Case Report
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Emerging Hyperprolactinemic Galactorrhea in Obsessive Compulsive Disorder with a Stable Dose of Fluoxetine

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While fluoxetine (FXT) is a frequently prescribed selective serotonin reuptake inhibitor (SSRI), with few major side-effects; altered serotonergic transmissions in hypothalamic pathways might lead to a distressing, and often embarrassing, manifestation of galactorrhea by altering prolactin release in those on FXT. We report here a case of FXT-induced hyperprolactinemic galactorrhea developing late into treatment on a stable regimen, who responded well to subsequent replacement with sertraline. Based on present finding, we suggest that while SSRIs may share similar mechanisms of action, there exist individual differences in their effects on prolactin secretion pathways.

KEY WORDS: Fluoxetine; Galactorrhea; Hyperprolactinemia; Selective serotonin reuptake inhibitors.

INTRODUCTION

Many psychotropic drugs have been found to cause galactorrhea (GLH) via their actions on dopamine system and consequent disinhibition of prolactin secretion.[1)] Effect of selective serotonin reuptake inhibitors (SSRIs) in this regard is less clear. They have been proposed to reduce dopaminergic transmission via both direct[2)] and indirect[3)] mechanisms. Interestingly, some authors have also proposed a normoprolactinemic pathway towards GLH, though data is less clear regarding this.[4)] Fluoxetine (FXT) is one of the oldest SSRI and approved as a first line drug by US Food and Drug Administation for use in major depressive disorder, panic disorder, premenstrual dysphoric disorder, bulimia nervosa and in obsessive compulsive disorder (OCD). Available literature on relationship between FXT and GLH is sparse, and here we present a female OCD patient, treated with FXT who was subsequently found to have GLH and hyperprolactinemia.

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CASE

A 31-year-old unmarried woman, without significant family/personal history or medical comorbidity, presented with complaints of fear from dirt, excessive checking and washing behaviors and repeated intrusive thoughts, gradually deteriorating for 2 years. She acknowledged the thoughts to be her own, and that they were unnecessary and baseless; but also expressed her inability to resist them at all. The thoughts did cause her severe anxiety. Because of an increase in severity, she had discontinued her job for last 3 months and was having difficulty in sleeping at night. At presentation, she was restlessness with psychomotor agitation, and had anxious, irritable affect. Enquiries regarding thought possession revealed severe obsessions and compulsion. She was diagnosed as obsessive-compulsive disorder according to ICD 10. Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[5)] score was 30 which showed 'extreme' symptoms severity. Her physical examination and laboratory tests including blood biochemistry, electrocardiogram, and radiological examinations were within normal limits. Her treatment was started with FXT (20 mg/day) according to available treatment guidelines,[6)] and it was decided to keep a watch for further deterioration of anxiety symptoms due to activating side-effects of FXT. The treating team decided to use short-term clonazepam cover for anxiety symptoms,[6)] but the patient did not require this rescue regimen. After

two weeks of initiation, FXT was hiked to 40 mg/day. After 3 weeks of increasing FXT to 40 mg/day, there was significant improvement in Y-BOCS score (Y-BOCS=19), and she was advised to continue the drug at this dose. We used an immediate-release formulation of FXT in our patient.

After 8 months, the patient came with 3-months' amenorrhea and 15-days' history of milky, non-hemorrhagic bilateral breast discharge on 40 mg/day FXT. The discharge had begun after 7 and a half month of hiking FXT to 40 mg/day, and was first noted by the patient who brought this to clinician's notice. Her serum prolactin level was investigated for and found to be 122 ng/ml. Her physical manifestations were highly suggestive of hyperprolactinemia associated with amenorrhea and GLH. Her urea, creatinine, thyroid-stimulating hormone, free-T4 and beta human chorionic gonadotropin were all normal; and thus we excluded underlying kidney disease, hypothyroidism or pregnancy as possible causes of GLH.

Treatment was first modified by discontinuing FXT over one week and adding clonazapam 0.5 mg/day to decrease anxiety. Sertraline was started after allowing for 7 days' washout time after last dose of FXT, and slowly built up-to 200 mg/day over next 2 weeks.[7] Two months after initiation of Sertraline, and one and a half month after a dose of sertraline 200 mg/day was reached, her serum prolactin level normalized (12 ng/ml) and menstrual abnormalities were resolved. Over next 10 months, the patient remained on same therapeutic regimen and continued to be mentally stable with regular menstrual cycles and no GLH.

DISCUSSION

Sexual dysfunction, headache and nausea have been reported sparingly with FXT,[8] while GLH and amenorrhea are considered rare with SSRIs.[7] In past, uncontrolled studies and case reports describing GLH with SSRIs have reported varied degrees of alterations in prolactin levels[7,9-11]; except few case reports like that by Canan *et al.*,[12] which described a 29-year old woman with generalized anxiety disorder who developed unilateral normo-prolactinemic GLH after initiation of FXT therapy. Most evidences implicate prolactin in GLH caused by SSRIs, though the exact mechanisms by which SSRIs cause hyperprolactinemia and its clinical consequences such as GLH (neuroendocrine effects) remain elusive.

Prolactin is secreted by the anterior pituitary under hypothalamic regulation through a complex series of connections. The periventricular and medial hypothalamic subdivisions of hypothalamus are the main regions associated with prolactin homeostasis.[13] Periventricular subdivision contains dopaminergic cells, which project to anterior pituitary and inhibit prolactin release. Medial subdivision contains paraventricular nucleus (PVN) with different populations of neurosecretory cells producing oxytocin, vasopressin, vasoactive intestinal peptide (VIP) and thyrotropin-releasing hormone, which have stimulatory effects on prolactin release.[13] Serotonergic neurons project to these structures from dorsal raphe nucleus and modulate prolactin release.[13] Currently, it is thought that elevated serotonin levels consequent upon SSRI might stimulate prolactin release in two ways: excess serotonin might directly stimulate postsynaptic 5-HT receptors in hypothalamic PVN[2] leading to prolactin release via release of secretagogues like oxytocin and VIP[13]; or it might inhibit dopaminergic transmission at tuberoinfundibular dopaminergic neurons (TDN),[3] easing the brakes on hypothalamic lactotrophs and causing prolactin release. The later might either be due inhibitory effects of volume transmission of serotonin in the vicinity of these neurons, or post-synaptic 5-HT receptors mediated activation of GABAergic cells in the region and subsequent inhibition of TDN.[13]

In our case normal vital signs, systemic and radiological examinations direct towards FXT as the causative factor. A long gap between starting of FXT therapy and onset of amenorrhea may be explained by the long half-life of FXT and its metabolites; resulting in gradual accumulation in body, especially in brain.[14] Further, although SSRIs share similar mechanisms of action at serotonin transporters, individual molecules differ in their overall therapeutic profiles, and overall spectrum of side effects. Thus, individual patients often react very differently to one particular SSRI than the other. Sertraline shares similar serotonin reuptake inhibitor properties of FXT, but additionally inhibits dopamine transporters.[15] The net effect is increased dopamine availability at the synapses, which might be responsible for improvement in GLH via normalization of prolactin secretion in our case.

A growing number of individual case reports could be signifying a strong association of SSRIs with prolactin abnormalities. Therefore, knowledge of their effect on prolactin homeostasis is extremely important. This calls for a meticulous study in future with large sample size and proper control group along to shed further light on pathophysiology and prevalence of hypaerprolactinoma due to SSRIs.

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