IJSCIA

International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 4 | Issue: 1 | Jan – Feb 2023 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v4i1.20

Internal and External Behavior Outcomes in Children with Congenital Adrenal Hyperplasia: A Systematic Review

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ABSTRACT

Introduction: Congenital adrenal hyperplasia (CAH) is autosomal recessive disorders that disrupt adrenal steroidogenesis. Congenital adrenal hyperplasia (CAH) has been shown to potentially affect psychological adjustment. However, the behavior effect on glucocorticoid treatment in CAH patient remain unclear. The aim of this systematic review was to assess the internal and external behavior problems in CAH children due to glucocorticoid treatment. ***Methods:*** The systematic review was carried out using the PRISMA framework and the search strategy was based on the population, intervention, control, and outcome (PICO) model. The relevant article was search from Cochrane, Google Scholar, PubMed, Science Direct, Springer Link, Wiley Online Library Databases from February and March 2022. ***Results:*** Six studies were included in this review. The primary domain identified are internal and external behavior from the CBCL questionnaire. Three studies compared the external and internal behavior of CAH children with glucocorticoid treatment to healthy control, two studies post-natal, and one study during prenatal. Three other studies compared CAH with glucocorticoid treatment and the CAH control group. ***Conclusion:*** Children with CAH had better behavioral outcomes, especially in internal behavior in glucocorticoid-exposed children.

Keywords: behavior problems; congenital adrenal hyperplasia; glucocorticoid treatment.

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder. CAH is a common disease that is affected by the background of various racial and ethnic. The most common variant is due to 21-hydroxylase deficiency that is caused by cortisol biosynthesis defect with or without defect in androgen excess and aldosterone synthesis [1]. The prevalence of classical forms explained to range from 1:5000 to 1:15,000 [2].

The clinical feature of the classical type is salt-wasting and simple virilizing. Salt-wasting is characterized by salt loss, hyponatremia, hyperkalemia, dehydration, shock, and ambiguous genitalia. The varying degree of clitoris enlargement, posterior labial fusion in females, and pseudo-precocious puberty in males are the typical symptom of the simple virilizing (SV) type [3]. Genital ambiguity in CAH is caused by 21-hydroxylase deficiency and leads to difficulties in sex assignment after delivery, potentially complex reconstructive genital surgery, and parental distress [4].

Glucocorticoid is used to prevent prenatal virilization in female fetuses with CAH. Several studies reported that dexamethasone at a dose of 20 μg/kg/day initiated before 6–7 weeks post conception significantly suppresses fetal androgen production and effectively prevents or reduces prenatal virilization [5].

Dexamethasone is glucocorticoids that play an important role in memory consolidation and retention [6]. A previous study showed that a long-acting DEX post-natal treatment significantly increased the risk for mood disorders (depression and anxiety). Hence, several studies reported that prenatal DEX treatment impacted the long-term neurocognitive and behavioral impact [7].

The CBCL (Child Behavior Checklist) is one of a family of screening tools developed by Thomas M. Achenbach starting in the 1960s. This checklist is a screening tool for suspicion of an emotional or behavioral problem with a child 6-18 years of age. There are also three summary scores, first is Internalizing Problems, which consists of summarizing the Anxious or Depressed, Withdrawn or Depressed, and Somatic Complaints scores. Second, Externalizing Problems consists of translating the Rule-Breaking Behavior and Aggressive Behavior scores). and the total Problems score, summarizing all eight syndrome scale scores. The interpretation is based on the T Score and percentile score. The Percentile scores below the 95th percentile is normal range, between 95th and 98th percentile is borderline range, and above the 98th percentile is considered to be in the clinical range [8].

A recent study reported that a parenteral questionnaire assessed long-term emotional and behavioral development.

