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Summary information of human health hazard assessment of existing chemical substances（VI）

Shigeta, Y.[1], Iso, T.[2], Inoue, K.[2], Hirose, A.[2], Matsumoto, M.[1]

Department of Pathology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia[1]
Department of Medical Microbiology and Parasitology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia[2]

ABSTRACT— A clinical descriptive study was done to determine the sociodemographic, laboratory and clinical characteristics of patients with congenital adrenal hyperplasia (CAH) referred to Hospital Putrajaya, a tertiary endocrine centre in Malaysia. Electronic laboratory data of 51 CAH patients were obtained. The demographics and clinical details of the study population were acquired from a questionnaire completed by parents of participants. There were 25 males (49%) and 26 females (51%), of which, 58.8% were Malays. Median age of participants was 4 years whilst median age at diagnosis of CAH was two years. Parental consanguinity was documented in three patients (5.9%). Patients originated from Johor (19.6%), Selangor (19.6%), Negeri Sembilan (17.6%) and Kedah (13.7%). Majority of patients were diagnosed after one week of life (80.4%) although more females were diagnosed under the age of one week compared to males (p=0.041). Most females presented with ambiguous genitalia (42.3%) [p=0.001] whereas 72% of males presented with salt wasting (p=0.003). No significant associations between race and all other variables, though interestingly three Malay patients presented with ambiguous genitalia and hypertension. Equal gender distribution noted as expected in an autosomal recessive condition, although not in keeping with other Asian countries. Early diagnosis in females attributed to obvious genital ambiguity at birth. Varied clinical presentation, although in minority, necessitates genetic studies for prompt diagnosis and treatment. Considering that majority of patients presented with salt wasting and the age at diagnosis was delayed, the introduction of a neonatal screening programme is essential in Malaysia.

KEYWORDS: Congenital adrenal hyperplasia, 21-hydroxylase, Salt wasting, Multiethnic, Malaysia

1. INTRODUCTION

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder of adrenal steroid hormone biosynthesis with two major phenotypes; classic and non-classic CAH. The most common form is due to 21-hydroxylase (21-OH) deficiency, which accounts for 95% of CAH. Classic CAH is the more severe form of the disease affecting very young children and can be subclassified as salt wasting (75%) or simple virilising (25%), reflecting the degree of aldosterone deficiency [1]. Non-classical CAH is milder and usually presents during late childhood or early adulthood [2], [3]. Clinical features of CAH depend upon the position of the defective enzyme in the steroid synthetic pathway, which determines the pattern of hormones and precursors produced.2 Mutation in 21-OH enzyme (CYP21A2) blocks conversion of 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol, which in turn causes adrenal insufficiency and compensatory elevation of adrenocorticotropic hormone (ACTH). ACTH elevation causes adrenal hyperplasia and additional precursor synthesis. Precursor excess is shunted into the androgen synthesis pathway, causing virilisation in females and premature sexual development in males. Adrenal crisis is a medical emergency in salt-wasting CAH, which usually occurs within 14 days of birth if the disorder is untreated [3], [4]. The worldwide incidence of CAH due to 21-OH deficiency based on neonatal screening is 1:14,199 live births.4 High rates of classic CAH have been reported in the Yupic Eskimos of Alaska, the

French island of La Réunion, Brazil and the Philippines.4 However, non-classic CAH is more common than classic CAH, with a frequency of one in 100 in a heterogenous New York population [5] and is more frequent in certain ethnic populations, such as Jews of Eastern European origin, Hispanics, and Yugoslavs [4]. 11-beta-hydroxylase (11β-OH) deficiency, the second most common cause of CAH, accounts for 5–8% of CAH patients and increased rates are found among Moroccan Jews [4]. The incidence of 11β-OH deficiency was reported to be one in 100,000 among Caucasians [6]. 11β-OH deficiency impairs conversion of 11-deoxycortisol to cortisol. An accumulation of 11-deoxycorticosterone will lead to mineralocorticoid excess with hypertension. Affected female infants can present with ambiguous genitalia [7]. Serum 17-OHP and androstenedione levels provide the most sensitive index of biochemical control. In cases where neonatal screening is not available and 21-OH deficiency is suspected clinically, a synacthen test with measurements of cortisol, 17-OHP and androgens before and one hour after exogenous administration of ACTH (0.25mg intravenous bolus of cosyntropin) can be performed after the first 24–48 hours of life. This test should not be performed during the initial 24 hours of life as it may give rise to false-positive results [2]. To date there are limited data on CAH in Malaysian population. Considering the incidence of CAH varies according to ethnicity and geographical area, the imminent need to know the racial distribution in a multiethnic population like Malaysia is essential. Thus, the aim of this study is to determine the sociodemographic, biochemical and hormonal characteristics and the clinical presentation of CAH patients in selected paediatric population in Malaysia.

