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Management of Childhood Congenital Adrenal Hyperplasia-An Integrative Review of the Literature

Louise Fleming, PhD, RN,

Assistant Professor, University of North Carolina at Chapel Hill School of Nursing, 437 Carrington Hall; CB #7460, Chapel Hill, NC 27599

Marcia Van Riper, PhD, RN, FAAN, and

Professor and Chair of Family Health Division, University of North Carolina at Chapel Hill School of Nursing

Kathleen Knafl, PhD, FAAN

Frances Hill Fox Distinguished Professor, University of North Carolina at Chapel Hill School of Nursing

Abstract

Congenital adrenal hyperplasia (CAH) is an endocrine condition that requires parents to administer steroids up to three times daily, supplementing maintenance doses with oral or injectable doses during times of illness. The purpose of this integrative review was to explore the management, care and associated health issues for children with CAH as well as the family response to the condition. Four literature indexes were searched with 39 articles included. Four themes emerged: 1) health and development related issues; 2) effects of excess androgens; 3) life experience of CAH; and 4) managing and averting adrenal crisis. Families having a child with CAH face complex concerns related their child's growth, the fear of adrenal crisis events, and the consequences of atypical genitalia for affected girls. Future studies should focus on interventions that provide guidelines to increase parental preparedness in managing adrenal crises as well as creating support systems for affected girls.

Keywords

congenital adrenal hyperplasia; atypical genitalia; adrenal crisis; adrenal crisis; adrenal insufficiency

Introduction

Classic congenital adrenal hyperplasia (CAH) is a rare, life threatening, endocrine disorder that affects boys and girls equally. CAH has an incidence in the United States of approximately 1 in 15,000 live births annually (Speiser et al., 2010). Management of CAH requires parents to administer oral steroids, typically hydrocortisone, up to three times daily.

corresponding author: C-919-272-7174, F-919-843-0841, lkflemm@email.unc.edu.

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If a child is prescribed too much hydrocortisone, side effects can include growth suppression, obesity and other cushingoid features. If the dose of hydrocortisone is not sufficient, children with CAH are at a high risk for precocious puberty, which can also lead to stunted growth. Determining the proper dosage of steroids is typically achieved by obtaining routine laboratory work and measuring height, weight, and bone age every 3–6 months in a growing child (Merke & Bornstein, 2005; Speiser et al., 2010). Additionally, stress dosing (doubling or tripling the oral steroid dose) is required when the child is experiencing an acute illness, such as fever or a broken bone. An emergency intramuscular (IM) injection of hydrocortisone is required when a child is unable to tolerate oral medications and/or if signs of adrenal crisis are present (Merke & Bornstein, 2005; Speiser et al., 2010; Witchel & Azziz, 2011). The need for stress dosing, either orally or by injection, related to simple viral and bacterial childhood illnesses is frequent and unpredictable, often requiring parents to make complex treatment decisions (Merke & Bornstein, 2005).

Girls born with CAH often experience virilization, which results in atypical genitalia at birth, due to elevated testosterone related to adrenal dysfunction. Boys born with CAH have typically appearing male genitalia (Witchel & Azziz, 2011). Families having a girl with CAH may face multiple surgeries into adolescence if parents, in consultation with their daughter's physicians, make the determination that reconstructive feminizing genitoplasty is warranted. (Witchel & Azziz, 2011).

There are multiple challenges for practitioners and families regarding the treatment and monitoring of children with CAH including: achieving optimal glucocorticoid replacement; height and weight difficulties; excess testosterone exposure; and the need for stress dosing during times of illness (Kim, Ryabets-Lienhard & Geffner, 2012; Merke & Bernstein, 2005; Speiser et al., 2010). In addition to these physiological concerns, children with CAH and their families must also manage the psychosocial and behavioral aspects of chronic illness, such as dealing with school personnel who are unfamiliar with the condition and the possible stigmas associated with chronic illness and, for girls, atypical genitalia (Schaeffer et al., 2010; Speiser et al., 2010). The purpose of this integrative review was to explore the management and care, associated health issues, and growth and developmental consequences for children with CAH as well as the family response to the condition.

Methods

Based on established guidelines for conducting integrative reviews (Whittemore & Knafl, 2005) and in consultation with a university health sciences librarian with expertise in web-based searches, four literature indexes were searched for articles published in peer reviewed journals from January 1, 2000 to June 1, 2015. Databases searched included PubMed, CINAHL, PsycINFO, and Family and Society Studies Worldwide using the following search terms: congenital adrenal hyperplasia and family (or parents or siblings) as well as adrenal crisis and parents. The words family, parents, and siblings were truncated for maximum results.

Empirical articles meeting the following criteria were included in this review: 1.) focus on CAH management, experience, and health outcomes for children under 18 years, and 2.) written in the English language and published between 1/1/2000 and 6/1/2015, and 3.) peer reviewed. Articles were excluded if they: 1.) focused exclusively on pathology, 2.) addressed other adrenal disorders or other disorders that may result in atypical genitalia, and 3.) focused on non-classical or rare types of CAH. The initial search yielded 470 articles (Figure 1). After further screening of the article titles, 389 were then excluded, leaving 81 articles from the initial search. Additional review of the abstracts and full text excluded an additional 55 articles, mainly due to a focus on pathology, non-empirical studies, and studies that included adults, leaving 26 articles. Thirteen additional manuscripts that met the criteria were added based on review of the reference lists of relevant research articles, resulting in a total of 39 research reports (encompassing 39 separate studies). A structured template was used to extract relevant information about the research (author/title, research purpose, location of study, participant information, data collection methods, and findings) and study results pertinent to the aims of the review. Data analysis was completed using a systematic approach consisting of sorting, categorizing, and summarizing data in an effort to create meaningful conclusions about the state of the knowledge (Whittemore & Knafl, 2005).

Results

Thirty-nine empirical research studies met the criteria and were included in this review. Thirty-four studies used a quantitative design, four used a mixed methods design, and one study used a qualitative design. These studies had global representation. Of the 39, fifteen were conducted in the United States (U.S.), thirteen in Europe (with the majority of European studies conducted in the United Kingdom (U.K.)), eight in Asia (Jordan, Turkey, India, and Malaysia), three in Brazil, and one in Australia. One study was conducted jointly in the U.K. and the U.S.

