

## WILL MY CHILD GROW UP AND BE NORMAL?

### Physical Growth and Endocrinal Disorders during Pubertal Maturation in Girls with Epilepsy

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**PURPOSE:** This study investigated the effect of epilepsy or antiepileptic drugs or both on the physical growth, pubertal development, and androgenic status of girls with epilepsy between ages 8 and 18 years.

**METHODS:** Sixty-six female patients with epilepsy, their mean ages  $13.47 \pm 3.5$  years, were included. Anthropometric measurements, staging of pubertal maturation, and clinical manifestations of hyperandrogenism were assessed, as well as measurement of serum levels of testosterone, dehydroepiandrosterone sulfate, sex hormone-binding globulin, and free androgen index. Of the included patients, 44 had transabdominal ultrasonic examination of the ovaries, and fasting serum insulin levels were measured. Forty healthy age-matched girls served as a control group.

**RESULTS:** Patients showed reduced mean height percentile compared with controls ( $z = 2.07$ ;  $p = 0.04$ ), which was negatively correlated with the duration of their epilepsy. Patients showed increased frequency of obesity, especially postpubertal girls taking valproate (67%), who also showed higher insulin levels ( $t = 8.01$ ;  $p = 0.0003$ ). Patients showed increased frequency of clinical hyperandrogenemia in the different stages of puberty. High levels

of testosterone and dehydroepiandrosterone sulfate were found in girls with epilepsy, especially pubertal and postpubertal girls. Hyperandrogenism (clinical and/or laboratory) was most affected by the types of antiepileptic drugs, with higher incidence in patients taking valproic acid compared with those taking enzyme-inducing antiepileptic drugs ( $\chi^2 = 9.16$ ;  $p = 0.01$ ). Eighteen percent of the patients were diagnosed as having polycystic ovary syndrome. No difference was found in the types of seizures, degree of seizure control, types of antiepileptic drugs, or insulin levels between patients with and those without polycystic ovary syndrome.

**CONCLUSIONS:** Longer duration of the disease has a negative impact on the stature of girls with epilepsy. Postpubertal girls taking valproic acid are more liable to obesity, which is associated with increased incidence of hyperinsulinemia. Clinical or laboratory evidence or both of hyperandrogenism is seen at a high frequency in patients, especially with the use of valproic acid. Furthermore, girls with epilepsy especially in the postpubertal stage of sexual maturation, have a high prevalence of polycystic ovary syndrome, independent of the type of antiepileptic drug or the characteristics of the epilepsy disorder.

### COMMENTARY

Will my child grow up and be normal? This is a question that parents often ask when the diagnosis of epilepsy is made, but do clinicians always understand what the question implies? For most physicians, comfort and familiarity are found in quoting statistics about chances for seizure control and potential for medication discontinuation. If appropriate, issues like driving and involvement in various sports or other activities are addressed, while promoting the concept that the child be allowed as much independence as possible and that the parent minimize overprotection. Epileptologists, as well, have a general confidence about discussing questions regarding intelligence and learning problems.

But do clinicians recognize that parents are sometimes asking if their children will be able to have normal families of their own when they grow up? Most frequently, the topic is addressed when young women are approaching the childbearing

years, as it is a time when relevant neuroendocrine issues are considered—issues that, perhaps, should have been addressed earlier. However, similar issues commonly are ignored in boys and men, yet, for all of these young people, living a normal life encompasses many factors, including normal growth and sexual function.

The recent article by El-Khayat and colleagues on pre- and postpubertal girls is a companion piece to an earlier study of male sexual development (1). Both reports examine the physical and hormonal development of young people with epilepsy; these articles, unfortunately, are part of a long and sometimes confusing literature of cross-sectional studies that often provide conflicting information. In brief, the report on sexual development in males with epilepsy indicates that this patient population may be adversely affected in a number of ways, including lower testicular volume, shorter penile length, higher total testosterone but lower free testosterone, and increased estradiol.

This article by El-Kayhat et al. is a study of girls with epilepsy, ages 8 to 18 years. As has been true of so many articles on this subject, the design of the study and the power to detect the cause of the problem must be examined. However, it is known that seizures, particularly temporal lobe seizures, appear to have an impact on menstrual cycles (5), and both menstrual cycles and their irregularities may influence seizure control (6). The debate about polycystic ovary syndrome continues in this article; the authors found a high prevalence of polycystic ovary syndrome, without a relation to the type of antiepileptic drug or type of epilepsy.

Regarding normal physical growth, El-Kayhat et al. report that the girls with epilepsy were shorter in stature than controls and that a significant negative correlation existed between the duration of epilepsy and height for both the prepubertal and postpubertal girls. In the previous study on boys, shorter stature was seen in the older patients, although this finding was reportedly not associated with duration of the disorder. Nonetheless, the issue of the effect of epilepsy and its treatment on height is not resolved. Studies from the 1980s concluded that, on a population basis, linear growth of people with epilepsy was normal, but subgroups raised a concern: those with earlier onset and those taking phenytoin (2). Questions regarding epilepsy and growth have persisted, and findings are confounded by various methods used to assess growth and bone health, such as the recently developed total body bone mass density measured by dual energy x-ray absorptiometry scan. Guo et al. found that short stature, low bone mineral density, and reduced bone formation were associated with long-term valproate (VPA) and lamotrigine therapy and provided the additional new insight that these problems may be affected by reduced physical activity of the children (3). Guo et al., and many other authors, lament the absence of well-controlled, longitudinal designs that would resolve the issue of the effect of epilepsy and epilepsy treatment on height. Too many questions remain. Are children with epilepsy at risk because of the type of seizure disorder they have; age at onset with respect to their maturation; medication(s); diet; or because they are not engaged in appropriate physical activity?

Both reduced physical activity and shorter stature are a concern for the obese patient, with or without epilepsy. In the current article, El-Khayat et al. noted that postpubertal girls being administered VPA are more liable to obesity, which is associated with increased incidence of hyperinsulinemia. The issue of decreased sensitivity to insulin in girls with epilepsy was not addressed in this article. In a rare prospective longitudinal study of VPA, Novak and colleagues (4) assessed children before treatment and at follow-up. A significant increase in body mass index and in weight  $z$  scores was demonstrated. Many of the children were heavy at the study onset, and an elevated initial weight  $z$  score was most strongly correlated with increase in weight, which suggests that a predisposition toward weight gain may exist in children with epilepsy. Furthermore, the data

raise the question of whether these children already were insulin insensitive before treatment onset and whether treatment initiates a clinical increase in plasma insulin.

Debates persist over whether one antiepileptic drug is better than another with respect to hormonal health (7,8), and longitudinal (rather than cross-sectional) studies of lamotrigine and VPA are in process (9). Until pharmacogenomics can facilitate the choice of medication best suited to the individual patient, clinicians must rely on the cogent and simple recommendations of investigators, such as El-Khayat et al. When is an individual patient at risk? Certainly, when he or she has reached the current guideline for obese, that is, a body mass index greater than 25 kg/m<sup>2</sup>. With adolescents, monitoring the velocity of growth and obtaining a fasting insulin level and lipid profile seems prudent. Evidence of hyperandrogenism or menstrual irregularities, either at baseline or during treatment, warrants investigating sex-hormone profiles, which can, in turn, inform drug selection and patient monitoring. Better collaboration with endocrinologists and gynecologists likely will improve patient outcome. Young patients need to feel that they can, indeed, grow up to be normal and that clinicians are providing them with the best possible chance for healthy sexual maturation and establishment of their own families.

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