LONG-TERM PROGNOSIS IN ADULT MALES WITH CLASSICAL 21-HYDROXYLASE DEFICIENCY

Hori N, Hasegawa T, Sasaki E, Inokuchi M, Sato S*, Matsuo N**

Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan; *Saitama Municipal Hospital, Saitama, Japan; **National Center for Child Health and Development Hospital, Tokyo, Japan

(Aims) We investigate long-term prognosis in adult males with classical 21-hydroxylase deficiency (21OH), and analyzed factors related to long-term prognosis.

[Subjects and Methods] Subjects: twelve 21OH patients with final heights, aged 14-31 (median 19.9) years. Parameters for long-term prognosis: (1) final height (FH) SD score (2) testicular volume by orchidometer (3) presence or absence of adrenal rest tumor (tumor) by palpation and/or ultrasonography. Factors related to prognosis: (1) median 17 hydroxyprogesterone (17OHP) except for the first admission and on adrenal crisis (2) clinical phenotypes as salt-wasting (SW) or simple virilizing (SV).

[Results] 1) long-term prognosis: FH was -3.43 to 0.66 (median -1.63) SD, and FH - target height -3.13 to 1.52 (median -1.90). Testicular volume was 20 to (median 15) mL, being <12 mL (10 percentile in Japanese healthy 16 yr boy) in 4 subjects. Tumor was present in 6 subjects. Factors related to long-term prognosis: median 17OHP was 0.90 to 87.0 (median 14.9) ng/mL. Eight were SW and 4 SV. None of the parameters were affected by median 17OHP and clinical phenotypes.

[Discussion] FH was not normalized, as previously reported. Spermatogenesis may be defective, warranting semen analyses. Short-term control of 21OH was not related to long-term prognosis. Further studies are required if other factors may affect the long-term prognosis.

ABNORMAL STEROIDGENESIS IN THREE PATIENTS WITH ANTYLEY-BIXLER SYNDROME: COMBINED DEFICIENCIES OF 17a-HYDROXYLASE, 17,20-LYASE AND 21-HYDROXYLASE

Adachi M, Asakura Y, Tachibana K

Department of Endocrinology & Metabolism, Kanagawa Children’s Medical Center

Aim: To clarify the nature of abnormal steroidogenesis in Antley-Bixler syndrome (ABS). Patients & Methods: Endocrinological evaluation was done in three ABS patients: case 1, 4 year-old girl; case 2, 14 year-old male; and case 3, 17 year-old male. Case 1 had urogenital sinuses and case 3 had bilateral orchiopey. Results: All patients showed remarkably elevated progesterone (P4), corticosterone (B), and 17OHP. After rapid ACTH stimulation, whereas P4 and B further increased, 17OHP and other 17-hydroxysteroids failed to respond, suggesting decreased 17a-hydroxylase activity. Activity of 17,20-lyase seemed partially impaired, since all patients showed hypergonadotropinemia and androstenedione in case 2 and 3 was lower. High 17OHP value was considered to be partly of testis origin, since high 17OHP persisted even after dexamethasone treatment in case 2. In addition, disorders 21-hydroxylase activity was inferred, because prepubertal case 1 also showed high 17OHP, coupled with elevated 17OHP/11DOFP and 17OHP/DHC. Discussion: Our three ABS cases showed complex abnormality in steroidogenesis, indicating combined 17aOHase/17,20-lyase/21OHase deficiency. Mutation(s) of a novel regulator gene, other than FGF2, that control both these enzymes and skeletal morphogenesis may be responsible for this unusual association.

NOVEL MUTATIONS IN THE CYP21B1 GENE IN JAPANESE PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA DUE TO 11-β-HYDROXYLASE DEFICIENCY

Katsumata N, Fujita K, Nishiy T, Ikami A, Kagemi M, Tanaka T

Department of Endocrinology and Metabolism, National Research Institute for Child Health and Development, "Department of Pediatrics, Osaka-City General Hospital, "Department of Pediatrics, Hiroshima Red Cross Hospital, "Sapporo City Institute of Public Health

Congenital adrenal hyperplasia (CAH) due to 11-β-hydroxylase deficiency is a rare autosomal recessive disorder, which is caused by mutations in the CYP21B1 gene, and comprises approximately 1% of CAH cases in Japan. In the present study, we analyzed the CYP21B1 gene in two Japanese families with 11-β-hydroxylase deficiency. The proband of Family 1 was a girl, who was born with masculinization of external genitalia. She was diagnosed as having 11-β-hydroxylase deficiency based on typical clinical and endocrinological findings during the neonatal period. Her younger brother was examined during the neonatal period because of the family history, and was also diagnosed as 11-β-hydroxylase deficiency. The proband, the only one patient, in Family 2 was a 9-year-old boy, who presented sexual precocity and hypertension. He was diagnosed as having 11-β-hydroxylase deficiency based on typical clinical and endocrinological findings. Genetic analyses of CYP21B1 were performed in these patients. The patients in Family 1 were demonstrated to have compound heterozygous mutations, a novel duplication of nt 1052-1074 of the cDNA with a K386R substitution (dup1238bp) in the paternal allele, and a novel deletion of codons 458 and 459 (Δ458A,459) in the maternal allele. The patient in Family 2 was found to be homozygous for a novel missense mutation P442R (CCC→CCC). The functional expression study confirmed that all the mutations markedly abolished the 11-β-hydroxylase activity. In conclusion, we have identified three novel mutations (dup1238bp, Δ458A,459 and P442R) in the CYP21B1 gene causing 11-β-hydroxylase deficiency.

CONGENITAL ADRENAL HYPOPLASIA AND MENTAL RETARDATION: IMPORTANCE OF THE IL1RAPL GENE ANALYSIS

Sasaki B, Hasegawa T (Keio University); Muroya K (Tokyo Dental College Ichikawa General Hospital); Kamimaki T (Shinshu Municipal Hospital); Yorifuji T (Kyoto University); Inaom Y (Nippon University Hikarigaoka Hospital); Kinoishi E (Nagasaki University); Ogata T (Tokyo Electric Power Company Hospital)

[Background] Congenital adrenal hypoplasia congenita (AHC) is frequently associated with mental retardation (MR). Here, we report on congenital gene syndrome involving DAX-1 for AHC and IL1RAPl for MR.

[Subjects] Family A: The elder brother had severe adrenal crisis at one month of age, and exhibited profound MR with brain atrophy. The younger brother had moderate MR, despite the lack of adrenal crisis. The mother and the sister had mild MR. Family B: The boy exhibited mild adrenal crisis at two months of age, and had mild MR in the absence of brain atrophy. The mother was free from MR.

[Family C: The brother had adrenal crisis in the neonatal period but showed normal mental development.

[Deletion analysis] PCR analysis for 20 loci on Xp21-22 and FISH analysis for DAX-1 and IL1RAPl were performed, showing a <6 Mb deletion involving DAX-1 and IL1RAPl in the brothers of family A, a <4 Mb deletion involving DAX-1 and disrupting IL1RAPl in the boy of family B, and a <1.5 Mb deletion involving DAX-1 but not IL1RAPl, in the brothers of family C. The three females in family A and family B were heterozygous for the deletions.

[X-inactivation analysis] Methylation pattern of the AR gene was examined by the standard method, revealing random X-inactivation in the three females in family A and family B.

[Discussion] The results suggest that male patients with contiguous gene syndrome involving DAX-1 and IL1RAPl show MR irrespective of the episode of adrenal crisis, and that reduced expression of IL1RAPl caused by random X-inactivation in heterozygous females results in variable degree of mental development. IL1RAPl analysis is recommended in families of males with AHC and MR.