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THE INCIDENCE AND PRESENTATION OF CONGENITAL ADRENAL HYPERPLASIA

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INTRODUCTION

- Worldwide, the reported incidence of congenital adrenal hyperplasia (CAH) ranges from 1:10,000 to 1:20,000 live births and it is more prevalent in small, genetically isolated populations [1]. 21-hydroxylase deficiency (caused by mutations in *CYP21A2)* accounts for more than 95% of cases [1].
- There is a wide spectrum of severity of illness at presentation ranging from life threatening salt-wasting in infancy to milder simple virilising and non-classical presentations [2].
- 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 [3].

AIM

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

METHOD

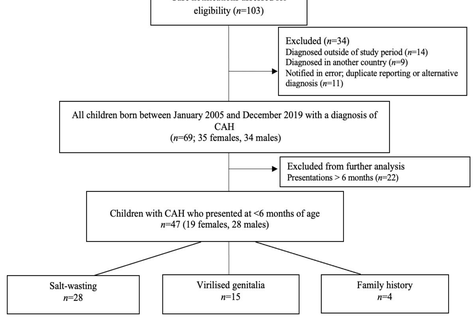
- A national, anonymised, retrospective study was performed to identify all children diagnosed with CAH in the Republic of Ireland between January 2005 and December 2019 inclusive.
- Cases were identified through contacting all Paediatric Endocrinologists and Endocrine Clinical Nurse Specialists in the Republic of Ireland.
- The overall annualised incidence of CAH in the Republic of Ireland was calculated using the annual birth rate provided by the Central Statistics Office (CSO).
- Given that the aim of this study was to characterise clinical presentations of CAH, the descriptive and statistical analyses thereafter focused on presentations before the age of 6 months.
- 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 (IQR) 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 incidence of CAH

- There were 1,018,056 live births in the Republic of Ireland between January 2005 and December 2019
- 69 children born in this period were diagnosed with CAH, giving an overall annualised incidence of **1:14,754 or 0.07 cases per 1000 births**.

Flow diagram of case notifications, excluded cases and early clinical presentations



Infants diagnosed before six months of age

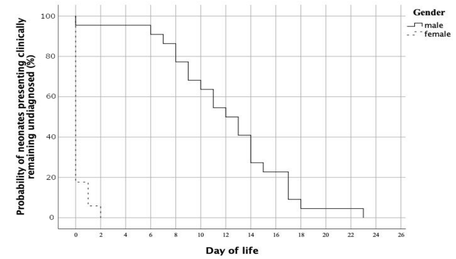
- Of the 47 early presentations, 39 (83%) presented in the first thirty days and 24 (51%) before day ten. Females presented at a median of 0 days [IQR 0-1] and males at 14 days [IQR 9-21] (p=<0.001).
- The median time to 17OHP result from sampling was 6 days [IQR 4-10] and the median age at 17-hydroxyprogesterone (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.
- 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, 0 females).

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

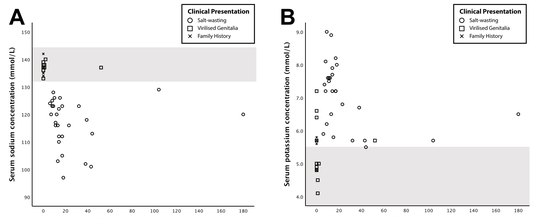
Variable	Total, *n*=47	Salt-wasting, *n*= 28	Virilised genitalia, *n*=15	Family history, *n*=4
Sex, female: male, n	1:1.5	1:27	N/A	3:1
Age at presentation, median days [IQR]	9 [0-17]	14 [10-30]	0 [0-1]	0 [0-0]
Age at biochemical diagnosis, median days [IQR]	15 [5-26]	23 [15-45]	5 [3-8]	0 [0-2]
Age at 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]*†	124 [116-136]	120 [112-123]	137 [134-138]*	136 [134-140]
Serum potassium at presentation, mmol/L, median [IQR]* Ω	6.5 [5.7-7.6]	7.2 [6.2-.7.8]	5.0 [4.8-6.4]*	5.7 [5.0-5.8]
Length of admission, median days [IQR]	11 [6-14]	12 [8-17]	11 [4-12]	5 [3-7]

*Serum sodium from the day of clinical presentation were not available for two infants presenting with virilised genitalia. Serum potassium from the day of clinical presentation was not available for four infants presenting with virilised genitalia.
†Reference range 133-144mmol/L
ΩReference range 3.5-5.5mmol/L
N/A=Not applicable

Kaplan-Meier survival graph of probability of remaining undiagnosed in children presenting clinically in the first thirty days of life, stratified by gender



Serum sodium (A) and potassium (B) concentration according to day of life at presentation, shown according to the reason for clinical presentation



*Serum sodium from the day of clinical presentation were not available for two infants presenting with virilised genitalia.
The shaded area represents the normal range, 133-144mmol/L.

*Serum potassium from the day of clinical presentation were not available for four infants presenting with virilised genitalia.
The shaded area represents the normal range, 3.5-5.5mmol/L.

CONCLUSIONS

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 (NBS), rapid access to 17OHP testing is required to ensure prompt diagnosis when a clinical suspicion of CAH is raised.

CAH screening has been recommended [1,4], as it reduces mortality and adverse outcomes from late diagnosis and is cost effective [5].

We recommend that NBS for CAH should be added to the Irish National Newborn Screening Programme to identify children prior to the development of the clinical complications described in this study.

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