Adrenogenital syndrome and buphthalmos

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The adrenogenital syndrome is a rare genetic disorder in which there is a failure of one of the enzymes involved in the production of corticosteroids by the adrenal cortex. The condition is an autosomal recessive. Buphthalmos is an uncommon ocular condition, and it would be surprising if buphthalmos and the adrenogenital syndrome were to co-exist in the same patient. This paper describes two such patients.

The synthesis of physiological corticosteroids in the adrenal cortex begins with the hydroxylation of progesterone to form 17-hydroxyprogesterone by the action of 17-hydroxylase. The 17-hydroxyprogesterone is converted to compound S (11 de-oxy 17-hydroxy-corticosterone) by 21-hydroxylase. Finally, the compound S is converted to cortisol by the action of 11-hydroxylase. The most important cause of the adrenogenital syndrome is 21-hydroxylase deficiency, and affected patients present shortly after birth with vomiting and dehydration associated with electrolyte deficiency. As a result of the block in the normal production of the corticosteroids, there is a deficiency of compound S and cortisol, and possibly of aldosterone. Compensatory overproduction of ACTH occurs; as a result there is overproduction of progesterone and its end-product pregnenediol. Excess production of androgens may cause virilization in the female at birth, but in the male child the condition may not be so easily diagnosed by virilization criteria. Treatment, which has to be instituted immediately, consists of the use of corticosteroids of glucocorticoid and mineralocorticoid types. The aim of treatment is to replace the deficient endogenous corticosteroids and suppress the excess ACTH production. The dose of steroids given is monitored by the clinical responses, and by frequent estimation of the serum electrolytes and excretion of urinary 17-hydroxy-ketosteroids, and 17-ketosteroids.

Case reports

Case 1, a male born on February 10, 1964, by breech delivery. The birth weight was 4 lb. 6 oz. He was born of unrelated parents, and was a member of a dizygous pair of twins. The twin sister is also affected with adrenogenital syndrome. There are four other siblings (2 male and 2 female), and one elder brother also has adrenogenital syndrome.

The patient presented with collapse and failure to thrive one week after birth, and was treated with 9- α -fluorocortisone, DOCA, and dexamethasone. On April 4 a moon-faced appearance was noted. A clinical note of prominent eyes was made on June 2. On August 7 he was referred to the Eye Department with an irritable right eye.

Examination

He was examined on August 13 under Pentothal and nitrous oxide anaesthesia, with scoline as muscle relaxant, and positive pressure ventilation. The right eye was described as having buphthalmos, with corneal oedema, deep anterior chamber, and an intraocular pressure of 66 mm. Hg (Schiotz). The corneal diameters were not measured.

Treatment

Diamox 65 mg. was given four times a day and gutt. pilocarpine 2 per cent. and eserine 0.5 per cent. three times a day to both eyes. On August 16, a right goniotomy was carried out. Later the left eye showed a hazy cornea and on September 9 a left Scheie's operation was carried out. On November 11, the right eye became cloudy; a diagnosis of recurrence of buphthalmos was made and on November 18 a right Scheie's operation was carried out. Thereafter the right cornea remained clear.

Progress

Examination under general anaesthesia on October 10, 1965, showed the ocular tension to be 15 mm. Hg (Schiötz) in both eyes, with cupping of the right optic disc. On March 17 the right corneal diameter was 13.5 mm. and the left 11.5 mm. The ocular tension was 18 mm. Hg (Schiötz) in both eyes, with a cupped right disc.

On August 15, 1966, a right convergent squint was noted, and on May 8, 1968, a right medial rectus recession was carried out. On December 4 the applanation tension was 17 mm.Hg in the right eye and 15 mm.Hg in the left.

On February 28, 1969, when the child was 4 years old, the visual acuity was recorded as 6/60 in the right eye and 6/6 in the left.

Case 2, a male born at term on May 20, 1967, of healthy parents weighed 8 lb. 10 oz. at birth. There is one healthy sibling, but one child died at 10 days of age and the *post mortem* examination showed enlarged adrenal glands.

At 7 days he failed to feed, looked lethargic, and began to lose weight. The serum electrolytes showed potassium 9.8 mEq/litre and sodium 125 mEq/litre. The genitalia were normal. He was treated with hydrocortisone, cortisone, and dexamethasone. The serum potassium fell from 9.8 to 4.8 mEq/litre, and the serum sodium rose from 128 to 134 mEq/litre. The ketosteroid excretion fell from 5 to 1.4 mg./24 hrs, and the 17-hydroxycorticosteroids from 2.9 to 0.8 mg./24 hrs. He was sent home at 2 months of age on dexamethasone 0.5 mg. daily, 9- α -fluorohydrocortisone 0.05 mg. daily, and salt 5 g. daily. A Cushingoid facies was noted at 5 weeks of age. Subsequently, on September 13, 1969, hydrocortisone 10 mg. three times a day was substituted for dexamethasone.

