"I'm fine; I'm just waiting for my disease"

The new and growing class of presymptomatic patients

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This issue of *Neurology*® contains a case report[1] describing a young man with Pompe disease, a lysosomal/glycogen storage disorder caused by deficiency of the acid α-glucosidase enzyme (GAA). As a clinical case, it provides a prospective history of the early and asymptomatic years of a patient with late-onset Pompe disease. The patient described is also emblematic of a new trend that neurologists, medical geneticists, and other clinicians are facing in patient diagnosis—that is, the presymptomatic diagnosis of a serious and progressive disorder in an individual who is currently healthy.

When Pompe disease presents in infancy, the classic form results in cardiomyopathy, hypotonia, and respiratory insufficiency leading to death, usually before 12 months. Enzyme replacement therapy (ERT) has been available for these infants since 2006, and early initiation can improve cardiac and motor function in a subset of affected patients, allowing these children to survive what previously had been a fatal disease. Later-onset forms of Pompe disease are generally restricted to skeletal and respiratory muscles with slow progression, but also with potential early death. In these patients, ERT can further slow disease progression but the benefits appear to be less dramatic than those observed in some infants. ERT is exceedingly expensive and must be continued lifelong, at least until alternative treatments are developed.

In this report, a serendipitous and early diagnosis of late-onset Pompe disease was made in a 1-year-old boy. Based on our current understanding of Pompe disease, his genotype and lack of cardiac involvement would put him in that later-onset group whose disease course and response to ERT is less predictable. The patient has had 2 decades of meticulous ongoing clinical surveillance including functional assessments (clinical quantitative strength and pulmonary function testing) and diagnostic tools (muscle MRI and in vivo NMR spectroscopy measures of muscle glycogen) to evaluate his skeletal muscle. These detailed and specialized assessments appear justified, even in a healthy and physically strong individual, before committing the patient and society to a treatment that costs about $350,000 a year for adults, requires specialized resources, has adverse effects, and will need to be provided indefinitely.

After 20 years of follow-up, quantitative muscle and strength testing have been normal, though he has reported "mild" decrease in quadriceps strength. Therefore, he and his physicians may soon be discussing initiation of ERT. Up to this point, he has enjoyed good health with no significant weakness or signs or symptoms of Pompe disease. Still, it has been a life additionally burdened by the knowledge of his diagnosis. Is the promise of earlier treatment (albeit of uncertain efficacy) worth the knowledge that at some point the healthy life being enjoyed might disappear?

The availability of newborn screening, genetic testing, and improvements in diagnostic procedures have made these presymptomatic diagnoses more commonplace. Neurologists are diagnosing Alzheimer disease at earlier stages in individuals who are still independent and functioning and likely to remain so for years.[2] Since 2005, states have been screening newborns for a wider array of inborn errors of metabolism and are under pressure to screen for potentially treatable lysosomal storage disorders such as Pompe disease and Krabbe disease. The difficulty in both Pompe and Krabbe disease screening programs is that while they are designed to identify severe early-onset cases where treatments appear effective, far more individuals are identified with later-onset disease for which treatments and management decisions are much less clear.[3–5]

Timmermans and Buchbinder[6] recently described the distress and upheaval experienced by families whose infants test positive for metabolic disorders in the course of newborn screening. These infants appear normal, but their confirmatory testing is not reassuring. They suggested that the term "patients-in-waiting" be used to describe children in this difficult threshold between appearing healthy but also

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having a disease diagnosis or clear liability for disease. In their study, families found it challenging to know how to treat their children normally when there were so many potential risks to be considered. Many of these disorders are so rare that the kind of reassurance that comes with expert knowledge and experience is impossible to offer. The stress and anxiety felt by families when their children are given presymptomatic diagnoses is typically shared by the specialists following these patients.

In the case of Pompe disease, what can be done to improve the situation where later-onset disease is diagnosed early? Improved markers of disease progression are needed. Muscle MRI and NMR spectroscopy would be more useful if validated against direct biochemical analysis of muscle glycogen content and objective muscle strength. Biomarkers such as angiotensin-converting enzyme insertion/deletion polymorphism[7] and urinary glucose tetrasaccharide[8] may also help predict Pompe disease progression, but require further investigation. The role of developing GAA antibody and the long-term safety and efficacy of ERT need greater study. Of greatest importance, rather than single patient observations, natural history studies of later-onset Pompe disease should be supported. Pharmaceutical company registries may prove somewhat useful in this regard, but independent registries would be preferred, and even then are no substitute for prospectively carried out, controlled natural history studies.

"Patient-in-waiting" is an apt description for this particular case. The current practice of medicine is ill-equipped to support and advise individuals who are "affected" yet currently well, diagnosed yet still not diseased. For Pompe disease, a treatment is available, perhaps lessening the blow of presymptomatic diagnosis. However, treatments are not available for some of the conditions being diagnosed presymptomatically. Some patients and families may be able to cope with this state of diagnostic limbo without undue distress. But for others, the healthy good years may be less good because of the dread of what will come.

DISCLOSURE

Dr. Kwon has received research support from the NIH; spends 20% of her clinical time overseeing the care of patients in her hospital's newborn screening clinic; and is a member of the Krabbe Consortium, a group of child neurologists, geneticists, and state health officials who meet to discuss clinical follow-up for patients identified in the New York State Krabbe disease newborn screening program. Dr. Steiner serves on a data safety monitoring board for the NIH; has received funding for travel and speaker honoraria from Actelion Pharmaceuticals Ltd; serves as Deputy Editor for *Genetics in Medicine*, Editor for *Biochemical Genetics*, and Associate Editor for the *Journal of Inherited Metabolic Disease*; has a patent pending re: Use of novel derivatization technique for MS analysis of sterols; and serves as a consultant for Actelion Pharmaceuticals Ltd, BioMarin Pharmaceutical Inc., Genzyme Corporation, Shire plc, the NIH, the U.S. Department of Health and Human Services–HRSA, Autism Speaks, the Smith Lemli Opitz Foundation, and the OI Foundation.

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