A Clinical and Molecular Genetic Study of Children with Hypophosphatemic Rickets (HR)

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Objective : A group of diseases including X-linked HR (XLH), autosomal dominant HR (ADHR), hereditary HR with hypercalciuria and tumor-induced osteomalacia shares common clinical and biochemical features, and, can be categorized as HR. Recently, dramatic advances in our understanding of the molecular bases of HR have been achieved. In this study, a clinical and molecular genetic study was performed in children with HR.

Methods : Total 17 unrelated children were included in this study. The clinical data were reviewed retrospectively, and mutational analysis of PHEX and FGF23 genes was carried out.

Results : The male to female ratio was 3 : 14. The median age of onset was 20 (10?35 mos) mos. The family history was positive in 5 patients. All patients had rachitic bony deformities, and dental abscess or caries were noted in 6 cases. Initial serum calcium and phosphorus were 9.5±0.7 and 2.5±0.4 mg/dL, respectively, and alkaline phosphatase 727±207 IU/L. The serum 25(OH)D3 and 1,25(OH)2D3 were 28±14 ng/mL and 44±20 pg/mL, respectively. The tubular reabsorption and transport maximum of phosphate were 48.9±22.6% and 1.33±0.56 mg/dL of GFR, respectively. Hypercalciuria was not detected in any cases before treatment. All cases were treated with oral vitamin D and phosphorus, and 12 received orthopedic management. The standard deviation score of the height improved from -2.23±1.00 to -1.70±1.09 ($p<0.05$) after 2 years of treatment, but complete catch-up growth was not achieved in most cases. During the follow-up, intermittent hypercalciuria was noted in 14 cases, hypercalcemia in 7, nephrocalcinosis in 10 and hyperparathyroidism in 4. Renal glycosuria was detected in 6 and intermittent microscopic hematuria in 4. The PHEX gene analysis revealed 7 different mutations in 8 patients including 2 missense mutations, 2 nonsense mutations and 3 short deletions. And a heterozygous T239M change in the FGF23 gene was detected in 3 cases with normal PHEX gene. There was no correlation between the phenotype and genotype.

Conclusion : The current treatment of HR brings only partial improvement for the final growth, and it is frequently accompanied by several complications. So, regular close monitoring of the calcium metabolism is essential. About a half of the patient were genetically diagnosed as XLH associated with the PHEX gene mutations. However, some proportion of patients with normal genetic study suggests the possibility of other causative gene(s) which remains to be identified.