—Case Reports—

Valproate-Induced Polycystic Ovary Syndrome in a Girl with Epilepsy: A Case Study

Yasuhiko Kawakami[1,2], Shuichi Fujii[2], Gen Ishikawa[3], Atsuko Sekiguchi[4], Akihito Nakai[4] and Masato Takase[2]

[1]Department of Pediatrics, Nippon Medical School Musashi Kosugi Hospital, Kanagawa, Japan
[2]Department of Pediatrics, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan
[3]Department of Gynecology, Nippon Medical School Chiba Hokusoh Hospital, Chiba, Japan
[4]Department of Gynecology, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan

Background: Polycystic ovary syndrome (PCOS) is a common ovulatory disorder that can be induced by sodium valproate (VPA).

Patient: We report a case of PCOS that developed in a 15-year-old girl with idiopathic epilepsy after she took VPA. VPA administration stopped her seizures, but it also led to weight gain and amenorrhea, and the patient was diagnosed with PCOS on the basis of diagnostic imaging and serological examination results. Cessation of VPA administration led to reduced weight gain and restored menstruation.

Conclusions: The risk of PCOS developing in patients with epilepsy is known to be high, and the association of VPA with PCOS is well established, so if physicians feel this is the best drug to prescribe for female patients with epilepsy, they should carefully monitor the patients' weight and menstruation, and immediately perform ovarian imaging and hormonal examinations if any abnormalities are observed.
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Key words: sodium valproate, polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is known to occur more frequently in women taking sodium valproate (VPA) for epilepsy than in the general female population[1]. The symptoms of PCOS include menstrual disorders (including amenorrhea), infertility, miscarriage, and hirsutism[2]. PCOS is characterized by any 2 of the following: oligomenorrhea or amenorrhea, hyperandrogenism or hyperandrogenemia, and polycystic ovaries[2,3]. The diagnostic criteria for PCOS define hyperandrogenemia as elevated serum total testosterone, free testosterone, or androstenedione levels[3].

The purpose of this case report is to highlight the problem of PCOS induced by VPA to medical staff treating patients with epilepsy.

Case Report

The patient was a 15-year-old girl who had been born uneventfully at 40 weeks of gestation weighing 3,060 g. There was no family history of neurological disorders or epilepsy, and her developmental milestones were normal, although she experienced a small number of episodes of febrile seizures in infancy. At the age of 12 years, however, she experienced her first unprovoked generalized tonic-clonic seizure (GTCs) and was brought to our clinic. Electroencephalography (EEG) showed diffuse spikes and wave complexes (SWCs) (**Fig. 1**), but magnetic resonance imaging (MRI) of the brain revealed no abnormalities (data not shown). No medication was prescribed, because this was her first experience of epileptic seizures. However, she had another episode of GTCs 6 months later, and a third episode 2 months after that. VPA (1,000 mg, 18.2 mg/kg/day) was administered orally. At this point, the patient was 13 years and 1 month old (height: 163 cm, weight: 55 kg, BMI: 20.7). After 6 months of treatment with VPA, the patient's EEG

Correspondence to Yasuhiko Kawakami, Department of Pediatrics, Nippon Medical School Musashi Kosugi Hospital, 1–396 Kosugi-cho, Nakahara-ku, Kawasaki, Kanagawa 211–8533, Japan
E-mail: kawakami@nms.ac.jp
Journal Website (http://www2.nms.ac.jp/jnms/)

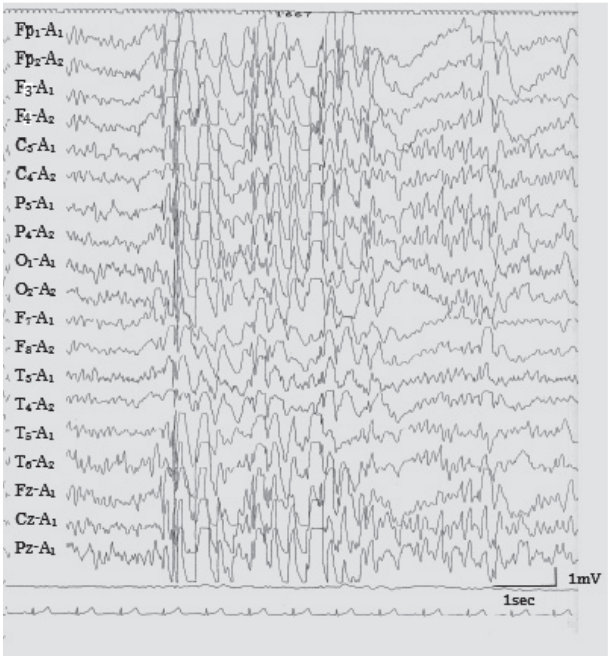

Fig. 1 Electroencephalography (EEG) taken when the patient was 12 years and 6 months old shows diffuse spike and wave complexes.

readings were normal, and she had experienced no epileptic seizures since she started taking VPA.