Across the 39 studies, four focus areas were identified: 1.) health and development issues associated with a diagnosis of CAH (n=10 studies); 2.) physical and psychosocial consequences for the child resulting from prenatal exposure to excess androgens (n=18 studies); 3.) the life experience of having CAH for those affected and their families (n=7 studies); and 4.) times of acute illness and managing and averting adrenal crisis (n=4 studies).

Health and Development Issues Associated with CAH

Children with CAH are steroid dependent for life, and the goal of daily maintenance treatment is to replace deficient levels of cortisol and/or aldosterone while minimizing androgen excess, preventing virilization, optimizing growth, and protecting fertility. If children are prescribed excess hydrocortisone, side effects can include growth suppression and obesity. If the dose of hydrocortisone is insufficient, children are at a high risk for precocious puberty and adrenal crisis (Merke & Bornstein, 2005).

Ten studies focused on aspects of CAH that lead or have the potential to lead to negative health outcomes (Table 2.1). Of the ten, five articles focused on growth issues, both height and weight. Obesity was found to be a significant problem in children with CAH (Volkl,

Simm, Beier, & Dorr, 2006; Mendes-dos-Santos et. al, 2011; Cetinkaya & Kara, 2011; Moreira et al., 2013). Mendes-dos-Santos et al. (2011) concluded in their cross sectional, retrospective study that height in these children was similar to unaffected children of the same age, yet children with CAH had higher body fat, which tended to be visceral. Similarly, Moreira et al. (2013) found that children with CAH presented with a higher prevalence of obesity and metabolic syndrome, but child weight was not correlated with glucocorticoid treatment. Cetinkaya and Kara evaluated the effects of glucocorticoid doses on bone mineral density in their 2011 study and found that children with CAH had higher BMIs than controls. The bone ages of children who were poorly controlled (when looking at 17 hydroxyprogesterone (17-OHP) levels) as well as those who had been diagnosed later were higher than tightly controlled, early-diagnosed groups. Additionally, treatment of glucocorticoids did not influence bone mineral density in children with CAH.

Using a descriptive design, Bonfig, Schmidt, and Schwartz analyzed linear growth patterns in children with CAH treated with low doses of hydrocortisone during early years of life (2011). In their cohort of fifty-one children, birth length was above average in both boys and girls, possibly due to increased androgens in utero. Treating these children with lower levels of glucocorticoids in infancy did not accelerate bone age and growth, and they were able to achieve height within the target range as they grew. However, final height in these children was still below genetic potential (Bonfig et al., 2007). Lin-Su, Harbison, Lekarev, Vogiatzi, and New (2011) evaluated whether growth hormone alone or in combination with a leutinizing hormone releasing hormone agonist (LHRHa) would increase final height in children with CAH, as LHRHa can effectively suppress puberty, preserving the ability for continued growth. These findings indicate that for CAH children experiencing precocious puberty and short stature, growth hormone alone or in combination with LHRHa is an effective therapy for improving height; however, males experience less height benefit than females.

Due to a variety of factors, children with CAH are at risk for vascular problems (Harrington, Pena, Gent, Hirte, & Couper, 2012). Using a cross-sectional design, Harrington and colleagues examined vascular function and increased carotid intima thickness (cIMT) in children with CAH compared to healthy children. They found that children with CAH have significant vascular and smooth muscle dysfunction, and this level of dysfunction was comparable to the healthy subjects that were mild to moderately obese.

Nabhan and colleagues (2006) studied the incidence of urinary tract infections (UTIs) in children with CAH, hypothesizing that girls were at higher risk of such infections secondary to structural genitourinary anomalies. These investigators concluded that the incidence of UTIs in children with CAH was similar to that of the general population; furthermore, there was not a significant increase in UTIs if genital surgery was delayed in affected girls.

Finally, one study investigated the behavioral health of children with CAH. Idris et al. (2014) studied behavioral outcomes in children with CAH compared to a non-affected, control group. They found a higher incidence of parent reported child problems including anxiety, depression, somatic complaints, social and attention problems, and aggressive behavior when compared to controls. Internalizing behavior problems were seen more often

in boys compared with controls, but girls with CAH had similar psychosocial adjustment to their control counterparts.

Physical and Psychosocial Consequences from Exposure to Excess Androgens

Both female and male children born with CAH are exposed to high concentrations of androgens, such as testosterone, in utero; while males do not typically show any outward physical signs of this exposure, females typically have atypical genitalia at birth to varying degrees, which often leads to a diagnosis in females shortly after delivery. The majority of the studies reviewed (18) addressed the potential impact of excess androgen exposure on the physical genitalia characteristics and psychosocial presentations of children with CAH. (Table 2.2)

The aim of a 2004 retrospective study in Turkey was to describe the experience of gender (re) assignment in genotypical female patients with CAH. Seventy female patients were studied with 21 of them having been reared “male.” Nine had been surgically reassigned as females, with a mean age of seven months at the time of surgery. The study identified difficulties related to surgical complications and family emotional strain in attempting to change the gender of female patients with CAH when they were older than 2.5 years of age at the time of surgery (Ozbey, Darendeliler, Kayserili, Korkmazlar & Salman, 2004).

Another study (Al-Maghribi, 2007), based in Jordan, evaluated the clinical features of all patients with CAH treated at a major medical center from 1996–2006. Among the 39 females born with CAH, 27 had experienced atypical genitalia. Seven of these chose not to have reconstructive surgery and six of these had hysterectomies and gonadectomies to keep their “male genders.” Although the majority of these female children had reconstructive surgery and were raised as girls, which is the typical treatment course in the United States, fifteen percent were genetically identified as female, but physically reconstructed, and raised as male. There were no other studies found that described these types of surgical measures to preserve male identity.

