

Study of Social and Cognitive Functioning in Children with Congenital Adrenal Hyperplasia

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Abstract

Background: Congenital adrenal hyperplasia (CAH) is a genetic problem of steroidogenesis in adrenals. Due to a particular enzyme deficiency causing lack of steroids, negative feedback involving hypothalamic-pituitary-adrenal axis is lost. This would result in increased production of adrenocorticotrophic hormone and corticotropin-releasing hormone which may have their effects on learning and memory. CAH is the most common cause of hyperandrogenism which may influence the psychological behavior in girls leading to psychiatric manifestations such as aggressiveness and attention-deficit hyperactivity disorder (ADHD). The prevalence of these behavioral and cognitive impairment is studied here.

Aims and Objectives: Aims and objectives of the study were to study the social and cognitive functioning in children with CAH on treatment and to determine the prevalence of aggression and ADHD in CAH children.

Materials and Methods: In total, 55 children from 2 to 12 years satisfying the criteria were enrolled in the study. Complete history recorded, physical examination done, and blood 17-hydroxyprogesterone and bone age were measured. Materials used include social adaptive behavior from Vineland social adaptive behavior scale, child behavior checklist to look for any aggressiveness, intelligence quotient (IQ) assessment using - Gesell's for children between 2 and 3 years, Binet Kamat test for children 3-6 years, and Malin's intelligence scale for more than 6 years.

Observation and Results: About 53% of the population had adequate adaptability and 40% of them had moderately low adaptability. 7% had low adaptability. 20% of the total study population were found to be aggressive as per child behavior checklist. Aggressiveness and gender were not dependent to each other in CAH. 15% of the total population had attention-deficit hyperactivity disorder (ADHD), 16% of the girls, and only 10% of the boys had ADHD. 53% of the total population had only borderline IQ levels IQ distribution pattern among the two sex is not much different from the total with a $P = 0.4375$.

Conclusion: From our study, we conclude that nearly half of the children with CAH had only borderline IQ and low social adaptability. Hence, all CAH patients should be subjected to psychological and cognitive assessment at least once a year.

Key words: Adaptability, Aggressiveness, Cognition, Congenital adrenal hyperplasia, Hyperandrogenism

INTRODUCTION

Adrenal glands are two small endocrine structures located just above the kidneys. Congenital adrenal hyperplasia (CAH) is a genetic problem involving steroidogenesis

resulting in enzyme deficiencies in adrenal gland. The accumulated metabolites due to the enzyme deficiencies are the cause for symptoms in CAH, in addition to steroid deficiency. Hypothalamic-pituitary-adrenal axis is essential for production and regulation of adrenal steroids. Adrenocorticotrophic hormone (ACTH) has a pulsatile release, and more secretion is during the early morning hours. In CAH, when this axis is disturbed the negative feedback is lost¹ and hence would result in increased production of ACTH and corticotropin-releasing hormone (CRH). These abnormally elevated hormones have their effects on learning and memory through their action on amygdale.²

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CAH and Effects on Social Functioning

CAH is a disorder where female babies are born with excess of male sex hormones, and hence naturally a sexual dimorphic behavior could be expected from these girls. There are certain personality traits which are specific for a particular sex. For example, traits such as dominance and assertiveness are more specific for men whereas tender-mindedness and empathy are more specific for girls. Hence in conditions causing hyperandrogenism as in CAH, there had been modifications in these behaviors. Increased male pattern behavior and increased aggressiveness may occur in these group of children. There had been studies quoting that early hormonal environment is one of the most powerful determinants of sex differences in personality. Affected girls especially have increased tendency to have a male playmate, male activity preferences and increased tendency to fight and physical aggression.³ Androgen excess in the early periods of brain development will affect the neural differentiation, cell survival and neural connectivity and neurochemical characterization.⁴

There are also proved evidences stating increased incidence of psychiatric disorders such as autism and attention deficit hyperactive disorder in these children.⁵ This may be again because of the hyperandrogenic state. In general, males tend to have more incidence of psychiatric disorders owing to their natural androgenic state. Early androgen exposure has also lead to the predisposition of these children to specific learning disabilities.⁶ There are multiple domains in which a child with CAH may have deficit including communication, socialization, and daily living skills. Physiological cause for these increase in aggression and male-typical behavior is increase in androgen receptors in medial amygdaloid nucleus in children having high prenatal androgen exposure. In many studies, it has been quoted that when these children are exposed to a negative situation, amygdala would be hyperactive than a normal person. Melanocortin-4 receptors are mainly involved in the modulation of anxiety and depression-like behavior in amygdala. CAH is a condition where there is increased ACTH and CRH. These hormones would act on these receptors situated in amygdala and cause those psychiatric symptoms and aggression.

