ISSN 2472-1972

Adverse Outcomes and Economic Burden of Congenital Adrenal Hyperplasia Late Diagnosis in the Newborn Screening Absence

Mirela Costa de Miranda,[1] Luciana Bertocco de Paiva Haddad,[2] Guiomar Madureira,[1] Berenice Bilharinho de Mendonca,[1] and Tania A. S. S. Bachega[1]

[1]Developmental Endocrinology Unit, Laboratório de Hormônios e Genética Molecular/LIM42, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil 05403-900; and [2]Liver and Gastrointestinal Transplant Division, Department of Gastroenterology, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil 05403-000

Objective: To establish short- and long-term adverse outcome frequencies related to a late diagnosis of congenital adrenal hyperplasia (CAH) in the absence of newborn screening (NBS) and to determine respective treatment costs, which have never been reported.

Design: A retrospective analysis of a CAH cohort diagnosed without NBS.

Methods: We evaluated medical record data concerning 195 patients (141 females) diagnosed with CAH through clinical suspicion and confirmed using hormonal and *CYP21A2* analysis, who were followed from 1980 to 2016 at Sao Paulo University. We measured mortality, dehydration, mental impairment frequencies, and hospitalization length outcomes in the salt-wasting form; the frequency of genetic females raised as males in both forms, frequency of depot GnRh analog (GnRha) and GH therapies in the simple virilizing form, and related outcome costs were calculated.

Results: Mortality rates and associated costs, varying from 10% to 26% and from $2,239,744.76 to $10,271,591.25, respectively, were calculated using the Brazilian yearly live-births rate, estimated productive life years, and gross domestic product. In the salt-wasting form, 76% of patients were hospitalized, 8.6% were mentally impaired, and 3% of females were raised as males (total cost, $86,230/salt-wasting patient). GnRha and growth hormone were used for 28% and 14% of simple virilizing patients, respectively, and 18% of females were raised as males (preventable cost, $4232.74/simple virilizing patient).

Conclusions: A late CAH diagnosis leads to high mortality and morbidity rates, notably increasing public health costs, and may result in physical and psychological damage that is not easily measurable.

Key Words: congenital adrenal hyperplasia, economic evaluation, newborn screening, delayed diagnosis, high morbi-mortality

Abbreviations: 17-OHP, 17-hydroxyprogesterone; CAH, congenital adrenal hyperplasia; CI, confidence interval; CP, cerebral palsy; GnRha, GnRh analog; HC, hydrocortisone; ICU, intensive care unit; NBS, newborn screening; Na, sodium; SUS, Brazilian public health system; SV, simple virilizing; SW, salt wasting; VSL, value of a statistical saved life

Received 31 July 2019
Accepted 15 November 2019
First Published Online 21 November 2019
Corrected and Typeset 6 Februry 2020

Congenital adrenal hyperplasia resulting from 21-hydroxylase deficiency (CAH) is a common autosomal recessive disease characterized as impaired cortisol and/or aldosterone synthesis and excessive adrenal androgen secretion [1]. The worldwide CAH incidence has been reported to range from 1:10,000 to 1:18,000 live births in screened populations [2], which is similar to the incidence in Brazil [3–6].

The disease presents a spectrum of clinical manifestations, classified as salt-wasting (SW), simple virilizing (SV), and nonclassical forms. Only SW and SV are the objective of screening programs because these forms present with severe manifestations in the neonatal period [7]. In the SV form, fetal androgen exposure leads to external genitalia virilization in females, often resulting in incorrect sex assignment at birth. If not treated, postnatal virilization continues in both sexes, resulting in pseudo-precocious puberty and short final height [8,9]. In the SW form, aside from the hyperandrogenic manifestations, the clinical presentation involves neonatal hyponatremic dehydration, followed by shock and death in the absence of treatment. Male newborns are more susceptible to severe SW crises in unscreened populations [1,7].

CAH is suitable for inclusion in public newborn screening programs because the measurement of 17-hydroxyprogesterone (17-OHP) levels involves an inexpensive screening test, CAH is a relatively frequent rare disease, and early diagnosis and treatment significantly reduces morbidity and mortality [7]. Although there have been reported false-negative cases [10], CAH newborn screening (CAH-NBS) has shown good efficacy in detecting classical patients. However, the high frequency of false-positive results remains a major issue [2, 11], especially in preterm newborns [12]. Neonates with positive screening results should undergo additional tests to confirm the diagnosis; however, this confirmation process increases screening costs. To date, the only rationale included in economic evaluations for CAH-NBS has been prevention of death resulting from SW crises. This mortality rate has not been well established; however, the risk has been reported to be very low in populations with high levels of health care. Therefore, CAH-NBS has not been considered to be a cost-effective diagnostic tool [13]. With modern ultrasonography, identification of atypical genitalia through routine gestational ultrasound can lead to a prenatal CAH diagnosis, which could reduce the need for CAH-NBS. However, diagnosis using ultrasound is only possible in affected female fetuses, and affected males cannot be diagnosed using this method [14].

Currently, CAH-NBS is undertaken across all 50 states in the United States, in 35 other countries, and in some regions of 17 additional countries. Although it is an Endocrine Society recommendation, there is no worldwide consensus on implementation within national public health systems, and some countries, even developed ones such as the United Kingdom and Canada, do not universally undertake CAH-NBS in their public health systems [15, 16]. There are limited data regarding the benefits of early CAH diagnosis [17]. Some studies have assessed long-term use of CAH-NBS and have evaluated the decline in mortality rates when comparing screened and unscreened populations [18–20].

