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Increased mortality in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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Abstract

Context: Reports on mortality in patients with congenital adrenal hyperplasia (CAH) are lacking.

Objective: To study mortality and causes of death in CAH.

Design, Setting and Participants: We studied patients with CAH (21-hydroxylase deficiency, n=588; *CYP21A2* mutations known, >80%), and compared them with controls (n=58800). Data were derived through linkage of national population-based registers.

Main Outcome Measures: Mortality and causes of death.

Results: The mean age of death was 41.2±26.9 years in CAH patients and 47.7±27.7 years in controls (P<0.001). Among CAH patients 23 (3.9%) had deceased compared to 942 (1.6%) of controls. The hazard ratio (and 95% confidence interval) of death was 2.3(1.2-4.3) in CAH males and 3.5(2.0-6.0) in CAH females. Including only patients born 1952-2009, gave similar total results but only patients with salt-wasting or with unclear phenotype had an increased mortality. The causes of death in CAH patients were adrenal crisis (42%), cardiovascular (32%), cancer (16%), and suicide (10%). There were seven additional deaths in CAH individuals with incomplete or reused personal identification number that could not be analyzed using linkage of registers. Of the latter all except one were deceased before the introduction of neonatal screening in 1986 and most of them in the first weeks of life, probably in an adrenal crisis.

Conclusions: CAH is a potentially lethal condition and was associated with excess mortality due to adrenal crisis. The salt-wasting phenotype seemed to have worse outcome also in children and adults due to adrenal crisis and not only before the introduction of neonatal screening.

Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder affecting one of the enzymes necessary for the adrenal synthesis of cortisol. More than 95% of all CAH cases have 21-hydroxylase deficiency, characterized by decreased cortisol and aldosterone levels and simultaneously increased production of adrenal androgens and steroid precursors (1-3). Untreated the condition is lethal in severe cases due to salt crisis and hypoglycemia. Females with salt-wasting (SW) or simple virilizing (SV) phenotype, i.e. classic CAH, have varying degrees of virilization of the external genitalia at birth. In contrast, males have no obvious signs of CAH at birth but males with SVCAH usually present with clinical symptoms of androgen excess at 2–4 years of age. Neonatal screening for CAH has been established in many countries to improve early detection and prevent neonatal salt-crisis and death. In Sweden a nationwide neonatal screening program for CAH was introduced in 1986, and 1 in 9000 infants has been found to be affected (4). Non-classic (NC) CAH is often not detected through the neonatal screening, thus reliable data on the frequency of the NC phenotype are absent but it is estimated to be substantially more common (1, 5). Most individuals with NCCAH are probably never diagnosed, but if they are it is usually due to symptoms and signs of androgen excess, including infertility, explaining why mostly females are diagnosed (5).

With the introduction of glucocorticoid treatment in the 1950s patients with classic CAH were able to survive. The need for glucocorticoid treatment is life-long and mineralocorticoids are often used, especially in the more severe cases. Once CAH has been diagnosed and treated, survival has been presumed to be normal. However, fatal adrenal crises are seen in clinical practice. Moreover, the physiological circadian rhythm of cortisol cannot be completely mimicked with oral glucocorticoids. During the last decades the awareness of the long-term risks of the disease and its treatment have increased (1-3), with reports on cardiometabolic risk factors (6-14), decreased bone mineral density (10, 12, 14-17) and risk of fractures (15, 16), psychiatric morbidity (18), and affected quality of life (10, 19-24). Increased risk of tumors, especially adrenal (25-28) and testicular (25, 29-31), have also been reported, however, only rarely malignant tumors (32, 33). It has been assumed that without neonatal screening mortality in CAH is elevated due to fatal adrenal crisis in undiagnosed boys with SW CAH. An increased female to male ratio in the most severely affected in the UK (34),

and in CAH populations in general have been interpreted as evidence of this (2). However, in a Swedish study we showed an increased survival for both males and females with SWCAH with the introduction of screening, and a persisting female preponderance among the mild cases, predominantly late diagnosed (4). Only one study has reported on mortality in patients with different forms of CAH (very few patients older than 35 years) and described an increased mortality at ages 1 to 4 years in girls with ethnicity from the Indian subcontinent (35).

The aims of the present study were to investigate the mortality and causes of death in a large cohort of patients with CAH due to 21-hydroxylase deficiency, and whether the outcomes differed between the phenotypes, as well as before and after the introduction of the nationwide neonatal screening.

