CYP21A2 Gene Mutation in South Indian Children with Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder; 21 hydroxylase deficiency is the most common cause accounting for 95% of cases [1]. The extent of the enzyme impairment and the clinical phenotype of the disease are determined by the severity of the genetic defect in the *CYP* 21 gene [2]. We present here the gene mutations seen in patients with CAH from Chennai, India, presenting to the department of Pediatric endocrinology at Kanchi Kamakoti CHILDS Trust Hospital, Chennai, India from August 2013 to July 2014. Children diagnosed with classical congenital adrenal hyperplasia (salt-wasting phenotype) based on the clinical features, serum electrolytes, 17 hydroxy progesterone levels and molecular genetic analysis, and followed during the study period were included. Informed consent was obtained and the study was approved by the Institutional ethics committee. Molecular genetic testing of *CYP21A2* gene was performed at All India Institute of Medical Sciences, New Delhi.

Abnormal genotype in *CYP21A2* gene was detected in 6 (4 boys) out of 10 children with CAH screened. Their clinico-laboratory characteristics are shown in ***Table* I**. 8 base pair deletion in exon 3 of *CYP21A2* gene was the commonest mutation seen in 4 children, followed by 12 g deletion mutation in Intron 2 in the remaining two. Mutation was not detected in four children. All children were treated with hydrocortisone and fludrocortisone, and are doing well at follow-up. Boys with CAH were diagnosed later than girls in our study which is similar to an earlier study by Bajpai, *et al*. [3], thus stressing the need to rigorously implement neonatal screening of all children which will enhance the earlier diagnosis of less severe forms of CAH, reduce the virilization in classical forms

TABLE I CLINICO – LABORATORY PROFILE OF CHILDREN WITH CAH

Patient Number	*Sex*	*Age at diagnosis*	*Consanguinity*	*Clinical features*	*Serum Na^+ (mmol/L)*	*Serum K^+ (mmol/L)*	*Serum 17OHP (ng/dL)*	*Genotype*
1	M	2 mo	3 degree	Vomiting, failure to thrive	128	6.5	3000	8 base pair deletion in exon 3 of CYP21A2 GENE
2	M	35 d	2 degree	Vomiting, failure to thrive	110	7	31760	Homozygous 8 base pair deletion in exon 3 of CYP21A2 GENE
3	M	2 mo	3 degree	Vomiting, loose stools, failure to thrive	107	7.6	2900	8 base pair deletion in exon 3 of CYP21A2 GENE
4	M	15 d	Non consanguineous	Vomiting, failure to thrive, skin hyperpigmentation	120	7.6	4590	Heterozygous 8 base pair deletion in exon 3 of CYP21A2 GENE
5	F	At birth	Non consanguineous	Ambiguous genitalia (Prader stage III)	115	7.9	3100	Homozygous 12 mutation in Intron 2 of CYP21A2 GENE
6	F	2 mo	Non consanguineous	Vomiting, loose stools, dehydration, shock, failure to thrive, genital ambiguity (Prader stage II)	130	6.3	2200	Homozygous 12 mutation in Intron 2 of CYP21A2 GENE

and promote normal growth. Vomiting and failure to thrive were the most common clinical presentation seen in both genders in our series, similar to an earlier observation by Begum, *et al*. [4].

To date there are approximately 100 different mutations reported in *CYP 21* gene including deletions, point mutations and insertions. Severe mutations are associated with classical CAH whereas milder mutations are associated with non-classical CAH [5,6]. Marumudi, *et al*. from New Delhi reported Intron 2 mutation as the most common mutation in patients with CAH [7]. Mathur, *et al*. [6] from New Delhi reported Ile173Asn followed by intron 2 splice and Gln 319 stop mutations in children with classical CAH. In our series, 8 bp deletion in exon 3 of the *CYP21A2* gene was the most common (66.7%) followed by 12 g mutation in Intron 2 of the *CYP21A2* gene [IVS2-13A/C>G]. As complete sequencing of *CYP21A2* gene is expensive and is available only in select laboratories, knowledge of common mutations prevalent in our population helps us to make a reliable pre-, peri- and post-natal diagnosis, and also to offer genetic counseling to the affected families.

