REVIEW ARTICLE

Management of Infants with Congenital Adrenal Hyperplasia

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Treatment of congenital adrenal hyperplasia (CAH) requires lifelong replacement of glucocorticoids with regular follow up to manage associated morbidities. The current review focuses on follow-up and management of infants diagnosed with classical CAH pertinent to Indian context. Early initiation of oral hydrocortisone in divided doses is recommended after diagnosis in newborn period, infancy and childhood. Fludrocortisone is recommended for all infants with classical CAH. All infants should be monitored as per protocol for disease and treatment related complications. The role of prenatal steroids to pregnant women with previous history of CAH affected infant for prevention of virilization of female fetus is controversial.

Keywords: *Adrenal crisis, Complication, Glucocorticoid, 17OHP, Mineralocorticoid*.

Congenital Adrenal Hyperplasia (CAH) due to 21-hydroxylase deficiency is a potentially life-threatening endocrine disorder if not diagnosed and treated timely. The disorder has variable phenotypic expressions ranging from overt symptomatic disease with signs of acute adrenal insufficiency and virilization at birth in female infants [salt-wasting (SW) CAH], to only virilization in female babies and precocious puberty in boys without features of adrenal insufficiency [simple-virilizing (SV) CAH], to non-classical CAH which may remain asymptomatic or present during adolescence with features of hyper-androgenism.

Newborn screening for CAH has emerged as a useful and practical tool to detect affected babies at birth. The prevalence of CAH in India is reported 1 in 5762 babies as per newborn screening data [1]. This data may not be a true incidence figure in India due to regional variations across different study centres and absence of confirmatory testing available for all screen positives. Newborn screening helps in early diagnosis, correct gender assignment and timely initiation of corticosteroid therapy thereby reducing mortality. The treatment of classical CAH is lifelong with steroids. Patients with CAH may develop complications as part of their disease and as side-effects of long term steroid therapy. The most significant of these are the ill-effects on linear and pubertal growth. Therefore, it is essential to initiate appropriate and early therapy and formulate a plan of regular follow-up.

We, herein, discuss the strategies for treatment and follow-up of infants with classical CAH (21-hydroxylase deficiency; SW and SV-CAH), applicable in the Indian context. The scope of this review is limited to management after diagnosis in newborn period till early childhood and does not cover details of management of other endocrine morbidities in CAH like precocious puberty or growth failure.

METHODS

A group of experts in Pediatric endocrinology and newborn screening (Delhi Pediatric Endocrinology Newborn Screening Group) met in September, 2017 and decided to carry-out this review to guide CAH management in the country. The present review is limited to management of infants with classical CAH with 21 hydroxylase deficiency. A semi-structured literature search strategy was used. The primary database used to search information was Medline through PubMed. The search was performed in September 2017 and repeated in January 2019 to include data from Indian subcontinent. Both MeSH and keyword-based inputs were searched for articles pertaining to management of CAH in childhood. Systematic reviews, meta-analysis and randomized controlled trials were given priority. Articles pertaining to the management of advanced endocrinal issues like precocious puberty, short stature and adulthood problems were not included.

Drug-therapy

Oral Hydrocortisone is recommended as the first line replacement therapy in classical CAH during childhood.

Agent- Glucocorticoid replacement is the cornerstone of replacement therapy in CAH. The drug of choice in children is hydrocortisone. This drug should be administered in tablet form which can be crushed and mixed with milk or liquid as fresh preparation before administration. The medicine should not be left dissolved or suspended in liquid for later use as there may be uneven drug delivery [2]. Other potent forms of glucocorticoids like prednisolone and dexamethasone are not recommended for use in early childhood years but can be used in post-pubertal and adult patients. Young patients with CAH who were administered prednisolone showed poor suppression in morning serum 17OHP levels and short adult height, suggesting overdosing and poor clinical outcomes [2,3].

Route - Oral hydrocortisone is effective with high bioavailability. The absolute bioavailability after oral dose was 94% after morning dose in CAH subjects [4].

Hydrocortisone should be administered in physiological doses of 10-15mg/m^2/day during infancy.

Dosage of hydrocortisone is chosen to simulate normal physiological cortisol production rate. Normally, this rate is higher during neonatal period and infancy. The endogenous cortisol production rate is estimated to be approximately 5.7-7.4 mg/m^2/day. Thus, a recommended dose of 10-15 mg/m^2/day would achieve the physiological cortisol production after accounting for first pass metabolism and bioavailability [5]. Physiological doses would promote attainment of normal growth potential without adverse effect on growth [6]. The use of more potent alternative glucocorticoids like prednisolone (4-6 mg/day) or dexamethasone (0.25-0.5 mg/day) is reserved for post-pubertal patients to permit once- or twice-daily administration [7].