A 2002 study in Germany (Woelfle et al.) examined sixteen highly virilized females in an effort to better understand specific problems these girls face. The authors concluded that there were five main concerns experienced in this population of sixteen virilized females with CAH: 1.) delayed diagnosis (due to an assumption of the child being a male rather than female), 2.) gender assignment, 3.) surgical procedures, 4.) short stature, and 5.) precocious puberty. Similarly, a 2010 study in India used a case study approach to report the effect of steroid therapy during infancy and early childhood on the appearance of the external genitalia of girls with CAH (Kulshreshtha et al., 2010). It was unclear if the three girls in the study had a definitive diagnosis of CAH according to the standards used for diagnosis in the United States, as steroids were not initiated until after two months of age. However, the authors believed that these girls did, in fact, have CAH and concluded that there was improvement in the external appearance of the girls’ genitalia with post-natal steroid therapy.

Four cross-sectional studies conducted in Sweden and in the United States examined toy preferences in children with CAH. In both the Servin et al. and Wong et al. (2003, 2013)

studies, girls with CAH were more interested in masculine toys such as cars and construction toys versus feminine toys such as dolls and tea sets. In the Wong study, which also looked at parental encouragement of sex-typical toy play, parents of girls in both CAH and control groups encouraged girl-typical toy play; however, parents reported encouraging less girl-typical, and more boy-typical, toy play in girls with CAH than in control females. The authors speculated that this could be due to the fact that parents simply encourage their children to play with toys that the child naturally prefers. Servin et al. (2003) examined the degree of masculinization for girls with CAH in regards to play behavior and attempted to identify playmates by asking the girls whom their “best friends” were. Two thirds of girls with severe masculinization reported a boy as their best friend, where most of the girls with milder forms of CAH and all of the control girls reported girls as their best friend. In addition, the group of girls with CAH who had the most masculinization spent significantly more time playing with masculine toys than girls with less masculinization.

A 2005 study by Pasterski investigated 65 children with CAH, as well as controls, to assess toy choices. As in the Servin and Wong studies, Pasterski et al. found that girls with CAH displayed more male-typical toy choices than controls, whereas boys with and without CAH did not differ. Similarly, a 2002 study (Nordenstrom et al.) not only investigated toy preferences in girls with CAH, but also explored a relationship between the degree of disease severity, reflected in CYP21 genotype, and the degree of masculinization with toy play and preferences. They too found that girls with CAH played more frequently with masculine type toys than controls; additionally, a higher degree of androgen exposure in utero did correlate was significantly correlated with an increased preference of masculine toys.

A 2004 study explored if girls with CAH had problems with gender identity due to increased androgen exposure prenatally and hypothesized that if the gender identity of girls with CAH was determined by prenatal androgen exposure, one would expect indications of increased gender confusion or gender dysphoria to be evident in childhood (Meyer-Bahlburg et al., 2004). As expected based on previous studies, girls with CAH scored significantly more masculine than controls on all scales used when looking at gender behavior; however, there was an absence of gender confusion/dysphoria. These results vary slightly from those of Berenbaum and Bailey (2003) who found that the vast majority of girls with CAH had similar responses (on a nine-question interview) to those of control girls. Girls with CAH, as also reflected in Meyer-Bahlburg’s study, did not express true gender confusion and articulated no discomfort in being a girl. Beltz, Swanson, and Berenbaum (2011) explored the relationship between androgen levels and occupational interests in males and females with CAH and found that females with CAH did have more interest in occupations that historically have been favored by males such as engineering and science.

Pasterski et al. (2015) studied 153 children total (43 females and 38 males with CAH as well as unaffected relative controls) to investigate potential cross gender identification in girls who were exposed to androgens prenatally. There was one of four studies evaluating the physical and psychosocial consequences of exposure to excess androgens that used a mixed methods approach in which standardized measures as well as a short parent and child interview were conducted. The study found that girls exposed to high levels of androgens in

utero due to CAH showed increased cross gender identification as well as cross gender role behavior, when compared to female controls (Pasterski et al., 2015).

The ability to understand and remember the spatial relations among objects has also been studied in children with CAH. In the general population, males typically outperform females in tests of spatial ability (Berenbaum, Bryk & Beltz, 2012). Comparison of the spatial abilities in males with and without CAH have yielded inconclusive results. A 2003 study found that females with CAH had increased spatial ability compared to unaffected females and had scores that resembled unaffected males and males with CAH. However, a 2012 study found males with CAH scored lower than their unaffected brothers in spatial ability (Hines et al., 2003; Berenbaum et al., 2012). The results of these studies investigating male and female spatial ability are somewhat conflicting, which makes it challenging to draw definitive conclusions.

Knickmeyer et al. (2006) investigated whether autistic traits among boys and girls with CAH are increased as a result of exposure to excess androgens. The Autism Spectrum Questionnaire (AQ) was given, and females with CAH scored significantly higher than unaffected females, in large part due to increased scores on subscales measuring social skills and imagination. However, none of the females in the study had AQ scores that met the cut off for suspicion of a clinical diagnosis of autism among the general population. Males with CAH did not differ from unaffected males on the total AQ or on any of its subscales.

Finally, four studies evaluated possible personality differences in children with CAH due to excess androgen exposure. Females with CAH tended to display increased aggressive behavior and activity levels in childhood compared to unaffected, female controls (Pasterski et al., 2007; Mathews, Fane, Conway, Brook & Hines, 2009). However, such results in males were less conclusive with one study reporting no significant differences in either aggressive behavior or activity level (Paterski et. al, 2007) in males with CAH and their unaffected male relatives while another study found males tended to display less dominant, less rough and tumble play and show increased “tender minded” characteristics (Mathews et al., 2009).

Prenatal treatment of dexamethasone (Dex) in pregnant women at risk for having a child with CAH was introduced decades ago (Nimkarn & New, 2009) with the understanding that taking steroids during pregnancy reduces the risk of virilization in the unborn female fetus with CAH by reducing the level of circulating adrenal androgens. Maryniak et al. (2014) studied 33 females in Poland ranging from 6–23 years of age from families in which there was a risk for CAH; 17 girls whose mothers were treated prenatally with Dex (9 affected and 8 unaffected after birth) and 16 females with CAH whose mothers were not treated prenatally. The purpose of the study was to assess cognitive development and social and emotional function in girls treated with dexamethasone prenatally compared to girls whose mothers were not treated prenatally. The authors found that prenatal treatment with Dex was associated with significantly better cognitive functioning (based on measures including an intelligence scale as well as memory and verbal learning tests) in girls with CAH. However, treating mothers whose girls were unaffected (in utero prior to knowing if they will have CAH or not) can cause the risk of unfavorable influence on the development of certain cognitive functions. As reflected in other studies (Beltz et al., 2014; Maryniak et al., 2014;

Nordenstrom et al., 2002; Pasterski et al., 2005; Servin et al., 2003; Wong et al., 2013), girls with CAH whose mothers did not receive Dex had more male “interests” than girls who did not have CAH and girls with CAH whose mothers received Dex while pregnant.

