Valproate, Hyperandrogenism, and Polycystic Ovaries

A Report of 3 Cases

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Background: Reproductive endocrine disorders characterized by menstrual disorders, polycystic ovaries, and hyperandrogenism seem to be common among women treated with sodium valproate for epilepsy.

Objective: To describe the development of valproate-related reproductive endocrine disorders in women with epilepsy.

Design: Case report.

Patients: Three patients developed a reproductive endocrine disorder during treatment with valproate. It was characterized by hyperandrogenism and polycystic ovaries in all cases, and it was associated with weight gain and menstrual disorders in 2 of the 3 women.

Results: Replacing valproate with lamotrigine resulted in a decrease in serum testosterone concentrations in all 3 women. The polycystic changes disappeared from the ovaries in 2 of the women after valproate therapy was discontinued, and the 2 women who had gained weight and developed amenorrhea while being treated with valproate lost weight and resumed menstruating after the change in medication.

Conclusions: The 3 cases presented here illustrate the development of reproductive endocrine disorders after the initiation of valproate therapy in women with epilepsy. The disorders were characterized by hyperandrogenism and polycystic ovaries in all cases, and were associated with weight gain and menstrual disorders in 2 of the 3 women. An evaluation of ovarian structure and function should be considered in women of reproductive age being treated with valproate for epilepsy, especially if they develop menstrual cycle disturbances during treatment.

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RECENT REPORTS have shown that reproductive endocrine disorders characterized by menstrual disorders, polycystic ovaries (PCO), and hyperandrogenism seem to occur frequently among women being treated with sodium valproate.1,2 These disorders are often associated with obesity, hyperinsulinemia, and low serum levels of insulin-like growth factor binding protein 1 (IGFBP-1), which may promote valproate-related hyperandrogenism.2,3 However, these disorders also occur in most lean valproate-treated women.2,3 Hyperandrogenism has also recently been reported in prepubertal and pubertal girls taking valproate for epilepsy.4 Serum insulin and testosterone levels return to normal 2 months after valproate is replaced with lamotrigine, whereas weight loss is much more gradual after discontinuing valproate therapy.5

There are no longitudinal studies on the development of valproate-related reproductive endocrine disorders in women with epilepsy. We present here 3 cases illustrating the development of hyperandrogenism and PCO in women after starting valproate treatment for epilepsy. In 2 of the cases, the disorders were associated with weight gain and menstrual disorders. These cases also show the reversibility of some of these changes after valproate treatment is discontinued.

REPORT OF CASES

The essential clinical features of the 3 women during and 1 year after discontinuation of valproate treatment are given in the Table. All the patients were clinically examined by the authors before and after valproate was replaced with lamotrigine. The retrospective data were collected from the hospital records of Oulu University Hospital, Oulu, Finland.

ULTRASOUND EXAMINATION OF THE OVARIIES

Transvaginal ultrasound examination was performed using an SSA-270A apparatus (Toshiba Co, Tokyo, Japan) equipped with a 6-mHz curvilinear probe (PVF-651VT). The endometrium, uterus, ovaries, and ovar-
ian follicles were scanned, and all results were stored as hard copies. The volume of the ovary (in cubic centimeters) was calculated using the prolate ellipsoid formula:

\[
\text{Volume} = \frac{4}{3} \pi \times (\text{Dimension 1})^\frac{2}{3} \times (\text{Dimension 2}) \times (\text{Dimension 3})^\frac{1}{3}
\]

The ovarian follicle size was determined by measuring its maximum diameter. The follicles of different sizes were counted. The ultrasonographic criteria used for the diagnosis of PCO were described by Adams et al.6

PATIENT 1

Epilepsy

Patient 1 had her first epileptic seizure when she was 8 years old. Her epilepsy can be classified as juvenile myoclonic epilepsy (JME), characterized by absence seizures, myoclonic seizures in the morning, and generalized tonic-clonic seizures. Electroencephalography (EEG) findings showed features consistent with the JME diagnosis: generalized spike-polyspike wave bursts and photosensitivity.

