NEUROENDOCRINE DYSFUNCTION IN WOMEN WITH EPILEPSY OR BIPOLAR DISORDER: IMPLICATIONS FOR PATIENT MANAGEMENT

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ABSTRACT

Neuroendocrine dysfunction is prevalent among women with epilepsy or bipolar disorder. The manifestations of neuroendocrine dysfunction can include insulin resistance, hyperinsulinemia, dyslipidemia, and obesity—all of which are risk factors for coronary artery disease. Hyperandrogenism, another common neuroendocrine finding, is associated with anovulation, fertility loss, and altered sex drive. Because of the serious health consequences of neuroendocrine dysfunction, women with epilepsy or bipolar disorder should be monitored carefully for signs or symptoms so that appropriate intervention can occur. Many aspects of neuroendocrine dysfunction can be controlled or prevented through lifestyle intervention and pharmacotherapy. To date, data have not established a causal relationship between use of anticonvulsants and reproductive endocrine dysfunction in women with epilepsy or bipolar disorder; although a possible contributory role cannot be ruled out. The possible benefits of a change in antiepileptic medication should be weighed carefully against the risks of adverse events and poor efficacy of alternative therapeutic options.

Women with epilepsy are less fertile1 and suffer from more menstrual irregularities, gynecologic syndromes,2,3 and reproductive endocrine disorders3,4 compared with women without epilepsy. Reproductive endocrine dysfunction is especially common in women with temporal lobe epilepsy3,5 but is also prevalent in women with generalized epilepsy.6 Bipolar disorder is also characterized by neuroendocrine dysfunction as reflected primarily in dexamethasone nonsuppression and blunted thyrotropin-stimulating hormone, prolactin, and growth hormone responses.7,13 Like women with epilepsy, women with bipolar disorder have more menstrual irregularities compared with their healthy counterparts.14 This paper discusses the implications of neuroendocrine dysfunction for the management of patients with epilepsy or bipolar disorder.

REPRODUCTIVE ENDOCRINE DYSFUNCTION IN WOMEN WITH EPILEPSY OR BIPOLAR DISORDER

Neuroendocrine dysfunction in women with epilepsy or bipolar disorder could arise from one or more of several causes.15,16 First, disease-related abnormalities of brain centers involved in endocrine control may explain reproductive endocrine disorders in these women. The pathophysiological substrate of epilepsy and bipolar disorder may overlap with brain areas regulating neuroendocrine function such that disease-associated brain abnormalities contribute to endocrine dysfunction and vice versa. Electrical activity associated with seizures, particularly those arising from temporal limbic areas, affects plasma levels of neuroendocrine hormones.17

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Neuroendocrine abnormalities may also arise from effects of medications on peripheral endocrine glands. Data from animal studies show that anticonvulsants can alter ovarian morphology and influence steroidogenesis. The degree to which these changes arise from a direct effect of medications on endocrine glands has not been determined. Clinically relevant effects of anticonvulsants on gonads have not been demonstrated in humans.

Anticonvulsants may also affect concentrations of biologically active hormones by displacing them from hormone-binding proteins or by altering hormone metabolism. For example, carbamazepine, phenobarbital, and phenytoin reduce steroid hormone concentrations by inducing the breakdown of steroid hormones and increasing the production of sex hormone-binding globulin (SHBG). On the other hand, valproate, a hepatic enzyme inhibitor, may increase steroid hormone levels.

Weight gain and obesity play a pivotal role in causing endocrine abnormalities in women with epilepsy and bipolar disorder. Weight gain may contribute to the development of hyperinsulinemia that leads to insulin resistance, which in turn may stimulate the ovaries to overproduce androgens and lead to lipid abnormalities. In addition, weight gain may contribute to hyperandrogenism by stimulating steroid production by means of adipose tissue. It is theorized that obesity acts via the same mechanisms and may also play a key causative role in polycystic ovary syndrome (PCOS). More than 40% of women with PCOS are obese. Anticonvulsants, including carbamazepine, valproate, vigabatrin, and gabapentin, cause weight gain that can be substantial in some patients. The weight gain, particularly when associated with or leading to obesity, reduces insulin sensitivity and may lead to the development of a PCOS-like condition. The extent to which weight gain associated with the use of antiepileptic drugs contributes to insulin resistance has not yet been determined.

**Evaluating the Patient for Possible Endocrine Dysfunction**

It is important that the clinician monitor the patient for signs and symptoms of neuroendocrine dysfunction in epilepsy due to its frequent occurrence. Although neuroendocrine dysfunction appears not to be as manifest or as common in bipolar disorder as it is in depression, it does occur. Therefore, many of the principles that apply to providing care for women with epilepsy also apply to women with bipolar disorder.

