augmenting agent, there was no reduction in the HAM-D score even after four weeks of treatment, suggestive of non-responsiveness. Here, the response was defined as ≥50% reduction in the HAM-D Score (Lin et al. 2013).

The turnaround was when the patient developed unusual and atypical symptoms of menorrhagia, galactorrhoea, and extrapyramidal symptoms in response to low dose antipsychotics. The relevant published literature suggested a temporal association of galactorrhoea, hyperprolactinemia symptoms with drugs like olanzapine, and escitalopram (Miller & Sebastian 2005). But the hyperprolactinemia observed with a dose of 20 mg of olanzapine per day has a corresponding prolactin level of less than 100 µg/L (Mendhekar et al. 2004, Miller & Sebastian 2005). Though the existing studies have reported no change in prolactin levels with SSRIs, few cases with galactorrhea and hyperprolactinemia with a dose of escitalopram 10 mg were reported. Hence, from the EPS symptoms and galactorrhoea, the likely possibilities of drug-induced or secondary Parkinsonism, prolactin-secreting tumor, treatment-resistant depression, and pregnancy were considered.

Prolactinoma, a common pituitary gland tumor, was initially considered to be the primary diagnosis in view of the unexpected high level of serum prolactin. Prolactinoma is a common occurrence in 10-25% of women with secondary amenorrhea or oligomenorrhea, 30% of women with galactorrhoea or infertility, and in 75% of women with amenorrhea and galactorrhoea (Vilar et al. 2019). Microprolactinoma (>90%) is the most common pituitary tumour followed by macroprolactinoma (<8%). Galactorrhoea occurs in approximately 80% of women with prolactinoma. Therefore, for a conclusive diagnosis, the MRI brain was done to confirm pituitary gland pathology, which was reported to be normal. Hence ultimately, we concluded the evaluation with a rare diagnosis of Idiopathic Hyperprolactinemia (Table 2).

Further, we administered bromocriptine 2.5 mg due to its cost-effectiveness and efficacy. Bromocriptine at doses of 2.5-7.5 mg/day, among the commonly used medications; often achieves hormonal control in 60% to 80% of patients with considerable side effects such as nausea, vomiting, constipation, dizziness, headache, and compulsive behavior (Molitch et al. 2017). Besides, the drug Cabergoline at doses of 0.5-2.0 mg/week achieves

**Table 2.** Levels of prolactin in different conditions (Schlechte 2003, Vilar et al. 2019)

Drug-induced serum PRL level: <100 µg/L
Microprolactinoma serum PRL level: <250 µg/L
Pregnancy serum PRL level (third trimester): <233 µg/L
Physical and psychological stress: <40 µg/L
Non-prolactin-producing macroadenomas (Compressing the pituitary stalk or hypothalamus): <200 µg/L
Prolactin-producing adenomas: >200 µg/L
Hook effect: >10000 µg/L, a saturation of antibodies, (false negative )

a hormone level of 80-90% and is associated with side effects similar to bromocriptine. Since these medications increase the compulsive behaviors such as excessive gambling and hypersexuality (in about 5% of patients), we recommended the use of the Yale-brown obsessive-compulsive scale before and after starting medication and patient was explained regarding the possible adverse effects. For women with oligomenorrhea or amenorrhea who do not wish to become pregnant, estrogen in the form of oral contraceptives or other estrogen plus progestin regimens is a reasonable therapeutic option.

For the patients of Idiopathic Hyperprolactinemia with normal MRI scans, serum prolactin levels should be monitored every 6 to 12 months. If prolactin levels increase or symptoms due to the hyperprolactinemia emerge or worsen, an MRI is needed for reevaluation of the tumor size and should be thence managed accordingly. For evaluation, in this case, we used several rating scales due to the complex psychopathology and the non-availability of the neuropsychological test battery. The heterogeneity of the tests was used to evaluate the different functions (Korali et al. 2003). There is only scanty literature related to neuropsychiatric manifestations, etiology, pathogenesis, and treatment guidelines of idiopathic hyperprolactinemia. Thus, this report highlights the importance of considering Idiopathic Hyperprolactinemia in a patient with atypical symptoms and cases of TRD.

## CONCLUSION

Idiopathic hyperprolactinemia (IH) is a rare endocrine disorder associated with neuropsychiatric manifestations. This condition should be considered in patients with TRD. It requires a multi-disciplinary approach and vigilant care in clinical practice.

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### Contribution of individual authors:

Kumari Padma & Ramdas S Ransing: study design, data collection, first draft.

Swati Sonawane, Sagar Nanaware & Unmila T N: data collection.

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