Medroxyprogesterone acetate in the treatment of seizures associated with menstruation

An 8-year-old girl who had a generalized seizure disorder from the age of 5 had an early onset of normal puberty and developed exacerbation of seizures and behavioral abnormalities during menstrual periods. The neurologic examination demonstrated only mild mental subnormality; a pneumoencephalogram showed slight ventricular dilatation. Oral medroxyprogesterone acetate (MPA) decreased seizure activity slightly. Subsequently following three biweekly injections of depot-MPA, the patient's menses ceased, and she became seizure-free for 4 months. There was associated improvement in behavior and school performance. Serum gonadotropin values remained normal, and no side effects were observed, except for increased appetite and weight gain.

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THE ASSOCIATION of an increased severity and frequency of seizures prior to or during menses in female epileptic patients has been repeatedly observed.[1,2] Often referred to as "catamenial" epilepsy, an exacerbation of seizure activity with menstruation occurs in up to 50 per cent of epileptic women.[3] Although the etiology remains unclear, water retention, electrolyte changes, and both direct and indirect hormonal influences have been suggested as contributing factors.

Livingston[4] in 1966 achieved complete control of seizures in three of five women 32 to 38 years of age) with catamenial epilepsy by means of continuous oral administration of norethynodrel and mestranol (Enovid) in doses sufficient to stop menstrual bleeding. Side effects included headaches and behavioral changes which necessitated withdrawal of therapy. Complete control of seizures using norethynodrel and mestranol has also been reported in one patient each by Groff[5] and by Sanchez Longo and Gonzalez Saldaña.[6]

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CASE REPORT

Patient S. S., an 8-year-old left-handed Caucasian girl, was born after a difficult 27 hour labor. Growth and development were normal until 5 years of age, at which time generalized seizures were first noted. Physical examination showed normal development, growth in height and weight at the ninety-seventh percentiles, and

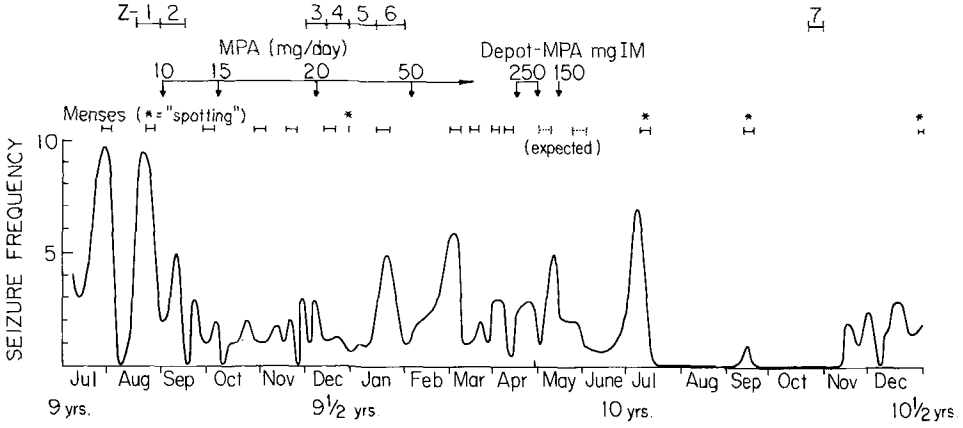

Fig. 1. The patient's clinical course over 18 months. Zones 1 to 7 (*Z*) refer to collection periods for luteinizing hormone and follicle-stimulating hormone as listed in Table I. Note increase in daily seizure frequency prior to and during menses before onset of therapy with MPA and cessation of seizures for 4 months after intramuscular injection of depot-MPA.

mild mental subnormality (I.Q. 80). Phenobarbital (15 mg. three times a day) was started and seizure frequency remained at about three per week.

Between 8 and 9 years of age she had a growth spurt of 20 cm. associated with the onset of puberty, with early breast buds, a female pubic hair pattern, and normal early pubertal genital changes.

Menses began at 9 years of age and were associated with an increase in seizure activity 1 to 2 days prior to bleeding and throughout the length of the period of about 7 days. The average frequency of epileptic attacks between menses was 0 to 4 per day and during the menstrual period, 7 to 10 per day.