On June 19, 1970, he was referred to the Eye Department with an irritable left eye and buphthalmos was diagnosed. He was treated with Diamox 65 mg. four times a day and gutt. pilocarpine 2 per cent. twice a day to both eyes.

Examination

He was examined under general anaesthesia (using nitrous oxide, scoline and positive pressure ventilation) and hazy corneae and deep cupping of the left optic disc were observed. The applanation tension was 14 mm.Hg in the right eye and 20 mm.Hg in the left. The corneal diameters were 14 mm. right and 15 mm. left. A 24-hr urinary amino acid estimation showed slight generalized amino aciduria.

Progress

On July 8, 1970, the applanation tension was 25 mm.Hg in the right eye and 28 mm.Hg in the left. A left Scheie's operation was then carried out. Examination under general anaesthesia on July 15 showed an intraocular pressure of 38 mm.Hg in the right eye and a right Scheie's operation was carried out on the same day.

Post-operatively the pressure has remained controlled and both blebs are draining. A gonioscopy under general anaesthesia using Worst's lens on September 9, 1970, showed open angles, with patchy depigmentation of the peripheral iris. Vascular arcades were prominent on the anterior iris surface. Schlemm's canal could be seen to be full of blood in the left eye.

Discussion

Buphthalmos may be associated with local ocular abnormalities, such as persistent primary hyperplastic vitreous, Axenfeld's anomaly, and aniridia; alternatively, buphthalmos may be associated with the phakomatoses, such as the Sturge-Weber syndrome, or neurofibromatosis. The only common metabolic disorder associated with buphthalmos is Lowe's syndrome of buphthalmos, amino aciduria, and mental deficiency. It is interesting to note that the second patient showed a generalized slight amino aciduria. Franceschetti (1962), however, found amino aciduria in 46.4 per cent. of 63 cases of buphthalmos. The association of buphthalmos with adrenogenital syndrome does not appear to have been described previously.

The incidence of buphthalmos was stated by Duke-Elder (1969) to be between 0.01–0.04 per cent. of ophthalmic patients. On the other hand Childs, Grumbach, and Van Wyk (1956) found the incidence of adrenogenital syndrome to be 1 in 67,000 live births in the State of Maryland, U.S.A. Buphthalmos and adrenogenital syndrome are therefore rare conditions unlikely to co-exist by chance in the same patient, but as they have been found in two patients in the same area the occurrence is unlikely to be fortuitous. That the association appears not to have been described earlier is due to the fact that, until the advent of systemic steroids and modern biochemistry, patients with congenital adrenogenital syndrome died shortly after birth, before the onset of buphthalmos could be observed.

Two possibilities occur: that the relationship between buphthalmos and adrenogenital syndrome is genetic, or that the occurrence of buphthalmos in cases of adrenogenital syndrome is due to treatment with systemic steroids.

The latter theory, that the buphthalmos is due to the administration of systemic steroids, is at first sight attractive. However, most authors agree that the rise in intraocular pressure is much less marked after treatment with systemic steroids than after the use of local steroids. Williamson, Paterson, McGavin, Jasani, Boyle, and Doig (1969) examined 148 patients with rheumatoid arthritis who were treated with systemic steroids and found only one case of steroid glaucoma. Bernstein and Schwartz (1962), after examining 48 patients receiving long-term steroid therapy, concluded that there was a small but statistically significant increase in intraocular pressure. Buphthalmos does not appear to have been described earlier with systemic steroid treatment, but Hofmann and Hauser (1964) described a case of juvenile glaucoma in a 10-year-old boy who was given systemic steroids for lupus erythematosus. Duke-Elder (1969) goes so far as to suggest that, if glaucoma occurs with local steroid therapy, systemic therapy may be substituted for local therapy.

It seems, therefore, that there is probably a genetic relationship between buphthalmos and adrenogenital syndrome, especially as the former, like the latter, is frequently inherited by means of a recessive gene. Patients with adrenogenital syndrome do not show other genetically related defects, apart from abnormalities of the urogenital tract.

From a practical point of view it is of little consequence whether the buphthalmos is due to steroid overdosage or to a genetic abnormality; in both cases the dose of steroid given should be as low as is compatible with the child's health and vitality. All who have the responsibility for looking after cases of adrenogenital syndrome should be aware of buphthalmos as a possible complication.

Summary

Two instances of buphthalmos occurring in cases of adrenogenital syndrome are described. It is suggested that these conditions are associated, and that the association is probably genetic.

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