Worsening Depression in a Patient with a Granulosa Cell Tumor

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Increased estrogen levels are likely to play a role in depression. The steroid hormone estrogen can modulate turnover of neurotransmitters by enhancing serotonin and noradrenaline levels. Estrogen is also involved in the regulation of serotonin receptor number and function.[1]

Oscillating estrogen levels during the postmenopausal period or caused by an estrogen-producing tumor may herald a recurrence or a worsening of the depressive episode in a woman with a previous diagnosis of depression. Both high and low levels of estrogen have been associated with the occurrence of depressive symptoms, and the variability in estrogen may cause depression.[2,3] This suggests that exploring the hypothalamic-pituitary-gonadal axis in depression may yield areas of research in psychosomatic medicine and psycho-oncology.

At present, evidence-based pharmacologic options are being studied for treating estrogen-sensitive depression. This article offers information on the pharmacological treatment and characteristics of depression in a woman with a previous diagnosis of major depression who is experiencing extreme fluctuations of estrogen levels.

CASE

A sexagenarian white woman had achieved full remission of her unipolar depression and was following up every 3 months with her clinician for psychotherapy and pharmacologic management. Her medication regimen included citalopram and bupropion, on which she was stabilized for 15 years. Her stability had deteriorated with the coincidence of hyperestrogenism.

The patient was diagnosed with granulosa cell tumor (GCT) of the ovary, which accounts for 2% to 3% of ovarian malignancies. GCTs are distinct from other ovarian cancers in their hormonal activity because they have the ability to secrete estrogen, inhibin, and anti–Mullerian-inhibiting substances.[4] The increase in circulating estrogen may account for the re-emergence of the patient's depression.

DISCUSSION

Depression results from a disruption of normal brain neurochemistry. Numerous studies have shown that decreasing levels of estrogen can result in depression.[1-3] However, there is little evidence to suggest that the same situation exists for elevated estrogen. Fluctuating estrogen levels appear to play a role in depression because estrogen has direct effects on neurotransmitter turnover and signaling, and also modulates prefrontal cortex (PFC) function and nitric oxide (NO) production in the hippocampus.[5]

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Estrogen is involved in the regulation of serotonin receptor levels and function, along with increasing the levels of circulating serotonin and norepinephrine. Across a woman's reproductive life, both fluctuating levels and low levels of estrogen have been associated with depressed mood.[3] Changes in serotonergic activity during the female hormone cycle appear correlated with variations in estrogen levels. It is well known that during menopause, fluctuating and declining levels of estrogen are associated with an increased risk of new-onset and recurrent depressive episodes and that there is strong support for a beneficial effect of estrogen-containing hormone treatment in depressed perimenopausal women.[1]

As the prevalence of depression in women is twice that in men, estrogen fluctuation causes women to be more vulnerable to affective disorders. Mood disturbances are more likely to occur during significant hormonal transitions (puberty, premenstrual, postpartum, perimenopause, and menopause).[6] Estrogen exerts a positive control on the production of NO in the hippocampus via the estrogen receptor-beta activating neuronal nitric oxide synthase (nNOS), which increases NO in the hippocampus. NO, in turn, phosphorylates cAMP response element binding (CREB) protein in the hippocampus, which results in behavior modification and possible potentiation of depressive symptoms.[6]

Additionally, genetic variation in the estrogen receptors may modify estrogen signaling, thus influencing a woman's susceptibility to developing depression. Specific estrogen receptor polymorphisms exert their biological effects in large part through intracellular activation of estrogen receptor-alpha (*ESR1*) and estrogen receptor-beta (*ESR2*). Expression of these polymorphisms results in varying levels of estrogen that can induce or worsen depression.[1]

Fluctuating estrogen levels also directly affect the PFC, which has a role in decision making, social functioning, cognitive behavior, and personality expression. Increasing levels of estrogen have been shown to affect the PFC,[7] thereby resulting in depression with decreased decision-making ability, decreased social functioning and alterations in personality expression. Cognitive function of the PFC becomes markedly impaired under conditions of stress. It is possible that estrogen up-regulates the factors that lead to PFC dysfunction, as estrogen has been shown to facilitate dopamine expression, norepinephrine release, and receptor expression.[1]

Mood disturbances are more likely to occur during significant hormonal transitions.

Estrogen may also amplify the stress response by altering norepinephrine (NE) adrenoreceptor expression. When estrogen is bound to the NE 1-alpha receptor in the PFC, estrogen can act as a transcription factor and thus stimulate PFC dysfunction. Therefore, higher levels of estrogen exert a greater effect on PFC dysfunction, resulting in depressive symptomatology.[7]

This case illustrates how an excess of estrogen worsens or initiates an episode of depression de novo. Consequently, the neuroendocrine system of a female patient poses challenges to the medical team confronted with the physiological symptoms of fluctuating estrogen levels in addition to the psychiatrist's efforts at managing depressive symptoms that have become increasingly complex.

The treatment of the psychiatric symptoms in this case must also be targeted toward the management of increased estrogen levels. Estrogen deficiency is best treated by hormone replacement, and GCTs are primarily treated surgically to normalize estrogen levels. The correction of estrogen levels through pharmacological and surgical interventions would most likely improve the mood symptoms that were unresponsive to antidepressant treatment alone.

In the case described here, the woman with early menopause had previously been effectively managed with an antidepressant and adjuvant hormone replacement therapy, and a woman with an estrogen-secreting tumor would most likely benefit from a reduction of her estrogen levels. Clinicians should carefully assess patients for underlying medical problems and hormonal imbalances that can exacerbate depression. After a thorough assessment, a multidisciplinary treatment approach to depression is necessary to achieve a resolution and/or remission of symptoms in estrogen-sensitive women.

CONCLUSION

Physicians need to recognize the importance of fluctuating estrogen levels in patients with a background

of depression. From the literature, it is evident that there is a hormonal vulnerability to depression.[1-3,6-8] However, field studies have not yet been conducted to determine the decreased severity of depression when estrogen levels are corrected.[8]

The association of mood symptoms and estrogen variation has become a focus of research. Estrogen fluctuation can play a multifaceted role in depression, as estrogen affects neurotransmitter turnover and receptor levels, as well as directly affecting behavior via NO production in the hippocampus, which can affect decision-making capacity, cognition, personality expression, and mood via its effects on the PFC.

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