Common neuroendocrine abnormalities include menstrual irregularity (which occurs frequently in women with epilepsy and those with bipolar disorder), infertility, obesity or weight gain, hirsutism, and galactorrhea. The clinician should be alert to any changes in menstrual cyclicity or body weight and should regularly question patients with epilepsy or bipolar disorder about menstrual abnormalities, hirsutism, galactorrhea, and fertility. Menstrual irregularity can be assessed by asking the patient to keep a chart of the days of menstruation for at least 6 months. Female infertility, defined as inability to conceive after more than 12 months of regular unprotected intercourse and exclusion of male causes, can be assessed by obtaining a clinical history.

**Methods used to detect and diagnose common neuroendocrine irregularities include clinical laboratory tests, pelvic ultrasonography, and pituitary imaging (Table).** Although an isolated abnormality may not suggest a neuroendocrine disorder, clusters of abnormalities or repeated abnormal values are causes for investigation.

**Approaches to Managing Neuroendocrine Abnormalities**

Both nonpharmacologic and pharmacologic approaches can be useful in managing neuroendocrine abnormalities. Treatment approaches to neuroendocrine disorders should address the patient's short-term goals (eg, establishment of fertility, reduction of hirsutism) as well as reducing long-term health risks, such as obesity and insulin resistance.

**Nonpharmacologic Approaches**

Diet, exercise, and, if appropriate, weight reduction constitute the cornerstone of management for any patient affected by insulin resistance. Weight loss can also help to reestablish normal menstrual cycles and reduce hirsutism. The nonpharmacologic measures are particularly important in the management of PCOS in order to reduce the long-term health risks posed by the disorder. The benefits of weight loss in PCOS are illustrated by results of a recent study in 28 overweight women with the disorder. Twelve weeks of dieting followed by a 4-week weight-maintenance
phase was associated with a 7.5% decrease in weight and a 12.5% decrease in abdominal fat—effects that were accompanied by improvements in menstrual cyclicity, lipid profiles, and insulin sensitivity.

**PHARMACOLOGIC APPROACHES**

The goals of pharmacologic management, where appropriate, include correction of hyperandrogenemia, management of metabolic abnormalities, and the induction of ovulation.\(^{15}\)

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**Table. Testing for Signs or Symptoms of Neuroendocrine Dysfunction**

<table>
<thead>
<tr>
<th>Test</th>
<th>Method</th>
<th>Abnormal Findings</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH, FSH</td>
<td>Measurement of serum levels</td>
<td>LH/FSH ratio &gt;2</td>
<td>Suggestive of PCOS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FSH &gt;35 IU/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LH &gt;11 IU/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LH &lt;7 IU/mL</td>
<td></td>
</tr>
<tr>
<td>Prolactin</td>
<td>Measurement of morning resting serum levels (when patient is not postictal)</td>
<td>&gt;20 µg/L</td>
<td>Level may be slightly increased in patients with epilepsy Rule out thyroid or pituitary tumor Medications may impact prolactin levels</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Measurement of serum level from blood taken during mid-luteal phase of menstrual cycle</td>
<td>&lt;6 nmol/L</td>
<td>Low levels indicate anovulation, common causes of which are PCOS, hypophyseal adenoma, and hyperprolactinemia</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Measurement of serum level on days 3 to 6 of menstrual cycle</td>
<td>&gt;2.5 nmol/L</td>
<td>Common causes include PCOS, valproate, and nonclassical adrenal hyperplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;4.0 nmol/L</td>
<td>Rule out adrenal/ovarian tumor</td>
</tr>
<tr>
<td>17-OH progesterone</td>
<td>Measurement of serum level</td>
<td>&gt;200 ng/dL when progesterone is &lt;3 ng/dL</td>
<td>Conduct ACTH stimulation test</td>
</tr>
<tr>
<td>DHEAS</td>
<td>Age 20 to 29 years, &gt;3800 ng/mL</td>
<td>Age 30 to 39 years, &gt;2700 ng/mL</td>
<td>Rule out nonclassical adrenal hyperplasia</td>
</tr>
<tr>
<td>Glucose/insulin</td>
<td>Fasting, morning levels; glucose/insulin ratio</td>
<td>Fasting glucose &gt;7.8 mmol/L</td>
<td>Suggestive of diabetes Suggestive of reduced insulin sensitivity; associated with obesity and PCOS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glucose/insulin ratio &lt;4</td>
<td></td>
</tr>
<tr>
<td>Pelvic ultrasonography</td>
<td>Transvaginal or transabdominal on day 3 to 9 of the menstrual cycle</td>
<td>&gt;10 peripheral cysts, 2 to 8 mm diameter in 1 ultrasound plane, thickening of ovarian stroma Other structural abnormalities of ovaries</td>
<td>Polycystic ovaries, variably associated with PCOS Tumors, atrophy, multifollicular ovaries</td>
</tr>
</tbody>
</table>

LH = luteinizing hormone; FSH = follicle-stimulating hormone; PCOS = polycystic ovary syndrome; ACTH = adrenocorticotrophic hormone; DHEAS = dehydroepiandrosterone sulfate.