Standardized parent-completed were used Child Behavior Check List (CBCL). On the other hand, a study reported that postnatal DEX treatment had negative effects, especially in girls, when comparing untreated, hydrocortisone-treated, and DEX-treated preterm children. Thus, neonatal DEX treatment, but not hydrocortisone treatment, resulted in more problem behavior, as assessed by the Child Behavior Check List (CBCL). The scores were similar to those observed in untreated children born preterm [9]. To the best author's knowledge, this is the first systematic review that investigated internal and external behavior outcomes in children with CAH due to glucocorticoid treatment.

MATERIALS AND METHODS INCLUSION AND EXCLUSION CRITERIA

Internal and External Behaviour Outcomes in Children with Congenital Adrenal Hyperplasia was systematic review between February and March 2022. Published reported from Cochrane, Google Scholar, PubMed, Science Direct, Springer Link and Wiley Online Library were quantitative, qualitative, and mixed methods were all considered.

No age restrictions were imposed, and all methods of measurement (self-report and parent-report) were included. Unpublished dissertations, case reports, review articles, editorial, and meeting abstracts were excluded.

Further exclusion criteria were: (a) studies that did not use CBCL criteria, (b) studies that did not present Internal and External Behaviour Outcomes as a group, with results not being displayed separately for CAH the current study has applied to ensure that our procedures, including record collection, extraction of data, quality evaluation and statistical analysis, adhere to the PRISMA guideline from Preferred Reporting Items for Systematic Examination (PRISMA) [10].

SEARCH STRATEGY

Several scientific references (Cochrane, Google Scholar, PubMed, Science Direct, Springer Link, and Wiley Online Library) were searched for studies assessing the Internal and External Behaviour Outcomes in Children with Congenital Adrenal Hyperplasia until March 29, 2022. We did limit the language of publication. If publication papers were not found in both English and Indonesian, we did not include this in our study. In addition, the following keywords were used to perform a systemic search: ["congenital adrenal hyperplasia" or" CAH" or"], or "Adrenal Syndrome"] and ["Internal and external behavior"] and ["CBCL"] and ["Children" or "Pediatric"]. If we did find documents with the same study details, we included only documents with larger samples in our search strategy. Additionally, the following information of interest was extracted from each paper: (1) first author name, (2) year of publication, (3) sample size of case and control, (4) age of participants, (5) ethnicity, (6) main findings. To provide high-validity data, two independent authors performed the data extraction to avoid human error. If a discrepancy was found, we performed a discussion together.