Hydrocortisone should be supplemented in thrice daily schedule. The morning dose should be given as early as possible in the morning.

Hydrocortisone has a short half-life of 1.8-2 hour with extensive protein binding (90-95%), which contributes to the non-linear pharmacokinetics of the drug. The maximum suppression of adrenal hormones occurs after 2-4 hours of morning or afternoon dose and till 6-8 hours of evening dose of hydrocortisone [8]. The best time to administer hydrocortisone to achieve adrenal suppression is morning, which corresponds to the body's circadian rhythm. Delaying the evening dose till night time does not improve suppression of morning serum 17OHP levels and is not recommended [8]. The attainment of normal serum cortisol levels with twice daily and thrice daily hydrocortisone was 15% and 60%, respectively [5]. It is recommended to administer hydrocortisone in three divided doses with morning dose administered as early as possible. Modified/ extended release hydrocortisone preparations are not advisable for pediatric use [9].

Stress doses of steroids to be continued during illness and stressful situations in all patients of CAH.

Patients with classical CAH fail to produce adequate endogenous steroids, thus requiring supplemental doses of steroids during periods of stress. Data from 2298 visits of 156 patients with CAH showed incidence of adrenal crisis at 7.55 per 100 patient-years [10]. Gastrointestinal and upper respiratory tract infections were the commonest triggers with lower age, lower hydrocortisone dose and higher fludrocortisones dose as risk factors for total illness episodes [10]. All patients with CAH should be administered higher doses of hydrocortisone at 50-75 mg/m^2/day during stress (approximately 3-5 times of daily oral dose). This may be given in intravenous form in sick children or may be given orally in those who are less sick and can take orally. The usual stress dose varies from 25 mg during infancy to 50 mg in childhood [2]. All children should be given a disease card (***Web* Box I)**, which mentions about their condition and should be produced by the parents anywhere they take the affected child for treatment. The card should ideally always accompany the child, such as at school, home, picnic etc.

The diagnosis of adrenal crisis is based on clinical suspicion as symptoms are nonspecific and include weakness, lethargy, abdominal pain, nausea, vomiting, shock, and rarely seizures. Management of adrenal crisis is a medical emergency, and should receive protocolized management ***(Box I)***.

Fludrocortisone should be supplemented in all infants with classical CAH irrespective of genotype/ phenotype. All infants with salt losing should be prescribed oral salt supplements 1-3 g day.

Fludrocortisone should be supplemented in all babies with classical CAH including those with SV-CAH (lower doses required in SV-CAH) [6,7]. Supplementation of fludrocorticsone reduces requirement of corticosteroid and optimizes final height outcomes. The doses prescribed are not dependent upon weight of the infant. The requirement for mineralocorticoids is higher during infancy at 0.05-0.2 mg/day and decreases as the child grows. The drug should be started at a lower dose initially and titrated according to serum electrolytes and blood pressure. A higher dose of fludrocortisone carries the risk of hypertension, edema and hypokalemia. Fludro-cortisone has a long half-life thus a single daily administration suffices [11].

A salt intake of 1-3 g/day (5-10 mmol/kg/day) is recommended in SW-CAH to replace the hyponatremia

Box I Protocol for Management of Adrenal Crisis

Clinical features

- Non-specific- lethargy, poor feeding, vomiting, abdominal pain, shock.
- Diagnosis based on high index of clinical suspicion.
- May obtain history of preceding viral disease, minor illness.

Management

i. Maintain airway, breathing and circulation.
ii. Restore intravenous hydration by intravenous route using a wide bore needle.Infuse isotonic saline at 20 mL/kg over 10 minutes if signs of shock are present (maximum upto 60 mL/kg).
iii. Further fluid replacement to be guided by clinical signs of shock or over-hydration. Newborns should be continued on 1.5-2 times fluid as maintenance therapy (half normal saline in 5% dextrose solution).
iv. Check and correct hypoglycaemia. Administer 5 mL/kg of 10% dextrose if low blood sugar is detected.
v. Administer Intravenous hydrocortisone at 50-100 mg/m^2 bolus followed by 50-100 mg/m^2/d in four divided doses (6 hourly). Usual dose in newborn babies is approximately 25 mg bolus followedby 5-6 mg every 6 hourly.
vi. Continue intravenous route till patient is fit to consume orally.
vii. Check and correct any dyselectrolytemia.
viii. Monitor vitals, intake, output and sensorium.
ix. Mineralocorticoid replacement may be resumed when patient is stable and shifted to oral hydrocortisone maintenance doses.

