SHORT COMMUNICATION

Raised 17-Hydroxyprogesterone Levels in Congenital Adrenal Hyperplasia

Sahar Iqbal and Aysha Habib Khan

ABSTRACT

Congenital adrenal hyperplasia (CAH) refers to autosomal recessive diseases resulting from deficiency of enzymes involved in the production of cortisol by the adrenal glands. This study was designed to determine the frequency of suspected congenital adrenal hyperplasia patients by evaluating the laboratory data of blood 17-OHP. The study was conducted at Chemical Pathology Section of Department of Pathology at the Aga Khan University, Karachi. The basic demographic data of 2282 subjects was recorded, screened for blood 17-OHP levels from January 2007 to December 2010. A cutoff of ≥ 4 ng/ml was considered as suggestive of CAH. The results showed 17-OHP levels ≥ 4 ng/ml were found predominantly among infants (14.4%) and in females (18.2%).

Key words: *Congenital adrenal hyperplasia. 17-hydroxyprogesterone. Cut off value.*

Congenital adrenal hyperplasia (CAH) refers to autosomal recessive diseases resulting from deficiency of enzymes involved in the production of cortisol by the adrenal glands. More than 90% of cases of CAH are caused by 21-hydroxylase enzyme deficiency (21-OHD).

Neonatal screening program for blood 17-hydroxy-progesterone (OHP) levels are intended to identify CAH cases of classical and non-classical forms in affected children before the complication of salt wasting crises arises and for early diagnosis of late non-specific presentation, respectively. Screening of non-classical CAH through testing blood (17-OHP) levels is the cornerstone for early diagnosis as disease presentation is non-specific as well as late in onset. Levels of 17-OHP > 4 ng/ml is a characteristic feature for disease suspicion in non classical form in contrast to the diagnostic levels of 200 ng/ml in classical form of CAH.[1]

The non-classic form is one of the most common autosomal recessive diseases in some ethnic groups and one of the reasons of high prevalence of CAH throughout the world.

The objective of this study was to determine the frequency of raised 17-OHP among different age groups and gender by evaluating the laboratory data of baseline blood 17-OHP levels.

This observational retrospective study was conducted at Chemical Pathology Section, Department of Pathology of the Aga Khan University Hospital (AKUH). Laboratory data of 5853 samples tested for blood 17-OHP levels was examined. The samples were collected between 2007 to 2010, at the main laboratory of AKUH in Karachi and its 188 phlebotomy centres located in four provinces of Pakistan. Subjects of all ages and gender with first time and baseline 17-OHP blood levels performed at the clinical laboratory were included. Those with any follow-up blood 17-OHP levels or stimulated with adrenocorticotropic hormone were excluded. 17-OHP results were grouped on the basis of locations of subjects, from where the test was ordered into Sindh, Baluchistan, Punjab and Khyber Pakhtunkhwa (KPK). Subjects were further categorized into four different age groups and three gender groups and frequency was observed for each age group and gender.

The study was approved by institutional ethical review committee. Analysis of 17-OHP concentrations was made with radioimmunoassay using Coat-A-Count kit (Diagnostic Product Corporation, USA). The assay sensitivity of 17-OHP was 0.1 ng/ml and intra- and inter-assay CVs were 7.9 and 12%, respectively. The 17-OHP value of ≥ 4 ng/ml was considered consistent with 21-OHD enzyme deficiency or suspected CAH.[2] Data was edited and analyzed by using Statistical Package for Social Sciences (SPSS) version 19. Frequencies were measured for age groups, gender and distribution of suspected subjects with CAH among four provinces of Pakistan. Chi-square or Fisher exact test used where applicable, p-value < 0.05 was considered significant.

There was an annual increasing frequency of blood 17-OHP levels screening (16.3%, 16.9%, 20.4% and 46.4% through the years from 2007 to 2010 respectively). An increasing annual trend, for frequency of subjects with suspected CAH (blood 17-OHP levels ≥ 4 ng/ml) as 5.1%, 6.5%, 7.1% and 15.7% respectively through the years 2007 to 2010. In general, screening for CAH was

Department of Pathology and Microbiology, The Aga Khan University Hospital, Karachi.

