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High-risk screening for Fabry disease in patients with chronic kidney disease of undetermined cause

Yura Chae[1], Jongho Son[1], Eun Sil Koh[1], Chul Woo Yang[2], Sungjin Chung[1]
[1]Department of Internal Medicine-Nephrology, The Catholic University of Korea, Yeouido St. Mary's Hospital, Korea, Republic of
[2]Department of Internal Medicine-Nephrology, The Catholic University of Korea, Seoul St. Mary's Hospital, Korea, Republic of

Objectives: The difficulty in recognizing Fabry disease due to its highly variable and nonspecific phenotype, low prevalence rate and lack of positive family history in some cases signifies that a diagnosis of this condition could be missed or delayed in many of patients with Fabry nephropathy. Therefore, Fabry disease needs to be considered and tested in patients with chronic kidney disease (CKD) with no definite cause and when no biopsy has been performed, even in no familial cases.

Methods: Based on the results of biochemical screening of α-galactosidase A in subjects with renal impairment and/or proteinuria without family history of Fabry disease, a confirmatory genetic test was performed in male subjects with low enzyme activity of α-galactosidase A and in female subjects with activity lower than 1.5 times normal limit.

Results: During the period from June 2018 to November 2019, enzymatic activity was measured in 493 dried blood spot samples of 284 males and 209 females. Among them, 19 males and 65 females, who had low or low normal enzyme activity, were recommended to be verified by the genetic test. We detected 3 subjects carrying genetic variants of exon possibly linked to late onset disease (c.196G>C and c.322G>A). Furthermore, c.-10C>T (g.1170C>T) polymorphism in the 5' untranslated region of exon 1 were found in 10 hemodialysis or kidney transplant patients, which frequency is higher than in patients with non-dialyzed CKD. Intriguingly, a few subjects with c-10C>T were found to carry a complex intronic haplotype (c.-10C>T, c.369 + 990C>A, c.370-81_370-77delCAGCC, c.640-16A>G, c.1000-22C>T).

Conclusions: As the importance of early treatment in patients with Fabry disease has been generally recognized, the introduction of widespread screening of at-risk patients with CKD may be needed. In addition, further investigation is required to elucidate the mechanism involved in the change of α-galactosidase A gene expression in presence of specific frequent polymorphisms.