Two cost-effective analyses concerning CAH screening have been conducted in the United States; both reached differing conclusions. Effectiveness was measured in terms of years of life saved and, through assuming varying mortality rates, 1 analysis concluded that CAH-NBS was cost-effective, whereas the other did not [13, 21]. Neither analysis considered other adverse outcomes of late diagnosis. It has been suggested that the cost-effectiveness of CAH screening might involve other benefits of early CAH detection, including correct sex assignment in cases of atypical genitalia; however, reliable estimates regarding long-term outcomes are still lacking [22].

Understanding the short- and long-term costs of care associated with delayed CAH diagnoses is important for analyzing the cost-effectiveness of NBS implementation. In particular, information concerning how treatment costs are altered when disease progression is prevented through NBS could be valuable for future economic analysis. For example, the incremental direct costs related to neonatal hospitalization in patients with the SW form, therapies undertaken because of erroneous sex assignment at birth, and precocious puberty should be included.

Table 1. Procedures Involved in CAH Diagnosis and Treatment and Their Respective Prices, Extracted from SUS Table of Procedures, Medications, and Orthoses, Prostheses and Special Materials [25]

Procedure	Price in US$
Hospitalization of medium to high complexity (payment per hospitalization)	$70.77
ICU diaries (payment per day)	$155.99
Hormonal Therapy of transexualizing process (payment per month)	$15.33
Hysterectomy with bilateral adnexectomy and colpectomy under transexualizing process	$366.70
Testicular prosthesis	$107.35
Genitoplasty	$122.09
Autogenous urethroplasty	$144.02
Leuprorelin 11.25 mg (price per ampoule bottle)	$273.26
GH (somatropin) 12 UI (price per ampoule bottle)	$33.97
Specialized medical consultation	$3.07
17-OHP laboratory measurement	$3.12
Sodium laboratory measurement	$0.57
Potassium laboratory measurement	$0.57
Renin laboratory measurement	$4.05
Testosterone laboratory measurement	$3.19
Androstenedione laboratory measurement	$3.54
Bone age radiography	$1.84
Hydrocortisone 10 mg (price per tablet)	$0.15
Fludrocortisone 100 mcg (price per tablet)	$0.12
Dexamethasone 0.5 mg (price per tablet)	$0.05

Abbreviations: 17-OHP, 17-hydroxyprogesterone; ICU, intensive care unit; SUS, Brazilian public health system.

The frequency of adverse outcomes in a large CAH unscreened population and their respective treatment costs have not been reported in the literature. In this study, we aimed to perform a cost of illness study comprising a CAH cohort diagnosed according to phenotype as a first step to conduct a comprehensive economic evaluation of CAH-NBS implementation.

1. Methods

A. Population

Data were retrospectively evaluated through a medical records review of 195 patients with CAH (females, n = 141; males, n = 54), who had been followed from 1980 to 2016 at the Hospital das Clínicas, Sao Paulo, Brazil. After the purpose and nature of all the procedures used had been explained, consent was obtained from each patient. This study was approved by the Ethics Committee responsible for research projects at the Hospital das Clínicas Medical School of Sao Paulo University.

A diagnosis of the SV form was made according to confirmation of atypical genitalia in females [23] and sexual precocity in males. Patients with the SW form also presented with hyponatremic dehydration in the first weeks of life. All patients had increased basal 17-OHP levels. Serum 17-OHP, androstenedione, and plasma renin activity levels were measured using radioimmunoassay. Serum cortisol, testosterone, and gonadotropins levels were measured using immunofluorometric assays. The CAH genotype was determined through *CYP21A2* analysis [24].

B. Cost analysis

The cost analysis was based on data derived from the Brazilian public health system (SUS). Prices were obtained directly from the SUS Table of Procedures, Medications, and Orthoses, Prostheses and Special Materials management system, in accordance with International Classification of Diseases, 10th revision [25] (Table 1), converted to United States dollars

Table 2. Characteristics of the Brazilian CAH Nonscreened Cohort Over Decades

	% SW Form	% Males	% Dehydration at Diagnosis	Mean Sodium (mEq/L)	% Genital Atypia Recognition at Birth
<1989, group 1	42.6	25	87	119.9	64
1990–1999, group 2	61.8	28.6	81	121.3	87
>1999, group 3	69.7	39.1	87	122.3	79

% SW form: group 1 vs group 2, $P = .012$; group 1 vs group 3, $P = .014$; group 2 vs group 3, $P = .68$.
% Males: group 1 vs group 2, $P = 0.065$; group 1 vs group 3, $P = 0.08$; group 2 vs group 3, $P = 0.85$.
Abbreviations: CAH, congenital adrenal hyperplasia; SW, salt wasting.

from Brazilian reals (end of 2016, US$1.00 = R$3.26) [26]. Two prices were not available at SUS Table of Procedures, Medications, and Orthoses, Prostheses and Special Materials: hydrocortisone (HC) (10 mg/tablet = $0.15) [27] and dexamethasone (0.5 mg/tablet = $0.17).

C. Time horizon

The frequency of adverse outcomes was analyzed from the time of clinical diagnosis until patients reached 19 years of age.

D. Costs involving standard treatment

Standard treatment was set according to Endocrine Society Guidelines [7] and was calculated as the mean daily HC dose used until bone age maturation. Subsequently, we calculated the mean daily dexamethasone dose until a patient reached 19 years of age. The mean daily fludrocortisone dose was also calculated. Standard follow-up consisted of 4 consultations per year with serum hormone measurements [1, 7, 28]. The number of patients who had undergone feminizing genitoplasty was calculated (i.e., those with Prader III-V) [29].

