

Congenital Adrenal Hyperplasia in The Bahamas due to 21-Hydroxylase Deficiency

S Peter¹, G McDigeon², P Sandiford², T Smith³

ABSTRACT

Objective: To determine the frequency of 21-hydroxylase deficiency in The Bahamas and the spectrum of this disorder.

Methods: Patients referred for evaluation of virilization, precocious puberty, ambiguous genitalia and salt wasting had blood taken for 17-hydroxyprogesterone (17-OH progesterone) which was measured by Enzyme-Linked Immunosorbent Assay (ELISA).

Results: Nine patients had elevated 17 – OH progesterone levels – confirming 21-hydroxylase deficiency. Range of levels was 174.9nmol/l to 81678.7 nmol/L (normal less than 13 nmol/L). There were six females and three males and the age at diagnosis ranged from 21 days to 16 years. Five had precocious development, three had salt wasting, and there was one with virilization. One of the salt wasters had ambiguous genitalia. Incidence of 21-hydroxylase deficiency – 20/100 000; salt wasting – 35/100 000; the prevalence of 21-Hydroxylase deficiency 10/100 000).

Conclusion: The frequency of 21-Hydroxylase deficiency in The Bahamas is one of the highest worldwide.

Hiperplasia Suprarrenal Congénita en las Bahamas por Déficit de 21-Hidroxilasa

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RESUMEN

Objetivo: Determinar la frecuencia del déficit de 21-hidroxilasa en las Bahamas y el espectro de este problema.

Métodos: A los pacientes remitidos para evaluación de virilización, pubertad precoz, genitales ambiguos, y pérdida de sal, se les extrajo sangre para medir la 17-hidroxiprogesterona (17-OH progesterona) mediante un inmunoensayo enzimático (ELISA).

Resultados: Nueve pacientes tuvieron niveles elevados de 17-OH progesterona, confirmando el déficit de 21-hidroxilasa. El rango de niveles fue de 174.9nmol/l a 81678.7 nmol/L (normal menos de 13). Había seis hembras y tres varones, y la edad al momento del diagnóstico oscilaba entre los 21 días y los 16 años. Cinco mostraban desarrollo precoz, tres presentaban pérdida de sal, y uno exhibía virilización. Uno de los pacientes con pérdida de sal presentaba también genitales ambiguos. Incidencia del déficit de 21-hidroxilasa – 20/100 000. (Incidencia de la pérdida de sal – 35/100 000. Prevalencia del déficit de 21-hidroxilasa – 10/100 000).

Conclusión: La frecuencia del déficit de 21-hidroxilasa en las Bahamas es una de las más altas a nivel mundial.

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INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders due to deficiency of one of the five enzymes required for the synthesis of cortisol and aldosterone in the adrenal cortex. The enzymes involved are 21-

hydroxylase, 11-hydroxylase, 17-hydroxylase and 3-b-hydroxysteroid dehydrogenase. The most common enzyme defect is 21-hydroxylase that accounts for 90% of cases. The fundamental defect in CAH is the inability to synthesize cortisol adequately. Inefficient cortisol synthesis signals the hypothalamus and pituitary to increase Corticotrophin releasing hormone (CRH) and adrenocorticotrophin hormone (ACTH) respectively (Figs. 1, 2)

As a result, the adrenals become hyperplastic and produce an excess of sex hormone precursors, which do not require 21-hydroxylation for their synthesis. These pre-

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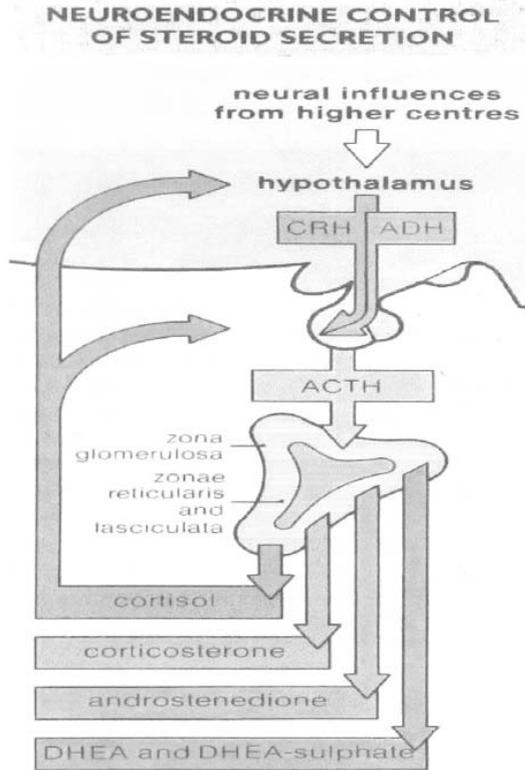


Fig. 1: Neuroendocrine control of steroid secretion.

cursors, progesterone and 17-hydroxyprogesterone, are further metabolized to active androgens – testosterone and dihydrotestosterone – and to a lesser extent oestrogens – oestrone and oestradiol. The net effect is prenatal virilization of girls and rapid somatic growth with early epiphyseal fusion in both genders. Severe enzyme defects with less than 1% of normal activity result in markedly reduced synthesis of aldosterone. These patients develop life-threatening hyponatraemic dehydration and are called “salt wasters”. Defects of 1–5% of enzyme activity produce simple virilization. A mild non-classical form occurs with enzyme defects of 50–80%. These females present with hirsutism and infertility as adults (Table). The 21-hydroxylase gene CYP21 is

		SPECTRUM	
		Classical	Non – Classical
Salt Wasting	Virilization		9
9 Enzyme Activity 9			Enzyme Activity
<1 % Normal 21 – OH Activity	1–5% 21 – OH Activity		50 – 80% 21 – OH Activity

Table: 21-OH represents 21-hydroxylase activity

located on the short arm of chromosome 6. A pseudogene *cyp21p* is located down stream close to *cyp21*. Diseases resulting from mutations are due to *cyp21p* acquiring portions of *cyp21*. Fourteen mutations causing diseases have been described (1–4). The objective of the study was to determine the frequency of 21-hydroxylase deficiency in The Bahamas and the spectrum of this disorder.