CAH and Cognition

Cognition includes process of thinking, reasoning, memory, comprehension judgment, and problem solving. There are innumerable number of studies stating that steroid hormones influence cognitive functioning.⁷ Cognitive functioning and intelligence is directly related to social adjustment and aggression. As these group of children have social maladjustment and aggression, intelligence assessment becomes essential. There are innumerable scales for assessment of intelligence quotient (IQ):

1. Wechsler's intelligence scale for children
2. Malin's intelligence scale for Indian children⁸
3. Binet-Kamath test (BKT)
4. Seguin-form board test
5. Wais adult intelligence scale.

And scores based on which cognitive impairment can be categorized into:

1. 90-110 - Normal
2. 70-89 - Borderline impairment
3. 50-69 - Mild impairment
4. 35-49 - Moderate impairment
5. 20-34 - Severe impairment
6. <20 - Profound impairment.

CAH is the condition which carries the risk for both hormonal imbalance starting from the intrauterine life and steroid treatment both of which may have an effect on cognition. Studies have quoted that high androgen levels were shown to impart changes in the synaptic plasticity in hippocampal CA1 cells in juvenile rats. In the same study, it also been clearly stated that elevated androgens may reduce social cognitive performance. Androgens also delay cerebral maturation in the prenatal and perinatal periods especially of the left cerebral hemisphere which would lead on to abnormalities in neuronal migration or abnormal connectivity.⁹ High levels of ACTH levels may also reduce the emotional learning and memory.¹⁰ This action is exerted mainly through their action on melanocortin receptors in amygdala. Studies have also quoted decreased amygdala volume in CAH patients. Steroids used for the treatment of CAH can exert their effect on cognition through two ways – (1) Organizational alteration and (2) activational alteration. Children with salt-wasting type have lower IQ compared to simple virilizing type.¹¹ The cause may be due to the diffuse brain injury during episodes of hypotension and hyponatremia which would further impair their IQ. There had been documented white matter lesions in magnetic resonance imaging leading to visuospatial impairment which is essential for solving arithmetic problems. Hence, their visuospatial and cognitive skills are also poor.

There had been many studies regarding the growth and physical features in CAH. Recent studies suggest that children with CAH also suffer from behavioral and cognitive disorders. Since there had been very few studies on behavioral and cognitive functioning in India, we proceed on with this study.

Aims and Objectives of the Study

Aims and objectives of the study were to study the social and cognitive functioning in children with CAH on treatment and to determine the prevalence of aggression and ADHD in CAH children.

MATERIALS AND METHODS

- Design of the study: Descriptive study (cross-sectional)
- Place: Pediatric Endocrinology Department, Institute of Child Health, Department of Child Guidance Clinic, ICH
- Period of the study: February 2015 to August 2015
- Sample specifications:
 - Case definition: All clinically and biochemically confirmed cases of CAH on treatment.

Inclusion Criteria

- All children from 2 to 12 years who were diagnosed as CAH and on treatment.

Exclusion Criteria

- Other causes of growth abnormalities: Familial short stature, growth hormone deficiency, nutritional causes, chronic systemic diseases
- Chronic medications unrelated to CAH
- Known psychiatric illness
 - Sample size - All children with above inclusion criteria who presented during the study period.

Ethical committee clearance was obtained from the institutional review board.

Maneuvre

Children of age 2-12 years diagnosed to have CAH and satisfying the inclusion and exclusion criteria were recruited into the study, after obtaining informed parental consent.

Subjects with CAH those satisfying the inclusion and exclusion criterion were enrolled into the study. Detailed history regarding the type of the disease, age of diagnosis, family history, developmental history, period of drug intake, and compliance were taken. Physical examination done and X-ray for bone age and blood 17-hydroxyprogesterone (17OHP) levels were done.

Following this, psychological assessment done:

1. Social adaptive behavior from Vineland social adaptive behavior scale
2. Child behavior checklist (CBCL) to look for any aggressiveness
3. IQ assessment using:
 - Gessel's for children between 2 and 3 years
 - BKT for children 3-6 years
 - Malin's intelligence scale for more than 6 years.