Subjects and Methods

Subjects

The national registry of individuals with CAH (4) was used to identify 545 CAH patients with 21-hydroxylase deficiency and complete personal identification number born between 1910 and 2009. In more than 80% of the cases the diagnosis was genetically verified. An additional 43 individuals had received the diagnosis of CAH at least three times in the National Patient Register (NPR) using the International Classification of Diseases ICD-8 (255.01, 255.08), ICD-9 (2552, 255C) and ICD-10 (E25.0), and had not subsequently been given other diagnoses, i.e. Addison's disease, Cushing's syndrome, acromegaly, or received glucocorticoid treatment due to malignancies. Thus, 588 patients with CAH due to 21-hydroxylase deficiency were included. However, in the national CAH registry there were 14 additional patients that could not be included in the registry study due to incomplete or reused personal identification number, or death before the introduction of the complete personal identification numbers. Seven of them were known to have deceased and the details known about them were noted.

The patients were divided in genotype groups depending on the most common *CYP21A2* mutation analyses performed as previously described (4, 28), including a detailed

description of all the different mutations in this cohort (4), denoted: null, I2splice, I172N, P30L and V281L. In compound heterozygotes, the mildest mutation defined the genotype group. Null is associated with the SW phenotype, I2 splice is most often associated with the SW phenotype, I172N typically leads to SV, while V281L results in NCCAH. P30L results in a phenotype with a severity in between SV and NC, but was in this study defined as SV. CAH individuals with unknown *CYP21A2* mutations were given a clinical classification (SW, SV, or NC) if clinical data were available that clearly could be used for classification. Patients with genetically verified or clinically diagnosed NC disease were combined and categorized as the NC group.

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

Study protocol

We used a matched cohort design, with exposure defined as having the diagnosis of CAH in the national CAH registry or in the NPR. We identified 100 unexposed individuals per CAH patients, matched by birth year, sex, and place of birth in the Total Population Register. Patients who had immigrated to Sweden were matched with unexposed individuals who had also immigrated.

All Swedish citizens have a unique personal identification number, which enables linkage of population-based registers. All CAH patients and their controls were given an anonymous code number by Statistics Sweden before linkage with the registers. The Swedish Cause of Death Registry (held by the National Board of Health and Welfare) contains all deceased persons registered in Sweden and the year they died, regardless if the death occurred within or outside the country (www.socialstyrelsen.se/register/dodsorsaksregistret). The registry does not include stillborn babies or persons without complete personal identification number. Emigrated Swedes, who are no longer registered in Sweden, are not included. The Swedish Cause of Death Registry contains data from 1952 and is updated each year. More than 99% of deaths are reported in the registry and the diagnoses are given according to the ICD classification. At the time when the data was retrieved, not all causes of death from 2010 were available. The age and year of the death, gender, pheno- and genotype, cause of death, and if the person had been born before or after the introduction of the Swedish nationwide

neonatal screening program was recorded. The Migration Register (Statistics Sweden) with all migrations since 1901 was used to control for migration.

Statistical analysis

A matched cohort design was used where the survival analysis and the risk of being deceased were calculated by Cox regression with results reported as Hazard Ratios (HR) and 95% Confidence Intervals (95%CI). Other comparisons between two groups were made using Students *t*-test or Mann–Whitney rank-sum test; the former results reported as mean±SD, the latter as median (range). Chi-square was used in frequency table calculations. A CI not surpassing 1.0 or a P-value <0.05 were considered significant. SAS version 9.3 software package was used.

Results

Characteristics of the patients and controls

The characteristics of this cohort have been reported previously in detail (18, 24). All 588 included CAH patients (253 males, 335 females) had been diagnosed with 21-hydroxylase deficiency and the median age was of 26.0 (range 0–92) years at the last observation time. The severity could be established in 482 patients (82%). SW phenotype was diagnosed in 240 patients (135 females), SV phenotype in 167 patients (91 females), and NC phenotype in 75 patients (56 females). The number of individuals in the most common genotype groups was: null, n=100 (59 females); I2 splice, n=122 (67 females); I172N, n=130 (72 females); P30L, n=24 (12 females); and V281L, n=56 (42 females). Three hundred and five CAH individuals (178 females) were born before the introduction of the national neonatal screening in 1986. Matched controls for sex, year and place of birth were included from the Total Population Registry (n=58 800). Of the 14 patients that had an incomplete or reused personal identification number six had SW phenotype (four females, one with null genotype) and one had SV (male, I172N) and seven (three females) had unknown clinical severity.