2. MATERIALS AND METHODS

Fifty-one patients with a diagnosis of CAH were recruited into this clinical descriptive study during their 3 - 4 monthly clinic visits to the paediatric endocrine clinics at Hospital Putrajaya over a period of 12 months. Hospital Putrajaya is currently the tertiary paediatric endocrine centre in Malaysia. Informed written consent was obtained from parent of each subject who participated in this study, in accordance with the Helsinki Declaration. The study was approved by the Research and Ethics Committees of both Universiti Putra Malaysia (ref. no: UPM/FPSK/PADS/T7-MJKEtikaPer/ F01(JPAT_NOV (09)07 dated 04/03/2010) and the Ministry of Health Malaysia (NMRR09-474-4011). All patients diagnosed with CAH who were referred to the paediatric endocrine clinics at Hospital Putrajaya were included. The demographics and clinical details of the study population were obtained from a questionnaire completed by parents of participants. Pre- and post-treatment laboratory data were acquired from the electronic laboratory information systems of Hospital Putrajaya. Patients with unrecorded data (missing data) were excluded from statistical analysis. Confidentiality of patients was ensured. Routine biochemical tests, such as sodium and potassium, were measured by standard laboratory methods on an automated biochemistry analyser, Synchron LX20 Pro (Beckman Coulter, Massachusetts, USA). Serum cortisol was determined by electrochemiluminescence immunoassay on the Roche Cobas e411 analyser (Roche Diagnostics, Mannheim, Germany). Serum 17-OHP and plasma renin were measured using DPC Gamma Counter C-12 (Diagnostics Products Corporation, California USA). Serum testosterone and ACTH were measured by chemiluminescence immunoassay on IMMULITE® 2000 XPi system (Siemens Medical Solutions Diagnostics, Erlangen, Germany). Statistical calculations were performed using the standard statistical software package, IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp. Shapiro-Wilk test was used to assess sample distribution due to small sample size (less than 100). Skewness and kurtosis values were also used to assess normality of data. Non- parametric tests were used for analysis of variables as they were not normally distributed, and median values with 25 to 75 percentiles were used. Mann-Whitney U test and/or Kruskall Wallis test were used to test the probability of any significant difference between groups. Associations between qualitative variables were determined by Chi-square test, Fisher's exact test and SAS Exact Contingency Table. In all statistical analyses, p value of < 0.05 (95% confidence interval) was considered to be statistically significant.

3. RESULTS

The demographics and clinical details of the study population (n = 51) are summarised in Table 1. There were 25 males (M) (49%) and 26 females (F) (51%). Majority were Malays (58.8%) - 15M, 15F; 29.4% were Chinese (7M, 8F); 7.8% were Indian (1M, 3F) and 3.9% of other races were categorised under Others (2M). Median age of patients was 4.1 years with an interquartile range (IQR) of 6, ranging from 1 to 16 years whilst median age at diagnosis of CAH was two years (IQR = 1), ranging from 0 to 4 years. Parental consanguinity was documented in three patients (5.9%). Majority were diagnosed after one week of life (80.4%). 31 families had only one child affected with CAH (17 Malays, 8 Chinese, 4 Indians, 2 others), 17 families had two children with CAH (10 Malays & 7 Chinese) while three Malay families had three children with CAH. The patients mainly originated from Johor (19.6%), Selangor (19.6%), Negeri Sembilan (17.6%) and Kedah (13.7%). However, the highest percentage of CAH diagnosis was made at Hospital Tuanku Jaafar, Seremban, Negeri Sembilan (15.7%). Forty-one patients (80.4%) were further investigated for CAH based on clinical presentation whereas the other 10 (19.6%) were based on a positive family history. Clinical presentation comprised of ambiguous genitalia (23.5%), ambiguous genitalia and salt wasting (5.9%), ambiguous genitalia and hypertension (5.9%) simple virilising (13.7%) and salt wasting (51%). For the laboratory investigations of the study population, the number of patients (n) differed for each analyte due to unrecorded data and thus were not included in statistical analysis (Table 2).

