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The presentation of congenital adrenal hyperplasia in an unscreened population

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Abstract

Background: The aim of this study was to describe the incidence and spectrum of early clinical presentations of congenital adrenal hyperplasia (CAH) in an unscreened population.
Methods: A national retrospective observational study was undertaken to identify all children diagnosed with CAH in the Republic of Ireland, between January 2005 and December 2019. Reporting clinicians completed anonymized clinical questionnaires.
Results: There were 103 cases of CAH reported and 69 cases met the study inclusion criteria. The estimated annualized incidence of CAH in the Republic of Ireland was 1:14,754 or 0.07 cases per 1,000 live births. Forty-seven children presented clinically in the first six months of life, but only 17 of these had a confirmed diagnosis by day 10. Of these early presentations, there were 28 infants with salt-wasting, 15 females presented with virilized genitalia and four infants were detected due to a family history of CAH. Female infants presented at a median age of 0 days [IQR 0–1] and males at 14 days [IQR 9–21]. Seventy-eight percent of salt-wasting presentations occurred after day 10. Delays in clinical presentation, biochemical diagnosis and treatment initiation were identified.
Conclusions: The incidence of CAH is higher in Ireland than in other unscreened populations. In the absence of screening, clinicians should be aware of the possibility of CAH and appropriate investigations should be urgently requested. Life-threatening salt-wasting is the most frequent clinical presentation and many cases could be detected prior to decompensation if newborn screening were introduced.

Keywords: congenital adrenal hyperplasia; disorders of sex development; newborn screening; 17-hydroxyprogesterone; salt-wasting.

Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders that cause impaired steroidogenesis and are associated with excess androgen production. It is the most common form of primary adrenal insufficiency in children [1] and of 46XX disorders of sex development (DSD) [2]. Worldwide, the reported incidence of CAH ranges from 1:10,000 to 1:20,000 live births [3] and it is more prevalent in small, genetically isolated populations [4]. 21-hydroxylase deficiency (caused by mutations in *CYP21A2*) accounts for more than 90% of cases [5]. There is a wide spectrum of severity of illness at presentation ranging from life-threatening salt-wasting in infancy to milder simple virilizing and non-classical presentations. The diagnosis of CAH may be delayed in an unscreened population, as clinical presentations may mimic other more common conditions and milder cases may not be detected until later in childhood.

Newborn screening for CAH reduces time to diagnosis [6], morbidity, and mortality [7, 8], and is recommended by international endocrine societies [3, 9]. The primary aim of screening is to detect cases of classical 21-hydroxylase deficiency (salt-wasting and simple virilizing) prior to decompensation with salt-wasting or adrenal crisis. Female infants may often be identified more easily in the newborn period due to virilization of external genitalia secondary to androgen excess. In contrast, male infants may not manifest any clinical signs at birth but present later with life threatening salt-wasting adrenal crisis. Undiagnosed CAH has been described as a cause of apparent sudden infant death syndrome [7, 10] and newborn screening for CAH can be associated with reduced infant mortality [11, 12], less severe hyponatraemia at

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presentation and shorter duration of initial hospital admission [13]. It also facilitates detection in girls whose virilization may not always be diagnosed clinically [14] or where the etiology of virilized genitalia is unclear [15]. In children with milder enzyme deficiencies, screening can identify those who may otherwise present later in childhood with precocious puberty, advanced skeletal maturation or subfertility [16, 17]. Some cases of 11β-hydroxylase deficiency [18] and 3β-hydroxysteroid dehydrogenase deficiency [19] may also be identified through screening.

Despite the availability of newborn screening for CAH, and its role in identifying infants prior to the development of critical illness, this is not implemented in all countries. While CAH screening is established in the United States and more than 40 countries [20], it has not been introduced in the United Kingdom. Reasons for this include concerns about the acceptability of the screening test [21] and a report that did not identify increased mortality in an unscreened population [22]. Although false negative cases have been reported with newborn screening [23], the high frequency of false positive cases is of greater concern [12, 24, 25] as this may lead to unnecessary investigations and parental stress.