E. Costs of adverse outcomes related to late diagnosis

E-1. Patients with the SW form

1. To determine early death cost, the human capital method was used, which considers the productivity loss associated with premature mortality [30]. The expected productive life in Brazil was estimated to be 34.5 years in 2010. This measure represents the average number of years that a 15-year-old person would remain in the labor market if, during his or her active life, he or she was exposed to mortality rates and economic activity levels according to the age group applicable in 2010 [31]. The mortality rate was calculated by comparing the SW form frequency in our unscreened cohort with those identified in other cohorts screened in Brazil [3, 5]. The number of infant deaths per year was calculated using Brazilian yearly live-births data [32], the SW form incidence, and the calculated mortality rate. The number of years lost was multiplied by the Brazilian gross domestic product *per capita* [33]. A discount rate of 5% [34] was applied to the estimated loss of future productive years.
2. Concerning hospitalization, the number of patients hospitalized because of dehydration was considered. The amount paid by the SUS has a fixed value for ward hospitalizations, regardless of duration. The costs concerning the intensive care unit (ICU) are paid for each day; therefore, the mean length of stay in the ICU was considered.
3. Regarding laboratory diagnosis for nonhospitalized patients, measurement data concerning serum 17-OHP, testosterone, androstenedione, renin, and electrolytes levels were determined.
4. To determine mental impairment resulting from an SW crisis, the number of patients with cerebral palsy (CP) or intellectual disability was identified. Total cost was extracted

from a United States Centers for Disease Control and Prevention survey that had been undertaken to determine costs associated with development disabilities [35].
5. Sex assignment error at birth concerned females who had been raised socially as males. This has been calculated as the costs of masculinization surgery and of androgen replacement from puberty to 19 years old [29, 36].

E-2. Patients with the SV form

1. The use of expensive medications was determined according to the number of patients who had received GnRh analog (GnRha) and GH, as well as the mean doses and treatment duration.
2. Sex assignment error at birth was considered similarly to patients with the SW form.
3. The diagnosis workup was similar to patients with the SW form. For those diagnosed after the age of 2 years, this was added to the cost of bone age radiography.

G. Statistical analysis

Data are expressed as averages and confidence intervals (CIs) and frequencies in percentages. Comparisons between averages were made using a Student *t*-test and between frequencies using chi-square tests. Statistical significance was set at $p < 0.05$, and *SPSS Statistics* version 22 software was used.

3. Results

A. Estimating mortality and its costs

The cohort comprised 195 patients (SV, n = 90; SW, n = 105), of whom 54% were identified as having the SW form. Given clinical awareness of CAH has varied throughout recent decades, the results were stratified according to the year of birth, as follows: group 1, born before 1989; group 2, born between 1990 and 1999, and; group 3, born after 1999 (Table 2). Only group 1 presented a significantly lower SW frequency (43%); however, the female-to-male ratio was similar among the groups. The mortality rate varied from 10% to 26%, which was obtained through subtracting the SW frequency of groups 2 and 3 (64%) from the 75% to 90% found in cohorts screened elsewhere [3, 5].

We considered that, given there had been 3,017,668 yearly live births [32] and a varying CAH incidence reported of 1:10,320 [4] and 1:14,967 [5], a mortality rate of 10% to 26% would result in 15 to 68 newborn deaths yearly, respectively. This figure, multiplied by a Brazilian growth domestic product *per capita* of $9001 [33] and 34.5 average productive years of work in Brazil [31] at a 5% discount rate resulted in a cost varying from $2,239,744.76 to $10,271,591.25 from lives lost annually.

B. Diagnosing and treating patients with the SW form

Atypical genitalia was recognized at birth in 54 of 74 females; however, this finding was associated with a precocious diagnosis in only 17 patients. Another 6 females were assigned as males at birth, of whom 2 were raised socially as males because their parents' decision and had undergone a masculinizing process following prolonged psychotherapy.

Neonatal SW crises occurred in 84% of patients (males, 100%; females, 77%). The mean sodium (Na) level was 117.7 mEq/L (95% CI, 113.2-122.2) in males and 123.2 mEq/L (95% CI, 120-127) in females ($P = .04$). The mean age at diagnosis was 38.8 days (31.1-46.4); 31 days (22–40) in females and 49 days (36–62) in males ($P = .036$). Nine patients (3 males, 6 females) developed severe neurological impairment requiring specialized care, of whom 2 presented with CP.

Hospitalization occurred in 91% of the dehydrated patients during a mean length of hospital stay of 38 days (30.3-47.4), and 36% had stayed in the ICU (mean, 23 days; 13.2-32.1). Six patients (5 males) had undergone multiple hospitalizations before diagnosis, resulting in a mean of 1.11 for hospitalizations/patient (1.02-1.2).

All costs related to adverse outcomes and treatment concerning the SW form are described in Table 3.

The mean cost per SW patient, considering only hospitalization outcomes, was $1087.14 ($676.47-$1497.81).

The costs of neurological sequelae calculated per person were $1,014,000 for mental retardation and $921,000 for CP [35]. The total cost of mental impairment was $85,142.86 per patient with the SW form.

The mean cost concerning a patient with the SW form, considering outcomes resulting from a late diagnosis, was $86,230 (95% CI, 85,819.32-86,640.67).

Regarding standard therapy, the mean HC dose was 14.4 mg/d (13.2-15.6), until 14.6 years of age (9.4-19.8). Subsequently, the mean dexamethasone dose until 19 years of age was 0.3 mg/d (0.27-0.34). The mean fludrocortisone dose was 57.4 mcg/d (55.2-59.5). Data regarding feminizing genitoplasty were obtained in 68 females, of whom 66 had undergone this procedure and 2 had slight genitalia virilization. The mean cost involving standard treatment from the time of diagnosis to 19 years of age was $3119.04 per patient ($2702.1-$3626.74).