SUBJECTS AND METHODS

There is only one Endocrine Clinic in The Bahamas, which started in February of 2001.

Patients referred for evaluation of virilization, precocious development, ambiguous genitalia, salt wasting had blood drawn for 17-hydroxyprogesterone levels. 17-hydroxyprogesterone was measured by Lab Corp USA by an enzyme linked immunosorbent assay (ELISA). Population statistics were obtained from the 2000 population census. The incidence was determined by patients seen over a period of 12 months, 2002 – 2003. The prevalence was determined by all patients registered in the Endocrine Clinic with this disorder.

RESULTS

Nine patients had elevated 17-OH progesterone levels, confirming 21-hydroxylase deficiency. Range of levels – 174.9 nmol/l to 81678.7 nmol/l (normal less than 13 nmol/L).

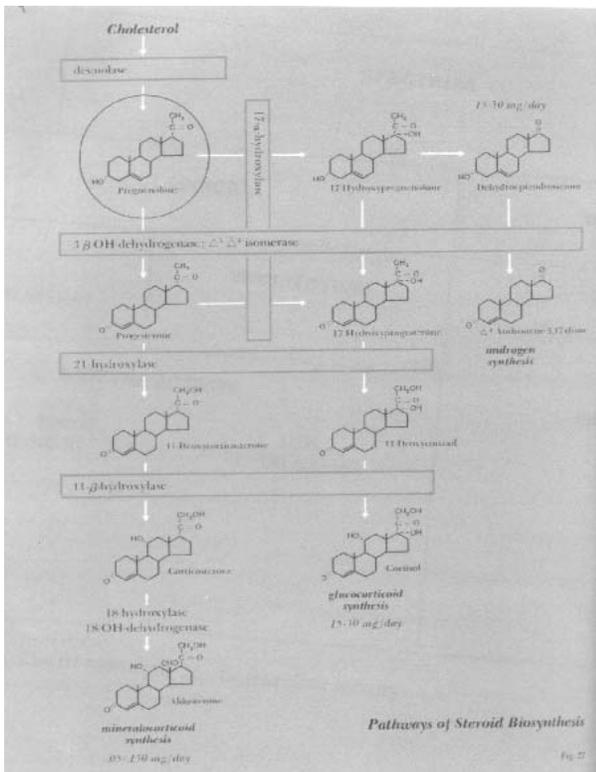


Fig. 2: Pathways of steroid biosynthesis.

There were six females and three males whose age at diagnosis ranged from 21 days to 16 years.

Five had precocious development, three had salt wasting, and one had virilization. One of the salt wasters had ambiguous genitalia.

During the twelve-month period from 2002 to 2003, seven of these patients were diagnosed. Five females and two males age ranged from 21 days to 5 years. Four females and one male had precocious development, *eg* pubic hair, breast development and one male had pubic hair and an adult sized penis. One male and one female had salt wasting. The 2000 population census showed a total population of 310 000 with 5908 persons being under one year of age. The incidence of salt wasters was 35/100 000. Persons between 0–5 years was 35 369. The incidence of 21-hydroxylase deficiency was 20/100 000. The population 0–16 years was 89 329. Thus the prevalence of 21-hydroxylase was 10/100 000.

DISCUSSION

Prior to this study the highest incidence of classic CAH reported occurred in two geographically isolated populations, the Yupik Eskimos of Western Alaska (1/280) and the French island of La Reunion in the Indian Ocean (1/2100). The incidence in other populations ranges from 1/10 000 to 1/18 000 (5).

The findings of this audit confirm that The Bahamas has the third highest incidence of classic CAH worldwide of adults. This is most likely the result of a “limited gene pool” in The Bahamian population. The Bahamas is an archipelago of 700 islands and Cays with only 13 being inhabited. The population at the 2000 census is 310 000 with 85% being of African ancestry. There is not as much genetic admixture in The Bahamas as compared to the neighbouring Caribbean countries. In Jamaica with a population of over 10 times that

of The Bahamas, only approximately six cases of classic CAH are seen nationwide (Personal Communication – Gabay). The prevalence rate in The Bahamas is underestimated because of the recent inception of an Endocrine Clinic. The incidence rate is also underestimated since (ACTH) stimulated 17-hydroxyprogesterone levels were not measured in the patients referred to the Endocrine Clinic.

It is now well established that early diagnosis by screening programmes significantly reduces morbidity and mortality from this disorder (6). Therapy is simple and cheap with the administration of glucocorticoids and mineralocorticoids orally. Hopefully these data will encourage the Ministry of Health to initiate a screening programme at the public hospitals.

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