The Life Experience of Having CAH for Those Affected and Their Families

Children with CAH often experience challenges such as missed school, frequent times of illness, isolation, and a decreased quality of life (Source deleted for blinded review; Boyse et al., 2011; Yau et al., 2015). Seven studies, one of which was qualitative, focused on the experience of having CAH from the perspective of either the child with CAH, family members, or both (Table 2.3). Three of the studies focused on parents of children with CAH in developing countries: Sri Lanka, Vietnam and India (de Silva et. al., 2014, Armstrong, Henderson, Hoan & Warne, 2006; Bhakhri & Jain, 2011). Parents in the three countries reported misconceptions and confusion about medication administration and general knowledge of the disorder. The authors concluded that there is a strong need for more support groups to help parents better understand the condition and their child’s special health care needs (Armstrong, Henderson, Hoan & Warne, 2006; Bhakhri & Jain, 2011). The de Silva study (2014) examined depressive symptoms in parents of children with CAH and found over half of the parents of children with CAH were classified as having symptoms of depression that did not subside with the passage of time.

In the United States, Boyse et al. (2014) conducted a small, qualitative study (6 parents from 4 families) examining the experience of having CAH for children and their families and identified multiple challenges facing families having a child recently diagnosed with CAH. These included problems communicating with health care providers, especially regarding understanding of the diagnosis and treatment options and the need for decision making regarding genital surgery in girls. Additionally, parents reported a lack of social support offered by health care providers. These challenges left parents feeling overwhelmed and isolated as well as concerned that their knowledge of how to manage the condition was insufficient (Boyse et al., 2014).

Three additional studies examined aspects of families’ quality of life related to their child’s CAH diagnosis. Sanches et. al (2012) investigated the physical, social, and societal functioning of children with CAH and their parents in The Netherlands through parent report. Parents reported that their child with CAH experienced few negative effects from the condition, with children participating (as unaffected children would) in typical school and leisure activities, but commented on the need for increased parental preparation for adrenal crisis events from providers. Gilban, Alves and Beserra (2014) evaluated the health related quality of life (HRQoL) of children and adolescents with CAH in Brazil. This was one of the few studies that used measures completed by both parents and affected children. Based on the data from both parents and children, they found a loss of HRQoL in children and teens with CAH, especially in the physical dimension (when compared with unaffected controls), which was in agreement with the assessment made by their parents. There were no statistically significant differences in quality of life between boys and girls with CAH however. Finally, Yau et al. (2015) evaluated the HRQoL in children with CAH, with a specific focus of comparing children with CAH and children with another endocrine

condition (hypothyroidism). Based on both parent and child reports, children with CAH had an overall decrease in HRQoL compared to both healthy children and children with hypothyroidism in school functioning.

Acute Illness and Managing and Averting Adrenal Crisis

Four studies focused on acute illness, stress dosing, and adrenal crisis experiences and management in children with CAH (Table 2.4). Three of the four examined the role that physical stress, such as exercise and acute illness, had on glucose regulation in children with CAH. In a randomized, double blind, crossover study from 2004, Weise et al. examined whether an extra dose of hydrocortisone would help normalize blood glucose levels in patients with CAH during exercise. Children with CAH do not mount the normal exercise-induced glucose response due to lack of cortisol production with physical activity (Weise et al., 2004; Green-Golan et al., 2007). The authors concluded that children with CAH do not benefit from additional hydrocortisone during short-term exercise, as the extra hydrocortisone did not increase blood glucose levels. Supporting these findings, a 2010 study examined blood glucose levels and physical symptoms during typical acute viral or bacterial illnesses at home (Keil, Bosmans, Van Ryzin & Merke). These authors found that children with CAH who were being “stress dosed” appropriately during common childhood illnesses were at risk for hypoglycemia during the illness. This suggests the need for additional glucose supplementation in addition to “stress dosing” during times of illness (Keil et al., 2010). Finally, a 2011 study assessed 60 caregivers’ knowledge of CAH, adrenal crisis, and stress dosing as well as their confidence in responding to adrenal crises (Source deleted for blinded review). The majority of caregivers responded that their child experiences a “crisis” situation one to two times per year. Caregivers had an accurate, basic understanding of the disorder. Those parents who received both a written instruction guideline and a demonstration by clinicians on how to stress dose, both orally and via an injection, scored significantly higher when looking at self-efficacy (Source deleted for blinded review).

Discussion

Studies that met the inclusion criteria for this integrative review were primarily conducted using quantitative methods and were cross-sectional and descriptive in nature, with the sample population usually coming from either one institution or one city. One limitation of these studies is that most only use only samples from one institution, which typically has a group of pediatric endocrinologists treating children with CAH in a similar manner regarding medication dosing, family education, etc. As a result, the studies may not have reflected the full range of treatment protocols being used for children with CAH, making it difficult to determine the variation in growth patterns. Many of the studies used structured measures, yet did not report on their reliability and validity. Only one out of 39 studies involved an intervention (Lin-Su et al., 2011). This study examined the effect of growth hormone on final height in children with CAH, but was not a randomized, controlled study. Since most children with CAH do not require growth hormone treatment, its applicability to the general CAH population is limited.

There were limitations to the studies discussed in this review. All of the investigators whose research focused on stress dosing for acute illnesses (such as the flu or ear infections) and adrenal crisis events either acknowledged having a small sample size (Keil et al., 2010; Source deleted for blinded review) or had a sample size less than 10 (Weise et al., 2004; Green-Golan et al., 2007). There were five studies that investigated body weight in children with CAH; however, only the Volkl et al. study accounted for parental BMIs and inquired about daily dietary intake for these children, making it difficult to know the comparative impact of CAH and environmental factors on the child's weight.