The total cost concerning the patients with the SW form, from the date of diagnosis to 19 years of age, including standard treatment and adverse outcomes, was $89,349.04 (95% CI, 88,521.42-90,267.41), excluding costs related to neonatal death.

C. Diagnosing and treating patients with the SV form

Among the 90 patients with the SV form, 67 (73.6%) were females. Atypical genitalia was identified at birth in 28 (44%) patients. Sixteen of 67 females (25%) were assigned at birth as males, and 10 of 16 (63%) were raised as males and underwent a masculinization process after extensive psychological evaluation.

The mean age at diagnosis was 5.7 (3.9-7.4) years, and 58 patients (64%) were diagnosed after 2 years of age. Males were diagnosed through hyperandrogenic manifestations in 92% of patients, with only 2 diagnosed because of familial history. Atypical genitalia motivated the diagnosis in 34 of 67 (51%) females, and precocious pubarche was observed in 16 patients (24%).

Advanced bone age at diagnosis was found in 45% of patients (males, 90%; females, 33%). The mean difference between bone age and chronological age was 5.2 (4.4-5.9) years. GnRha was used in 25 (28%) patients, for a mean period of 3.8 years (95% CI, 3.08-4.5). GH was used in 13 (14%) patients for a mean period of 3.2 years (2.4-4.0) and the mean dose was 5.9 UI/d (4.9-6.8).

Considering adverse outcomes in patients with the SV form, such as the masculinization process, the laboratory and radiography examinations required to confirm the diagnosis, and the GnRha and GH therapies, a total cost of $380,931.13 ($265,485.90-$660,903.48) was calculated, at $4232.57 per patient ($2949.84-$7343.37). All costs related to adverse outcomes and treatment for the SV form are described in Table 4.

Regarding standard therapy, the mean HC dose until bone maturation was 16.8 mg/d (14.8-18.6) and the mean chronological age at bone maturation was 13.2 years (10.6-18.5). The mean dexamethasone dose until 19 years of age was 0.38 mg/d (0.3-0.47). Among the females, 47 of 55 (85.5%) had undergone feminizing genitoplasty. The mean cost involving standard follow-up until 19 years of age was $1689.74 per patient (95% CI, 1,160.79-2586.55).

The mean total cost for a patient with the SV form until 19 years of age, including diagnosis workup, standard treatment, and adverse outcomes, was $5922.48 (95% CI, 4110.80-9930.09).

Table 3. Costs Description for the SW Form

105 Salt Wasters								
Costs of Late Clinical Diagnosis Outcomes								
	Point Estimate	**Range (95% CI)**		**Unitary Value**		**Total Value**	**Range**	
Girls with wrong sex assignment	2			Hysterectomy/bilateral oophorectomy	$366.70	$3812.50		
				Urethroplasty	$144.00			
				Testicular prosthesis	$107.30			
				Androgen Replacement (12–19 y)	$1288.10			
					$1906.20			
Mental retardation	7			$1,014,000.00		$7,098,000.00		
Cerebral palsy	2			$921,000.00		$1,842,000.00		
Hospitalization	80			$70.80		$6291.00	$5765.70	$6816.40
Average hospitalizations before diagnosis	1.11	1.0	1.2					
Hospitalization in ICU	29			$155.90		$102,466.50	$59,871.20	$145,061.80
Length of ICU hospitalization (d)	22.7	13.2	32.1					
Laboratory examinations to diagnosis	105			$15.00		$1579.60		
Total						$9,054,149.60	$9,011,028.90	$9,097,270.30
Total per patient						**$86,230.00**	**$85,819.30**	**$86,640.70**
Costs of Standard Clinical Follow-up								
	Point Estimate	**Range (95% CI)**		**Unitary Value**		**Total Value**	**Range**	
Medical consultations	4/y			$3.07		$24,474.70		
Laboratory	4/y			$15.04		$120,048.20		
Age at final height achievement	14.6 y	9.4 y	19.8 y					
Hydrocortisone	14.37 mg/d	13.2 mg/d	15.6 mg/d	$0.15		$120,837.50	$71,162.80	$177,685.60
Dexamethasone	0.3 mg/d	0.27 mg/d	0.34 mg/d	$0.05		$5,377.30	0	$13,110.30
Fludrocortisone	57.39 mcg/d	55.2 mcg/d	59.5 mcg/d	$0.12		$48,704.50	$46,867.20	$50,541.90
Genitoplasty	66			$122.08		$8057.28		
Cost of standard treatment from diagnosis to 19 y in all patients						$327,499.60	$283,720.60	$380,807.80
Cost of standard treatment from diagnosis to 19 y per patient						$3119.00	$2702.10	$3626.70
Total costs from diagnosis until 19 y (outcomes and treatment)						**$9,381,649.20**	**$9,294,749.50**	**$9,478,078.10**
Costs from diagnosis until 19 y per patient						**$88,349.00**	**$88,521.42**	**$90,267.41**

Abbreviations: CI, confidence interval; ICU, intensive care unit; SW, salt wasting.