Social Adaptive Behavior

Vineland social adaptive behavior scale is used for obtaining a composite score which roughly corresponds to the social quotient. Subdomain raw scores are computed

from identification of basal and ceiling items. Domains include receptive, expressive, written language, personal, domestic, community communication, daily living skills, and socialization. Standardized scale score (V-scale score) is determined based on age and domain standard score is then obtained. Then, sum of all these domain standard scores is obtained based on this scoring social adaptive levels are classified as:

Adaptive level	V-scale	Standard score
Low	1-9	20-70
Moderately low	10-12	71-85
Adequate	13-17	86-114
Moderately high	18-20	115-129
High	21-24	130-160

CBCL

CBCL estimates the externalizing disorders and internalizing disorders in children. It classifies them into normal range, borderline and in clinical range based on the scores obtained. Separate list of questions for boys and girls and also for children <6 years and more than 6 years exist in CBCL. somatic problems, anxious/depressed/withdrawn, social, thought problems, attention problems, hyperactivity, rule breaking behavior, and aggressive behavior were included in the study. In our study, aggression is given importance and concluded either child is aggressive, borderline aggressive or normal.

Gessel's Child Behaviour Schedule

From the age of 4 months, the child's development can be assessed based on motor development, language development, adaptive behavior, and personal-social behavior. The developmental age and its corresponding development quotient can be derived. In this study children between 2 and 3 years this test is administered.

BKT for General Mental Abilities

BKT is applied to all children above 3 years of age for obtaining IQ. For each age, 6 standardized questions are present and based on the child's performance their mental age is calculated. Basal age (where all 6 items are correct) and terminal age (where all 6 items are failed) is calculated. Mental age is calculated from the number of items which are being answered between the two basal and terminal age. In this study children between 3 and 6 years this test is administered.

Malin's Intelligence Scale for Indian Children

Malin's test is applied to children from 6 to 15 years of age for IQ; in this study, age group of 6-12 years this test is done. This is an Indian adaptation of Wechler's intelligence scale for children. Full-scale IQ comprises 11 subsets – 6 for verbal intelligence which includes

information, comprehension, arithmetic, similarities, vocabulary, and digit span. 5 for performance intelligence which includes picture completion, picture arrangement, block design, object assembly, coding, and mazes.

Statistical Methods

The history, anthropometry, physical examination findings, psychological examination, and laboratory investigations were collected from the children included in the study and recorded in data collection form. The data entered in the excel sheet. Data analysis was performed using epidemiological information package in computer. Frequencies, means, percentage, standard deviations, fisher's exact test, coefficient of correction values, and *P* value were calculated using SPSS software frequencies.

OBSERVATION AND RESULTS

In total, 55 children with CAH on treatment were studied in the age group between 2 and 12 years. In this study, as shown in Table 1, 53% of the population had adequate adaptability and 40% of them had moderately low adaptability. 7% had low adaptability. Social adaptive behavior was not associated with types of disease at *P* = 0.5648. The difference was due to chance. 20% of the total study population was found to be aggressive as per child behavior checklist as in Figure 1. Aggressiveness was not associated with types of disease at *P* = 0.7309. The difference was due to chance. There was no statistical significant association between aggressiveness and gender at *P* = 1.000. That is, aggressiveness and gender were not dependent to each other in CAH. 15% of the

total population had ADHD as in Table 2. ADHD was not associated with types of disease at *P* = 0.696. The difference was due to chance. In our study, 16% of the girls and only 10% of the boys had ADHD. However, the difference is not statistically significant as the *P* = 1.000.

About 53% of the total population had only borderline IQ levels as in Table 3. IQ range was not associated with types of disease at *P* = 0.5473. The difference was due to chance. IQ distribution pattern among the two sex is not much different from the total with a *P* = 0.4375 and hence not statistically significant.

DISCUSSION

This study is conducted at Endocrinology Department of Institute of Child Health and Hospital for Children between the period of February 2015 and August 2015. We studied the social and cognitive functioning in CAH children. CAH is the most common cause of hyperandrogenism in children. Incidence of the disease is as high as 1 in 15,000.

In total, 55 children with CAH between 2 and 12 years of age were enrolled into the study. Among them, *n* = 45 (82%) were females and only *n* = 10 (18%) were males. Salt wasting type constituted the majority about *n* = 34 (62%). Simple virilizing type was only *n* = 21 (38%). Social adaptive behavior of these children was studied using Vineland adaptive behavior scale. *n* = 29 (53%) of the kids had adequate adaptive behavior. *n* = 22 (40%) of the kids had moderately low adaptive behavior. Among these 22 kids, seven kids had been on excess steroid dose than recommended and 17OHP levels seen among these 22 showed eight of them with high levels and eight had less than normal range. *n* = 4 (7%) of the kids had low adaptive levels. Among these four kids, one kid had been on excess steroid dose than recommended and two of them had 17OHP levels less than normal range. Comparing the two varieties of disease, simple virilisers have better adaptive levels than salt wasters, though not statistically significant.

