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Editorial Comment

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Fabry Disease: The Role of Screening for Early Diagnosis

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Fabry disease (FD) is a rare X-linked inherited genetic disorder caused by a mutation in the GLA gene, leading to a deficiency or absence of an enzyme activity called alpha-galactosidase A. This enzyme is responsible for breaking down globotriaosylceramide (Gb3) in glycosphingolipid metabolism. Globotriaosylceramide and its deacylated derivative globotriaosylsphingosine (lyso-Gb3) accumulate progressively in lysosomes of various cell types and affect various organs and tissues. Therefore, FD is considered a multi-systemic disease with neurological, kidney, cardiac, ocular, and dermatological manifestations. Early symptoms often include neuropathic pain, abdominal pain, and hot and cold intolerance, while end-organ damage such as chronic kidney disease (CKD), early stroke, and cardiomyopathy can lead to life-threatening complications and premature death.[1]

Fabry disease is a rare disease, and timely diagnosis is quite challenging, as with other rare diseases. The clinical presentation of FD is highly variable, and the symptoms can be nonspecific and overlap with other diseases, making it difficult to diagnose. Unfortunately, many patients are evaluated by several different medical specialists and are often given the wrong diagnosis before being diagnosed with FD. There is a significant diagnostic delay of up to 20 years from symptom onset.[2] This delay is likely due to the lack of awareness of the disease and the wide spectrum of clinical presentations, especially in females. A suspicion of FD arises from the evidence of clinical manifestations and the family history. Therefore, a detailed history including family history and examining clinical signs and symptoms related to FD are essential in the diagnosis of FD. Biochemical, genetic, and histopathological tests (whenever possible) should be incorporated into the diagnostic work-up. In general, new cases detected by clinical suspicion based on clinical manifestations are classic males in FD. In females and individuals with genetic variants, the diagnosis can be challenging. Since the diagnosis of a new patient with FD is difficult in clinical practice, different screening strategies have been frequently conducted in different populations.

Newborn screening for FD has gained some interest in recent years; however, several concerns exist, and it is still not universally accepted. Nevertheless, case-finding studies among high-risk populations are crucial for identifying new patients. The term high-risk includes those patients with at least one sign or symptom of FD. Patients with an unknown etiology of CKD or left ventricular hypertrophy or hypertrophic cardiomyopathy or cerebrovascular events are the main high-risk patient groups. Clinicians caring for patients suffering from CKD, heart disease, or stroke are likely to encounter individuals with undiagnosed FD.

In this issue of the Journal, Demirelli B et al[3] address the importance of screening patients with CKD. They report the results of 470 patients with CKD and 47

patients with a family history of FD mutation. The overall prevalence of FD in patients with CKD was 0.6% (3 of 494 patients). Although it has not been completed so far, family screening of three index cases was conducted and enabled to diagnosis of additional eight patients with Fabry mutation in this case-finding study. In the same line with previous study, Saray S and colleagues,[4] in this issue of the Journal, a total of 950 high-risk patients were identified using a questionnaire in patients with signs and symptoms suggestive of FD. A controversial mutation (p.D313Y) was detected in only 1 female patient (0.7%). Previously, several case-finding studies have been performed in high-risk populations in Türkiye. However, the true incidence and prevalence of FD are not known. Systematic screening studies for the FD in the general population may help to determine it. Previous FD screening studies in patients with CKD from our country have reported a prevalence ranging from 0.2% to 0.95%.[5,6] These findings emphasized that FD should be considered and tested in patients with CKD with no definitive cause of kidney disease. Identifying an index case allows to recognize the disease within a family. Once an index case is identified, a complete family pedigree analysis should be conducted to identify at-risk family members. Family screening can be especially helpful for finding patients earlier in their disease course. It is estimated that 5-10 family members are detected mutation positive around an index case. In conclusion, a considerable number of patients with one of the major symptoms of FD can be identified by screening.

Overall, the diagnosis is often delayed because of the rarity and the nature of the disease in FD. Early diagnosis and treatment are crucial in managing the symptoms and preventing devastating complications. Therefore, raising awareness among clinicians about FD is crucial to ensure timely diagnosis and access to early therapy. Many efforts have been made to increase the awareness of FD among physicians since 2010. With the initiation of enzyme replacement therapies, the number of patients diagnosed with FD has increased in many centers in Türkiye. The disease may be more prevalent than estimated. Screening programs allow the early diagnosis and lead to the initiation of specific therapies before the onset of progressive organ damage.

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REFERENCES

1. Ezgu F, Alpsoy E, Bicik Bahcebasi Z, et al. Expert opinion on the recognition, diagnosis and management of children and adults with Fabry disease: a multidisciplinary Turkey perspective. *Orphanet J Rare Dis*. 2022;17(1):90. [CrossRef]
2. Martins AM, Kyosen SO, Garrote J, et al. Demographic characterization of Brazilian patients enrolled in the Fabry Registry. *Genet Mol Res*. 2013;12(1):136-142. [CrossRef]
3. Demirelli B, Boztepe B, Betül Öğütmen M. Fabry disease screening in patients with proteinuria or chronic kidney disease and defining a novel mutation: A single-center experience. *Turk J Nephrol*. 2024 [Epub Ahead of Print].
4. Saray S, Çeltik A, Atay G, Aşçı G, Seziş Demirci M, Yılmaz M. Screening for the frequency of Fabry disease in patients followed up in the nephrology outpatient clinic. *Turk J Nephrol*. 2024 [Epub Ahead of Print].
5. Turkmen K, Guclu A, Sahin G, et al. The prevalence of Fabry disease in patients with chronic kidney disease in Turkey: the TURKFAB study. *Kidney Blood Press Res*. 2016;41(6):1016-1024. [CrossRef]
6. Yalın SF, Eren N, Sinangil A, et al. Fabry disease prevalence in renal replacement therapy in Turkey. *Nephron*. 2019;142(1):26-33. [CrossRef]