Table 4. Costs Description for the SV Form

90 Simple Virilizers							
Costs of Late Clinical Diagnosis Outcomes							
	Point Estimate	**Range (95% CI)**		**Unitary Value**		**Total Value**	**Range**
Girls with wrong sex assignment	12			Hysterectomy/bilateral oophorectomy	$366.70	$22,874.97	
				Urethroplasty	$144.00		
				Testicular prosthesis	$107.35		
				Androgen replacement (12–19 y)	$1288.14		
					$1906.19		
Use of leuprorelin	25			$273.25 per ampoule bottle of 11.75 mg		$103,493.93	$84,144.06 $122,843.80
Length of leuprorelin treatment	3.79 y	3.08 y	4.5 y				
Use of GH	13			$33.97 per ampoule bottle of 12 Ui		$253,101.56	$157,006.21 $513,724.05
Length of GH treatment	3.2 y	2.4 y	5.6 y				
Mean GH dose per day	5.9 U	4.9 U	6.8 U				
Laboratory examinations to diagnosis	90			$15.04		$1353.93	
Patients diagnosed after 2 y of age, submitted to bone age radiography	58			$1.84		$106.73	
Total cost of outcomes						$380,931.10	$265,485.90 $660,903.50
Total costs of outcomes per patient						$4232.60	$2949.90 $7343.40
Costs of Standard Clinical Follow-up and Treatment							
	Point Estimate	**Range (CI 95%)**		**Unitary Value**		**Total Value**	**Range**
Medical consultations	4/y			$3.07		$20.978.30	
Laboratory (17-OHP, A4, testosterone)	4/y			$9.86		$67,466.20	
Age of bone maturation	13. 2y	10.6 y	18.5 y				
Hydrocortisone	16.8 mg/d	14.5 mg/d	18.6 mg/d	$0.15		$50,276.50	$9,81.10 $125,227.20
Dexamethasone	0.38 mg/d	0.3 mg/d	0.47 mg/d	$0.05		$7617.80	$507.90 $13,379.90
Genitoplasty	47			$122.08		$5737.80	
Total costs of standard follow-up and treatment						**$152,076.60**	**$104,471.30 $232,789.50**
Costs of standard follow-up and treatment per patient						$1689.70	$1160.80 $2586.50
Costs from diagnosis until 19 y, including outcomes, follow-up, and treatment						**$533,007.70**	**$369,957.20 $893,692.90**
Costs from diagnosis until 19 y (outcomes, follow-up, and treatment) per patient						$5922.30	$4110.60 $9929.90

Abbreviations: 17-OHP, 17-hydroxyprogesterone; A4, androstenedione; CI, confidence interval; SV, simple virilizing.

4. Discussion

Economic evaluations guide policy decisions through providing relevant data and projected estimations of long-term clinical and economic outcomes [37]. Costs and benefits have been assessed to establish the effectiveness of NBS in terms of reduced risk of death and/or of severe morbidity [38]; however, the cost-effectiveness evaluation of CAH-NBS has only focused on the mortality rate. It has been claimed that the lack of data on the costs of long-term disability resulting from late diagnosis should be addressed to improve the quality of evaluations for implementing NBS [22]. In developed countries, CAH is reasonably diagnosed by clinical means [17], which may not always be the case in developing countries [39–41]. This paper presents, for the first time to the best of our knowledge, the frequencies and costs of adverse outcomes in a population diagnosed using clinical means.

The primary goal of CAH-NBS is to prevent an SW crisis and death. The risk of death for patients with the SW form in the absence of NBS ranges widely across Europe and North America, from 0% to 9% [17], which differs markedly from the 10% to 26% range estimated in our cohort. However, those risk evaluations were performed among populations with high standards of CAH clinical awareness, and it is possible there was some underestimation in relation to undiagnosed cases. The observation of increased CAH incidence after CAH-NBS implementation and of unbalanced female-to-male and SW-to-SV ratios in some nonscreened populations [42–45] support our findings of increased CAH mortality from unrecognized SW crises. In our cohort, males corresponded to approximately 30% of patients in both SW and SV forms, indicating that especially males had likely not been diagnosed.

It is expected that a clinical diagnostic workup, knowledge of this disease, and patient care would likely improve with time [46, 47]. Our cohort comprised patients followed for at least 30 years and, when we compared data with regard to 3 different decades, only a partial improvement was found, suggested by the increasing SW form and male proportions in more recent decades (Table 2). However, no differences in the rates of dehydration, hospitalization, atypical genitalia recognition, and mean serum Na levels at diagnosis were observed, pointing out that a clinical diagnosis of CAH remains suboptimal.

Calculating the value of a statistical saved life (VSL) is challenging. In this study, we selected an income-based human capital method, as has been adopted in other cost-of-illness studies [30, 48]. Current United States regulatory agency practice uses a VSL estimate of approximately $9 million to value an averted death [48]. Considering these data, our estimation of VSL was comparable.

SW crisis is life-threatening in the first 2 weeks of life; clinical diagnosis in our SW cohort occurred much later in both sexes. Males were diagnosed >2 weeks later than females. Similar results have been shown in other populations [18, 41, 42, 49]. It has been reported that NBS might be cost-effective only for males because females are clinically diagnosed through atypical genitalia [13, 50, 51]. Among our females with the SW form, only 21% were prevented from developing dehydration because of clinical recognition of the disease, highlighting that females are also at risk of death from a late diagnosis.

The patients with the SW form presented with low serum Na levels and a long length of hospitalization, suggesting severe SW crises among these patients. Severe salt loss may result in learning disabilities and/or cerebral lesions [52, 53]. We identified 8.6% of our cohort as having mental impairment, which also carries a considerable economic burden because disabled patients receive financial support and multidisciplinary specialized care that is state funded. Data concerning this total cost are not available for the Brazilian population; therefore, we used international data provided by the United States Centers for Disease Control and Prevention that has estimated the direct and indirect economic costs associated with 4 development disabilities [35]. Even though the costs in this study were calculated based on economic data published elsewhere, we emphasized the frequency of these outcomes and their role in accessing CAH-NBS cost-effectiveness evaluation.