In order to better understand the presentation of CAH in an unscreened population, this study aimed to characterize the severity of illness in infants at diagnosis of CAH in the Republic of Ireland over a 15-year period.

Materials and methods

The Ethics Committee of Children's Health Ireland approved this study. A national, anonymized, retrospective study was performed to identify all children diagnosed with CAH in the Republic of Ireland between January 2005 and December 2019 inclusive. Cases were identified through contacting all Pediatric Endocrinologists and Endocrine Clinical Nurse Specialists in the Republic of Ireland.

Case notifications were reviewed by an expert panel (NPM/CPH) to determine whether the case met the inclusion criteria. A child was considered to have a diagnosis of CAH if they had a typical clinical feature (adrenal insufficiency, virilized external genitalia, family history, precocious puberty, advanced bone age, hypertension, or signs of androgen excess) and a diagnostic biochemical or genetic investigation (urine steroid profile, elevated 17-hydroxyprogesterone (17OHP) levels, and/or genotyping of *CYP21A2*). Cases were included if they met the diagnostic criteria, were born in Ireland and were diagnosed during the study period. Cases were excluded from the study if an alternative diagnosis was likely, they were born outside of the study period or they were born in another country.

The overall annualized incidence of CAH in the Republic of Ireland was calculated using the annual birth rate provided by the Central Statistics Office [26]. The number of children born each year who were diagnosed with CAH was compared to this annual live birth rate.

Given that the aim of this study was to characterize clinical presentations of CAH, the descriptive and statistical analyses thereafter focused on early presentations. We defined early presentations as those presenting before the age of six months, as these infants were more likely to have severe salt-wasting or virilization at presentation. Cases were grouped according to their reason for clinical presentation. The age at first clinical presentation was defined as the day the patient presented with symptoms prompting investigation and subsequent diagnosis. The day of birth was designated as day zero. Infants with a measured serum sodium concentration below the reference range at presentation were considered to have salt-wasting.

Additional data collected included symptoms and signs at initial presentation, birth weight and gestation, biochemical data (including time to 17OHP result availability), genetic test results and radiology reports. Clinical management at initial presentation including need for resuscitation, duration of hospitalization, need for intensive care management or transfer to another unit was reviewed.

Statistical analyses were performed using SPSS 26.0 (SPSS Statistics, IBM Corporation, Armonk, NY). Non-normally distributed continuous data were presented as median and interquartile range and compared using one-way ANOVA tests. Categorical data were presented as proportions. Mann–Whitney U tests were used to compare independent variables. A p value of <0.05 was considered statistically significant.

Results

Overall study population

All 14 Pediatric Endocrinologists in the Republic of Ireland provided data and 103 cases were notified. Thirty-four cases were excluded as they did not meet the inclusion criteria (Figure 1). There were 1,018,056 live births in the Republic of Ireland between January 2005 and December 2019 and 69 children born in this period were diagnosed with congenital adrenal hyperplasia, giving an overall annnualized incidence of 1:14,754 or 0.07 cases per 1,000 births.

Of the 69 children born between January 2005 and December 2019 and diagnosed with CAH, 35 were female (51%) and 34 were male. Forty-seven children (68%) were of Irish ethnicity, 8 (12%) were of 'other white' ethnicity, 4 (6%) were Asian, 4 (6%) were of 'other' or 'mixed' ethnicity, 3 (4%) were from the Irish Travelling community and 3 (4%) were African black. The following subtypes were identified: 21-hydroxylase deficiency (n=67) and 11β-hydroxylase deficiency (n=2). Forty-one percent of all clinical presentations of CAH were salt-wasting (n=28) and 79% of males presented with salt-wasting. There were 22 females (63% of females) detected following presentation with virilized genitalia. A further six infants were screened for CAH due to a known family history. 13 children (4 males and 9 females) presented later in childhood with precocious puberty, and one presented with hypertension. The majority (68%) of children presented in the first six months of life, with no salt-wasting presentations occurring beyond this age.

