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Substitution therapy in adult patients with congenital adrenal hyperplasia

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Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive inherited disorders caused by defective steroidogenesis. Steroid 21-hydroxylase deficiency (21OHD) is its most prevalent form, accounting for over 90% of all cases. Clinically classic 21OHD is characterised by glucocorticoid deficiency and adrenal androgen excess with (salt wasting form) or without (simple virilising form) additional mineralocorticoid deficiency. Life-saving glucocorticoid substitution therapy has been available since the 1950s and enables long-term survival, and potentially, a good quality of life. However, care of adult patients with classic congenital adrenal hyperplasia is challenging for two main reasons: firstly, there is no glucocorticoid preparation available mimicking circadian cortisol release and adaptation to stress and secondly, management of adult patients is still in its infancy. There is no evidence-based treatment and experienced centres, taking care of larger patient cohorts, are only emerging. In this article we aim to guide physicians on the treatment and monitoring of adult patients with 21OHD, based on the clinical studies available and our own clinical experience.

Background

Congenital adrenal hyperplasia is one of the most common genetic diseases affecting approximately 1:10,000 to 1:20,000 newborns [32,41,57]. It comprises a group of defects in adrenal steroidogenesis

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with subsequent cortisol deficiency caused by mutations in genes encoding one of the enzymes or cofactors for cortisol biosynthesis. As mutations in the gene *CYP21A2*, encoding for the enzyme 21-hydroxylase, are by far the most common affecting more than 90% of all patients, this article will focus on 21OHD. So far, over 100 mutations causing 21OHD have been described, however only 10 mutations account for 90% of all cases [29,32].

Steroid 21-hydroxylase converts 17-hydroxyprogesterone into 11-deoxycortisol and progesterone into 11-deoxycortisone [34]. Both are glucocorticoid and mineralocorticoid precursors for the biosynthesis of cortisol and aldosterone. Excessive steroid precursor accumulation prior to the enzyme block is converted to androgen precursors. The lack of cortisol leads to increased ACTH secretion by the pituitary, stimulating adrenal growth and thereby resulting in adrenal hyperplasia. Furthermore it increases steroid precursor accumulation leading to adrenal androgen excess. Clinically, female patients with classic 21OHD suffer from prenatal virilisation of the external genitalia, and both sexes are at risk for life-threatening adrenal crises during their entire life. Suboptimal treatment in childhood and adolescence causes short stature and disturbance of pubertal development. In adults, bone, metabolic and cardiovascular health may be compromised and adrenal neoplasia and testicular adrenal rest tumours are common phenomena [3,10,12,17,19,20,22,31,48,56,57,59,61,62,68,69,77]. Many patients also suffer from reduced fecundity [11,58,73].

Traditionally we distinguish between classic and non-classic 21OHD. Classic 21OHD is defined by cortisol deficiency with the need of life-long hormone substitution. Furthermore, classic 21OHD can be divided into the severe salt-wasting form which is also lacking mineralocorticoid synthesis and the simple virilising form with sufficient aldosterone synthesis. Non-classic 21OHD is characterised by a partial enzyme defect resulting in sufficient cortisol biosynthesis but symptoms due to enhanced precursor accumulation prior to the enzyme block. This results in elevated 17-hydroxyprogesterone and 21-deoxycortisol concentrations converted into adrenal androgens and androgen precursors with subsequent mild androgen excess. It is important to note that these classifications are somewhat arbitrary. In reality disease severity is a continuous spectrum defined by the underlying residual enzyme function. An enzyme function of about 1–2% is sufficient to prevent salt-wasting, whereas a residual enzyme activity of 20–50% function restores cortisol and aldosterone biosynthesis.

Steroid 21OHD follows an autosomal recessive trait implying that two alleles need to be affected in order to be disease causing. A good genotype–phenotype correlation of about 80% has been described [5,30,33,36,50,72,74,80]. This mainly holds true for children with the severe salt wasting form of CAH and the non-classic form, whereas for the simple virilising form and in adults a wide phenotypical variability has been observed [37,50]. Most of the patients are compound heterozygous, i.e. they have two different mutations one on each allele. In such a constellation generally the less affected allele is responsible for the phenotype [32].

Since the introduction of newborn screening programmes in almost all Western countries, classic 21OHD is diagnosed in the first week of life leading to timely initiation of life-saving glucocorticoid therapy. Thanks to neonatal screening, nowadays salt-wasting crises in the first few weeks of life rarely happen. Non-classic 21OHD typically is not detected by neonatal screening, but rather, because of symptoms due to androgen excess such as premature pubarche, it is sometimes detected in childhood, and more commonly in adolescence or young adulthood due to acne, hirsutism, menstrual disorders and subfertility [39,45,49]. Some patients with non-classic 21OHD however, may not even be diagnosed or require treatment during their entire lifetime, in particular most male patients with non-classic 21OHD remain asymptomatic and undiagnosed [47].

Treatment in classic 21OHD is required to restore glucocorticoid and mineralocorticoid deficiency as well as to correct adrenal androgen excess. Optimal glucocorticoid and mineralocorticoid substitution in theory should avoid disease associated comorbidities and enable good quality of life and normal life expectancy. This goal is not yet reached, as patients with classic 21OHD show increased comorbidities [3,10,12,17,19,20,22,31,48,56–59,61,62,68,69,77] and increased mortality [21]. In non-classic 21OHD, treatment “only” aims at resolving symptoms caused by adrenal androgen excess, typically hormone substitution is not necessary. For treatment in non-classic 21OHD glucocorticoids can be used, but therapeutic goals can also be achieved by cosmetic measures, antiandrogens as well as by anti-androgenetic oral contraceptives [40,79].