In both Brazilian screened and nonscreened cohorts, errors in gender assignment were observed for 6 of 74 (8%) females in our cohort and for 1 of 24 (4%) females in a screened cohort [3]. NBS results provided early diagnosis and correction of this error [3], whereas, in its absence, 12 patients (SW, n = 2; SV, n = 10) were raised as males and underwent a masculinization process involving cost burdens, invasive surgical procedures, and psychological challenges such as poor self-image, infertility, and impaired sexuality [36].

Traditionally, the SW form has been the main concern of the NBS program; however, our data showed that the SV form also involves challenges concerning delayed diagnosis. The low male-to-female ratio suggests that, in this clinical form also, males are underdiagnosed and are, therefore, at risk of adrenal crisis during stressful conditions. The mean age at diagnosis of 5.7 years was sufficient to warrant signs of virilization and advanced bone maturation in almost 50% of patients. It has been reported that classical patients present with a loss of potential final height [8, 9], especially associated with increased androgen levels and advanced bone maturation during infancy [54]. This outcome is likely to have driven the frequent use of expensive therapies such as GnRha and GH in our cohort, which could have been avoided with an earlier diagnosis.

In this study, we used the Brazilian public health system's economic data to calculate the treatment costs of the relevant adverse outcomes. Large variations in costs may occur among different countries; however, we considered it important to describe the dramatic frequencies of late diagnosis-related adverse outcomes in the absence of NBS. These outcomes have a national economic impact and on patients' quality of life, which are likely to occur in differing nonscreened populations.

The findings in this study support the international endorsement of CAH-NBS. A clinical diagnosis of CAH is only possible in symptomatic neonates and cannot be made reliably in both sexes, which can lead to delayed treatment and severe sequelae. These consequences increase the costs of treatment, including measurable factors, such as longer hospitalizations for hyponatremic dehydration and expensive medications to improve final height. Furthermore, the absence of early diagnosis could result in unnecessary physical, psychological, and neurological damage to patients that is not easily measurable.

To date, the only rationale included in economic evaluations concerning CAH-NBS has been prevention of deaths from neonatal SW crises. We estimated that the mortality rate could be as high as 26% in our population; however, because the mortality rate varies widely in other populations, there is uncertainty concerning the cost-effectiveness of CAH-NBS. Considering our results, we recommend that the cost-effectiveness of CAH-NBS should be determined in relation to additional benefits of early detection, which have remained unassessed in the literature before this study. Further studies comparing costs and benefits of both clinical and screening diagnoses should be undertaken.

Acknowledgments

The authors thank Dr. Scott Grosse for his valuable insight.

Financial Support: M.C.d.M. was supported by *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES) Social Demand Grant; T.A.S.S.B. and B.B.d.M. were partially supported by CNPq grants #3030288/2015-0 and #303002/2016-6, respectively.

Additional Information

Correspondence: Mirela Costa de Miranda, Av. Dr Eneas de Carvalho Aguiar 155 2o andar bloco 6 Cerqueira Cesar, São Paulo, Brazil 05403-900; E-mail: mirelacdm@yahoo.com.br.

Disclosure Summary: All authors declare no conflicts of interest.

Data availability: The data that support this study's findings are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

References and Notes

1. White PC, Bachega TA. Congenital adrenal hyperplasia due to 21 hydroxylase deficiency: from birth to adulthood. *Semin Reprod Med.* 2012;**30**(5):400–409.
2. White PC. Neonatal screening for congenital adrenal hyperplasia. *Nat Rev Endocrinol.* 2009;**5**(9):490–498.
3. Hayashi GY, Carvalho DF, de Miranda MC, Faure C, Vallejos C, Brito VN, Rodrigues AS, Madureira G, Mendonca BB, Bachega TA. Neonatal 17-hydroxyprogesterone levels adjusted according to age at sample collection and birthweight improve the efficacy of congenital adrenal hyperplasia newborn screening. *Clin Endocrinol (Oxf).* 2017;**86**(4):480–487.
4. Silveira EL, dos Santos EP, Bachega TA, van der Linden Nader I, Gross JL, Elnecave RH. The actual incidence of congenital adrenal hyperplasia in Brazil may not be as high as inferred–an estimate based on a public neonatal screening program in the state of Goiás. *J Pediatr Endocrinol Metab.* 2008;**21**(5):455–460.
5. Nascimento ML, Cristiano AN, Campos Td, Ohira M, Cechinel E, Simoni G, Lee Jv, Linhares RM, Silva PC. Ten-year evaluation of a neonatal screening program for congenital adrenal hyperplasia. *Arq Bras Endocrinol Metabol.* 2014;**58**(7):765–771.
6. Kopacek C, de Castro SM, Prado MJ, da Silva CM, Beltrão LA, Spritzer PM. Neonatal screening for congenital adrenal hyperplasia in Southern Brazil: a population based study with 108,409 infants. *BMC Pediatr.* 2017;**17**(1):22.
7. Speiser PW, Azziz R, Baskin LS, Ghizzoni L, Hensle TW, Merke DP, Meyer-Bahlburg HF, Miller WL, Montori VM, Oberfield SE, Ritzen M, White PC; Endocrine Society. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2010;**95**(9):4133–4160.
8. Brunelli VL, Russo G, Bertelloni S, Gargantini L, Balducci R, Chiesa L, Livieri C, De Sanctis C, Einaudi S, Virdis R, Saggese G, Chiumello G. Final height in congenital adrenal hyperplasia due to 21-hydroxylase deficiency: the Italian experience. *J Pediatr Endocrinol Metab.* 2003;**16**(Suppl 2):277–283.
9. Van der Kamp HJ, Otten BJ, Buitenweg N, De Muinck Keizer-Schrama SM, Oostdijk W, Jansen M, Delemarre-de Waal HA, Vulsma T, Wit JM. Longitudinal analysis of growth and puberty in 21-hydroxylase deficiency patients. *Arch Dis Child.* 2002;**87**(2):139–144.
10. Sarafoglou K, Banks K, Kyllo J, Pittock S, Thomas W. Cases of congenital adrenal hyperplasia missed by newborn screening in Minnesota. *JAMA.* 2012;**307**(22):2371–2374.
11. Olgemöller B, Roscher AA, Liebl B, Fingerhut R. Screening for congenital adrenal hyperplasia: adjustment of 17-hydroxyprogesterone cut-off values to both age and birth weight markedly improves the predictive value. *J Clin Endocrinol Metab.* 2003;**88**(12):5790–5794.
12. Coulm B, Coste J, Tardy V, Ecosse E, Roussey M, Morel Y, Carel JC; DHCSF Study Group. Efficiency of neonatal screening for congenital adrenal hyperplasia due to 21-hydroxylase deficiency in children born in mainland France between 1996 and 2003. *Arch Pediatr Adolesc Med.* 2012;**166**(2):113–120.
13. Yoo BK, Grosse SD. The cost effectiveness of screening newborns for congenital adrenal hyperplasia. *Public Health Genomics.* 2009;**12**(2):67–72.
14. Achermann JC, Domenice S, Bachega TA, Nishi MY, Mendonca BB. Disorders of sex development: effect of molecular diagnostics. *Nat Rev Endocrinol* 2015;**11**(8):478–488.
15. Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP, Meyer-Bahlburg HFL, Miller WL, Murad MH, Oberfield SE, White PC. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2018;**103**(11):4043–4088.
16. Therrell BL, Padilla CD, Loeber JG, Kneisser I, Saadallah A, Borrajo GJ, Adams J. Current status of newborn screening worldwide: 2015. *Semin Perinatol.* 2015;**39**(3):171–187.
17. Grosse SD, Van Vliet G. How many deaths can be prevented by newborn screening for congenital adrenal hyperplasia? *Horm Res.* 2007;**67**(6):284–291.
18. Brosnan CA, Brosnan P, Therrell BL, Slater CH, Swint JM, Annegers JF, Riley WJ. A comparative cost analysis of newborn screening for classic congenital adrenal hyperplasia in Texas. *Public Health Rep.* 1998;**113**(2):170–178.