When she reached her menarche at the age of 14 years and 2 months, she was 165 cm in height and weighed 60 kg (BMI: 22.0). She had a regular menstrual cycle of about 4 weeks. When she was 14 years and 9 months old, she was 167 cm tall and weighed 69 kg (BMI: 24.7). However, neither her health providers, her parents, nor the patient herself paid much attention to her weight gain. There were two reasons for this: her satisfactory clinical course, and the fact that she was focusing on high school entrance examinations.

After she gained admission to high school at the age of 15 years and 7 months (height: 167 cm, weight: 73 kg, BMI: 26.1), her EEG readings were normal (data not shown), and because she had had no seizures for 2 years and 6 months, VPA cessation was considered. At this point, her serum VPA levels had increased from 80 to 90 μg/mL, and she revealed that she had not menstruated for several months. A growth curve created around the same time also showed clear weight gain in the patient since the start of VPA administration (**Fig. 2**). This new clinical information led to suspicion of PCOS.

Ultrasonography and MRI of the abdomen showed multiple cysts in her ovaries (**Fig. 3-A, 3-B**). Her luteinizing hormone level was high (9.1 mIU/mL), and her follicle stimulating hormone level was normal (5.3 mIU/mL). Her total-testosterone (1.17 ng/mL) and free-testosterone (1.3 pg/mL) were within normal limits. Adrenal function was also within normal limits, as were her insulin level, blood glucose level, and lipid metabolism (data not shown). These finding met the diagnostic criteria for PCOS[3]. As soon as the diagnosis was confirmed, the dosage of VPA was reduced by 50% for 1 month, after which administration was terminated. The patient lost weight gradually and, 2 months after VPA cessation, menstruation resumed (**Fig. 2**).

Discussion

First reported in 1935[4], PCOS is a common ovulatory disorder estimated to affect 5% to 10% of the female population[5,6]. The risk of developing PCOS during VPA treatment is reportedly higher in women with epilepsy than in women with bipolar disorders, which may be due to an underlying neuroendocrine dysfunction related to seizure disorders[7]. Indeed, it has been reported that epileptic discharge itself may affect hypothalamic function via dysregulation of gonadotropin-releasing hormone pulse generators[8]. Other evidence shows that the incidence of PCOS is more common among women with epilepsy[9]. An association between the development of PCOS and all antiepileptic drugs (AEDs) is suspected, but it has been reported that PCOS develops more frequently in patients administered with VPA than in those taking any other medication for epilepsy[10,11].

PCOS has reproductive, metabolic, and cardiovascular components[2]. According to Ehermann, "Androgen excess and insulin resistance, both of which have strong genetic components, underlie much of the clinical presentation"[2]. The insulin resistance of PCOS appears to impart an increased risk of glucose intolerance, diabetes, and lipid abnormalities, and may enhance the development of vascular disease[12–15]. These metabolic abnormalities may have an indirect influence on reproductive functions, however, the detailed pathophysiology of PCOS remains unknown.

Other researchers have reported that stopping VPA administration leads to recovery of the menstrual cycle[16,17], so VPA cessation may be the best option for patients who develop PCOS.

In 2015, an International League Against Epilepsy task force recommended that restrictions on the use of VPA in women and girls be strengthened[18]. Separately, lamotrigine has been reported to be a viable substitute for VPA[19].

Since the 1990s, VPA has been used to treat patients in a manic state[20], and it has also been presented as an op-