Correspondence: Dr. Aysha Habib Khan, 116 A/II, 16th Street, Off Mohafiz, Phase VI, DHA, Karachi.
E-mail: aysha.habib@aku.edu

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performed for different age group and gender. However, first time screening was predominantly performed in female population and after 15 years.

Overall, 34.4% subjects with suspicion of CAH were observed to have 17-OHP blood levels ≥ 4 ng/ml. Majority of subjects with 17-OHP levels ≥ 4 ng/ml were from infant age group (≥ 1 month to ≤ 1 year). Mostly females were found positive for suspicion of CAH ($p < 0.001$). Variable percentages were observed for referrals of 17-OHP levels from different provinces but majority were referred from Sindh (73.4%). The demographic details of the subjects are shown in Table I.

Table I: Demographic features and distribution of subjects among different provinces of Pakistan tested for blood 17-OHP levels at the Aga Khan University, Clinical Laboratory during 2007 - 2010 (n = 2282).

Variables	Total subjects n = 2282 (%)	17-OHP levels ≥ 4 ng/ml n = 784 (34.4%)	*p-value
Age groups			
Up to 1 month	32 (1.4)	28 (1.2)	0.0001
> 1 month to ≤ 1 year	477 (20.9)	328 (14.4)	
> 1 year to ≤ 15 years	758 (33.2)	278 (12.2)	
> 15 years	1015 (44.5)	150 (6.6)	
Gender			
Male	756 (33.1)	363 (15.9)	0.0001
Female	1520 (66.6)	416 (18.2)	
Ambiguous	6 (0.3)	5 (0.2)	
Subjects distribution within country			
Sindh	1676 (73.4)	541 (23.7)	0.108
Punjab	524 (23.0)	209 (9.2)	
Baluchistan	9 (0.4)	3 (0.1)	
KPK	73 (3.2)	31 (1.4)	

**p-value < 0.05 is considered as significant*

In Pakistan, the data on CAH is very limited. The features reported from previous studies were about the complications due to delay in diagnosis and high degree of consanguinity and infertility in local population. However, none of the study determined the disease burden though expected to be high due to the high frequency of parental consanguinity.[3]

Most of the suspected cases were infants (14.4%), reflecting the importance of neonatal screening. However, it was observed that CAH screening was most commonly ordered in elder age group (after 15 years). This late screening may be explained by the late emergence of non-classical CAH signs and symptoms.

Variable frequency of referrals from different provinces of Pakistan was observed as shown in Table I. Higher frequency of cases with suspected CAH was observed from Sindh (23.7%) as compared to other provinces. The most likely reason of this higher frequency from Sindh may be dependent on numbers of referrals or the number of collection centres from the province (73.4%). In Sindh, 68% of the samples were collected from the (78) phlebotomy centres in Karachi and the main AKU Campus. An additional 5.4% of samples from other phlebotomy centres located in different cities of Sindh other than Karachi, but we found Karachi city as the main hub for 17-OHP referrals from Sindh province which may be due to the large number of phlebotomy centres in the area. From this laboratory data it is not possible to determine the ethinicity of suspected CAH cases, but it could be presumed that CAH exists throughout the country with variable frequency. This finding is also supported by the results of a previous study from Pakistan.[4]

The importance of establishing neonatal screening program for CAH is enhanced by the present data; however, the benefits of screening for any disease in a state are dependent on the existing healthcare system. The treatment or management of inborn disorders has not been acknowledged appropriately in Pakistan. Additionally, the existing healthcare system generally does not address complex issues commonly seen in genetic disorders including CAH patients.[5]

The true incidence of CAH in Pakistan remains unidentified due to the absence of new born screening program, diagnostic testing, and lack of disease awareness in the society and failure of case identification by primary physicians. There is a need for developing a team of experts in early identification and management of CAH to reduce the morbidity and mortality. A well structured and appropriate screening program should be instituted for the high risk groups and the general population. The establishment of CAH registry is also critical at regional or national levels for the identified cases and respective pre-natal treatment.

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