due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Euprolactinemic Galactorrhea with Paroxetine: Exploring the Missing Link

Sir,
Selective serotonin reuptake inhibitors (SSRI) are a group of antidepressants used in psychiatric conditions such as major depressive disorder, obsessive compulsive disorders, anxiety disorder, sexual disorders, etc. Paroxetine is an SSRI which also has concomitant norepinephrine reuptake inhibitory properties. Sexual dysfunctions including loss of libido, anorgasmia, and erectile dysfunction are the frequently described adverse effects with the use of SSRIs including paroxetine.

Iatrogenic hyperprolactinemia causing galactorrhea has been described with the use of SSRIs such as sertraline, escitalopram, fluoxetine, and paroxetine. However, galactorrhea in the context of a euprolactinemic state with the use of paroxetine is rarely cited, without any clear explanation of the underlying pathophysiology. We report a woman who was treated with paroxetine when she developed galactorrhea despite having normal serum prolactin levels. We also attempt to postulate the possible neurobiological explanation for this presentation.
A 35-year-old married woman presented to the psychiatry outpatient department with complaints of a “ball of air” that is felt to move around in her abdomen for the last 9 years, in a fluctuating pattern characterized by periodic exacerbations and remissions. She would often speak of harboring a major abdominal condition that led to doctor shopping and multiple investigations on demand over the last 9 years but with little benefit. She was also found to be having low mood, anhedonia, prominent depressive cognition, insomnia, and loss of appetite for the last 2 months.

She was provisionally diagnosed with hypochondriacal disorder with secondary depression. She was started on Tab. paroxetine and maintained on a dose of 25 mg/day. After 2 months, on follow-up, there was a substantial reduction in her somatic preoccupations along with improvement in her mood state. She, however, complained of whitish milky discharge from both her nipples for the last 2 weeks, which was not present earlier. She had otherwise normal menstrual cycles without any use of oral contraceptives and had no recent pregnancy or lactation for the last 6 years after her only child was born. She also had no local chest infections or trauma recently. We suspected either a local breast pathology or an endocrinal/pituitary cause for the presentation.

Fine-needle aspiration cytology (FNAC) examination with a specimen of breast discharge revealed findings suggestive of galactorrhea, while mammogram of both breasts revealed focal segmental branch duct dilatation without obvious intraductal growth bilaterally (Breast Imaging Reporting and Data System or BIRADS II), and both these pointed to galactorrhea. Routine blood investigations (complete hemogram, renal and hepatic function tests) were normal. An endocrinological profile was done, which revealed normal thyroid function tests (and, surprisingly, normal morning serum prolactin level (7.22 ng/mL). Brain imaging (MRI brain) ruled out any central pituitary cause of such a presentation.

Paroxetine was stopped, and she was prescribed nortriptyline 25 mg/day. Follow-up after 2 months revealed a significant reduction in the galactorrhea. However, there was worsening of her mood state and hypochondriacal concerns. We planned to re-challenge her with paroxetine 25 mg/day afresh, and this again resulted in a re-emergence of galactorrhea after 3 weeks of the re-challenge. Paroxetine was again stopped and finally she was maintained on Cap. venlafaxine 75 mg/day, which resulted in improvement of her psychiatric symptoms, with no further recurrence of galactorrhea. Venlafaxine was chosen in view of its efficacy in hypochondriacal and somatic symptoms and also its less propensity to cause hormonal side effects.\[5\]

Iatrogenic galactorrhea has been reported with the use of most SSRIs, including paroxetine. However, isolated galactorrhea with the use of paroxetine, with a normal menstrual cycle, in the context of a euprolactinemic state, is a rare clinical presentation.\[5\] In our case the patient developed galactorrhea after around 6 weeks of continuous intake of paroxetine 25 mg/day, which waned off after discontinuing it and re-emerged upon re-challenge. The causality was further strengthened by the findings in FNAC, mammogram, and MRI brain. We applied the Naranjo Adverse Drug Reaction Probability Scale\[6\] that yielded a score of 6, suggesting “probable” causality due to paroxetine.

Reports of galactorrhea due to paroxetine are available in the literature [Table 1]. It has been found to start within a few weeks to months of starting paroxetine and has been associated with both normal and raised serum prolactin levels. However, the current finding of iatrogenic galactorrhea in an euprolactinemic state needs to be understood from a neuroendocrinological perspective.

Paroxetine-induced galactorrhea can be understood by probable serotonergic inhibition on the dopaminergic neurotransmission mediated through two different pathways. The first is the presynaptic inhibition of tuberoinfundibular dopamine release by serotonergic receptors, and the second is through direct stimulation of hypothalamic postsynaptic serotonergic receptors that leads to the release of prolactin-releasing factors such as vasoactive intestinal polypeptide and oxytocin, which in turn leads to hyperprolactinemia.\[5\] However, in both these cases, serum prolactin will be raised since both these involve “dopamine-dependent” pathways.

The biological basis of an iatrogenic euprolactinemic galactorrhea state remains elusive, though two mechanisms can be proposed to explain the finding.

**Table 1: Published literature on paroxetine-induced galactorrhea**

| Authors                  | Paroxetine dose (mg/day) | Duration of paroxetine treatment before onset of galactorrhea (weeks) | Serum prolactin level |
|--------------------------|--------------------------|---------------------------------------------------------------------|-----------------------|
| González et al., 2000\[3\] | 40                       | 16                                                                  | Not mentioned/assessed |
| Bhattacharya et al., 2010\[3\] | 25                      | 6                                                                   | Normal                |
| Sertcelik et al., 2012\[5\] | 60                      | 2                                                                   | Normal                |
| Gulati et al., 2014\[6\] | 75                      | 11                                                                  | Raised                |
| Evremel et al., 2016\[7\] | 20                      | 28                                                                  | Raised                |
There are reports suggesting nondopaminergic involvement, where iatrogenic euprolactinemic galactorrhea has been implicated through thyrotropin releasing hormone hyper-responsiveness. Such a mechanism for galactorrhea was earlier proposed for escitalopram.\(^9\) Paroxetine being of similar chemical class as escitalopram can probably produce a euprolactinemic galactorrhea state through this mechanism. The other postulate is that it might be due to the isomeric variation of prolactin. Prolactin has different isomers, i.e., small, big, and big-big, having differences in bioactivity and immunoreactivity. Macroprolactinemia is a rarely cited condition in which there is a proportionately higher level of the big-big isomeric fraction. Elevation in the levels of macroprolactin, which is impermeable to the capillary membrane, can present with symptoms of galactorrhea with normal serum prolactin, though a literature search did not reveal any such isomeric change induced by paroxetine. Macroprolactinemia can also be associated with autoimmune thyroid conditions.\(^10\) A search for a possible autoimmune thyroid condition can be beneficial for this patient.

The exact causality of the finding is difficult to ascertain, though this report tries to highlight that paroxetine use can rarely cause galactorrhea which possibly involves a nondopaminergic explanation and clinicians need to be vigilant about the emergence of such symptoms.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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