Review Article

Congenital adrenal hyperplasia: Treatment and outcomes

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ABSTRACT

Congenital adrenal hyperplasia (CAH) describes a group of autosomal recessive disorders where there is impairment of cortisol biosynthesis. CAH due to 21-hydroxylase deficiency accounts for 95% of cases and shows a wide range of clinical severity. Glucocorticoid and mineralocorticoid replacement therapies are the mainstays of treatment of CAH. The optimal treatment for adults with CAH continues to be a challenge. Important long-term health issues for adults with CAH affect both men and women. These issues may either be due to the disease or to steroid treatment and may affect final height, fertility, cardiometabolic risk, bone metabolism, neuro-cognitive development and the quality-of-life. Patients with CAH should be regularly followed-up from childhood to adulthood by multidisciplinary teams who have knowledge of CAH. Optimal replacement therapy, close clinical and laboratory monitoring, early life-style interventions, early and regular fertility assessment and continuous psychological management are needed to improve outcome.

Key words: Bone health, cardio-metabolic risk, congenital adrenal hyperplasia, fertility, final height, glucocorticoids, neurocognitive outcome, quality-of-life

Introduction

Congenital adrenal hyperplasia (CAH) refers to a group of inherited autosomal recessive disorders that cause a deficiency in an adrenal enzyme, resulting in altered cortisol and aldosterone secretion. The loss of negative feedback inhibition by cortisol leads to increased hypothalamic-pituitary-adrenal axis activity and subsequent hyperplasia of the adrenal gland. The most frequent CAH variant, accounting for 95% of all affected patients, is 21-hydroxylase deficiency (21-OHD) and because of mutations in the CYP21A2 gene.

Different forms are recognized in CAH because of 21-OHD: Classic CAH, the most severe form comprises both salt-wasting and simple virilizing forms and the non-classic (NC) form that may be asymptomatic or associated with signs of postnatal or even adult onset androgen excess. The classic form has a frequency of about 1 in 10,000 to 1 in 15,000 in the general population, whereas the NC form is more common with an estimated incidence of about 1 in 1000.

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.119491

Treatment of CAH

Glucocorticoid (GC) and mineralocorticoid (MC) replacement therapies are the mainstays of treatment of CAH. According to the pediatric consensus statement, recommended GC replacement for children is with 10-15 mg/m^2/day of hydrocortisone divided into 3 daily doses. No such consensus exists for the management of adults with CAH. If a patient is in good control during adolescence taking hydrocortisone, he could continue this regimen. However, a minimum amount of long-acting GC may be added if adequate control is not achieved with hydrocortisone alone.[1,2]

All classic CAH patients should receive fludrocortisone at diagnosis and during the 1st years of life. The use of

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fludrocortisone in simple-virilizing CAH is recommended and allows management with lower doses of GC. Later, the need for on-going MC treatment should be assessed individually.[1,2]

Levels of 17-hydroxyprogesterone androstenedione and plasma renin activity are used to evaluate the adequacy of therapy in conjunction with clinical signs and symptoms of over-or under-treatment.

Long-term Outcome

With the availability of GC replacement allowing patients to reach adulthood, long-term effect of this disease and its treatment have become an important issue. Data concerning CAH adults have reported conflicting results. Most of the problems relate to final height, fertility, cardiometabolic risk, bone metabolism and psychoneurological issues.

Height Outcome

Evidence derived from observational studies suggests that patients with CAH due to 21-OHD often reach a reduced final height compared with their parentally determined target height. Treatment of CAH is often suboptimal and results of combination of hyperandrogenism and hypercortisolism states, both may compromise growth. Two extremely critical periods in this treatment include early infancy and puberty. In addition, central precocious puberty may develop in this population due to androgen activation of the hypothalamic-pituitary-gonadal axis, thus exacerbating premature epiphyseal fusion. Many other factors have been suggested as being additional predictors of growth.

Data related to the indications, efficacy and safety of height-enhancing drugs is limited. Patients with CAH can reach a final height that is within their genetic potential with traditional medical treatment. However, alternative protocols should be considered in a subset of CAH patients with poor height prognosis due to poor hormonal control, advanced skeletal maturation and central precocious puberty onset.[3,4]

Bone Mineral Status

Data are conflicting concerning the effect of long-term GC replacement therapy on bone mass and bone metabolism in patients with CAH. In adults, bone mineral density (BMD) has been reported to be normal, decreased or even increased. Nevertheless, the overall conclusion is in favor of preservation of bone integrity in patients on standard GC therapy (10-20 mg/m^2). Thus, unless there is a clinical suspicion of previous over-treatment with GCs; routine bone density measurements are unnecessary in the young adult with CAH. However, if there is evidence of over-treatment with GCs, BMD measurement is justified and osteoporosis prophylaxis such as physical activities, calcium and vitamin D intake could be considered.[4]

Similarly, markers of bone formation, especially osteocalcin, are reported to be low in adult CAH.[5] Although these markers are not recommended for use in diagnosis of osteoporosis, they seem to be useful for predicting future bone loss.