Medication

Patient 1 was originally treated with phenytoin, but because relief from seizures was not achieved, therapy with a combination of valproate and phenytoin was begun in 1975 (Table). Phenytoin was tapered from the therapy during 1981. Complete freedom from seizures was not achieved with valproate therapy alone, although at times there were seizure-free periods lasting a few years. She did not experience absence seizures or myoclonias during valproate therapy, but she occasionally experienced generalized tonic-clonic seizures in the morning.

Body Weight

At the time when valproate therapy was started in August 1975, the patient was 17 years old, weighed 23.3 kg (body mass index [BMI], 23.3 kg/m²), and had regular menstrual cycles. Her weight started to increase gradually and progressively after valproate therapy was begun. She weighed 75 kg (BMI, 27.2 kg/m²) in February 1982, 103 kg (BMI, 37.3 kg/m²) in November 1990, and 116 kg (BMI, 42.2 kg/m²) in November 1994.

Endocrine Function

Patient 1 was referred to the outpatient department of gynecological endocrinology at the University Hospital of Oulu because of secondary amenorrhea in February 1990. At that time her serum testosterone level was very high, 11.2 nmol/L (322.8 ng/dL); reference range, 0.4 to 3.1 nmol/L (11.5-89.3 ng/dL). Ultrasound findings of the ovaries revealed a few randomly situated cysts in both ovaries, which was not consistent with PCO. During the years 1990 to 1994, she was treated with progestins for some time periods, and during the treatment and thereafter she menstruated regularly for a while. Her serum testosterone level declined gradually during this time, and it was only slightly elevated (3.5 nmol/L [100.9 ng/dL]) in November 1994. In 1994, ultrasoundography findings of the ovaries showed subcapsular cysts in both ovaries consistent with PCO.

Restoration of Normal Body Weight and Endocrine Function After Replacing Valproate With Lamotrigine

In November 1994, patient 1 was referred to one of us (J.I.T.I.) for neurological evaluation by the gynecologist because she suspected that the patient’s amenorrhea, PCO, and hyperandrogenism could be related to valproate treatment. Lamotrigine therapy was started and valproate was tapered off over 2 months. During the first year after changing the medication, the patient experienced some tonic-clonic seizures, and also absence seizures and myoclonic jerks. The lamotrigine dose was gradually increased from an initial 200 mg/d to 600 mg/d. She has

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y</th>
<th>Medication</th>
<th>BMI, kg/m²</th>
<th>Menstrual Cycles</th>
<th>Testosterone, nmol/L (ng/dL)†</th>
<th>Ultrasonographic Findings of the Ovaries</th>
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<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>Phenytoin, valproate begun</td>
<td>23.3</td>
<td>Regular</td>
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<td>...</td>
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<td>Amenorrhea</td>
<td>11.2 (322.8)</td>
<td>A few randomly situated cysts; not PCO</td>
</tr>
<tr>
<td>1</td>
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<td>42.2</td>
<td>Amenorrhea</td>
<td>3.5 (100.9)</td>
<td>PCO</td>
</tr>
<tr>
<td>1</td>
<td>37§</td>
<td>Lamotrigine</td>
<td>36.0</td>
<td>Regular</td>
<td>2.5 (72.9)</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>Valproate begun</td>
<td>21.8</td>
<td>Regular</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>Valproate and oxcarbazepine</td>
<td>26.7</td>
<td>Amenorrhea</td>
<td>5.5 (158.5)</td>
<td>PCO</td>
</tr>
<tr>
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<td>24.3</td>
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<td>4.5 (129.7)</td>
<td>PCO</td>
</tr>
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<tr>
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<td>21.3</td>
<td>Regular</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>3</td>
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<td>21.3</td>
<td>Regular</td>
<td>7.5 (216.1)</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
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<td>Regular</td>
<td>2.5 (72.9)</td>
<td>PCO</td>
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<tr>
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<td>22.1</td>
<td>Regular</td>
<td>1.8 (51.9)</td>
<td>Normal</td>
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</tbody>
</table>