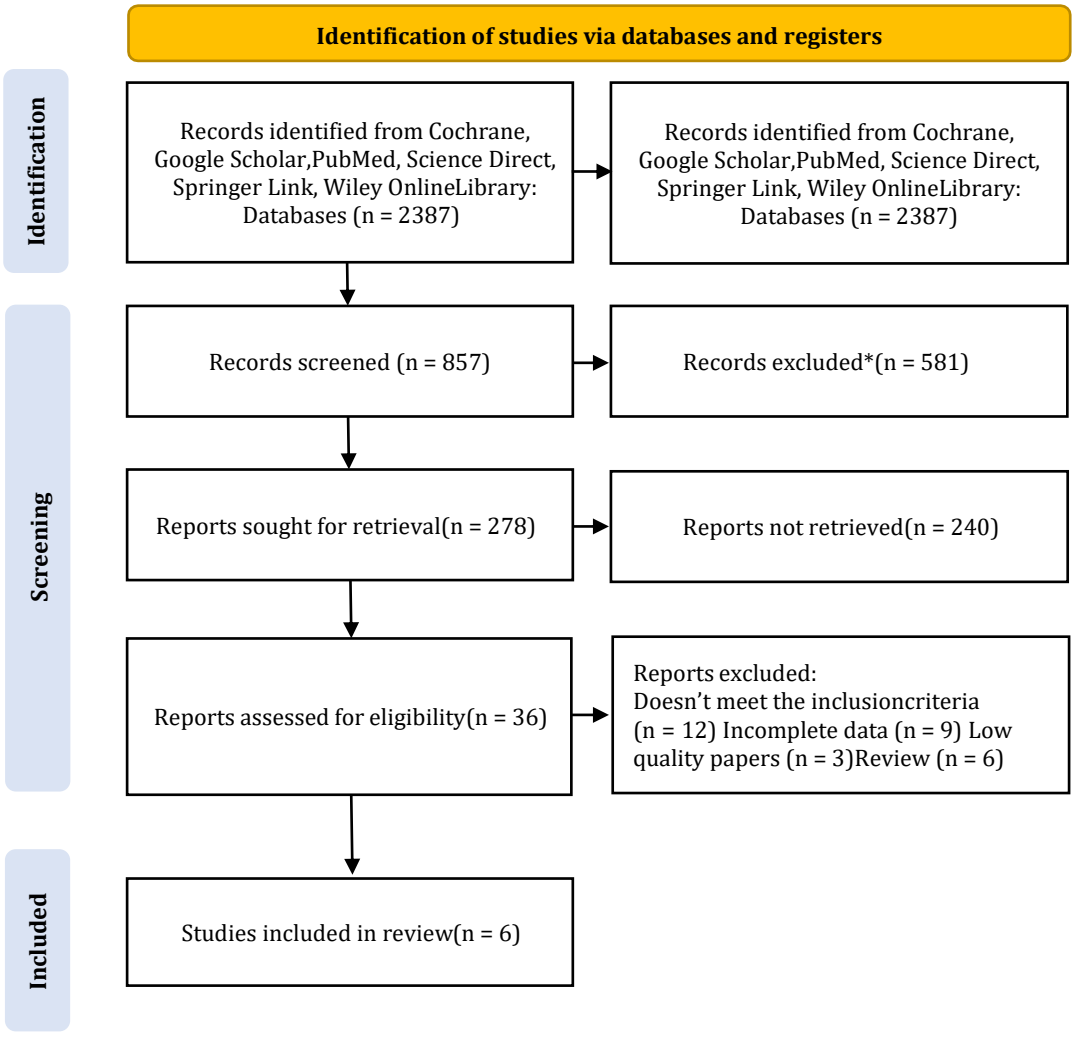

FIGURE 1: Illustrating the procedure for article inclusion and exclusion in a systematic review of psychological adjustment, quality of life, and self-perceptions of reproductive health in males with congenital adrenal hyperplasia *If automation tools were used, indicate how many records were exclude by a human and how many were excluded by automation tools.

ASSESSMENT OF METHODOLOGICAL QUALITY

The systematic search initially yielded 2387 articles and after the removal of duplicates, 857 records were screened for eligibility (Figure 1). By examining all titles, 278 studies were identified. Abstracts were assessed according to the agreed criteria, leading to the exclusion of 30 papers. Hence, a total of 6 articles were selected for full-text reading. Included and excluded articles were agreed on together regarding the criteria described by all authors, and 6 studies were finally included.

DATA EXTRACTION

Data were collected regarding the included authors, sample size, gender, Age range, Informant, country, methods, design, setting/context, and results/findings.

RESULTS

All articles were quantitative studies. The measures and domains investigated in each paper are described in Table 1. The main themes were identified: (1) internal, and (2) external behavior problems from the CBCL questionnaire. Six studies analyzed the internal and external behavior outcomes in children with CAH. Three of these studies compared CAH with glucocorticoid treatment and a healthy control group, and three other studies compared with the CAH group. Due to Post-natal glucocorticoid treatment, showed that CAH with glucocorticoid treatment has a different impact on higher problem behaviors on external and internal behavior than healthy control [10,11]. However, another study described that external and internal behavior have not significantly disturbances in healthy control compared with CAH with glucocorticoid treatment in the prenatal study [12].

Three other studies by Messina et al., trautmant et al., and hirvikosvki et al., investigated prenatal glucocorticoid treatment compared with the CAH control group [13,14,15]. There was a different impact that did not seem to cause major behavioral problems on external and internal behavior in CAH with glucocorticoid treatment compared with the CAH control group, according to trautmant et al. and hirvikosvki et al. study. On the other hand, Messina's study explains that glucocorticoid treatment was not significantly different, impacting more social problems on the external and internal behavior of CAH with glucocorticoid treatment compared with the CAH control group [14, 15].