4. DISCUSSION

The incidence of CAH in Asian populations is approximately 1:44,000, [5] which is relatively lower compared to worldwide figures. In 1994, a case survey in Malaysia using the birth rate of the Maternity Hospital- and the patients referred to the Paediatric Endocrine Unit of Hospital Kuala Lumpur found that the overall incidence of CAH was 1: 3,000 with approximately equal distribution among the Malay, Chinese and Indian populations, comprising 57%, 16%, and 13%, respectively [8]. In comparison, our study showed no significant change in distribution of CAH in Malay patients (58.8%), an increase in Chinese patients (29.4%) and a decrease in Indian patients (7.8%). Our study also took into account other ethnicities, which made up 3.9% of CAH patients. partially attributed this unexpected high incidence of a potentially salt-wasting disorder in a tropical country to consanguinity which is frequent in the Malay- and Indian-, but not in the Chinese community. However, in our study parental consanguinity was only documented in three patients, of whom two were Malays and one from other ethnicity. Furthermore, no significant association was found between ethnicity and consanguinity. Also hypothesised selective advantage of the heterozygote state as a possible cause. As expected in an autosomal recessive disorder, there was equal gender distribution among CAH patients in this study; 25 males (49%) and 26 females (51%). However, other retrospective studies in South East Asia have reported skewed male: female ratios, with female preponderance; rationale given was that the clinical manifestation was more obvious in females, hence the earlier consult [9]. In this study, although majority of patients were diagnosed after one week of life (80.4%), more females were diagnosed under the age of one week compared to males ($p=0.041$). The significant difference in the age at diagnosis between genders could be explained by the significant association between gender and clinical presentation (Table 3). Most females (42.3%) presented with ambiguous genitalia whereas 72% of males presented with salt wasting.

Female infants with classic CAH typically have genital ambiguity at birth because of exposure to high concentrations of androgens in utero. Characteristic findings include an enlarged clitoris, partly fused and rugated labia majora, and a common urogenital sinus in place of a separate urethra and vagina. The internal female organs, the uterus, fallopian tubes, and ovaries, are normal. Male infants however have no obvious signs of CAH at birth, except hyperpigmentation and possible subtle penile enlargement [4]. Thus, it is probably the ambiguous genitalia in females at birth that typically lead to early diagnosis and treatment.

Affected males may go undetected for several years, until symptoms and signs of androgen excess develop. The age at diagnosis in boys varies according to the severity of aldosterone deficiency. Patients with severe salt wasting present at 2–3 weeks of life with adrenal crises, which includes vomiting, weight loss, lethargy, dehydration, hyponatraemia, hyperkalaemia and shock. This problem is particularly critical in male infants who have no genital ambiguity to alert physicians to the possibility of CAH [4], [7].

5. CONCLUSION

We were unable to estimate the prevalence of CAH in Malaysia due to the limitation of this study being conducted in a single site tertiary centre and the small sample size. Based on the clinical and laboratory findings, the majority of CAH patients were likely to have 21-OH deficiency, the most common form of classic CAH. However, there were three patients who presented with ambiguous genitalia and hypertension, pointing to a diagnosis of 11β-OH deficiency. Thus, detailed biochemical and genetic studies should be done as part of management to further confirm the diagnosis in these patients. Considering that the age at diagnosis is delayed in the study population, it is imperative that the reason/s for the delay in diagnosis be ascertained to ensure timely treatment and avoidance of complications. More effort is also required to educate the public regarding the disease presentation. The introduction of a neonatal screening programme in Malaysia is essential so that CAH can be diagnosed early leading to fewer patients presenting with life-threatening adrenal crisis. This will ultimately lead to an improvement in the management of CAH patients, resulting in a better quality of life, lower morbidity and mortality, and finally a reduction in the health care cost in our country.

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