A trial of oral medroxyprogesterone acetate (MPA) (Provera, 10 mg. per day) was begun in an attempt to abolish menstruation, alleviate abusive behavior associated with menses, and hopefully improve seizure control. Because of lack of the expected response, the dose was increased to 20 and later to 50 mg. per day. This was accompanied by a slight decrease in seizure frequency; menses were modified but not abolished (Fig. 1). Seizure medications consisted of primidone, 250 mg. three times a day, and phenobarbital, 30 mg. three time a day, throughout the course of this observation. A previous attempt to control seizures with diphenylhydantoin, up to 300 mg. per day in combination with diazepam 15 mg. per day, was unsuccessful.

In order to circumvent hepatic degradation, oral MPA was discontinued and a total of three intramuscular injections of a depot preparation of MPA (250, 250, and 150 mg.) were given at intervals of 2 weeks. No further menses occurred except for light spotting at 2 months. Epileptic attacks first declined and then ceased altogether for 4 months. Social behavior during the seizure-free months was greatly improved and the improvement has persisted to the time of this report. Seven months after the three injections of depot-MPA, the patient again had zero to three generalized seizures per day and regular menstruation occurred at 12 months.

CLINICAL STUDIES AND OBSERVATIONS

Table I shows the values for luteinizing hormone and follicle-stimulating hormone as determined by a double-antibody radioimmunoassay carried out on serum and 24 hour urine extracts, by using the second international reference preparation of human menopause gonadotropins for dose interpolation.[7, 8] No suppression of gonadotropin levels is evident before, during, or after treatment with MPA. One midcycle peak in luteinizing hormone is seen in Zone 3.

Fig. 1 illustrates the patient's clinical course with changes in seizure frequency in relation to menstrual periods and MPA treatment. The pretreatment level of seven to ten seizures per day prior to or during menses decreased with oral MPA therapy to zero to four seizures per day, but after 4 months increased again to five to six per

Table I. Values for luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in serum and 24-hour urine specimens

*ZONE**		*Urinary LH (mI.U./ml.)*	*Serum LH. (mI.U./ml.)*	*Urinary FSH (mI.U./ml.)*	*Serum FSH (mI.U./ml.)*
Pre (MPA) treatment	1	1.5 ± 0.3	7.3 ± 0.7	5.7 ± 1.6	9.9 ± 0.3
Follicular phase with MPA	2	3.7 ± 2.3		7.6 ± 0.4	
Luteal phase with MPA	3		29.5 ± 16.5 (midcycle)	8.3 ± 2.9	15.5 ± 5.7
Follicular phase with MPA	4		8.5 ± 1.5	5.2 ± 1.7	16.4 ± 1.1
Luteal phase with MPA	5	10.6 ± 9.4	10.0 ± 3.0	—	13.4 ± 4.4
Follicular phase with MPA	6	2.0 ± 1.2			
Amenorrheic— no MPA	7		10.8 ± 0.4		17.5 ± 0.3

*Zones 1 to 7 refer to collection periods of serum and urine for determination of gonadotropins indicated in Fig. 1.

day during menses with oral doses of 20 and 50 mg. of MPA daily. Following depot-MPA treatment, one period occurred, during which the patient had seven seizures per day. She then became amenorrheic and seizure-free for 4 months, except for brief spotting associated with a temper tantrum 2 months after the depot-MPA injections. After 6 months, seizures recurred at zero to three per day and regular menses occurred after 12 months.

Serum levels of primidone and phenobarbital by gas-liquid chromatography showed no significant changes before, during, or after MPA therapy.

Electroencephalograms showed a diffuse dysrhythmia, with bilateral sharp waves and variable epileptiform discharges, but with no relation to phases of the menstrual cycle or MPA treatment. A pneumoencephalogram disclosed mild enlargement of both lateral ventricles with no shift of midline structures. The results of a brain scan and cerebral-spinal fluid examination were normal.