Mortality

The mean age of death in the cohort to the end of the study period was 41.2±26.9 years in CAH patients and 47.7±27.7 years in controls (P<0.001). The median age of death was 44.1 [0-91] years vs. 51.1 [0-94] years (P<0.001). From 1952 to 2010, 23 deaths (13 females) occurred among the 588 CAH patients (3.9%) compared to 942 deaths among the 58 800 controls (1.6%). The HR of dying was 2.3 (95% CI 1.2-4.3) in CAH males and 3.5 (95% CI 2.0-6.0) in CAH females compared to controls (Table 1). When analyzing the clinical severity, only the NC and patients with unclear severity had an increased mortality. However, when excluding the three CAH individuals (two girls and one boy) and controls that died during their first year of life, i.e. only analyzing those who survived the first year of life, mortality was similar between CAH patients and controls. Among patients and controls that were born from 1952, with full data coverage from the Swedish Cause of Death registry, the results were similar to the entire cohort (Table 1 and Figure 1). Patients with SW or with unclear phenotype had an increased mortality. The mortality after the first year of life was increased in females but not in males and when clinical severity was analyzed only patients with unclear severity had a significantly increased mortality.

Cause of death

The detailed causes of death in CAH patients are presented in Table 2. Among these one died in the 1950s (infant), one in the 1970s (>50 years old), four in the 1980s (mean age of death 21.3±20.7 years), three in the 1990s (38.3±25.0 years), nine in the 2000s (49±28.0 years), and five in 2010 (57±12.5 years). We had access to the cause of death in only one of the patients deceased in 2010, hence when we calculated the frequency the four patients with unknown cause were excluded. Eight out of 19 patients (42%) had died of adrenal crisis, six (32%) of a cardiovascular cause (four were cerebrovascular), three (16%) of cancer (two gastrointestinal, one leukemia), and two (10%) of suicide. However, in three of the cardiovascular deaths a severe infection was also reported on the death certificate and those cases may have been associated with adrenal crises. Thus, it is possible that at least 58% were related to or due to adrenal crisis.

There were seven additional deaths in the national registry of CAH individuals with incomplete or reused personal identification number (of a total of 14, i.e. 50%), thus those could not be analyzed using the Swedish Cause of Death Registry. Of these all except one were deceased before the introduction of neonatal screening and most of them in the first weeks of life. The deaths were most likely all related to adrenal crisis (Table 3).

Combining the cohort of 588 and the group of 14 individuals, two children that had been diagnosed through screening died in the neonatal period, one severely preterm and one with lactic acidosis (36). Hence, 1.6% (5/316) of the diagnosed CAH individuals died in the neonatal period before the introduction of neonatal screening compared to 0.7% (2/286) after the introduction (P=NS).

In controls the most common causes of death were cancer (31%), cardiovascular disease (27%), accident (11%), and suicide (10%). The only significant statistical difference compared to CAH patients was adrenal crisis (P<0.001).

Discussion

This is the first nationwide study investigating mortality in detail in CAH patients. We found an increased mortality with a 6.5 years earlier mean age of death in CAH patients compared to matched controls illustrating that despite the diagnostic advances and the available glucocorticoid and mineralocorticoid replacement, CAH is still a potentially lethal condition. However, the mean age of death seemed to increase during the decades from 21 years during the 1980s to 57 years in 2010.

In the entire cohort, the excess mortality in both CAH males and females combined was not significant when analyzing only the patients surviving the first year. However, as the Swedish Cause of Death Registry contains data from 1952 and onwards only patients and controls that survived until 1952 could be analyzed. If only patients born 1952 and later were analyzed the mortality in both genders of CAH was similar but in those surviving the first year only CAH females had an increased mortality. However, in both CAH males and females the mortality rate was similar but the female controls had lower rate than male controls resulting in a higher and significant hazard ratio for CAH females compared to their controls. Moreover, there were more women in the cohort which may increase the power in the calculations.