which results from steroid deficiency. A recent study reported similar dose requirement of fludrocortisone and hydrocortisone, height SDS and BMI SDS in salt supplemented (27%) and un-supplemented (72.7%) children with CAH, questioning the role of routine salt supplementation in CAH [12]. However, most clinicians prefer to supplement salt in SW-CAH during first year of life when fludrocortisone requirements are also high [11]. The normal family pot diet usually suffices for the sodium requirement after infancy.

Monitoring

All children with CAH should be monitored for steroid excess clinically. Physical examination should look for hyperpigmentation, cushingoid features, growth, distribution of body fat, presence of pigmented striae and blood pressure for hypertension.

The goal of glucocorticoid supplementation in CAH is to achieve physiological replacement with maximal height potential and prevention of adrenal crisis and virilization. There is no single indicator to optimally monitor the glucocorticoid dose. Physical indicators like weight, height, growth velocity, signs of virilization and degree of skeletal maturation are the key parameters for monitoring a child with CAH. Skin pigmentation decreases in patients once optimally controlled with suppression of serum ACTH levels. There should be no progression of virilization with good control. The follow-up visits are usually monthly for first three months, and then 3-4 monthly for first two years of life. The parameters to be evaluated at every follow up visit are highlighted in ***Table* I.** Annual skeletal age computation must be done after the age of two years.

TABLE I Monitoring of Children with Classical Congenital Adrenal Hyperplasia

Age, frequency	*Investigations*
First three mo,	Serum electrolytes*
monthly	Baseline serum 17-hydroxyprogesterone recorded
3-12 mo,	Serum electrolytes*
3-monthly	Serum 17-hydroxy progesterone** Serum androstenedione, total testosterone, ACTH[#] Plasma renin activity and aldosterone:renin ratio – optional
12 -30 mo	Serum electrolytes*
4-monthly	Skeletal age assessment annually after 24 mo of age Serum 17-hydroxy progesterone** Serum androstenedione, total testosterone, ACTH[#] Plasma renin activity and aldosterone:renin ratio – optional

*Clinical parameters to be performed at all visits: Weight, length, blood pressure, Genitalia, signs of virilization, Skin pigmentation, Cushingoid features; *Performed at all visits for all patients with classical CAH or those on mineralocorticoid supplementation; **Sample for serum 17OHP should be taken before the morning dose of glucocorticoid; [#]Serum androstenedione, total testosterone, ACTH (adrenocorticotropin hormone)- to be performed if feasible.*

A sudden spurt in growth velocity along with an accelerated bone age is an indicator of under-treatment even without other signs of androgen excess. This is related to increase in adrenal hormones that cause premature bone maturation [5,6]. In contrast, weight-gain, cushingoid features and poor growth velocity are pointers of steroid overdose that warrant a dose adjustment. Timely initiation of therapy during newborn period, use of physiological doses of steroids, and lower steroid doses during puberty have shown to optimize height outcomes in children [13]. Data on 81 Indian children with CAH (mean age 6.7 y) showed a mean height SDS as -0.6 on glucocorticoid replacement (hydrocortisone mean dose 14.6 mg/m^2/d) [14]. Height was most affected in SW-CAH than SV-CAH and in children less than two years than in older age [14]. Similar data was reported in 18/30 classical CAH Indian subjects with final height SDS at -2.06 (1.1) at mean age of 14.2 y [15].

In males, high levels of ACTH can also stimulate formation of testicular adrenal rest tumors (TARTs), which impair testicular function and can cause oligospermia [5]. Beyond five years of age, affected males should be screened for development of any TARTs by serial ultrasonography of testis to detect hypoechoic lesions. Usually these lesions are small, not clinically discernible, and regress with better titration of steroid therapy. Five out of 21 boys (age >5 y) in an Indian study [14] had TARTs on ultrasonography, which regressed in three boys on follow-up.

Hormonal profile for serum 17OHP should be done 3-monthly during infancy and subsequently every 6-12 month interval.