Following oral MPA therapy, a SU 4885 (Metapirone) test and 2 hour postprandial glucose values were normal. Right and left buccal smears showed a normal female chromatin pattern. The radiologic bone age advanced in spite of MPA therapy to 14 years. Blood coagulation studies (prothrombin time, partial thromboplastin time, and thrombin time) were normal.

COMMENT

The observations presented suggest that MPA raised this patient's seizure threshold by unknown mechanisms and was effective in spite of a lack of suppression of gonadotropin secretion. Although oral therapy was associated with a decrease in seizures, three intramuscular injections resulted in complete seizure control and amenorrhea.

Considerable controversy exists as to the mechanisms of catamenial epilepsy and the relative effects of progesterone and estrogen. Laidlaw[1] found a significant reduction of seizure activity during the luteal phase (with elevated serum progesterone) in the combined menstrual and seizure records of 50 epileptic women. Seizures increased before, during, and after menstruation (and physiologic lowering of progesterone). The administration of conjugated estrogens was thought to be a factor in exacerbating seizures and electroencephalogram abnormalities in 16 patients with epilepsy by Logothetis and associates.[10] Progesterone as well as estrogen levels are lowest during menstruation, and progesterone values drop more precipitously than estrogen prior to the onset of menses. Enhancement of seizure activity might, therefore, result in part from increased excitability because of lack of one or both hormones.

Costa and Bonnycastle[11] found progesterone to be superior to other steroids in rais-

ing the seizure threshold in dogs and thereby protecting them from agene-induced seizures. Conjugated estrogens (Premarin) applied directly to cat cerebral cortex produced surface "spikes."[12] Blackham and Spencer[13] found that progesterone accelerated the metabolism of phenobarbital, diphenylhydantoin, and diazepam in mice, whereas estrogen had the opposite effect.

A disturbance of hypothalamic or other subcortical processes may be associated with precocious puberty and electroencephalogram abnormalities. Liu and associates[14] reviewed the electroencephalograms of 42 children with "idiopathic" and 23 with "cerebral" (neurogenic) type precocious puberty. Those with seizure disorders showed slow activity and/or paroxysmal activity in electroencephalograms, but no correlation of the menarche or menses to the abnormalities was reported. Significantly, those children in the idiopathic group of precocious puberty had less prominent, but similar, abnormalities in spite of the lack of "hard" neurologic findings.

MPA has been used in the therapy of isosexual precocity with varying results. Kaplan and associates[15] found the depot preparation effective in producing amenorrhea in all of ten girls with vaginal bleeding. The injections were given biweekly (150 and 200 mg. in children over 4 years of age) for 1 to 4½ years. A suppression of gonadotropin secretion was observed in 65 per cent of the girls in whom luteinizing hormone and follicle-stimulating hormone values were elevated prior to MPA therapy. Even high doses of MPA failed to inhibit the advancement of bone maturation in these patients, suggesting incomplete suppression of gonadotropins by MPA.

Our patient showed no suppression of gonadotropins following oral and depot-MPA therapy. Rifkind and associates[16] treated five children with isosexual precocity with MPA (150 mg. intramuscularly biweekly): two responded, as did two castrate adults, with suppression of gonadotropins as measured by radioimmunoassay. Three children showed no response (2 girls, 5 and 7½ years old; one boy, age 11, with pineal tumor).

In contrast to the 19-norsteroid group of progestin compounds commonly used in oral contraceptives, MPA has no androgenic or estrogenic properties. Its use results in a decrease in breast size and reversal of estrogenic changes on the vaginal smear, as well as amenorrhea. Reiter and Kulin[9] have emphasized the potential morbidity of MPA during long-term administration, mostly due to its glucocorticoid actions. Also, a decrease in spontaneous fibrinolytic activity of the blood during treatment with parenteral MPA (150 mg. every third month) was reported by Brakman and associates[17] and Astedt.[18] Alterations of testicular histology and chromosomes have been associated with prolonged MPA administration in boys with constitutional precocious puberty by Camacho and associates.[19]

Experience of other investigators with oral contraceptives as well as the present data suggest that MPA may be a useful agent in the treatment of increased seizure activity with menstruation; however, caution is advised, pending further investigations of its mechanism of action, side effects, and clinical efficacy.

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