

## ADRENAL HYPERPLASIA AND CONGENITAL GLAUCOMA IN A FAMILY: REPORT OF A RARE CASE

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Congenital adrenal hyperplasia (CAH) is a common recessively inherited disorder of cortisol biosynthesis due to a deficiency of one of the enzymatic activities necessary for its synthesis. It has an average incidence of 1:5000,<sup>1</sup> the most common of which is 21-hydroxylase deficiency which represents about 95% of involved cases.<sup>1</sup> It is usually presented by salt-losing crises in 75% of classic cases, with ambiguous genitalia in females and precocious puberty in males.

Primary congenital glaucoma is also a recessively inherited disorder. A significant proportion of cases develop because of a defect in the permeability of the trabeculum to aqueous humor.<sup>2</sup> It has an average incidence of about 0.03%,<sup>3</sup> and it may lead to blindness in spite of medical and surgical treatment in very severe cases. To our knowledge, this is the third reported case worldwide with both of these disease combinations.<sup>4</sup>

### Case Report

A 5½-year-old girl, a product of full-term normal delivery with a birth weight of 3.4 kg., length 55 cm and head circumference of 35 cm, was found at birth to have severe bilateral congenital glaucoma and ambiguous genitalia. The deformed genitalia was in the form of large clitoris about 3 cm long, fused labioscrotal folds and no palpable gonads with normal 46 XX chromosomes. Pelvic ultrasound showed normal uterus and ovaries, and had increased urinary sodium. At two weeks of age, her serum 17-OH-progesterone was 22 ng/mL (normal <1.1 ng/mL), ACTH of twice the normal value and aldosterone of 104 ng/dL (normal 1-160 ng/dL).

The patient was treated with hydrocortisone 20 mg/m<sup>2</sup>/day and fludrocortisol (Flornif) with mild episodes of hyponatremia and hyperkalemia. Her blood pressure was normal, but there was no progress in the amount of virilization. She had normal growth parameters, and her

weight and height were around the 25th centile with normal bone age. At five years of age, while she was off steroids for 24 hours, she had synacthen stimulation test to confirm the diagnosis of 21-hydroxylase deficiency: pre-synacthen test serum 17-OH progesterone was 0.22 ng/mL, serum cortisol <0.036 µg/dL (normal morning: 6.3-19.4). Sixty minutes post-synacthen, her serum 17-OH progesterone went up to 4.9 ng/mL, serum cortisol <0.036 µg/dL, and 11 desoxycortisol (compound-s) <0.5 ng/mL (normal <8), testosterone <0.02 ng/mL (normal, 0.03-0.32). With regards to her eye problem, she had severe bilateral glaucoma and had three operations, unfortunately, she lost the vision in her left eye, and had to receive anti-glaucoma treatment for the right eye.

### Family History

The patient had first-degree consanguineous parents and three other affected members of her family (Figure 1). A 14-year-old brother who had severe bilateral congenital glaucoma became completely blind in both eyes after several operations had failed. He had normal blood pressure, normal growth parameters and normal virilization. A 10½-year-old sister also had ambiguous genitalia with large clitoris, labioscrotal fusion, and no palpable gonads. Another child who was a first cousin died at four months of age at home. The child also had ambiguous genitalia, probably following salt-losing crises, most likely with congenital adrenal hyperplasia.

### Discussion

To our knowledge, this is the third case reported worldwide with both congenital adrenal hyperplasia (21-hydroxylase deficiency) and primary congenital glaucoma. The first two cases were reported by Clements.<sup>4</sup> The most common type of congenital adrenal hyperplasia is 21-hydroxylase deficiency. Its gene is located in the short arm of chromosome 6 (6p21.3).<sup>6</sup> It has three types of presentation: classical salt-losing, classical non-salt losing, and non-classical late-onset type. In the first two types, girls may present with ambiguous genitalia and boys with precocious puberty. The third type, which is non-classical late onset, presents usually with hirsutism, amenorrhea and clitoromegaly. The mainstay of diagnosis is elevated 17-HO-progesterone level. In the salt-losing type, hyponatremia and hyperkalemia are commonly found at diagnosis, in

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FIGURE 1. The family pedigree.

addition to elevated serum renine and androgens levels. The golden standard therapy is steroids (hydrocortisone, prednisone, or dexamethasone) and fludrocortisone (in salt-losing type), and clitroplasty and vaginoplasty in virilized females.

Congenital glaucoma is also an autosomal recessive disease with evidence for genetic heterogeneity.<sup>6,7</sup> Its gene is located on the short arm of chromosome 2 (2p21) GLC3A and on 1p36.2-p36.1 GLC3B.<sup>8-11</sup> The diagnosis is basically clinical and the treatment is primarily surgical. The aim is either to create a more normal anterior chamber angle, to create an exit site for aqueous fluid to exit the eye, or to reduce aqueous fluid production. Long-term medical therapy may be necessary as well.<sup>3</sup>

We regard this rare combination as a coincidental occurrence, since the consanguinity rate is high in our community and these diseases are recessively inherited disorders. This is also supported by other members of the family being affected by these diseases, namely congenital glaucoma (her brother) or congenital adrenal hyperplasia (her sister). Further studies to identify the type of mutations in this family may turn out to be interesting.

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