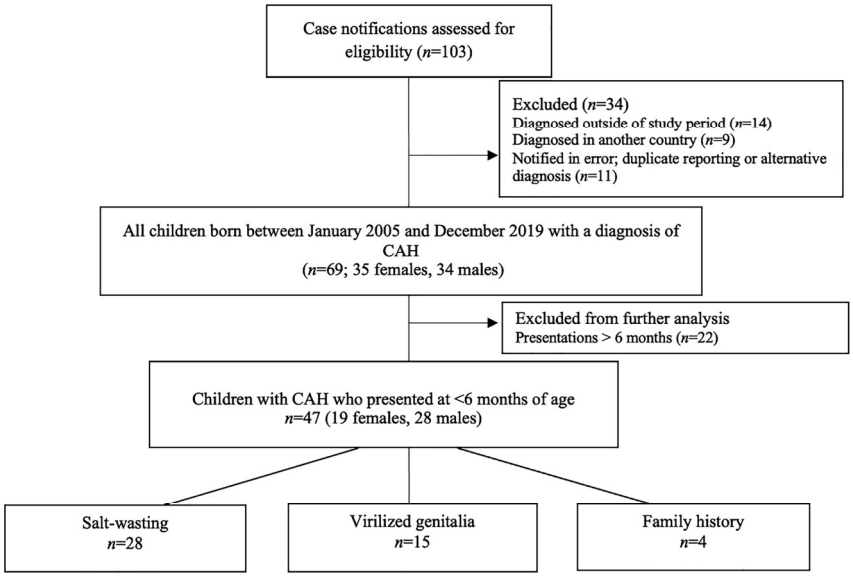

Figure 1: Flow diagram of case notifications, excluded cases and clinical presentations of CAH in the first 6 months of life.

Infants presenting before the age of six months

Forty-seven infants (28 males, 19 females) were diagnosed before the age of 6 months. Of these, 46 had 21-hydroxylase deficiency and 1 had 11β-hydroxylase deficiency. Sixty percent (n=28) of these early presentations were with salt-wasting. Thirty-two percent (n=15) were females presenting with virilized genitalia and eight percent (n=4) were identified due to a family history of CAH. The median birth weight was 3340 g [IQR 3,030–3,800] and 96% were born at term.

Of the 47 early presentations, 39 (83%) presented in the first thirty days and 24 (51%) before day ten (Figure 2). The median age at presentation was 9 days [IQR 0–17] (Table 1). Females presented at a median of 0 days [IQR 0–1] and males at 14 days [IQR 9–21] (p≤0.001). The median time to 17OHP result from sampling was 6 days [IQR 4–10] and the median age at 17OHP result was 15 days [IQR 5–26]. Only 17 infants had received a definitive diagnosis by day 10. Electrolyte abnormalities were more commonly seen in infants presenting later (Figure 3A and B).

Hydrocortisone treatment was initiated in 64% of infants before a biochemical diagnosis was made. Females commenced hydrocortisone treatment at a median age of 4 days [IQR 3–6], whereas treatment was delayed in males until a median age of 15 days [IQR 11–30] (p≤0.001). Male infants had more extensive investigations, required more fluid resuscitation (22 males, 0 females) and had more intensive care admissions (5 males and 0 females).