*BMI indicates body mass index; ellipses, not available; and PCO, polycystic ovaries.
†Reference range, 0.4 to 3.1 nmol/L (11.5-89.3 ng/dL).
‡Tapered off 6 years later.
§One year after valproate was replaced with lamotrigine.
now been seizure free for almost a year with a daily dose of 600 mg of lamotrigine.

During the first year after valproate was replaced with lamotrigine, her body weight decreased from 116 kg (BMI, 42.2 kg/m²) to 99 kg (BMI, 36 kg/m²); her serum testosterone level, from 3.5 nmol/L (100.9 ng/dL) to 2.5 nmol/L (72.0 ng/dL); and she started to menstruate regularly (duration of menstrual cycle, 30 days). Before the medication was changed, the ultrasononographic finding of both ovaries was consistent with PCO, but the structure of the ovaries returned to normal during the first year after tapering off valproate treatment; polycystic changes were no longer present in the ovaries (Figure).

PATIENT 2

Epilepsy

Patient 2 had her first epileptic seizure when she was 12 years old. Her epilepsy can be classified as cryptogenic simple partial epilepsy with secondary generalization. She had simple partial seizures with jerks in the left leg, mostly at night, and occasionally secondary generalized tonic-clonic seizures. Interictal EEG findings showed focal slow wave activity with right temporoparietal maximum. However, the findings in an ictal video EEG recording suggested that her seizures initiated from the left temporal lobe. The results of computed tomography and magnetic resonance imaging of the brain were normal.

Medication

Patient 2 was originally treated with carbamazepine and, because freedom from seizures was not achieved, phenytoin was added to her regimen after 18 months. Phenytoin therapy was tapered off 2 years later because of hepatotoxic effects. Valproate therapy was started in September 1991. In February 1992, carbamazepine was switched to oxycarbazepine. Freedom from seizures was not achieved with these medications, and the patient continued to experience several partial seizures and 1 to 2 secondarily generalized tonic-clonic seizures per month.

Body Weight

At the time when valproate therapy was started in September 1991, patient 2 was 16 years old. She weighed 57.5 kg (BMI, 21.8 kg/m²) and had regular menstrual cycles. Her weight started to increase gradually and progressively after starting valproate treatment. Her body weight was 62 kg (BMI, 23.4 kg/m²) in February 1993 and 71 kg (BMI, 26.7 kg/m²) in August 1993.

Endocrine Function

Patient 2 was referred to the outpatient department of gynecological endocrinology in the University Hospital of Oulu because of secondary amenorrhea in September 1993. She had had her last menstrual bleeding in January 1993. Biochemical studies showed mild hyperprolactinemia, and her serum testosterone level was elevated (5.5 nmol/L [158.5 ng/dL]). Ultrasonography findings of the ovaries revealed subcapsular cysts consistent with PCO. During the years 1993 to 1995 she was treated with bromocriptine because of hyperprolactinemia, and with progestins for some periods of time. Her serum prolactin level became normal under treatment with bromocriptine, but she continued to have hyperandrogenism and amenorrhea.