***RAMASWAMY GANESH, NATARAJAN SURESH, LALITHA JANAKIRAMAN AND #KARNAM RAVIKUMAR**
Departments of Pediatrics and #Pediatric Endocrinology, Kanchi Kamakoti CHILDS Trust hospital and The CHILDS Trust Medical Research Foundation, Chennai, Tamil Nadu, India.
**ganeped79@rediffmail.com*

REFERENCES

1. Huynh T, McGown I, Cowley D, Nyunt O, Leong GM, Harris M, *et al*. The clinical and biochemical spectrum of congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency. Clin Biochem Rev. 2009;30:75-86.
2. Dolzan V, Stopar-Obreza M, Zerjav-Tansek M, Breskvar K, Krzisnik C, Battelino T. Mutational spectrum of congenital adrenal hyperplasia in Slovenian patients: A novel Ala15Thr mutation and Pro30Leu within a larger gene conversion associated with a severe form of the disease. Eur J Endocrinol. 2003;149:137-44.
3. Bajpai A, Kabra M, Menon PS. 21-Hydroxylase deficiency: Clinical features, laboratory profile and pointers to diagnosis in Indian children. Indian Pediatr. 2004;41:1226-32.
4. Begum JA, Sarker AK, Hoque M, Mamum MAA, Mobarak MR, Biswas R, *et al*. Clinical profile of congenital adrenal hyperplasia(CAH): A treatable disease. Dhaka Shishu (Children) Hospital Journal. 2010;26:108-12.
5. Forest MG. Recent advances in the diagnosis and management of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Hum Reprod Update. 2004; 10:469-85.
6. Marumudi E, Sharma A, Kulshreshtha B, Khadgawat R, Khurana ML, Ammini AC. Molecular genetic analysis of CYP21A2 gene in patients with congenital adrenal hyperplasia. Indian J Endocrinol Metab. 2012;16:384-8.
7. Mathur R, Menon PS, Kabra M, Goyal RK, Verma IC. Molecular characterization of mutations in Indian children with congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency. J Pediatr Endocrinol Metab. 2001;14:27-35.

Pediatric Melioidosis in Southern India

Melioidosis in children is increasingly detected from the coastal region of Southern India during monsoon. We present 11 cases of melioidosis, ranging from localized to disseminated, treated successfully, barring one death. It calls for awareness and upgrading laboratory facilities for better diagnosis and management of pediatric melioidosis.

Keywords: *Burkholderia pseudomallei*, *Child, Lymphadenitis.*

Melioidosis, a disease caused by the soil-dwelling bacterium *Burkholderia pseudomallei*, has varied clinical spectrum ranging from mild localized illness to fulminating sepsis. Southern part of India is apparently a new 'hot spot' in the global map of melioidosis [1,2]. Childhood infections are increasingly being recognized, and are more localized affecting immunocompetant population [3,4]. This case series highlights the occurrence and presentation of the culture-confirmed cases of melioidosis among children, diagnosed at our institute between January 2007 and June 2014.

Pediatric melioidosis accounted for 8% of 140 cases of melioidosis diagnosed during this period. The median age was 7.5 years (range 3-18 y). Fever was the commonest presentation (100%) with a median duration of 10 days (range 2-90 d). Ten children presented with acute disease (≤2 mo), while one child had fever for three months. Melioidosis was restricted to head and neck region in five children (two submandibular abscesses, two suppurative cervical lymphadenitis and one suppurative parotitis), whereas six had disseminated disease. Hepatomegaly and splenomegaly were observed in three and two cases, respectively. Two children had diabetes mellitus, both of whom presented with severe systemic illness, but recovered. One child, who presented with septic shock, encephalopathy and acute respiratory