

Fabry disease in Poland

To the Editor This letter has been written to inform Polish medical community about the problems of patients with Fabry disease in our country.

Fabry disease (FD) is an ultrarare, devastating, and progressive X-linked inherited metabolic disorder, caused by a deficiency of the lysosomal enzyme α -galactosidase A.¹ Its pathogenesis is related to the lysosomal accumulation of globotriaosylceramide (GL-3) and other glycosphingolipids, leading to cellular and microvasculature dysfunction and subsequent organ damage.¹ The prevalence of FD is estimated at about 1:100 000 in the general population.¹ According to the latest annual report of the Polish Association for Families Affected by Fabry (in Polish, Stowarzyszenie Rodzin z Chorobą Fabry'ego), there are currently 73 confirmed cases in Poland,² indicating that the disease is underdiagnosed. The phenotypes of the disease can range from severe multiorgan manifestations, commonly found in men, to apparently asymptomatic courses observed in some women. However, progressive organ damage develops in both sexes. Particularly renal failure and severe cardiovascular events result in a shortened life-expectancy.¹

The first clinical symptoms usually develop in childhood. The diagnosis, however, is often delayed and properly established in adulthood. Therefore, internists should be aware of the typical symptoms of FD. The most characteristic early manifestations are episodes of burning pain in the distal extremities, accompanied by chronic paresthesias. Gastrointestinal symptoms are also common, like abdominal pain (often postprandial), diarrhea, nausea, vomiting, and anorexia. Other classic manifestations include skin lesions in the form of angiokeratomas and decreased ability to sweat with exercise, cold, and heat intolerance. The disease may also cause corneal lesions (cornea verticillata) or tinnitus and hearing loss.³ Confirmation of the disease in hemizygous males is based on the marked α -galactosidase A deficiency measured in leukocytes, plasma, or serum.¹ In heterozygous females, however, enzyme analysis is usually inconclusive due to random chromosome X inactivation. Therefore, in these subjects molecular testing (genotyping) is required.¹ On the other hand, the diagnosis of FD can be challenging in those with confirmed genetic mutation and absence of the characteristic FD features. Such situation might be observed in family members of some affected patients.¹

Enzyme replacement therapy (ERT) for FD was introduced in 2001. Two isoforms of human α -galactosidase are presently available: agalsidase alfa and agalsidase beta, both administered intravenously every other week. This therapy has been approved in most European and Asian countries, Australia and Canada, while in the United States, only agalsidase beta has been approved by the Food and Drug Administration.⁴ It has been documented that the ERT use in pediatric patients can significantly clear GL-3 deposits, ameliorate early symptoms of the disease, and improve the quality of life.⁴ This hopefully may prevent further disease progression and overt organ damage. The efficacy of ERT has been also demonstrated in clinical trials in adult FD patients, by stabilizing or slowing progression of severe organ damage, or even improvement of the function of affected organs.¹ It is still unknown, however, whether ERT might extend life expectancy in this disease.

Unfortunately, FD patients in Poland have no access to reimbursed ERT within our health care system, even if such treatment is recommended by European expert groups, at least in selected patients.⁵ Poland is the only country in the European Union that does not reimburse ERT in FD. Moreover, in Poland there are no specialized centers, which could provide comprehensive care for these individuals. Access to the diagnostic procedures is also very limited, particularly for adult patients, while molecular testing, according to our knowledge, is not available within the public health care service. In the last few years, a selected group of Polish patients (about 20) are continuing ERT as part of the so called "charity program" supported by pharmaceutical companies, after these patients had completed their participation in clinical trials. The remaining patients do not receive ERT, often despite severe and disabling symptoms, due to very high costs of such treatment (about 800 000 PLN per year).

At University Hospital in Krakow, the ERT is currently provided at the expense of pharmaceutical companies for 7 patients (4 men, 3 women). In these patients, we have observed a considerable stabilization of the clinical course, including renal and heart function, as well as a reduction in pain and gastrointestinal symptoms, resulting in a significant improvement in the quality of life. Moreover, in 3 patients, we have documented resumption of sweat production. However, the charity

program does not provide continuous access to the ERT. Recently, in our 56-year-old male patient, a 6-month treatment interruption was associated with a non-ST-segment elevation myocardial infarction, followed by an ischemic stroke related to the percutaneous coronary intervention.

Meanwhile, it is generally believed that only early medical intervention might improve long-term prognosis. Later, when irreversible organ damage occurs, it will likely be ineffective.¹ This finding imposes a significant psychological burden on our FD patients. Unfortunately, it seems that systemic solutions for diagnosis and treatment of rare diseases in Poland have come to a standstill in the last several years.

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Conflict of interest The authors declare no conflict of interest.

How to cite Bazan-Socha S, Kuczia P, Musiał J, Błażejewska-Hyżorek B. Fabry disease in Poland. *Pol Arch Intern Med.* 2018; 128: 567-568. doi: xxx.

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