Amongst the adrenal steroids, the three most commonly used markers for monitoring the adequacy of glucocorticoid treatment in CAH are 17-OHP, androstenedione and/or testosterone. The hormone evaluation can be performed in urine, blood, saliva or dried blood filter paper. The measurement of adrenal steroids is subject to wide variation as it depends upon time of sampling and interval from glucocorticoid administration. The diurnal variability is most marked for 17-OHP levels and relatively less for androstenedione and testosterone. Moreover, intra-individual divergence in measurement of 17-OHP can occur up to 40 folds. The single random hormone levels are difficult to interpret in isolation as there is considerable degree of overlap between the normal and poorly-controlled patients [16]. The use of consistently timed serum estimation of hormones is recommended for routine monitoring of children with CAH [7]. The serum levels of 17-OHP are usually maintained between 5-10 ng/mL. It is undesirable to achieve normal age appropriate 17-OHP levels with replacement doses of corticosteroids as that often leads to over-treatment. The dose adjustments of gluco-corticoids should be done in relation to the overall clinical context coupled with adrenal hormone measurements [2,7].

Measurement of serum androstenedione and serum testosterone add to the hormonal profile assessment in CAH and should be maintained in near normal range. Serum testosterone (total) levels can be used to monitor CAH in patients aged 6 month (beyond-minipuberty) to prepubertal age to maintain a level below 20 ng/dL [17]. Routine measurement of serum cortisol for monitoring therapy is not indicated. The plasma levels of ACTH are highest in the morning and fall abruptly after morning steroid dose. The goal of therapy is seldom to suppress ACTH production as that would lead to excess steroid dosing and side-effects of therapy. Thus, plasma ACTH values may not serve any benefit in monitoring adequacy of therapy.

The adequacy of mineralocorticoid therapy can be adjudged by monitoring blood pressure and serum electrolytes. Plasma renin activity (PRA) and aldosterone-to-PRA ratio are useful adjuncts to clinical monitoring where resources permit.

The mineralocorticoid axis can be monitored by measuring serum electrolytes (sodium and potassium) and blood pressure (***Table* I**).The aim of therapy is to maintain serum electrolytes and blood pressure in normal range. Inadequate mineralocorticoid dosing can manifest as salt craving and result in hyponatremia and hyperkalemia. Hypertension is usually asymptomatic and detected on examination. Monitoring of blood pressure should be done as per age, and gender, specific charts to detect hypertension, which can develop with overdosing of steroids. Plasma renin activity (PRA) is a sensitive marker of volume depletion. A high PRA level even with normal serum electrolyte concentrations is suggestive of inadequate replacement dose of fludrocortisone [18]. However, the logistics of sample collection, processing and measurement of PRA level preclude for its estimation in routine clinical practice.

Genital Surgery

Early genital surgery during infancy is recommended for severely virilized (≥ Prader stage 3) female babies.

Surgical correction of female genitalia is often indicated in extreme virilized states. The goals of corrective surgery are (*i*) improving the appearance of external genitalia to resemble normal female genitalia, (*ii*) conserve sexual and reproductive functions, (*iii*) achieve adequate urinary stream without incontinence. The decision for corrective surgery should never be taken in haste during early

newborn period. There is evidence to show that there may be partial regression of mild clitoromegaly after starting hydrocortisone replacement, thus averting the need of extensive surgical correction [19]. Genital surgery should be performed at a tertiary-level center, where expertise for genital surgery, urosurgery and endocrinology are available. Surgery must be conducted by experienced surgeons taking care to achieve as normal anatomical reconstruction with preservation of neurovascular bundle. Corrective surgery is indicated when patient has a high proximal junction between the vagina and urethra (^{3}Prader 3 stage) [2]. Corrective genital surgery includes vaginoplasty, clitoroplasty and labial surgery. Clitoroplasty done during infancy provides advantage of using phallic skin for vaginal reconstruction. Most children will need a staged repair [20]. There is no role of bilateral adrenalectomy in children with CAH.

Prenatal Steroids

Prenatal dexamethasone administration to pregnant woman with a prior CAH affected child for prevention of virilization of a female fetus should be considered experimental and offered after a complete discussion with the family about possible maternal adverse effects, variable genital outcome and unknown long-term side effects of dexamethasone therapy

Prenatal steroids (oral dexamethasone) may be administered to a mother having an earlier baby with CAH to prevent virilization of an affected female fetus in current pregnancy. Oral dexamethasone is not metabolized by the placenta and has shown to significantly decrease virilization in 75-85% cases if started before 9 weeks of gestation. The criteria for considering prenatal steroids are (*i*) history of previously affected sibling or first degree relative with known mutations, (*ii*) period of gestation less than 9 weeks, and (*iii*) aim to continue pregnancy till term with good drug compliance [2,7].