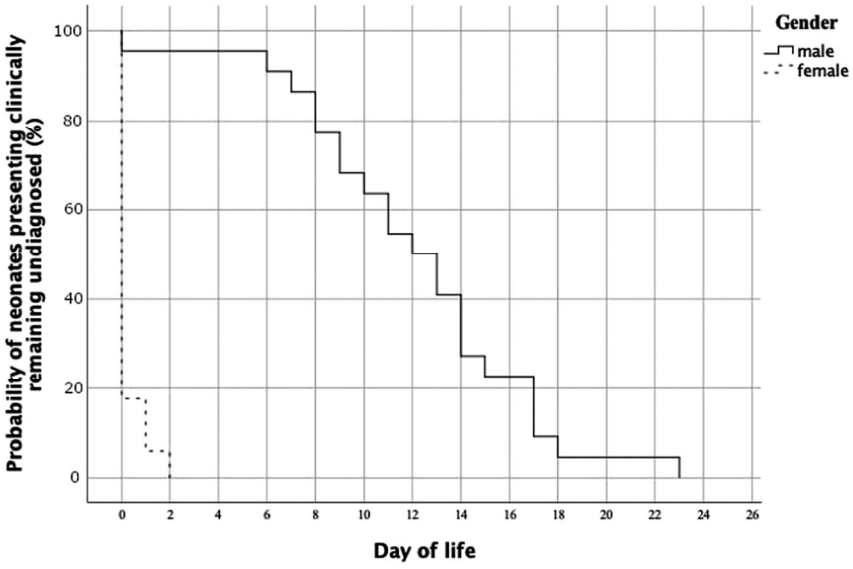

Figure 2: Kaplan–Meier survival graph of probability of remaining undiagnosed in children presenting clinically in the first thirty days of life, stratified by gender.

Table 1: Characteristics of patients presenting with congenital adrenal hyperplasia in the first six months of life.

Variable	Total, n=47	Salt-wasting, n=28	Virilized genitalia, n=15	Family history, n=4
Sex, female: male	1:1.5	1:27	NA	3:1
Age at presentation, median days [IQR]	9 [0–17]	14 [10–30]	0 [0–1]	0 [0–0]
Age at biochemical diagnosis, median days [IQR]	15 [5–26]	23 [15–45]	5 [3–8]	0 [0–2]
Age at hydrocortisone commencement, median days [IQR]	11 [5–18]	16 [11–37]	4 [3–6]	3 [3–5]
Serum 17OHP at presentation, nmol/L, median [IQR]	478 [300–755]	500 [299–800]	457 [230–567]	229 [54–635]
Serum sodium at presentation, mmol/L median [IQR][a,b]	124 [116–136]	120 [112–123]	137 [134–138][a]	136 [134–140]
Serum potassium at presentation, mmol/L, median [IQR][a,c]	6.5 [5.7–7.6]	7.2 [6.2–7.8]	5.0 [4.8–6.4][a]	5.7 [5.0–5.8]
Length of admission, median days [IQR]	11 [6–14]	12 [8–17]	11 [4–12]	5 [3–7]

[a]Serum sodium from the day of clinical presentation were not available for two infants presenting with virilized genitalia. Serum potassium from the day of clinical presentation was not available for four infants presenting with virilized genitalia. [b]Reference range 133–144 mmol/L. [c]Reference range 3.5–5.5 mmol/L.