Two of the studies dealing with the family experience were in developing countries where steroids were reported to be expensive based on the typical amount of family income, and parents in these studies reported that medication cost was a significant concern (Armstrong, Henderson, Hoan & Warne, 2006; Bhakhri & Jain, 2011). This particular difficulty is not likely to be as prevalent in more developed countries such as those in Europe or in Canada and the U.S.; thus, a similar study conducted in these countries could yield different results. Another cultural difference that was evident involved the 2007 study in Jordan (Al-Maghribi) in which surgery was done to preserve male appearance so the female with CAH could be reared male. This decision, which is not typical for a CAH female, could be based on cultural differences related to gender roles in middle eastern countries.

Overall, the literature reviewed reflected a heavy emphasis on gender behavior and identity, with little research on how families manage the social challenges associated with girls born with atypical genitalia. With the exception of the Wong et al. and Nordenstrom et al. studies (2013, 2002) which involved the use of some observational methods, investigators relied on parents' reports of their child's play preferences over the course of their development. In addition, very few co-variables (e.g. gender of other siblings) were addressed in the studies investigating the effects of androgens on gender-related play and toy preferences. For example, a girl with CAH having three older brothers might be living in an environment where most toys were boy-typical. In addition, the observers who were interpreting the play behavior of the children in the studies and their training were not described. Again, as reflected in previously discussed studies, investigators rarely collected data on aspects of family life such as marital status or parenting competence that could potentially influence child personality traits such as aggression and activity level. Since these studies focused on children, the lack of longitudinal studies, especially with regards to child preferences, is significant. The effects of excess prenatal androgens on both males and females with CAH have been studied in depth over the last fifteen years; however, there are few qualitative or mixed method studies on this issue. Atypical genitalia and the physical and emotional struggles associated with it are likely sensitive topics for research and the related effects might not be adequately represented in questionnaires and surveys completed by parents and children with CAH.

As stated, studies were focused primarily on potential health complications associated with CAH, emergency management of the disorder, and potential consequences of excess androgen exposure. Very few studies examined the implications of these significant problems on family response to their child's CAH. The lack of knowledge in this area limits

the conclusions that can be made about family management of the condition and the experiences of family members.

Future Implications for Practice and Research

While CAH has similarities to other chronic, life threatening illnesses such as type 1 diabetes and asthma, which have previously been studied through a family lens, more research is needed to identify the ways having a child with CAH intersects with family life. For example, when parents are not properly instructed on how to manage emergency situations associated with CAH, the result can be not only improper use of emergency medical services (EMS) services and emergency departments in hospitals, but also, and more significantly, serious injury to and possible death of the child. Understanding and identifying gaps in parent education by healthcare professionals, especially concerning times of adrenal crisis and surrounding the decision to have reconstructive genital surgery in girls, is necessary to promote positive outcomes for children with CAH and their families. In addition, parents of girls born with CAH likely feel the need to keep their child's diagnosis of CAH more private due to potential stigmatization, which adds another challenge to a disorder that is already complex to manage. Health care providers should recognize this difference and develop support systems designed specifically for girls born with CAH and their families that address both surgical decision making and long-term complications resulting from being born with elevated testosterone. Future studies with an emphasis on family experience and management would enhance the current state of the science and provide a much-needed window into interventions aimed at improving the lives of families and children with CAH.

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Figure 1.
Prisma flowchart

Table 2.1

Summary of Articles: Health Related Issues Associated with CAH Diagnosis

Author (Year)	Sample/Setting	Purpose	Study Design	Conclusions
Bonfig et al. (2007)	68 patients with salt-wasting CAH in one clinic	To determine final height outcome and influences of steroid treatment	Retrospective	Patients with CAH are able to achieve adequate final height with conventional therapy. Total pubertal growth is significantly decreased and treatment with prednisone results in decreased final height.
Bonfig et al. (2011)	51 patients with CAH ages birth to 3 years in Bavaria. Both genders.	To analyze growth patterns in children with CAH diagnosed by newborn screening and treated with relatively low doses of hydrocortisone during the first year of life.	Cross sectional/Descriptive	Birth length is above average in children with classical CAH, which might be the result of untreated hyperandrogenism in utero. Relatively low doses of hydrocortisone treatment in the first 3 years results in heights that achieve genetic height potential.
Centinkaya & Kara (2011)	26 children with CAH and 11 healthy controls ages 2–15 years in Turkey. Both genders.	To evaluate the effects of glucocorticoid doses on bone mineral density (BMD) in children with CAH and to investigate other factors influencing BMD	Cross sectional/Descriptive	Children with CAH have higher BMIs than healthy controls. The bone age of the poorly controlled group (looking at 17ohp), late diagnosed groups and male patients were higher than the tightly-controlled group, early diagnosed group and female patients.
Harrington et al. (2012)	14 patients with CAH and 28 obese and 53 healthy controls ages 9–20 in Australia. Both genders.	To establish whether children with CAH have reduced vascular function and increased carotid intima media thickness (cIMT) when compared to healthy and obese children.	Cross sectional/Descriptive	CAH children have significant vascular endothelial and smooth muscle dysfunction when compared to healthy controls. The vascular dysfunction was comparable to the subjects with mild to moderate obesity.
Idris et al. (2014)	49 patients between the ages of 6–18 that attend a medical center in Malaysia. Both genders.	To determine the status of the behavioral outcome in children with CAH compared to a control group of children without CAH and to identify the risk factors that may influence it	Cross sectional/Descriptive	There was a higher incidence of parent reported problems of anxious/depressed and withdrawn/depressed behaviors, somatic complaints, social, thought, and attention problems and rule-breaking, aggressive, internalizing and externalizing behavior among CAH children compared to controls. Internalizing behavior problems were higher in CAH boys compared with controls; CAH girls had similar psychosocial adjustment to the control group. Family income (the lower the income, the more behavior problems) and glucocorticoid dose (the higher the dose, the more behavior problems) were significantly related to parent reported problem behavior.
Lin-Su et al. (2011)	34 patients with CAH treated with GH with a mean age of 8 yrs in New York, USA. Both genders.	Examine whether growth hormone (GH) alone or in combination with leutinizing hormone releasing hormone antagonist (LHRHa) improved the final adult height in patients with CAH	Non randomized/Prospective with an intervention	GH alone or in combination with LHRHa improves final adult height in patients with CAH.
Medes-dos-Santos et al. (2011)	21 pre-pubertal patients ages 2–10 years old with CAH and 67 healthy controls in Brazil. Both genders.	To evaluate growth and body composition of patients with CAH and to compare them with healthy children	Cross sectional/Retrospective/Descriptive	Patients had growth recovery with mean height similar to the general population; however, they had higher body fat, which seemed to be visceral, since there was not difference between the skinfolds of both groups.