The increased mortality was mainly seen among patients with unclear severity of CAH. It could be speculated that these patients had not been in contact with a specialized center. All CAH patients personally known to us were included in the national CAH registry but the majority of those with unclear severity were not. The CAH diagnose in patients with unclear severity, and not included in the national CAH registry, were considered accurate as the diagnosis had been used several times in the NPR and the patients had not subsequently been given other diagnoses that could be misinterpreted as CAH. Moreover, the mortality rate was most certainly under-estimated as we have medical records of seven additional deaths, not included in the statistical calculations due to incomplete or reused personal identification number. Most of these patients died in the neonatal period before the screening. Of those diagnosed with CAH the neonatal mortality was, however not significant, more than doubled before the introduction of neonatal screening compared to after. We have previously shown a dramatic rise in the number of CAH patients diagnosed in the 1960s and 1970s, and after the introduction of the nationwide neonatal screening in 1986 the proportion of SW patients increased in both genders suggesting that most CAH cases probably died undiagnosed in the earlier period (4).

Our data are in parity with the only other published study examining mortality in diagnosed CAH patients (35). It reported an increased mortality, but subgroup analysis showed that mortality was only increased in young girls of Indian subcontinent ethnicity. However, the study was performed almost two decades ago with no genetic confirmation of diagnosis, it includes mainly children with very few patients older than 35 years, different variants of CAH were included, and only a few highly specialized centres participated with one centre including more than half of the CAH cohort. A later study found a significant female preponderance among the children with null genotype, mainly of Indian subcontinent ethnicity, indicating that the males may have died undiagnosed in the neonatal period (34). All these factors influence how the data should be interpreted. On the other hand, most of the eight deaths in the previous study seemed to be caused by adrenal crisis (35), which is in accordance with the present study.

Of note, half of the cases with a cardiovascular death had a severe infection as a co-diagnosis on the death certificate indicating that there may have been even more deaths related to adrenal crisis. The importance of increased glucocorticoid doses during severe illness, especially

during vomiting cannot be stressed enough. We have personal knowledge of at least one adult patient dying, probably unnecessary, because the patient did not increase the glucocorticoid dose and seek medical attention during a severe infection. This occurred despite repeated information to the patient and parents about the importance of increased stress doses. However, also during hospital admission there may have been room for improvement in optimizing the glucocorticoid doses as many of the deaths in the children were suspected or due to adrenal crisis and some of them may have occurred in hospitals. It has been discussed that some patients with CAH may not need treatment as adults, even patients with the SW form (37). Our data suggests that it may be questioned if patients not on treatment and lost to follow-up are still alive.

Three of the deaths within the first year of life occurred after the year 2000, thus the patients had been screened. However, as mentioned above, we know that the nationwide neonatal screening program saves lives as the proportion of the SW phenotype increased substantially after the introduction (4). Moreover, neonatal screening may also decrease future health issues, as indicated by a lower rate of psychiatric morbidity in CAH males after its introduction (18).

An increased risk of benign tumours in CAH patients, principally adrenal and testicular (25-31) has been reported. There has also been speculation on increased risk of malignant tumours (32, 33). Our study did not support this since only three of our patients (16%) died of a cancer, which was not in excess compared to controls (31%).

The major limitations of the present study are that all outcome data were derived from national registries. The number of deceased patients was limited as a result of the median age of only 26 years and most deaths occur at a much older age. Moreover, we could only include individuals with a complete personal identification number and patients included in the Swedish Cause of Death Registry from 1952. Despite the large cohort, the number of patients in the different severity subgroups was limited which may contribute to the non-significant effects among these patients. The ICD coding may have been inadequate. A pre-requisite to obtain approval by the Ethics committee was that all included individuals were anonymized to protect the integrity of the included individuals. Therefore, analyzing results on an individual level and compare with medical files was not possible. Moreover, it is likely that the study underestimates the mortality among patients with CAH born

before the screening since we know that not all patients were clinically diagnosed at that time. On the other hand, the strengths of this study are the unique national registry of CAH individuals covering almost all CAH patients diagnosed in Sweden, with most registered patients being both geno- and phenotyped, and the almost complete coverage of all deaths by the Swedish Cause of Death Registry.

In conclusion, CAH was associated with excess mortality mostly due to or related to adrenal crisis and not only during the first year of life but also among children and adults. This seemed to be related to the SW phenotype. The mean age of death increased among the CAH patients during the decades. There seemed to be room for improvements in the glucocorticoid stress treatment used in spite of the diagnostic advances and available glucocorticoid and mineralocorticoid replacement. Improved doctor awareness and patient education may reduce mortality.

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Figure Legend:

Survival probability of 550 CAH individuals with 21-hydroxylase deficiency compared with 55 000 age- and sex-matched controls, year of birth 1952-2009, i.e., from the commencement of the Swedish Cause of Death Registry in 1952.

