SHORT REPORTS

Increased bacterial antibody titres and IgA deficiency in epileptic patients

An association between epileptic seizures and increased serum bacterial antibody titres was recently reported in Finnish patients receiving carbamazepine and those receiving no drugs.¹

We studied bacterial antibody titres in Norwegian patients with epilepsy receiving long term treatment with phenytoin, many of whom had IgA deficiency.

Patients, methods, and results

Twenty eight Norwegian patients with epilepsy (16 male and 12 female patients, aged 10-50) were examined. All had been treated with phenytoin for at least a year, seven of them in combination with carbamazepine, phenobarbitone, or clonazepam. Four patients suffered from primary generalised tonic-clonic seizures, and 24 suffered from partial seizures. None had febrile convulsions. The causes of the epilepsy were perinatal brain lesions (12 patients), head injury (two patients), genetic predisposition (two patients), and unknown (12 patients). The 28 healthy controls were matched for age, sex, race, and geographical location.

Titres of antibodies to several bacterial antigens were measured by standard techniques. The results were considered to be positive when above the 98th percentile for a healthy Finnish population (see table).² Serum IgA, IgG, and IgM

Positive serological results in epileptic patients* and controls

Antibody test	Minimum measurement denoting positive result	Patients (n=28)	Controls (n=28)
Antistreptolysin O*	500 Todd units	2†	0
Antideoxyribonuclease B*	1/400	6	0
Antistaphylococcal	4.0 IU/ml	0	0
Teichoic acid antibody	1/8	0	1
Antibodies to <i>Yersinia</i> serotypes 3 or 9, or both	1/320	0	0
Widal test	1/320	0	0

* $p=0.023$ (Fisher's test of exact probability, two tailed) for streptococcal serology (6/28 v 0/28).

†Both patients also had positive antideoxyribonuclease B titres.

concentrations were determined by single radial immunodiffusion. The percentage of mononuclear cells with membrane bound immunoglobulins, E receptors, Fc receptors, complement receptors, and phagocytosing capacity were measured in peripheral blood from 14 patients and 13 controls.³ The mononuclear blood cells were also stimulated in vitro by phytohaemagglutinin.³

Six patients yielded positive results to the streptococcal antibody test, while all of the controls yielded negative results ($p<0.05$) (table). Nine patients had serum IgA deficiency ($\text{IgA}<0.05$ g/l), and another 10 patients had abnormally low serum IgA concentrations (0.05 g/l $< \text{IgA}<0.50$ g/l). Nine patients had normal serum IgA concentrations ($\text{IgA}>0.50$ g/l). The serum IgG concentration was normal in all patients, and the serum IgM concentration was normal or slightly decreased, but none of the patients had IgM deficiency. All the controls had normal serum immunoglobulin concentrations.

The percentages of mononuclear blood cell subpopulations with membrane bound immunoglobulins, E receptors, Fc receptors, complement receptors, phagocytosing capacity, and mononuclear cell response to stimulation with phytohaemagglutinin did not differ between the controls and the patients with and without streptococcal antibodies. Five of the seropositive patients suffered partial seizures, and one suffered primary generalised tonic-clonic seizures. There was no correlation between the presence of bacterial antibodies and other immunological or clinical values, including IgA deficiency and the frequency of epileptic fits. The patients who had increased streptococcal antibody titres showed a prevalence of respiratory tract symptoms similar to that seen generally in patients treated with phenytoin.⁴

Comment

Phenytoin may cause IgA deficiency in epileptic patients,⁵ which may lead to an increased risk of respiratory infections.⁴ As increased titres of bacterial antibodies were not related to IgA deficiency or any other immunological or medical factor in epileptic patients treated with phenytoin, and increased titres may also occur in untreated epileptic patients,¹ the increase in bacterial antibodies cannot be explained by IgA deficiency, treatment with phenytoin, or any of the other factors analysed. The frequency of infection is also greater in epileptic patients with normal immunoglobulin concentrations, as well as in epileptic patients with IgA deficiency who receive phenytoin, than it is in controls.⁴

The association between epileptic seizures and increased bacterial antibody titres remains unexplained, but possibly infections, even when clinically silent, may trigger epileptic seizures.