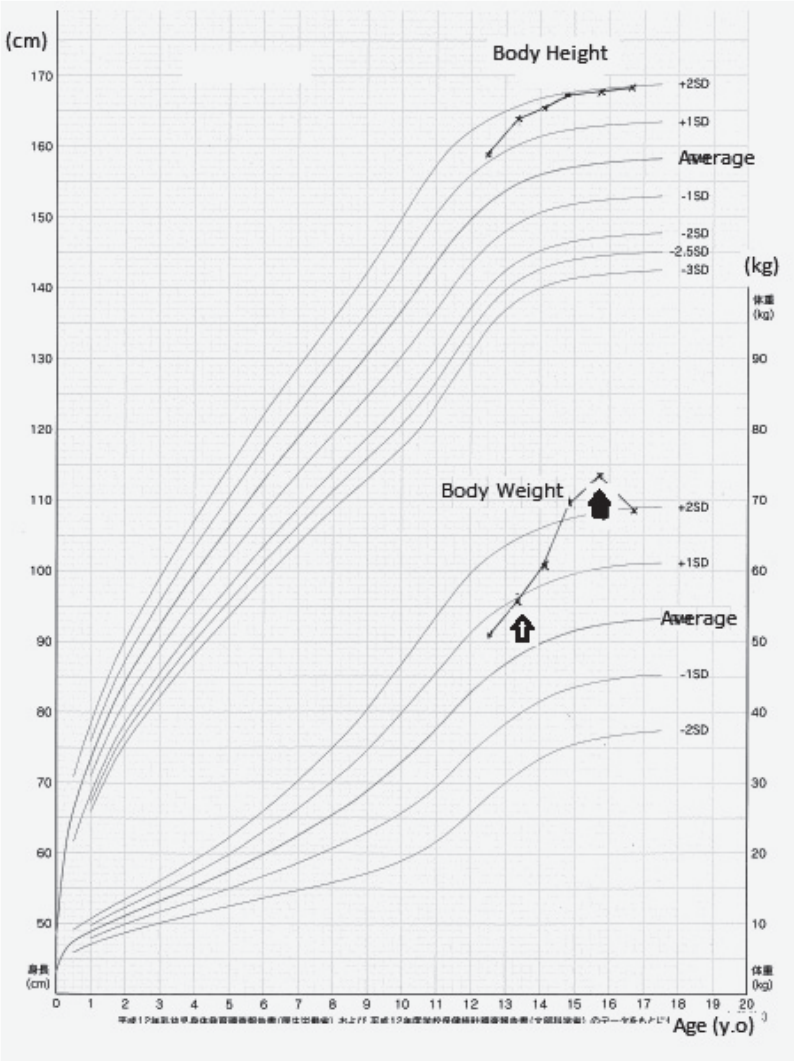

Fig. 2 Growth curve

Between the ages of 12 and 17 years, the patient's height ranged between 1 and 2 standard deviations above the mean height for her age group. However, her weight during sodium valproate (VPA) administration increased to over 2 standard deviations above the mean. It then decreased again after VPA administration was discontinued.

The outline arrow indicates the start of VPA administration (patient's age: 13 years and 1 month), and the black arrow the cessation of VPA (15 years and 7 months).

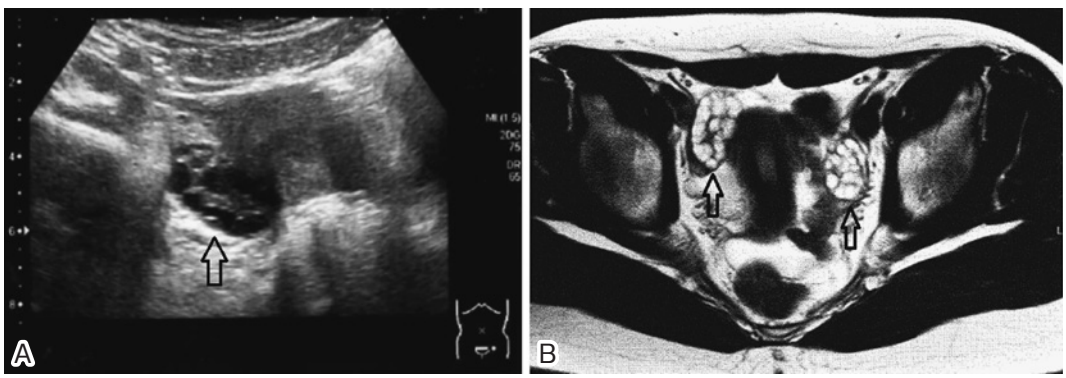

Fig. 3 Abdominal imaging showed multiple cysts in the patient's ovaries (**A**: ultrasonography, **B**: magnetic resonance imaging). The outline arrows indicate polycystic ovaries.

tion for treating migraine[21]. VPA is used for purposes other than the treatment of epilepsy, therefore, it has been administered to women even of reproductive age. Physicians would be well advised to bear in mind the risk of PCOS onset in women taking VPA and to immediately perform ovarian imaging and hormonal examinations if any abnormalities in menstruation develop. If VPA is the only viable medication for specific patients after the onset of PCOS, such obstetrical and gynecological treatments as Kaufmann therapy, Holmstrom therapy, or Pincus therapy should be considered[22].

Because of the role played by epilepsy itself in the development of PCOS[7], elucidation of the full pathophysiology of PCOS is eagerly awaited.

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Conflict of Interest: No conflict of interest is declared.

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