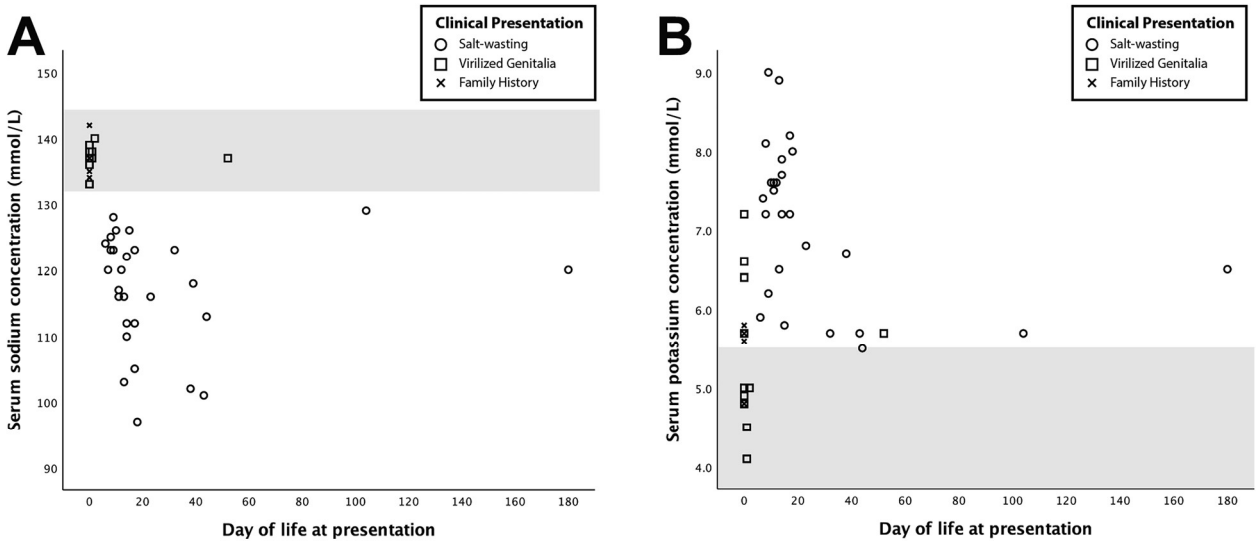

Figure 3(A): Serum sodium concentration according to day of life at presentation shown according to reason for clinical presentation. *Serum sodium from the day of clinical presentation were not available for two infants presenting with virilized genitalia. Figure 3 (b) Serum potassium concentration according to day of life at presentation shown according to reason for clinical presentation. *Serum potassium from the day of clinical presentation was not available for four infants presenting with virilized genitalia.

The median length of admission was 11 days for both genders.

Infants presenting with salt-wasting

There were 28 cases of salt-wasting CAH identified during the study period, all of whom presented before six months (Table 1). The majority presented after day 10 (n=22; 79%). In 20 cases (71%) CAH was not suspected at the time of first clinical presentation, with initial investigations focusing on suspected feeding issues, possible gastrointestinal or renal etiologies and sepsis evaluations. In a quarter of cases (n=7), the infant had previously presented to an emergency department or general practitioner with symptoms of vomiting, poor weight gain and lethargy and was discharged without investigation. Clinical features at presentation included; poor weight gain or weight loss (n=23), vomiting (n=12), lethargy (n=9), scrotal hyperpigmentation (n=5), and jaundice (n=4). The median weight loss from birth weight was 8% [IQR 5–14%].

Three infants presented with hypoglycemia. Metabolic acidosis was noted in 7 infants (37%) and significant renal impairment was seen in 5 (18%). All infants had

hyponatremia and hyperkalemia (Table 1). Nineteen infants had an abdominal ultrasound, with adrenal hyperplasia noted in 11 (58%) of these.

Twenty-two infants (79%) required fluid resuscitation and 26 (93%) received intravenous fluids. Five infants were admitted to intensive care, with a median length of stay of 3 days [IQR 2–4] and 11 infants (39%) required transfer to a tertiary care center. There were no reports of mortality.

Infants presenting with virilization

Fifteen girls presented with virilized external genitalia in the first six months of life and 14 of these were identified in the first 48 h of life. Clinical findings described included clitoromegaly, hyperpigmentation, posterior labial fusion, and labioscrotal folds.

Three infants who had normal electrolytes at presentation developed hyponatremia while awaiting confirmation of diagnosis. Fourteen ultrasounds were performed in this cohort and 8 of these identified features of CAH which expedited diagnosis. Nine (60%) infants had urine sent for urine steroid profile analysis, which indicated a diagnosis of CAH. The time to USP result availability was not reported.

One infant received intravenous fluids. There were no intensive care admissions within this group, but five children (33%) were transferred to a tertiary unit for assessment.

Infants presenting due to a family history of CAH

Four infants were identified because of a family history of CAH; three had received a prenatal diagnosis and two of these had been treated prenatally. Electrolytes and blood glucose monitoring were normal in this group. As these infants were diagnosed early in the newborn period, they were not treated with stress dose hydrocortisone or intravenous fluids and they did not require interhospital transfer or intensive care admission. They had minimal investigations and their median length of stay from birth was 5 days [IQR 3–7], significantly shorter than the other cohorts (p=0.01) (Table 1).

