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Fabry disease with genetic variants of unknown significance and concomitant immunoglobulin A nephropathy in a single center in China: case series and review

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Case Study : Aims Fabry disease (FD) is an X-linked inherited disease caused by GLA gene mutations. The clinical diagnosis and treatment of FD with genetic variants of unknown significance (VUS) is relatively difficult, we intend to report some cases with novel VUS mutations and concomitant immunoglobulin A nephropathy (IgAN) to improve the understanding of VUS. Methods The study investigated patients with genetically confirmed FD in our center retrospectively. Demographic data, medical history, physical examination, clinicopathological data, laboratory indicators, α-Gal A activity, lyso-Gb-3 level, DNA analysis, and information of family members were collected from all participants. Results Fourteen probands (37.79 ± 12.65 years, 8 males) and their family members were included in the study. Eleven probands represented missense mutations in GLA, 4 of whom showed VUS mutations, and the other 7 showed pathogenic or likely pathogenic mutations. Another 3 probands had deletion mutations in GLA, 1 of whom showed VUS mutation, others showed pathogenic mutations. Most probands presented renal (12/14) and cardiac (10/14) involvement, while a few probands had cutaneous (1/14), ocular (1/14), and peripheral nerve (3/14) involvement. One of the family members had cerebral infarction. Among the five probands with VUS mutations, one was concomitant with nephrotic syndrome with minimal change disease (MCD) of c.733T>C mutation, and 3 was concomitant with IgAN, 2 of whom had the same missense mutation (c.479C>A), and the other one had a deletion mutation (c.1032-1058 del). Conclusions The clinical manifestations of FD are heterogeneous. Our study indicated renal and cardiac system are mainly involved, while nervous, ocular, and cutaneous system are less involved. Comprehensive clinical evaluation, especially tissue-specific biopsy, is necessary for patients with VUS mutations for timely diagnosis and treatment. FD often coexists with nephrotic disorders, such as IgAN and MCD. The VUS mutation with c.479C>A seemed to be more likely concomitant with IgAN.