Author (Year)	Sample/Setting	Purpose	Study Design	Conclusions
Moreira et al. (2013)	33 patients ages 6–17 who attend a clinic in Sao Paulo, Brazil. Both genders.	To investigate the prevalence of obesity and metabolic syndrome in young patients with CAH and to correlated this prevalence with glucocorticoid treatment and family history	Cross sectional/Comparative	CAH patients presented a higher prevalence of obesity and metabolic syndrome, which were not correlated with the glucocorticoid treatment suggesting that obesity and familial predisposition are significant determining factors for an adverse metabolic profile in CAH patients.
Nabhan et al. (2006)	71 patients with CAH ages 15 and younger in Indianapolis, USA. Both genders.	Investigate the incidence of urinary tract infections (UTIs) in children with CAH and to determine whether there was a correlation between timing and type of genital surgery in girls	Cross sectional/Descriptive/Retrospective	The incidence of UTIs in children with CAH is similar to the general population. There is not a suggested increase in UTIs if genital surgery in girls is delayed.
Volkl et al. (2006)	89 children and adolescents with ages birth through 17 in Bavaria. Both genders.	Analyze BMI values, compared with population-based references, for children and adolescents with CAH	Cross sectional/Retrospective	Children and adolescents with CAH have a higher risk of obesity. Glucocorticoid dosage, chronologic age, advanced bone age maturation, and parental obesity contributed to elevated BMI SDS, whereas birth weight and length, serum leptin levels, used glucocorticoid, and mineralocorticoid dosage were not associated with obesity.

Table 2.2
Summary of Articles: Physical and Psychosocial Consequences from Exposure to Excess Androgens

Author (Year)	Sample/Setting	Purpose	Study Design	Conclusions
Al-Maghribi (2007)	The records of 73 children (39 were genetic females and 34 were genetic males) with CAH ages five months to 18 years in Jordan. Both genders	To evaluate the clinical features of all of the patients with CAH who were followed at the King Hussein Medical Center in Jordan from 1996–2006.	Descriptive/Retrospective	Among the 39 females with CAH, 27 had developed anomalies of the external genitalia; 20 of them underwent surgical interventions of their external genitalia. Fourteen genetically female patients were wrongly diagnosed as 'male sex' at birth due to severe virilization. Seven of them were reassigned 'female sex' socially, legally, and surgically; the parents of one of them (a four-year-old girl) wanted the surgical intervention postponed for two to three years. Hysterectomy and gonadectomy were carried out for 6 of the other 7 patients who chose to keep the male genders.
Beltz et al. (2011)	125 individuals: 46 females with CAH; 21 without and 27 males with CAH; 31 without ages 9–26 years in Mid-western USA. Both genders.	To explore the contribution of sex hormones on occupational interests in females and males with CAH compared to their same gender, unaffected siblings.	Cross sectional/Descriptive	Females with CAH had more interest in "things" versus "people" than unaffected females and variations among females were congruent with degree of exposure to androgens.
Berenbaum & Bailey (2003)	43 girls with CAH, 7 tomboys, and 29 sister/cousin controls ages 3–18 years in USA. All girls.	To study gender identity in girls with CAH in relation to characteristics of the disease and treatment, particularly genital appearance and surgery	Mixed Methods/Descriptive	Gender identity in girls with CAH was not related to degree of genital virilization or age at which genital reconstructive surgery was done.
Berenbaum et al. (2012)	58 males and females with CAH and 27 unaffected siblings ages 16–30 in mid-western USA. Both genders.	To study effects of early androgens on spatial and mechanical abilities in adolescents and young adults with CAH	Cross sectional/Descriptive	Increased spatial ability was enhanced for females with CAH compared to their unaffected sisters. Males with CAH showed reduced spatial abilities compared to their unaffected brothers.
Hines et al. (2003)	128 participants: 40 females and 29 males with CAH and 29 unaffected female and 30 unaffected male relatives of individuals with CAH ages 12–45 years in London. Both genders	To investigate the androgen influences on spatial abilities	Cross sectional/Descriptive	Females with CAH performed better than unaffected females on spatial ability tests and resembled unaffected males and males with CAH. Males with CAH showed unaltered performance on the targeting tasks, and impaired performance on the mental rotations tasks.
Knickmeyer et al. (2006)	60 individuals with CAH (34 females, 26 males), and 49 unaffected relatives age 12–45 years in London. Both genders.	To examine the hypothesis that autistic traits are increased following prenatal exposure to abnormally high levels of testosterone caused by CAH	Cross sectional/Descriptive	Females with CAH scored significantly higher than unaffected females on the total Autism Spectrum Quotient questionnaire, largely due to enhanced scores on subscales measuring social skills and imagination.
Kulshreshtha et al. (2010)	3 individuals with CAH age 2 to 4 years that attend a clinic in India. Females	To report on the effect of steroid therapy during infancy and early childhood on the appearance of the external genitalia of girls with CAH.	Longitudinal/Case Study	Unclear if patients in the study suffered from classical CAH, although that is the determination of the authors, despite none of the 3 children beginning steroid treatment until after the age of 2 months. There is improvement in the external appearance of genitalia with post-natal steroid therapy.
Maryniak et al. (2014)	33 females ranging from 6–23 years old from 19 at-risk CAH families (17 girls treatment prenatally with	To assess cognitive development and social and emotional function in girls prenatally treated with	Mixed Methods/Cross sectional	Prenatal treatment with dexamethasone in CAH unaffected girls can cause the risk of unfavorable

