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Case report

Ovarian failure in a young woman with galactosaemia

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Classical galactosaemia is an autosomal recessive condition characterised by an inactivity of galactose –1– phosphate uridyl transferase. This results in elevated levels of galactose and its metabolites which have been associated with damage to the lens, liver, brain and renal tubule. Only recently has it been appreciated that the ovaries may also be affected.

The patient described in this report was treated for galactosaemia from six weeks of age and investigated at 17 years with primary amenorrhoea. This patient demonstrates an unusual cause for hypergonadotrophic hypogonadism, namely galactosaemia, and is thought to be the first reported in Northern Ireland.

Case History. The patient presented at age four weeks with abdominal distension secondary to ascites and hepatosplenomegaly. She was not jaundiced. Reducing sugars were detected in her urine and the diagnosis of galactosaemia was confirmed by finding low levels in the erythrocytes of galactose –1– phosphate uridyl transferase (0.04 units/g Hb, normal range 14·25 units/g Hb) and an intermediate value in her parents (7.76 units/g Hb and 5.14 units/g Hb in mother and father respectively). A lactose-free diet was started at age six weeks.

At age 17 she was referred to the gynaecological endocrine clinic complaining of primary amenorrhoea. On examination she was 160 cm tall, weighed 50 kg, had stage 1 breast development,[1] stage 2 pubic hair development[1] and infantile external genitalia. Serum gonadotrophins were high (LH 50U/1, FSH 85U/1) and serum oestradiol was below the detection limit for the assay (60 pmol/l). This pattern of hypergonadotropic hypogonadism was demonstrated on three occasions indicating ovarian failure as the cause of her hypogonadism. At

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laparatomy there was a small uterus and normal fallopian tubes with bilateral streak ovaries. Histological examination of one complete ovary showed ovarian stroma and a small group of hilar cells. No follicles were present.

DISCUSSION

In the last few years reports have appeared describing ovarian failure associated with galactosaemia.[2, 3, 4, 5] This is not an invariable association since normal pregnancy in galactosaemic women has also been well documented.[3, 5, 6, 7] Galactosaemia is usually diagnosed in the first few days of life with feeding difficulties, diarrhoea, dehydration and a variable degree of jaundice. Our case was rather unusual, presenting at four weeks of life with abdominal distension due to ascites. This atypical presentation allowed a greater post-natal exposure to galactose than usual. The appearance of the ovarian biopsy in this case was similar to that of a streak ovary, no follicles being detected. It is not possible to say if this represents failure of ovarian development or regression of developed follicles. Kaufman et al showed an increased incidence of ovarian failure with increasing age at the time of diagnosis, suggesting that galactose or one of its metabolites has a direct toxic effect on the ovary and that early treatment may therefore improve the prognosis.[3] There is experimental evidence that this is so, since a toxic effect on ovarian development has been seen in animals fed a high galactose diet.[8] However, Steinmann et al were unable to show an association between age at the time of diagnosis and ovarian failure and suggested that self-intoxication by endogenously produced galactose may lead to ovarian damage.[9] They reported one child who subsequently developed ovarian failure even though she had apparently never been exposed to galactose in utero or in post-natal life. Robinson et al reported a case of hypergonadotrophic hypogonadism in a galactosaemic patient who was commenced on a galactose-free diet at birth.[10] Ovarian biopsy in this case revealed only a reduced number of primary follicles. These observations suggest that ovarian damage due to galactose may have occurred in utero. The authors, however, do not comment on the patients' dietary adherence and there remains the possibility that post-natal exposure to galactose may have occurred.

Alternative mechanisms of ovarian failure have also been suggested. Since the carbohydrate moieties of normal gonadotrophins contain galactosamine and galactose, it has been suggested that ovarian damage may be due to a structural aberration of either LH or FSH in the galactosaemic patient.[3] However, this seems unlikely since gonadotrophins appear to have normal bioactivity in galactosaemic patients.[3] The consensus of evidence is that ovarian damage is related to exposure to galactose. In order to reduce the risk of toxic damage to the ovaries and other tissues in pre-natal and post-natal life, galactose consumption should be avoided by those known to be at risk of conceiving a galactosaemic infant. Even with this precaution, one case of ovarian failure has been reported[9] and we must therefore await further evidence before the value of galactose restriction can be definitively stated. However, at present, the evidence is such that those females with normal ovarian function who either have galactosaemia or are known carriers, should be made aware of the risk to their offspring and should maintain a strict lactose-free diet while at risk of conception. This may reduce the risk of fetal ovarian damage and subsequent failure. Strict compliance to a lactose-free diet for female galactosaemic children should be advised from birth. Galactosaemic females with primary amenorrhoea should be screened promptly to exclude gonadal failure.

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