Aggressiveness is one of the features associated with hyperandrogenic state. Many studies have proved that girls with CAH are more aggressive than unaffected girls.⁷

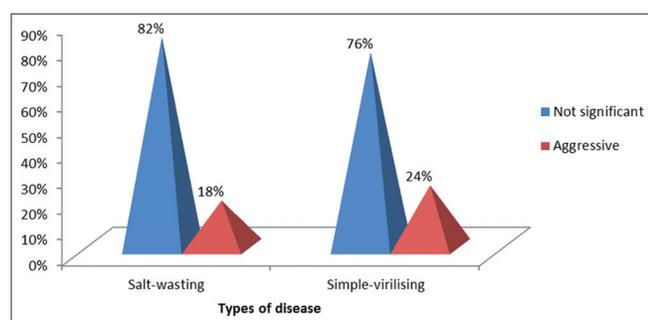


Figure 1: Aggressiveness in children and types of disease

Table 1: Distribution of social adaptive behavior among the study population

Social adaptive behavior	Types of disease			Fisher's exact test
	Salt-wasting (%)	Simple-virilising (%)	Total (%)	<i>P</i> value
Adequate	16 (47)	13 (62)	29 (53)	0.5648
Moderately low	15 (44)	7 (33)	22 (40)	
Low	3 (9)	1 (5)	4 (7)	
Total	34 (100)	21 (100)	55 (100)	

Table 2: Distribution of ADHD among the study population

ADHD	Types of disease			Fisher's exact test P value
	Salt-wasting (%)	Simple-virilising (%)	Total (%)	
No ADHD	28 (82)	19 (91)	47 (86)	0.696
ADHD	6 (18)	2 (9)	8 (15)	
Total	34 (100)	21 (100)	55 (100)	

ADHD: Attention-deficit hyperactivity disorder

Table 3: Distribution of IQ among the two types of CAH in the study population

IQ range	Types of disease			Fisher's exact test P value
	Salt-wasting (%)	Simple-virilising (%)	Total (%)	
50-70	1 (3)	1 (5)	2 (4)	0.5473
70-90	20 (59)	9 (43)	29 (53)	
90-110	13 (38)	11 (52)	24 (43)	
Total	34 (100)	21 (100)	55 (100)	

CAH: Congenital adrenal hyperplasia, IQ: Intelligence quotient

They have also stated that girls and boys with CAH do not differ much in aggressiveness. In our study, $n = 11$ (20%) of the affected kids were aggressive. Among the general population between 2 and 17 years, the prevalence of aggression is 2-16%. Among males, it is 6-16% and among females it is 2-9%. Our study has shown a higher proportion of patients with aggressiveness than in the general population. In our study, aggressiveness is screened from CBCL. Between the types of disease, $n = 5$ (24%) of the simple virilisers and $n = 6$ (18%) of the salt-wasters were aggressive. The difference is not statistically significant.

Incidence of ADHD among general population is 5-12%. In our study, about $n = 8$ (15%) of our population were found to have ADHD based on CBCL. Studies have shown higher incidence of psychiatric disorders such as ADHD and autism among these children.¹² Among the two disease types, salt wasters (18%, $n = 6$) were found to be more affected than simple virilisers (15%, $n = 2$). Comparing between boys and girls, in our study girls (16%, $n = 7$) were found to be more affected than boys (10%, $n = 1$) though not statistically significant.

Mean full-scale IQ in our study is 84.6 ± 9.8 , but in one study,¹² it was found to be 84.5. Among the total population about $n = 24$ (43%) of them had normal IQ scores. About $n = 29$ (53%) of the patients were in the borderline level in our study, salt wasters were more affected than simple virilisers, though not statistically significant. It has been

stated in other studies also that salt wasters have lower IQ scores than simple virilisers.¹¹ Between the two sex, not much of difference was noted. $n = 2$ (4%) of the total population had IQ scores between 50 and 70. Both were on excess steroid dose (>20 mg/m²). Their 17OHP levels were also uniformly very low. Among the 29 patients with borderline impairment, about $n = 12$ (41%) of them had very low 17OHP levels. Hence based on all these factors, the dose should be adjusted adequately to maintain the needed control over the hyperandrogenic state.

Major limitations of the study include:

1. Other hormonal assays like androstenedione in addition to 17OHP should have been measured for appropriate determination of hyperandrogenic state
2. Small sample size.

CONCLUSION

From our study, we found out that, nearly half of the children with CAH had only borderline IQ and low social adaptability. Hence, we could conclude that all CAH patients should be subjected to psychological and cognitive assessment at least once a year as they are more prone for cognitive impairment and psychiatric disorders like ADHD. Regular dosage modification should also be done based on clinical, biochemical, and psychological findings.

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