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Exposure to antiandrogen during pregnancy: case report

Idiopathic hirsutism is most effectively treated with antiandrogens such as cyproterone acetate.¹ Laboratory animals exposed to cyproterone acetate during fetal life, however, have shown abnormal sexual differentiation.² The risk of fetal malformations in man after cyproterone acetate medication during pregnancy is also thought to be high but few data are available. We present the case of a woman who was inadvertently prescribed cyproterone acetate during the first 17 weeks of pregnancy.

Case report

The patient was a 28 year old woman with oligomenorrhoea and hirsutism. She had previously been investigated for infertility and for a period treated with clomiphene citrate for induction of ovulation. Conception had not occurred, however, and the treatment was discontinued when she and her husband separated. One year later she complained about hirsutism. Routine investigations showed no obvious hormonal abnormality. Serum concentrations of the gonadotrophins testosterone and dehydroepiandrosterone sulphate were all within normal limits.

Cyproterone acetate (100 mg daily for 10 days) was prescribed in a reversed regimen together with ethinyloestradiol (50 µg daily for 21 days) as described by Hammerstein *et al.*³ When the patient was given her prescription she had had her last menstrual bleeding two weeks earlier. She began treatment two weeks later on the fifth day of the next menstrual period, which she regarded as normal. Menstruation did not occur again but she had been told that withdrawal bleeding might not occur every month. She continued the treatment until she came back to the clinic four months later and was found to be in the 17th week of pregnancy. Conception had plainly occurred at the time she had had her prescription.

The patient welcomed a baby but was concerned about the risk of fetal malformation due to the medication. Ultrasound scanning failed to disclose the sex or detect any genital malformation. Chromosomal analysis showed that the fetus was male and abortion was therefore induced in the 21st week. The fetus showed no signs of external or internal malformations.

Comment

Cyproterone acetate in high dosage has teratogenic effects with disturbed sexual differentiation in male laboratory animals.² In a study of low dose cyproterone acetate during pregnancy no obvious anatomical malformations occurred but adult animals had endocrine functional disturbances with partial androgen insensitivity.⁴ In man little is known about fetal outcome after treatment with cyproterone acetate during pregnancy. Low dose exposure (2 mg; Diane) did not induce any malformations in a male infant.⁵

Schering Company (personal communication) has information from 16 pregnancies, all normal, in which there was low dose exposure. The company is also aware of four pregnancies exposed to the Hammerstein regimen. Two normal girls were born after treatment with 50 mg cyproterone acetate daily during the first 10 and 18 weeks of pregnancy, respectively. Two boys were born after exposure to 100 mg cyproterone acetate daily but little is known about these pregnancies. One of them occurred in Britain (treatment for 20 weeks, child probably normal) and the other in the United States (data inadequate but possible exposure for six weeks, outcome unknown) (Schering Company, personal communication).

In our patient we considered that the male fetus was at particular risk of genital malformation because of the high dose and prolonged exposure to the antiandrogenic drug during a sensitive period of fetal life. Postabortal examination of the fetus, however, showed no sign of anatomical malformation, so the abortion may have been unnecessary. Nevertheless, normal genital anatomy does not exclude the risk of disturbed sexual function in adult life.⁴ The question what to advise should another patient be exposed to cyproterone acetate during early pregnancy remains open. Our case and the few available data from other patients suggest that apparently normal development may occur in a male fetus and that induced abortion may therefore not be absolutely necessary.

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Coagulation studies in cases of intrauterine death: overkill?

In many obstetric units coagulation profiles are performed on all women with abruptions, moderate to severe pre-eclampsia, and intrauterine fetal death. While not doubting their value in the first two cases, we wondered whether the routine use of these tests in all cases of intrauterine fetal death can be justified.