Diagnosis of CAH in fetus may be made preferably by molecular genetic testing of *CYP21A2* gene in chorionic villus cells. Genetic testing includes sequencing followed by deletion/duplication analysis, if no variant is identified. The aim of prenatal diagnosis is to start treatment early to prevent virilization of female fetus. Hence, pending confirmation of affected fetus, all high-risk pregnancies where prenatal therapy has been agreed upon after counseling are started on prenatal steroids by 5-6th week of gestation. Confirmation is done by chorionic villus sampling (CVS) or amniocentesis. CVS is advantageous over amniocentesis as it can be performed early around 9 weeks of gestation. As CAH is inherited as an autosomal recessive disease, the risk of affected fetus is 25%. Prenatal steroids, are beneficial only for affected homozygous or compound heterozygous females, hence 7/8 fetuses (boys and unaffected females) would unnecessarily be exposed to prenatal steroids raising ethical concerns [7,19]. The use of prenatal steroids is postulated to be associated with maternal complications like higher weight gain, edema and abdominal striae but not hypertension and gestational diabetes. The adverse fetal outcomes reported are spontaneous abortion, fetal demise, intrauterine growth retardation, liver steatosis and congenital malformations. Mild cognitive and behavioral abnormalities have been reported in children who received prenatal steroids.

A meta-analysis based on four observational studies, which included total 325 pregnancies, reported significant reduction in virilization in female babies who received prenatal dexamethasone. An increased incidence of edema and striae were found in mothers but no increased risk of stillbirths, spontaneous abortions, fetal malformations, neuropsychological or develop-mental outcomes were seen. However, as these studies were only observational and lacked long-term follow-up, the use of prenatal steroids is not recommended at present and may be started only after detailed discussion with the family [21].

Gender Assignment

Gender assignment should be done after expert opinion and appropriate counseling and discussion with the parents. Most babies with 46XX DSD with CAH should be assigned female gender at birth

Gender assignment may be difficult, and not always possible, immediately after birth. The parents should be appropriately counseled by the pediatrician regarding the nature of disease, including the need of karyotype and additional biochemical tests for confirmation of diagnosis. A recent review of 52 cases of CAH (42 simple virilizing, 10 salt-wasting) from India reported male gender assignment in one-fourth of simple virlizing CAH (median age 2 mo). All babies with SW-CAH presented earlier at median age at 0.4 mo, and were reared as females [22]. Similar data from Northern India showed male gender assignment in 17/49 (35%) of CAH, affected girls [14].

In patients with 46 XX DSD due to 21-hydroxylase deficiency, gender identity is generally female and fertility is possible. Hence, according to an International consensus guideline, female gender assignment is advised [23]. Appropriate pediatric surgery referral should be made for severely virilized females (Prader stage ≥3) for genital surgery in infancy [24].

CONCLUSIONS

Congenital adrenal hyperplasia is an endocrine disorder amenable to newborn screening and treatment. Early diagnosis and treatment have shown to improve growth,

final adult height, fertility, bone health and metabolic parameters in both girls and boys. Patients and parents must be educated about the appropriate use of steroids and the possibility of adrenal crisis. Treatment of CAH is lifelong and should be supported by a dedicated team of endocrinologists, geneticists, psychologists, surgeons and social workers.

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WEB BOX I Identification Card for Patients Affected with Congenital Adrenal Hyperplasia

- Name
- Date of birth
- Gender:
  Male
  Female
  Unassigned
- Father's name:
- Emergency contact number
- Diagnosis:
  CONGENITAL
  ADRENAL
  HYPERPLASIA
- Management if sick:
  - Check blood glucose, serum electrolytes
  - Check hydration, blood pressure, perfusion. Start Intravenous fluids if in doubt.
  - At home: Do not stop hydrocortisone or fludrocortisone.
  - Minor illness (like upper respiratory tract infection, acute diarrhea or mild fever): Double the dose of oral hydrocortisone in minor illness.
  - Moderate to severe illness (vomiting, fever >38.5 ^{o}C, lethargy, poor feeding, dehydration, surgery, trauma): Take 3-5 times the dose of oral hydrocortisone. May need intravenous steroids if hospitalized or poor oral acceptance.
  - Withhold oral fludrocortisone till taking increased dose of hydrocortisone. Continue increased dose of hydrocortisone till illness subsides.
  - Hospitalization: Administer intravenous hydrocortisone at 50-75 mg/m^2 stat if patient needs hospitalization.
  - Contact your doctor immediately after stabilization.