DISCUSSION

Congenital adrenal hyperplasia (CAH) is a hereditary disease caused by the lack of cortisol synthesis. Approximately 90% to 99% of cases of CAH are caused by 21-hydroxylase deficiency (21OHD). Excess glucocorticoid treatment can lead to poor growth. The mean age at onset of puberty in both males and females is slightly younger than the general population. Central precocious puberty can occur in a patient with inadequate treatment. Following the onset of puberty, in a majority of successfully treated patients, the milestones of further development of secondary sex characteristics, in general, appear to be normal [17].

A total of six studies analyzed the internal and external behavior outcomes in children with CAH treated with glucocorticoid in prenatal and postnatal conditions. Due to Postnatal glucocorticoid treatment, oner et al. and Idris et al. showed that CAH with glucocorticoid treatment impacts external and internal behavior differently than healthy control. The CBCL internalization problems score was associated with mean testosterone. Meanwhile, the externalization and total problems related to testosterone, surgeons' assessment, and mean hydrocortisone dose [11].

Patients with CAH had a higher risk of having an anxiety disorder. On the other hand, the prevalence of internalizing behavior problems included a combination of anxious/ depressed and withdrawn or depressed behaviors, and somatic complaints were higher in CAH boys compared with those controls. The family income and glucocorticoid dose might be associated with higher internalizing and externalizing behavior. High- dose glucocorticoid is reported to be associated with clinical disease severity. Boys are higher, especially in internalizing [12]. Those studies associated with Fardet et al. present a high risk for neuropsychiatric conditions, e.g., suicidal behavior, and increased risk for mood disorders, e.g., depression and anxiety caused by postnatal glucocorticoid treatment.

Prenatal androgen exposure in females affected with classical forms of CAH has a masculinizing effect on the development of the external genitalia and childhood behavior [17]. Four other studies by Messina et al., trautmant et al, hirvikosvki et al, and wallensteen et al. investigated prenatal glucocorticoid treatment compared with the CAH control group. There was a different impact on external and internal behavior in CAH with glucocorticoid treatment compared with the CAH control group [15,16]. The first-trimester prenatal treatment with glucocorticoid, used in treating children at risk of CAH, does not cause behavioral maladaptation during childhood. Both glucocorticoid -exposed and control children obtain a normal score on CBCL [16]. Those studies associated with the study by Maryniak et al. stated that there is no significant difference in cognitive behavior between CAH children with prenatal glucocorticoid treatment compared to the non-prenatal glucocorticoid treatment group [18]. Another study by Meyer et al. showed the same result [19].

On the other hand, Messina et al. and wallensteen et al. explained that glucocorticoid treatment did not significantly impact the external and internal behavior of CAH with glucocorticoid treatment compared with the CAH control group. Considering many uncontrolled factors, e.g., shared genetics, that remains to be elucidated, the results should be interpreted with caution when considering the effects of prenatal glucocorticoid exposure in CAH [20].

This study showed that postnatal DEX and glucocorticoid treatment resulted in more problem behavior, as assessed by the Child Behavior Check List (CBCL). The scores were similar to those observed in prenatal DEX, and glucocorticoid treatment are not significantly different in healthy control. The studies underscore the importance of psychological and social support for the patients and their families. We recommend that children with CAH undergo psychological screening, and those found to have abnormal screening results may benefit from further psychological evaluation and intervention. This systematic review also has some limitations. Some of the studies have small subjects that can cause different signification. Further study is recommended with a larger sample, dose-response analysis, and validation by directly examining the children.

CONCLUSION

The behavioral outcome in children with CAH negatively affected behavior problems with postnatal glucocorticoid treatment and did not cause major behavioral problems in prenatal glucocorticoid-exposed. This study showed the importance of psychological and social support for the patients and their families. The parents must be thoroughly informed about the benefits of the treatment for CAH as well as possible adverse effects and uncertainties. Prenatal and postnatal glucocorticoid-exposed children at risk for CAH should only be carried out in centers where proper follow-up of treated cases can achieve.