Patients, methods, and results

All stillbirths at Dudley Road Hospital in 1980-5 were studied. Those associated with conditions known to cause coagulation abnormalities—that is, abruptions and pre-eclampsia—were excluded. This left a total of 91 intrauterine deaths, for 82 of whom notes were traced and any coagulation investigations noted. In 77 women we were able to estimate the maximum possible time that the fetus had been dead (table).

Twenty women had no coagulation studies performed: 12 of these delivered soon after arrival, giving no time for any investigations. The remaining 62 women had some coagulation investigations. Fifty eight had their activated partial thromboplastin time measured. The range was 23-45 seconds (mean (SD) 34 (6.7) seconds). Fifty six had a prothrombin test. The range was 11-14 seconds; this was not appreciably different from control values. Fifty four had a platelet count. The range was $130-575 \times 10^9/l$ (mean 280 (98) $\times 10^9/l$). Twenty one had fibrin degradation products measured. Eighteen patients had a result of ≤ 10 mg/l, and three of >10 mg/l <40 mg/l. Fifteen had their fibrinogen concentrations measured. The range was 2.5-6.0 g/l (mean 3.7 (1.0) g/l). None of these values was clinically important or differed significantly from the normal

Approximate maximum time the fetus had been dead in utero

Time (days):	1	2-4	-7	-10	-13	-16	-19	-22	-28
No of patients:	19	15	22	2	1	8	1	8	1

range. None of the 82 patients had any symptoms that could be associated with coagulation problems.

Comment

During the 1950s diagnosing fetal death with certainty was sometimes difficult. Spontaneous labour was awaited, which resulted in some fetuses remaining dead in utero for many weeks. In reviewing 14 papers from this era (over 133 cases) we found only two cases in which coagulation abnormalities occurred within five weeks after presumed fetal death, one after four weeks¹ and one after 14 days.² A case was described in an unbooked patient 10 days after "movements ceased," but the clinical history and examination suggested a much longer period of intrauterine death.³

One study reported more than 100 women who had retained a dead fetus in utero for more than one week, 50 of them for longer than five weeks (range 5-19 weeks, mean eight weeks).⁴ Fibrinogen concentrations started to fall after three to four weeks, but this was not clinically important before five weeks. After five weeks about 25% of women developed defective haemostatic function. Hodgkinson *et al* found a clinically unimportant fall in fibrinogen concentration within two weeks, which recovered only to fall again weeks later.⁵ This fall in fibrinogen concentration might be similar to that which occurs after normal delivery.

Thus other reports suggest that within three weeks after fetal death no abnormalities are found by coagulation studies and no clinically important abnormalities are likely before five weeks; our data support these statements. The diagnosis of intrauterine death can now be made with certainty, and prostaglandins and oxytocin can reliably and safely empty the uterus. Consequently it is rare for dead fetuses to be left in utero for any length of time, as our study confirms. An on call "clotting screen" costs about £11, but the resulting delay in starting epidural anaesthesia and further distress to the mother must be considered.

We believe that routine coagulation screening when the fetus has been known to be dead for three weeks or less is not necessary from an obstetric or anaesthetic viewpoint. A policy of performing such investigations on those women with a fetus in utero for longer than this time, or where clinical indications or doubts exist, gives a good safety margin and would be more rational.

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Primary nocturnal enuresis in children with vesicoureteric reflux

Despite numerous reports on the prevalence of genitourinary tract abnormalities in enuretic children¹⁻³ there is no information about the prevalence of primary nocturnal enuresis in children who have anatomic abnormalities of the urinary tract. We evaluated the prevalence of primary nocturnal enuresis in 67 children who had vesicoureteric reflux.

Patients, methods, and results

Fifty patients with unilateral and 17 with bilateral primary vesicoureteric reflux were investigated (41 girls, 26 boys; age range 5-14, mean 8.1 years; 49 children were aged 9 or under). The severity of reflux was graded from I to V according to the international classification; 49 patients had grade I or II reflux and 18 grades III to V. Thirty four children had experienced a recent urinary infection and had been investigated for the first time by voiding cystourethrography. The remaining 33 children had a history of urinary infection between the age of 2 weeks and 3 years; they had undergone voiding cystourethrography at least twice as part