Discussion

In this study we have described the spectrum of clinical presentations of CAH in an unscreened population. The majority of children presented in the first 6 months of life, but only a quarter of all children with CAH were diagnosed by day 10. The most common clinical presentations of CAH were salt-wasting (which occurred predominantly in males), followed by virilized external genitalia in girls. The majority of salt-wasting presentations occurred after day 10 and was preventable. Delayed diagnoses, in the absence of newborn screening, led to repeated presentations, unnecessary (and potentially harmful) investigations (including blood cultures, lumbar punctures, metabolic investigations, and barium studies), significant cost and likely parental distress. Virilized girls generally presented earlier. However, even when a clinical diagnosis of CAH was suspected, there was a delay in biochemical confirmation of the diagnosis.

Our data highlights potential benefits of early detection in preventing severe clinical presentations of CAH. Consistent with other studies of unscreened populations [27, 28], most boys with CAH presented later than girls and following decompensation with salt-wasting. Contrary to earlier reports, our data and others [14, 29] suggest that CAH is not always detected clinically in girls and therefore newborn screening for CAH should include both male and female infants. In comparison with similar studies of unscreened populations in the United Kingdom [27] and Australia [28], the incidence of CAH is higher in Ireland and salt-wasting was a more common reason for clinical presentation.

Newborn screening for CAH has the potential to prevent clinical presentations with salt-wasting, expedite diagnosis in virilized females and reduce morbidity arising from later presentations [3, 20]. However, the implementation of newborn screening for CAH is not straightforward. Although many programmes have reported positive outcomes [14, 30–32], low positive predictive values remain problematic and this leads to the identification of many healthy infants who require additional testing [12, 25]. Current guidelines [3] recommend the measurement of 17OHP using a standardized immunoassay on dried blood samples, followed by secondary screening of elevated results by liquid chromatography-tandem mass spectrometry to improve specificity. Birth weight/gestational age cut-offs have been used as the false positive rate is known to be higher in preterm and low birth weight infants [3, 12]. The additional measurement of 21-deoxycortisol has also been shown to improve the positive predictive value and may be a superior analyte for consideration in contemporary screening programmes [33].

Strengths of this study include its comprehensive national data that span 15 years in an unscreened population. This is the first study to detail the spectrum and severity of presentations of CAH in Ireland and details the severity of illness at presentation in this population. In the absence of newborn screening, it is possible that our results underestimate the incidence of all CAH as many children with non-classical are likely to be missed. It is also possible that

infants with undetected salt-wasting CAH may have died and that their death registered as a sudden infant death, as has been reported by other authors [7, 10]. When performing this study, the authors contacted the National Pediatric Mortality Register of Ireland to determine if the records could be assessed for possible missed CAH cases. Reporting of 17OHP, electrolytes or adrenal size is not standardized at postmortem and therefore this aspect of the study was not possible.

Conclusion

CAH is a treatable genetic condition, which is associated with significant morbidity at the time of presentation in an unscreened population. In the absence of universal newborn screening, rapid access to 17OHP testing is required to ensure prompt diagnosis when a clinical suspicion of CAH is raised. CAH screening is cost effective [32], as it reduces mortality and adverse outcomes from late diagnosis. We recommend that newborn screening for CAH should be added to all newborn screening programmes to identify children prior to the development of the clinical complications described in this study.

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Author contributors: TAC conceptualised and designed the study, coordinated the data collection, performed data analyses and drafted the initial manuscript. CPH conceptualised and designed the study, provided critical statistical analysis support and revised the manuscript. JJB contributed to the interpretation of the findings and revised the manuscript. NPM conceptualised and designed the study, reviewed and edited the manuscript. All authors approved the final manuscript as submitted and are accountable for all aspects of the work.
Competing interest: TAC, CPH, JJB and NPM have no financial relationships relevant to this article to disclose.
Ethical approval: This study was approved by the Ethics Committee of Children's Health Ireland (19.016).
Informed consent: Not applicable.

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