Cessation of Epileptic Seizures and Improvement of Reproductive Endocrine Function After Replacing Valproate With Lamotrigine

In November 1995, patient 2 was referred to one of us (J.I.T.I.) at the outpatient department of neurology at the University Hospital of Oulu. At that time she had had 62 partial and 1 generalized epileptic seizures during the previous 142 days, according to her seizure calendar. Lamotrigine therapy was started and valproate treatment
was tapered off over 2 months. The patient became seizure free with a lamotrigine dose of 200 mg/d, and she has not had any seizures since. During the first year after valproate was replaced with lamotrigine, her body weight decreased from 65 kg (BMI, 24.3 kg/m²) to 55 kg (BMI, 20.6 kg/m²); her serum testosterone level, from 4.5 to 1.6 nmol/L (129.7 to 46.1 ng/dL) and she started to menstruate randomly (4 menstrual cycles in a year). Before the medication was changed, the ultrasonographic findings of both ovaries were consistent with PCO, and 1 year later, polycystic changes were still present in the ovaries. Bromocriptine therapy has been stopped, but her prolactin levels have been normal since replacing valproate with lamotrigine.

PATIENT 3

Epilepsy

Patient 3 had her first generalized tonic-clonic seizure when she was 15 years old. She has had myoclonic jerks in the morning since she was a child. She experienced 2 more generalized tonic-clonic seizures at ages 30 and 31 years and JME was diagnosed. Results of EEG showed features consistent with the JME diagnosis: generalized spike-polyspike wave bursts and photosensitivity.

Medication

Patient 3 began treatment with valproate in 1990. She experienced an additional 2 generalized tonic-clonic seizures while taking the drug.

Body Weight

When valproate treatment was begun in 1990, patient 3 was 31 years old; she weighed 58 kg (BMI, 22.1 kg/m²), and she had regular menstrual cycles. There were no major changes in body weight after starting valproate therapy, and her BMI was still 22.1 kg/m² in February 1994.

Endocrine Function

In 1992, patient 3 participated in a study on reproductive endocrine function in women with epilepsy in our hospital. At that time she had been undergoing valproate treatment for 18 months at 600 mg/d. She was menstruating regularly; however, her serum testosterone level was very high, 7.5 nmol/L (216.1 ng/dL). Ultrasonographic findings of the ovaries revealed no abnormalities. In 1994, she was still menstruating regularly. Her serum testosterone level had decreased to 2.5 nmol/L (72.0 ng/dL), but the findings in the ultrasonography of both ovaries were consistent with PCO.

Restoration of Normal Endocrine Function After Replacing Valproate With Lamotrigine

In February 1994, the serum testosterone level of patient 3 was 2.5 nmol/L (72.0 ng/dL), and she had developed both-sided PCO. Lamotrigine therapy was started and valproate was tapered over 2 months. During the first year after changing the medication, the patient experienced some myoclonic jerks. The lamotrigine dose was gradually increased from the initial 200 mg/d to 500 mg/d. She has now been seizure free with a daily dose of 500 mg of lamotrigine. During the first year after valproate was replaced with lamotrigine, her body weight did not change. However, her serum testosterone level decreased from 2.5 nmol/L (72.0 ng/dL) to 1.8 nmol/L (51.9 ng/dL). Moreover, her menstrual cycles remained regular, and the structure of the ovaries became normal during the first year after tapering off valproate treatment; polycystic changes were no longer present in the ovaries.

The 3 cases presented here demonstrate the development of a reproductive endocrine disorder in women treated with valproate. Two of the cases were symptomatic and were characterized by hyperandrogenism (elevated serum testosterone levels), polycystic changes in the ovaries, menstrual disorders, and weight gain. The third case was asymptomatic, with normal body weight and normal menstrual cycles. However, the third patient developed hyperandrogenism and, thereafter, PCO while taking valproate. We have previously reported the high frequency of these kinds of disorders in women taking valproate for epilepsy.1-3

The possible pathogenetic mechanisms leading to development of PCO and hyperandrogenism during valproate therapy are unknown. This is the case with polycystic ovarian syndrome in general as well. We have suggested that obesity and associated hyperinsulinemia and low serum IGFBP-1 levels could be implicated in the development of PCO and hyperandrogenism in women taking valproate.2,3,5 Insulinlike growth factor binding protein 1 is a locally important regulator of insulinlike growth factor 1, which is a well-known stimulator of ovarian androgen synthesis.7 Insulin decreases the synthesis of IGFBP-1 in the liver, and hyperinsulinemia is associated with low serum levels of IGFBP-1.8 In addition, elevated serum insulin levels decrease the synthesis of sex hormone-binding globulin and, as a consequence, increase the bioavailability of testosterone.