TEBLE 1: Overview and details about the included article of the present systematic review.

Reference	Sample Size	Gender	Informans	Recruitment site	Comparison Group	Internalising problem	Externalising problem	Outcome
Messina et al, 2020	57	13; m (5) f (8)	patients and parents	Swedish and Italian	CAH with DEX vs CAH	0.588	0.961	More social problems and withdrawn-depressed problems in DEX-treated.
Idris et al, 2014	91	49; m (20) f (29)	patients and parents	Malaysia	CAH with glucocorticoid vs health control	0.200	0.62	Glucocorticoid dose influencedby disease severity which in turn may affect the behavioral outcome.
Oner et al,2009	56	28; f (28)	patients and parents	Turkey	CAH with Hydrocortisone vs health control	0.063	0.015	Patients with CAH in hydrocortisone-treated hadsignificantly higher problem behaviors.
Wallensten et al, 2018	104	34; m (19) f (15)	patients and parents	Swedish	CAH withDEX vs health control	0.445	0.889	Prenatal treatment with DEX,as used in the treatment of children at risk of CAH, does not cause behavioral maladaptation during childhood.
Trautman et al, 1995	26	14	Parents	New York	CAH with DEX vs CAH	<0.002	<0.048	No gross behavioral disturbances Were seen in prenatal DEX treatment.
Hirvikoski et al, 2008	61	26; m (12) f (14)	patients and parents	Swedish	CAH with DEX vs CAH	0.319	0.895	Prenatal DEX treatment of CAH does not seem to cause major behavioural problems or psychopathology.

REFERENCE

[1] Merke, D. P., & Bornstein, S. R. (2005). Congenital adrenal hyperplasia. Lancet, 365(9477), 21252136

[2] Witchel, S.F. (2017) Congenital Adrenal Hyperplasia. Journal of Pediatric and Adolescent Gynecology, 30, 520-534. https://doi.org/10.1016/j.jpag.2017.04.001

[3] Niang, B., Ly, F., Ba, A., Mbaye, A., Boiro, D., Faye, P.M., Dieng, Y.J., Sow, A., Thiongane, A., Ba, I.D., Thiam, L., Fall, A.L. and Ndiaye, O. (2020) Congenital Adrenal Hyperplasia: Diagnostic Features in a Limited Resource Country, Senegal. Open Journal of Pediatrics, 10, 137-146. https://doi.org/10.4236/ojped.2020.101013

[4] MccCann-Crosby B, Placencia Fx, Adeyemi-Fowode O, et al. Challenges in Prenatal Treatment with Dexamethasone. Pediatr Endocrinol Rev. 2018; 16(1): 186–193.

[5] Hanna Nowotny, Uta Neumann, Véronique Tardy-Guidollet, S Faisal Ahmed, Federico Baronio, Tadej Battelino, Jérôme Bertherat, Oliver Blankenstein, Marco Bonomi, Claire Bouvattier, et al. (2022) European Journal of Endocrinology. 186(5). p.K17-K24

[6] McGaugh, J.L. and B. Roozendaal, Role of adrenal stress hormones in forming lasting memories in the brain. Curr Opin Neurobiol, 2002. 12(2): p. 205-10.

[7] Fardet, L., I. Petersen, and I. Nazareth, Suicidal behavior and severe neuropsychiatric disorders following glucocorticoid therapy in primary care. Am J Psychiatry, 2012. 169(5): p. 491-7.

[8] Claire R.McNellan, Daniel J.Gibbs, Ann S.Knobel, EmilyPutnam-Hornstein. The evidence base for risk assessment tools used in U.S. child protection investigations: A systematic scoping review. Elsevier. 2022. https://doi.org/10.1016/j.chiabu.2022.105887

[9] Ter Wolbeek, M., Kavelaars, A., de Vries, W.B., Tersteeg-Kamperman, M., Veen, S., Kornelisse, R.F., van Weissenbruch, M., Baerts, W., Liem, K.D., van Bel, F., Heijnen, C.J., 2015. Neonatal glucocorticoid treatment: long-term effects on the hypothalamus-pituitary- adrenal axis, immune system, and problem behavior in 14–17-year-old adolescents. Brain Behav. Immun. 45, 128–138.