Author (Year)	Sample/Setting	Purpose	Study Design	Conclusions
	dexamethasone (9 affected; 8 non affected) and 16 CAH affected females prenatally untreated, Poland.	dexamethasone compared to female CAH patients who were not subjected to prenatal therapy		influences on the development of some cognitive functions.
Mathews et al. (2009)	128 participants belonging to 1 of 4 groups: 1. Females with CAH 2. Unaffected female relatives 3. Males with CAH and 4. Unaffected male relatives ages 12–44 in the London area. Both genders.	To investigate influences of early androgen exposure on personality	Cross sectional/Descriptive	There are alterations in males and females with CAH in some personality facets that show sex differences. Females: tendencies to physical aggression and less tender minded. Males: less dominant, less rough and tumble play, more tender minded.
Meyer-Bahlberg et al. (2004)	Dexamethasone unexposed girls (15 with CAH and 30 without) and the dexamethasone unexposed boys without CAH ages 5–12 years old in the U.S. Both genders	To test in CAH girls of middle childhood the assumption that prenatal androgens determine the development of gender identity	Mixed Methods/Descriptive	Prenatal androgenization female fetuses lead to marked masculinization of later gender-related behavior, but the absence of any increased gender-identity confusion/dysphoria. This concludes that a direct determination of gender identity by prenatal androgens does not support a male gender assignment at the birth of the most markedly masculinized girls.
Nordenstrom et al. (2002)	40 females (from 35 families) with CAH in Sweden between the ages of 1–10.	To investigate the possible influence of disease severity (degree of fetal androgen exposure) on toy play and toy preference in girls with CAH.	Cross sectional/Observational	Girls with CAH played more frequently with masculine toys than controls. Additionally, the degree of disease severity reflected in CYP21 genotype (ie. degree of fetal androgen exposure) contributed to the degree of masculinization of toy play and preference, with a higher degree of fetal androgen exposure correlating to increased likelihood of preferring masculine toys.
Ozbeý et al. (2004)	70 female patients with CAH were counseled for gender assignment and had reconstructive surgery in Istanbul Turkey. Girls only.	To report experience of gender (re)assignment in genotypical female patients with CAH	Descriptive/Retrospective	49 were reared as female and 21 as male. Only 9 of these “males” could be reassigned as females (mean age 7.87 months). It is extremely difficult to correct the gender of patients with female CAH when they present > 2.5 years of age.
Pusterski et al. (2005)	117 children (34 females and 31 males with CAH; 27 unaffected sisters and 25 unaffected brothers) ages 3–10 and parents. Los Angeles, USA.	To assess the toy choices of young children with CAH and their unaffected siblings as well as the parental encouragement of sex-typed toy play.	Cross sectional/Observational	Girls with CAH displayed more male-typical toy choices than did their unaffected sisters, whereas boys with and without CAH did not differ. Mothers and fathers encouraged sex-typical toy play in children with and without CAH. Girls with CAH received more positive feedback for play with girls’ toys than did unaffected girls.
Paterski et al. (2007)	113 children (36 girls, 29 boys with CAH; 25 unaffected sisters, 21 unaffected brothers) ages 3–11 and their mothers from the U.S and U.K. Both genders	To provide more definitive information on the effects of early androgen exposure on aggression and activity level by using a larger sample than in prior studies and by using a standardized questionnaire measure of current behavior	Cross Sectional/Descriptive	Prenatal elevation in androgen that is experienced by females with CAH is associated with increased aggressive behavior and activity level in childhood. There were no significant differences in either aggressive behavior or activity level for boys with versus without CAH.
Pusterski et al. (2015)	153 children total. 43 females and 38 males with CAH and 41 unaffected female and 31 unaffected male relatives, aged 4–11, living in the United Kingdom (England, Northern Ireland, Wales, and Scotland)	To investigate potential cross-gender identification in girls exposed prenatally to high concentrations of androgens due to classical CAH.	Cross sectional/Mixed Methods	Girls with CAH had more cross-gender responses than female controls on all three measures of cross-gender identification as well as on a composite measure of gender identity independent of gender role behavior. Parent report showed 12.8% of the girls with CAH exhibited cross-gender behavior in all 5 behavioral domains compared to 0% of the children in the other three

Author (Year)	Sample/Setting	Purpose	Study Design	Conclusions
				groups combined. The researchers concluded that prenatal androgen exposure could play a role in gender identity development in healthy children, and may be relevant to gender assignment in cases of prenatal hormone disruption.
Servin et al. (2003)	26 girls affected with CAH and 26 unaffected girls ages 2–10 years in Sweden. Girls only	3 aims: 1 to replicate and extend previous findings of masculinization of behavior in girls affected by CAH. 2 to investigate a possible relationship between disease severity and toy play 3. to explore possible parental influences on the behavior of the girls	Cross sectional/Observational	Girls with CAH were more interested in masculine toys and less interested in feminine toys and were more likely to report having male playmates and to wish for masculine careers. Parents of girls with CAH rated their daughters' behaviors as more boy like than did parents of unaffected girls. A relationship was found between disease severity and behavior indicating that more severely affected CAH girls were more interested in masculine toys and careers. No parental influence could be demonstrated on play behavior.
Woelfle et al. (2002)	16 completely virilized females in Germany between the ages of 8–49 years	To better understand specific problems of female CAH patients with complete virilization and male sex assignment	Cross sectional/Descriptive	Patients with CAH and complete virilization have a high risk of being diagnosed late. There are significant negative challenges associated with gender reassignment. Gender identity is disturbed in some patients. Multiple surgical procedures are necessary and challenges with stature and precocious puberty are likely. Neonatal screening is of great importance to avoid some of these concerns.
Wong et al. (2013)	The adolescent–adult sample included 40 females and 29 males with CAH and 29 female and 30 male unaffected relatives age 12–45 years recruited from UK. The child sample included 37 females and 31 males with CAH and 27 female and 21 male unaffected relatives ages 3–10 years. Twenty-nine children with CAH and 13 unaffected relatives were recruited in the UK and 39 children with CAH and 35 unaffected relatives were recruited in Los Angeles, USA.	To assess parental encouragement of sex-typical toy play, as well as encouragement of spatial activities, in offspring with and without CAH. To evaluate the relationships between parental encouragement and offspring toy play and spatial ability.	Cross sectional/Observational	Females with CAH showed more boy-typical toy play and better targeting performance than control females, but did not differ in mental rotations performance. Males with CAH showed worse mental rotations performance than control males, but did not differ in sex-typical toy play or targeting. Reported parental encouragement of girl-typical toy play correlated with girl-typical toy play in all four groups.