19. Heather NL, Seneviratne SN, Webster D, Derraik JG, Jefferies C, Carll J, Jiang Y, Cutfield WS, Hofman PL. Newborn screening for congenital adrenal hyperplasia in New Zealand, 1994-2013. *J Clin Endocrinol Metab*. 2015;**100**(3):1002–1008.
20. Gidlöf S, Wedell A, Guthenberg C, von Döbeln U, Nordenström A. Nationwide neonatal screening for congenital adrenal hyperplasia in Sweden: a 26-year longitudinal prospective population-based study. *JAMA Pediatr*. 2014;**168**(6):567–574.
21. Carroll AE, Downs SM. Comprehensive cost-utility analysis of newborn screening strategies. *Pediatrics*. 2006;**117**(5 Pt 2):S287–S295.
22. Grosse SD. Cost effectiveness as a criterion for newborn screening policy decisions. In: *Ethics and Newborn Genetic Screening: New Technologies, New Challenges*. Baltimore: Johns Hopkins University Press; 2009:58–88.
23. Prader A. [Genital findings in the female pseudo-hermaphroditism of the congenital adrenogenital syndrome; morphology, frequency, development and heredity of the different genital forms]. *Helv Paediatr Acta*. 1954;**9**(3):231–248.
24. de Carvalho DF, Miranda MC, Gomes LG, Madureira G, Marcondes JA, Billerbeck AE, Rodrigues AS, Presti PF, Kuperman H, Damiani D, Mendonca BB, Bachega TA. Molecular CYP21A2 diagnosis in 480 Brazilian patients with congenital adrenal hyperplasia before newborn screening introduction. *Eur J Endocrinol*. 2016;**175**(2):107–116.
25. SIGTAP - Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos, Órteses e Próteses do SUS. http://sigtap.datasus.gov.br/tabela-unificada/app/sec/inicio.jsp. Accessed July 2017.
26. Banco Central do Brasil. http://www.bcb.gov.br/pt-br/#!/home. Accessed July 2017.
27. Ministério da Saúde. *Cipionato de Hidrocortisona, comprimidos de 10mg e 20mg, para tratamento da hiperplasia adrenal congênita de recém-nascidos diagnosticados no programa nacional de triagem neonatal - PNTN*. In. Vol **146**. Brasilía-DF: Comissão Nacional de Incorporação de Tecnologias – CONITEC; 2015.
28. Brasil. Secretaria de Saúde do Estado de São Paulo. Resolução SS – 74, de 29/7/2015. Institui o novo Protocolo de Diretrizes e de Diagnóstico Laboratorial da Hiperplasia Adrenal Congênita – HAC, no Estado de São Paulo. *In. Diário Oficial da União*. 2015:45–47.
29. Sircili MH, de Mendonca BB, Denes FT, Madureira G, Bachega TA, e Silva FA. Anatomical and functional outcomes of feminizing genitoplasty for ambiguous genitalia in patients with virilizing congenital adrenal hyperplasia. *Clinics (Sao Paulo)*. 2006;**61**(3):209–214.
30. Jo C. Cost-of-illness studies: concepts, scopes, and methods. *Clin Mol Hepatol*. 2014;**20**(4):327–337.
31. Correa CH. *Expectativa de Vida no Mercado de Trabalho Brasileiro*. In. Banco Central do Brasil: Trabalhos para Discussão Nº 389; 2015:1–47.
32. Ministério da Saúde - DATASUS. Sistema de Informação sobre Nascidos Vivos - SINASC. http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sinasc/cnv/nvuf.def. Published 2015. Accessed July, 2017.
33. Instituto Brasileiro de Geografia e Estatística - IBGE. Brasil em síntese. Contas Nacionais. PIB *per capta*. http://brasilemsintese.ibge.gov.br/contas-nacionais/pib-per-capita.html. Published 2015. Accessed July, 2017.
34. Harrison M. *Valuing the future: the social discount rate in cost–benefit analysis*. Canberra: Visiting Researcher Paper, Productivity Commission, April, 2010:1–192. Accessed July, 2017.
35. Centers for Disease Control and Prevention (CDC). Economic costs associated with mental retardation, cerebral palsy, hearing loss, and vision impairment--United States, 2003. *MMWR Morb Mortal Wkly Rep. 2004*;**53**(3):57–59.
36. Khattab A, Yau M, Qamar A, Gangishetti P, Barhen A, Al-Malki S, Mistry H, Anthony W, Toralles MB, New MI. Long term outcomes in 46, XX adult patients with congenital adrenal hyperplasia reared as males. *J Steroid Biochem Mol Biol*. 2017;**165**(Pt A):12–17.
37. Prosser LA, Grosse SD, Kemper AR, Tarini BA, Perrin JM. Decision analysis, economic evaluation, and newborn screening: challenges and opportunities. *Genet Med*. 2013;**14**(8):703–712.
38. Grosse SD, Thompson JD, Ding Y, Glass M. The use of economic evaluation to inform newborn screening policy decisions: the Washington State Experience. *Milbank Q*. 2016;**94**(2):366–391.
39. Sheikh Alshabab LI, AlebrahIm A, Kaddoura A, Al-Fahoum S. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency: a five-year retrospective study in the Children's Hospital of Damascus, Syria. *Qatar Med J*. 2015;**2015**(1):11.
40. Maiti A, Chatterjee S. Congenital adrenal hyperplasia: an Indian experience. *J Paediatr Child Health*. 2011;**47**(12):883–887.
41. Shetty VB, Bower C, Jones TW, Lewis BD, Davis EA. Ethnic and gender differences in rates of congenital adrenal hyperplasia in Western Australia over a 21 year period. *J Paediatr Child Health*. 2012;**48**(11):1029–1032.