[10] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021; 372:71.

[11] O. Oner, Z. Aycan, T. Tiryaki, D. Soy, E. Cetinkaya, E. Kibar. Variables Related to Behavioral and Emotional Problems and Gender Typed Behaviors in Female Patients with Congenital Adrenal Hyperplasia. Journal of Pediatric Endocrinology & Metabolism. 22, 143- 151 (2009).

[12] A. N. Idris, V. Chandran, S. Z. S. Zakaria, R. Rasat, Behavioural Outcome in Children with Congenital Adrenal Hyperplasia: Experience of a Single Centre, Hindawi Publishing Corporation International Journal of Endocrinology Volume 2014, Article ID 483718, 9 pages (2014). http://dx.doi.org/10.1155/2014/483718

[13] L. Wallensteen, L.Karlsson, V. Messina, A. Gezelius, M. T. Sandberg, A.Nordenstrom, T. Hirvikoski, S. Lajic. Evaluation of behavioral problems after prenatal dexamethasone treatment in Swedish children and adolescents at risk of congenital adrenal hyperplasia. https://doi.org/10.1016/j.yhbeh.2017.11.004

[14] V. Messina, T. Hirvikoski, L. Karlsson, S. Vissani, L. Wallensteen, R. Ortolano, A. Balsamo, A. Nordenström, S. Lajic, Good overall behavioural adjustment in children and adolescents with classic congenital adrenal hyperplasia. Endocrine 68:427–437 (2020). https://doi.org/10.1007/s12020-020-02244-1

[15] P.Trautman, H. F.L. Meyer-BahlburgG, J. POSTELNEK. M. I. New. Efeects of Early Prenatal Dexamethasone on The Cognitive and Behavioral Development of Young Children: Results of a Pilot Study. Psychoneuroendocrinology, Vol. 20, No. 4, pp. 439-449, 1995.

[16] T.Hirvikoski, A. Nordenstrom, T. Lindholm, F. Lindblad, E. M. Ritze, S.Lajic. Long-term follow-up of prenatally treated children at risk for congenital adrenal hyperplasia: does dexamethasone cause behavioural problems? European Journal of Endocrinology (2008) 159 309–316.

[17] Yau M, Gujral J, New MI. Congenital Adrenal Hyperplasia: Diagnosis and Emergency Treatment. [Updated 2019 Apr 16]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279085/

[18] Agnieszka Maryniak1, Maria Ginalska-Malinowska, Alicja Bielawska1, and Agnieszka Ondruch. Cognitive and social function in girls with congenitaladrenal hyperplasia — Influence of prenatallyadministered dexamethasone. Child Neuropsychology, 2014Vol. 20, No. 1, 60–70, http://dx.doi.org/10.1080/09297049.2012.745495.

[19] Meyer-Bahlburg, H.F.L., Dolezal, C., Baker, S.W. et al. Gender Development in Women with Congenital Adrenal Hyperplasia as a Function of Disorder Severity. Arch Sex Behav 35, 667–684 (2006). https://doi.org/10.1007/s10508-006-9068-9

[20] Claahsen-van der Grinten, H. L., Speiser, P. W., Ahmed, S. F., Arlt, W., Auchus, R. J., Falhammar, H., Flück, C. E., Guasti, L., Huebner, A., Kortmann, B., Krone, N., Merke, D. P., Miller, W. L., Nordenström, A., Reisch, N., Sandberg, D. E., Stikkelbroeck, N., Touraine, P., Utari, A., Wudy, S. A., White, P. C. (2022). Congenital Adrenal Hyperplasia-Current

[21] Insights in Pathophysiology, Diagnostics, and Management. Endocrine reviews, 43(1), 91–159. https://doi.org/10.1210/endrev/bnab016