Table 2.3
Summary of Articles: The Lived Experience of Having CAH for Those Affected and Their Families

Author (Year)	Sample/Setting	Purpose	Study Design	Conclusions
Armstrong et al. (2006)	58 parents of children age 1 month -17 years with CAH in Hanoi Vietnam. Both genders.	To provide more specific insights into difficulties faced by families with CAH living in Vietnam	Cross sectional/Descriptive	A child with CAH is a huge financial concern for parents. There is a need for both support groups and universal screening.
Bhakhri & Jain (2011)	28 individuals (17 males and 11 females) who are parents of 22 affected children aged < 5 years in New Delhi India.	To explore the perceptions and misconceptions of parents of children with CAH in India	Cross sectional/Descriptive	There is a great deal of misconceptions, practices and concerns prevalent among the parents of children in India affected with CAH. These include gaps in knowledge concerning CAH, steroid use, medication, and ambiguous genitalia.
Boyse et al. (2014)	4 mothers and 2 fathers from four separate families having a child with CAH (children's ages were 5–11 with 2 males and 2 females). USA.	To characterize early parent caregiver experiences and needs in CAH with a focus on contextual factors that can be modulated through education and support delivered by health care providers or via the newborn screening system.	Qualitative/Descriptive	Several themes emerged from the interviews including health communication problems, a lack of medical home and decision support, and a desire for parent-to-parent social support.
de Silva et al. (2014)	37 parents (26 mothers and 11 fathers) of children (both genders) with CAH who attended an endocrinology center in Sri Lanka.	To determine the depressive symptoms in parents of children with CAH	Cross sectional/Descriptive	59% of the parents of children with CAH were classified as having symptoms of depression, and these depressive symptoms did not abate with the passage of time.
Gilban, Alves, & Beserra (2014)	25 patients (age 5–18 years) with CAH in Brazil as well as their parents. There were 19 female patients and 6 were male. Among the 19 female patients, 2 identified as male. Brazil.	To evaluate the health related quality of life of children and adolescents with CAH	Cross sectional/Descriptive	There is a loss of health related quality of life in children and adolescents with classical CAH. The self-assessment was concordant in key areas with the assessment made by their parents. No differences were observed between genders or clinical presentation of the disease.
Sanches et al. (2012)	104 parents of children with CAH age 0–18 years as well as 24 adolescents with CAH living in The Netherlands. Both genders.	To investigate the physical, social, and societal functioning of children with CAH and their parents in a Dutch population.	Cross sectional/Descriptive	Children with CAH, according to their parents, experience few negative effects of the condition and they participate well in several areas such as school and leisure time. Improvements can be made concerning the measures parents and children must take to prevent an adrenal crisis.
Yau et al. (2015)	Children with CAH (n=33) as well as children with hypothyroidism (n=14) and their parents were recruited from a university based pediatric endocrinology clinic in Los Angeles, USA. Both genders.	To evaluate health related quality of life in children with CAH and investigate whether CAH poses an additional burden compared to other endocrine disorders.	Cross sectional/Descriptive	Compared to subjects with hypothyroidism, children with CAH self-reported lower health related quality of life in school domain scores. CAH children more frequently reported peers not wanting to be friends. There was a strong correlation between child self report and parent proxy report.

Table 2.4
Summary of Articles: Acute Illness, Stress Dosing, and Adrenal Crisis Experiences and Management

Author (Year)	Sample/Setting	Purpose	Study Design	Conclusions
Fleming et al. (2011)	60 caregivers of children ages 0–16 with CAH in Los Angeles, CA. Both genders.	To assess caregiver knowledge of CAH, adrenal crisis, and stress dosing and to assess their confidence in managing adrenal crisis and stress dosing of children with CAH. Further the relationship between caregiver knowledge and self-efficacy was examined.	Cross sectional/Descriptive	Caregivers had a good understanding of CAH but those that received both a written instruction guideline and a demonstration on how to give the hydrocortisone injection scored higher on both self efficacy of stress dosing and self efficacy of how to give the injection
Green-Golan et al. (2007)	6 adolescents with CAH ages 16–20yrs were compared with 7 age sex and BMI matched controls (16–23yrs) using a 90 min standardized ergometer test. National Institutes of Health in Bethesda, MD. Both genders.	To assess hormonal, metabolic, and cardiovascular response to prolonged moderate intensity exercise comparable to brisk walking in adolescents with classic CAH	Cross sectional/Observational	Patients with CAH have defective glycemic control evident in prolonged moderate intensity exercise. CAH patients have difficulty maintaining glucose levels as exercise duration increases.
Keil et al. (2010)	20 patients with CAH ages 3–10 enrolled in a long-term study at National Institutes of Health in Bethesda, MD. Both genders.	Examine blood glucose levels and symptoms of children with CAH during a physical stressor, such as a typical acute illness managed at home, and prospectively determine the frequency of hypoglycemia	Longitudinal	Children with CAH, despite receiving adequate glucocorticoid and mineralocorticoid supplementation, are at risk for hypoglycemia during common childhood illnesses.
Weise et al. (2004)	9 adolescent children with CAH and 9 adolescent children without CAH-done at National Institutes of Health in Bethesda MD	To examine whether an extra dose of hydrocortisone, similar to that given during other forms of physical stress, would normalize blood glucose levels during exercise in patients with CAH	Cross sectional/Observational	Patients with classical CAH do not benefit from additional hydrocortisone during short-term, high intensity exercise.