42. Balsamo A, Cacciari E, Piazzi S, Cassio A, Bozza D, Pirazzoli P, Zappulla F. Congenital adrenal hyperplasia: neonatal mass screening compared with clinical diagnosis only in the Emilia-Romagna region of Italy, 1980-1995. *Pediatrics.* 1996;**98**(3 Pt 1):362–367.
43. Nordenström A, Ahmed S, Jones J, Coleman M, Price DA, Clayton PE, Hall CM. Female preponderance in congenital adrenal hyperplasia due to CYP21 deficiency in England: implications for neonatal screening. *Horm Res.* 2005;**63**(1):22–28.
44. Gidlöf S, Falhammar H, Thilén A, von Döbeln U, Ritzén M, Wedell A, Nordenström A. One hundred years of congenital adrenal hyperplasia in Sweden: a retrospective, population-based cohort study. *Lancet Diabetes Endocrinol.* 2013;**1**(1):35–42.
45. Lee CT, Tung YC, Hsiao PH, Lee JS, Tsai WY. Clinical characteristics of Taiwanese children with congenital adrenal hyperplasia caused by 21-hydroxylase deficiency in the pre-screening era. *J Formos Med Assoc.* 2010;**109**(2):148–155.
46. Kovács J, Votava F, Heinze G, Sólyom J, Lebl J, Pribilincová Z, Frisch H, Battelino T, Waldhauser F; Middle European Workshop on Paediatric Endocrinology-Congenital Adrenal Hyperplasia Study Group. Lessons from 30 years of clinical diagnosis and treatment of congenital adrenal hyperplasia in five middle European countries. *J Clin Endocrinol Metab.* 2001;**86**(7):2958–2964.
47. Virdi NK, Green A. Congenital adrenal hyperplasia in Birmingham: a retrospective analysis (1958–1985). *J Inherit Metab Dis.* 1986;**9**(Suppl 1):152–155.
48. Grosse SD. Showing value in newborn screening: challenges in quantifying the effectiveness and cost-effectiveness of early detection of phenylketonuria and cystic fibrosis. *Healthcare (Basel).* 2015;**3**(4):1133–1157.
49. Van der Kamp HJ, Noordam K, Elvers B, Van Baarle M, Otten BJ, Verkerk PH. Newborn screening for congenital adrenal hyperplasia in the Netherlands. *Pediatrics.* 2001;**108**(6):1320–1324.
50. Van Vliet G, Czernichow P. Screening for neonatal endocrinopathies: rationale, methods and results. *Semin Neonatol.* 2004;**9**(1):75–85.
51. Brosnan CA, Brosnan PG, Swint JM. Analyzing the cost of neonatal screening for congenital adrenal hyperplasia. *Pediatrics.* 2001;**107**(5):1238.
52. Winfeld M, Patel P, Shah B, Nass R, Milla S. Early occurrence of cerebral white matter abnormality detected in a neonate with salt-wasting congenital adrenal hyperplasia. *J Pediatr Endocrinol Metab.* 2013;**26**(1-2):13–17.
53. Nass R, Baker S. Learning disabilities in children with congenital adrenal hyperplasia. *J Child Neurol.* 1991;**6**(4):306–312.
54. Muirhead S, Sellers EA, Guyda H; Canadian Pediatric Endocrine Group. Indicators of adult height outcome in classical 21-hydroxylase deficiency congenital adrenal hyperplasia. *J Pediatr.* 2002;**141**(2):247–252.