Accordingly, PCO and/or hyperandrogenism and menstrual disorders are more common in obese than in lean women treated with valproate.2,3,5 Although these conditions also occur in lean women without hyperinsulinemia who undergo valproate therapy,2,3 Similarly, women with PCO syndrome in general can be categorized into obese patients with hyperinsulinemia and lean patients with normal serum insulin levels.9 Two of the patients presented here gained weight during valproate therapy, and both of them had menstrual disorders. The third patient did not experience weight gain during the first 3 years of valproate treatment, nor did she have menstrual disorders. Hyperandrogenism in prepubertal, pubertal, and postpubertal girls taking valproate for epilepsy was not associated with obesity or hyperinsulinemia.4 Therefore, obesity and elevated serum insulin levels do not seem to be the factors initiating the pro-
Valproate-treated women with hyperandrogenism have also had normal serum luteinizing hormone levels, suggesting that valproate does not stimulate ovarian androgen synthesis predominantly via increased luteinizing hormone secretion. Serum luteinizing hormone levels were also normal in the 3 women described here. Consequently, it is possible that valproate has a direct effect on ovarian androgen production. High serum testosterone concentrations may be a factor leading to the arrest of follicular maturation and eventually to development of PCO in these women. In our first and third patients, elevated serum testosterone levels occurred earlier than the polycystic changes in the ovaries. Interestingly, serum testosterone levels seemed to decrease in all 3 patients before valproate therapy was discontinued. Therefore, a relationship between discontinuation of valproate treatment and the decrease in serum testosterone concentrations cannot be clearly established in these 3 cases.

Valproate-related weight gain seems to be progressive in girls and women with epilepsy. This was the case in 1 of the patients with weight gain described in this article as well. It is not known whether the lean women with PCO and/or hyperandrogenism in the previous studies had gained weight or not. Our second patient was not yet obese (BMI, <25 kg/m²) when her menstrual disorders started. However, she continued to gain weight, and at the time she was referred for gynecological examinations she was already obese (BMI, 26.7 kg/m²). In the first patient, the weight gain was progressive.

The role of epilepsy in the development of reproductive endocrine disorders in women with epilepsy has been examined. It has been suggested that reproductive endocrine disorders may be overrepresented among women with temporal lobe epilepsy and among women with primary generalized epilepsy. Patient 1 and patient 3 had primary generalized epilepsy (juvenile myoclonic epilepsy), and patient 2 had localization-related epilepsy with an apparent left temporal lobe focus. This shows that valproate-related PCO and hyperandrogenism can develop in association with both primary generalized and partial epilepsies. Patient 2 became seizure free after lamotrigine treatment was begun. Therefore, it is possible that the better seizure control also contributed to the improvement of endocrine function in this woman.

A prospective randomized study on the endocrine effects of valproate would be important to further investigate and confirm the relationship between the use of valproate and the occurrence of PCO and hyperandrogenism in women with epilepsy. However, such a study would take a long time to complete, and it is possible that it might take years for the results to be known.

The 3 cases presented here illustrate the development of a reproductive endocrine disorder after starting valproate therapy in women with epilepsy. The disorder was characterized by hyperandrogenism and PCO in all cases, and it was associated with weight gain and menstrual disorders in 2 of the 3 women. Significantly, lower fertility rates were recently reported in women with treated epilepsy than in the general population. Valproate treatment may be related to infertility in women with epilepsy. Therefore, evaluation of ovarian structure and function should be considered in women of reproductive age taking valproate for epilepsy, especially if they develop menstrual cycle disturbances during the treatment.

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