Table 1. Mortality in CAH individuals with 21-hydroxylase deficiency compared with age- and sex-matched controls (100 controls per case)

Deaths	Year of birth 1910-2009		Year of birth 1952-2009	
n	CAH 588	Hazard ratio (95% CI)	CAH 550	Hazard ratio (95% CI)
Total	23(3.9%)	**2.8(1.9-4.3)**	12(3.9%)	**3.2(1.8-5.6)**
Male	10(4.0%)	**2.3(1.2-4.3)**	5(2.1%)	**2.6(1.1-6.4)**
Females	13(3.9%)	**3.5(2.0-6.0)**	7(2.2%)	**3.7(1.7-7.9)**
SW	5(2.1%)	2.0(0.8-4.7)	4(1.7%)	**2.6(1.0-7.0)**
SV	4(2.4%)	1.3(0.5-3.5)	0(0%)	0(0->1000)
NC	3(4.0%)	**3.4(1.1-10.9)**	1(1.4%)	4.0(0.6-30.1)
Unclear severity	11(10.4%)	**6.9(3.8-12.8)**	7(7.2%)	**8.0(3.7-17.4)**
Surviving the 1st year				
Total	19(3.2%)	1.0(0.5-2.0)	9(1.6%)	**2.6(1.4-5.1)**
Male	8(3.2%)	1.2(0.5-3.2)	4(1.7%)	2.3(0.8-6.1)
Females	11(3.3%)	0.9(0.4-2.3)	5(1.6%)	**3.0(1.2-7.3)**
SW	3(1.3%)	2.6(0.3-20.4)	2(0.9%)	1.6(0.4-6.3)
SV	3(1.8%)	1.2(0.3-4.2)	0(0%)	0(0->1000)
NC	3(4.0%)	0.4(0.0-3.2)	1(1.4%)	4.4(0.6-32.9)
Unclear severity	10(9.5%)	1.1(0.5-2.8)	6(6.3%)	**7.1(3.1-16.3)**

CI, confidence interval. SW, salt-wasting. SV, simple virilizing. NC, non-classic. In those born 1910-2009, 585 CAH patients and 5871 controls survived the 1st year, while in those born 1952-2009 the numbers were 547 CAH patients and 54964 controls respectively.

Table 2. Characteristics and causes of death in CAH individuals with 21-hydroxylase deficiency.

Age span	Male/Female	Screening*	Phenotype	Genotype	Cause of death
0-1 m	1/1	1	SW, 2	Null, 1	Adrenal crisis, 2
				I2 splice, 1	
1 m-2 yrs	2/0	1	SW, 1	Unknown, 2	Adrenal crisis, 2
			Unknown, 1		
2-19 yrs	1/1	0	NC, 1	V281L, 1	Adrenal crisis, 2
			Unknown, 1	Unknown, 1	
30-49 yrs	3/4	0	SW, 2	Null, 1	Adrenal crisis, 2
			SV, 1	I2 splice, 1	Cardiovascular, 2
			Unknown, 4	I172N, 1	Suicide, 2
				Unknown, 4	Unknown, 1
50-69 yrs	3/4	0	SV, 2	I172N, 1	Cardiovascular, 2**
			NC, 1	Unknown, 6	Cancer, 3
			Unknown, 4		Unknown, 2
70-99 yrs	1/2	0	SV, 1	I172N, 1	Cardiovascular, 2**
			NC, 1	V281L, 1	Unknown, 1

	Unknown, 1	Unknown, 1

m, month. yrs, years. SW, salt-wasting. SV, simple virilizing. NC, non-classic. *neonatal screening. ** three cases had a co-diagnosis of infection, thus they may be related to adrenal crisis.

Table 3. Characteristics and causes of death in CAH individuals with 21-hydroxylase deficiency known to have deceased but with incomplete or reused personal identification number, thus not included in the statistical calculations and the Swedish Cause of Death Registry could not be used.

Age span	Male/Female	Screening*	Phenotype	Genotype	Cause of death
0-1 m	3/2	1	SW, 3	Null, 1	Adrenal crisis, 1
			Unknown, 2	I2 splice, 1	Unknown, 4**
				Unknown, 3	
2-7 yrs	1/1	0	SW, 2	Unknown, 2	Unknown, 2**

m, month. yrs, years. SW, salt-wasting. *neonatal screening. **suspected to be due to adrenal crisis