Adapted from Bauer et al. *J Neurol Neurosurg Psychiatry.* 2002;73:121-125, with permission from the BMJ Publishing Group.
Oral Contraceptives. Oral contraceptives may be useful in correcting hyperandrogenemia as reflected in the establishment of regular menstrual cycles, reduction in hirsutism, and improvement in acne. The patient should be made aware that oral contraceptives may need to be given for several months before benefits become apparent. In a study reported in 2002, the effects of combined oral contraceptives (21 days of treatment followed by a 7-day rest period for 12 months) were assessed in 28 adolescent girls with hyperandrogenism and 6 or fewer menses in the year prior to the study. Hirsutism significantly improved from the sixth month on. Levels of testosterone and androstenedione decreased, and SHBG increased. Total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol increased without a change in total cholesterol/HDL cholesterol ratio and LDL cholesterol/HDL cholesterol ratio.

Insulin Sensitizers. Insulin sensitizers have become increasingly important tools in managing insulin resistance. In addition to improving metabolic parameters, insulin sensitizers can help to improve fertility. In a randomized, double-blind, placebo-controlled trial, short-term therapy with the insulin sensitizer rosiglitazone enhanced both spontaneous ovulation and ovulation induced by clomiphene citrate in insulin-resistant, overweight, or obese women. The effect was accompanied by an increase in the level of SHBG.

Antiandrogen Agents. In some cases, addition of an antiandrogen medication, such as spironolactone, may be warranted. Because of possible teratogenic risk to the male fetus, antiandrogen medications should not be used without adequate contraception.

Gonadotropin-Releasing Hormone Agonists. Gonadotropin-releasing hormone agonists have been used to treat severe ovarian hyperandrogenism.

Isolated reports suggesting that certain anticonvulsant or antipsychotic medications can cause endocrine abnormalities has raised concern among some clinicians about the neuroendocrine safety of these medicines. Although these medications have been shown to affect the neuroendocrine system in animal and human studies, no anticonvulsant or antipsychotic has been established as causing clinically significant neuroendocrine dysfunction in women with epilepsy or bipolar disorder. However, women with epilepsy are seldom given antipsychotics, and antipsychotics have not been studied systematically in this patient population. Neuroendocrine dysfunction is common in women with epilepsy and bipolar disorder regardless of which anticonvulsant is prescribed. In many cases, reproductive endocrine dysfunction precedes initiation of anticonvulsant or antipsychotic therapy. According to most available data, no anticonvulsant or antipsychotic should be excluded from the range of treatment options available for women with epilepsy or bipolar disorder. However, the possibility that anticonvulsants and antipsychotics can cause or exacerbate neuroendocrine dysfunction should not be discounted. The obese patient or the patient who gains significant weight after initiating an antiepileptic medication should be monitored closely in view of the relationship of weight gain and obesity with neuroendocrine abnormalities. The possible benefits of a patient’s change in antiepileptic medication should be weighed carefully against the risks of adverse events and efficacy of alternative therapeutic options.

Conclusion

Neuroendocrine dysfunction is prevalent among women with epilepsy or bipolar disorder. The manifestations of neuroendocrine dysfunction include insulin resistance, hyperinsulinemia, dyslipidemia, and obesity, all of which are risk factors for cardiovascular disease. Hyperandrogenism, another common neuroendocrine finding, is associated with anovulation, fertility loss, and altered sex drive. Because of the serious health consequences of neuroendocrine dysfunction, women with epilepsy or bipolar disorder should be monitored carefully for signs or symptoms so that appropriate intervention can occur. Many aspects of neuroendocrine dysfunction can be controlled or prevented through lifestyle intervention and pharmacotherapy. To date, a causative role of anticonvulsants or antipsychotics in reproductive endocrine dysfunction in women with epilepsy or bipolar disorder has not been established; however, a possible contributory role cannot be ruled out. The possible benefits of a change of antiepileptic medication should be weighed carefully against the risks of adverse events and the efficacy of alternative therapeutic options.
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