Cardiovascular Risk and Metabolic Profile

More recently, attention has turned to cardiovascular risk factors in adults with CAH. Overall, studies demonstrate an increased prevalence of obesity, body composition alterations, hypertension, dyslipidemia, carbohydrate metabolism disorders and insulin resistance. More interestingly, some markers of subclinical atherosclerosis, such as a non-dipper status, endothelial dysfunction and increased intima-media thickness, were reported; even in children.[6,7]

It has been suggested that patients with CAH develop an unfavorable cardiovascular risk profile either because of the existence of hyperandrogenism in untreated or undertreated patients or because of the supra-physiological doses of GCs used to suppress androgen levels to normal values. Other factors, such as adrenomedullary dysfunction and alteration in leptin axis, may promote metabolic disorders and cardiovascular risk factors.

Female Fertility

Traditionally, reduced fertility rates have been reported in women with classic CAH, especially in those with the salt-wasting phenotype.

Subfertility in females with classic CAH is due to several contributing factors, including androgen excess, adrenal progesterone hypersecretion, consequences of genital reconstructive surgery, secondary polycystic ovaries syndrome and psychosexual factors.[8]

In contrast to this sub-fertility, pregnancies are commonly normal and uneventful. Thus, fertility rather than pregnancy rates seem to be reduced in women with classical CAH compared to the general population.

More recent reports show a significant increase in fertility rates, even among patients with classic CAH, possibly as a

result of earlier treatment of CAH, improved compliance with therapy and surgical advances in genital reconstruction.

Male Fertility

Previous studies showed that male patients with CAH have reduced fertility. These patients may develop hypogonadotropic hypogonadism due to high levels of steroids, which suppress the hypothalamic-pituitary-gonadal axis. More frequently, men with CAH have infertility because of testicular adrenal rest tumors (TARTs). Most authors now agree that TARTs develop from ectopic remnants of intra-testicular adrenal tissue stimulated by adrenocorticotropic hormone (ACTH) hypersecretion. However, such tumors were also reported in adequately or even overtreated patients with suppressed ACTH levels and other factors such as MC replacement adequacy could be involved in this tumorogenesis.

TARTs may be prevalent in up to 94% of CAH adults and may already appear during childhood. They can affect testicular function directly through mechanical compression of adjacent seminiferous tubules and/or indirectly (paracrine effect) via local steroid production which may be toxic to the Leydig cells and germ cells. Poor hormonal control and inadequate suppression of ACTH secretion are dominant etiological factors in the development of TARTs. Early intensifying GC therapy may lead to tumor regression and prevent fertility problems in CAH males.[8,9]

Neuro-cognitive Outcome

CAH constitutes an interesting natural model for studying interactions between hormones and the brain. Some studies suggest that patients with CAH who experienced adrenal crises are at risk for cognitive impairment. In addition, few studies have reported brain magnetic resonance imaging abnormalities affecting white matter signal, temporal lobe and amygdala/hippocampus structure and function.[10] The mechanisms involved in their pathogenesis seem related to hormonal imbalances during brain development and exposure to excess exogenous GCs. Clinical implications of such lesions remain unclear but could precede cognitive dysfunction. More extensive studies are required to define better the relationships between brain involvement and different CAH phenotypes and treatment regimens.

Quality-of-life

Recent studies, in contrast to previous observations, have demonstrated a reduction in the quality of life in patients with CAH, particularly in its social dimensions. Patients with CAH were more often single, were less sexually active, displayed more negative body image and had more negative self-image with regard to self-confidence, sociability and social acceptance. There are many factors that influence quality-of-life in patients with CAH, such as genital surgery procedure, mutation severity, short stature, increased weight and hirsutism.

Adrenal Tumors

The chronic enlargement of the adrenal glands in CAH is associated with increased prevalence of adrenal tumors, including massive myelolipomas.

Myelolipomas are benign non-functioning tumors, consisting of adrenal, adipose and hematopoietic tissues. Although the precise pathogenesis of myelolipomas remains unclear, prolonged stimulation with high levels of ACTH or adrenal androgens are assumed to have a causative role.

Conclusion

We conclude that adult patients with CAH have a number of issues due either to the disease or to its treatment. Most of the problems relate to final height, fertility, cardiometabolic risk, bone metabolism and psychoneurological issues. Patients with CAH should be regularly followed up from childhood to adulthood by multidisciplinary teams who have knowledge of CAH. Optimal replacement therapy, close clinical and laboratory monitoring, early life-style interventions, early and regular fertility assessment and continuous psychological management are needed to improve outcome.

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Cite this article as: Kamoun M, Feki MM, Sfar MH, Abid M. Congenital adrenal hyperplasia: Treatment and outcomes. Indian J Endocr Metab 2013;17:S14-7.

Source of Support: Nil, **Conflict of Interest:** None declared.