

Clomiphene as an Anticonvulsant Drug

A Case Report

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The effect of sex steroids on seizure disorders is controversial. Two controlled trials showed no effect^{1,2}; however, there are other descriptions of patients whose attacks were aggravated by oral contraceptives.^{3,4} Some experimental evidence suggests that estrogens increase the electrical excitability of the brain.⁵

Clomiphene citrate, an antiestrogen drug, has been used to treat oligospermia and asthenospermia.^{6,8} In contrast to its use in women for infertility, where the drug is taken for only five days each month, clomiphene is used in men for at least 25 days per month. Whether the drug is safe to use in either men or women with a seizure disorder is not known. If the evidence that estrogen adversely affects seizure disorders is correct, then this antiestrogen drug might have an ameliorative effect. However, there is some evidence that clomiphene may act as an estrogen in a man.⁹ Thus, its use for oligospermia in men with seizure disorders must be monitored closely.

This study describes a patient with an unstable seizure disorder who was treated with clomiphene for a male factor problem. A marked improvement in his spells was subsequently noted.

REPORT OF A CASE

A 33-year-old man sought improvement of marked oligospermia (sperm count, 0.5×10^6 /mL, with rare motility). He had been treated for a seizure disorder since age 13 years, and was taking 250 mg of valproic acid three times a day, 400 mg/day of mephenytoin, and 1,000 mg/day of primidone. Despite this therapy he was experiencing two major motor seizures per year and six to seven partial spells per day,

which were manifested by sudden staring and occasional kicking movements with the right foot.

The results of examination were completely normal. The serum level of follicle-stimulating hormone (FSH) was increased slightly at 25.5 IU/mL (normal, 5 to 25 IU/mL) and the serum prolactin level was 17.5 ng/mL (normal, 7 to 18 ng/mL).

The patient and his wife were advised that, in view of the increased FSH level and the poor spermogram results, the prognosis for improvement with clomiphene was poor. He was also advised of the possibility of worsening his seizure disorder. Despite these admonitions, the patient requested clomiphene therapy.

The patient was administered 25 mg/day of clomiphene citrate for 25 days each month, as is usually prescribed. Four months later there had been no improvement in his spermogram. However, he noted a marked improvement in the incidence of partial spells (zero to one per day) during the 25 days of taking the drug, only to experience the usual six to seven spells per day during the five days of cessation. The patient asked to take the drug without interruption.

Routine and sleep EEGs performed while the patient was taking clomiphene showed a basic rhythm at 7 cps with generalized paroxysmal spike and wave discharges of up to 20-s duration. An EEG taken two weeks after the patient stopped clomiphene therapy was unchanged. The serum blood levels of the anticonvulsant drugs were in therapeutic ranges for valproic acid at 72 μ g/mL (normal, 50 to 100 μ g/mL), primidone at 6.8 μ g/mL (normal, 5 to 12 μ g/mL), and mephenytoin at 6.2 μ g/mL (normal, 2 to 7 μ g/mL) and were the same whether or not he was taking clomiphene. Full seizure activity resumed during this hiatus in clomiphene treatment and promptly ceased when the drug was resumed. After 12 months of treatment there has been no improvement in the sperm count, but clomiphene therapy has been continued and is maintaining a greater than 90% suppression of his seizures. Thus far he has not had a major seizure while taking clomiphene.

COMMENT

Our patient showed a reproducible improvement in his seizure disorder with ingestion of clomiphene citrate, while exacerbations regularly recurred on stopping the drug. Its mech-

anism of action might be associated with suppression of electrical excitability of the brain because of the drug's antiestrogen nature. However, the evidence that estrogen aggravates convulsive attacks is far from conclusive. Perhaps it may potentiate the effects of valproic acid, mephenytoin, or primidone.

Whether clomiphene was beneficial only for this patient or is of potential use for other patients with seizures is not known. This case may encourage carefully controlled studies in a larger series. It will need to be determined whether clomiphene is helpful only for partial complex seizures, which this patient experienced, or for major motor seizures as well. Another interesting question is whether the drug will be beneficial for women as well as men.

We hope that this case report may serve to stimulate further and more definitive investigation of this drug. Since it may cause cystic gynecomastia in men and ovarian cysts in women, its efficacy should be evaluated first in carefully controlled studies before being used by physicians generally.

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