Diagnosis and management of lysosomal storage disorders.

Three key words: early, multidisciplinary, and network

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The European Commission on Public Health defines as rare diseases *life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them*.¹ The term *low prevalence* is taken as prevalence of less than 5 per 10,000 in the European Union. The definition is slightly different in the US (*any disease or condition that affects less than 200,000 persons in the United States, or about 1 in 1500 people*, according to the Rare Disease Act of 2002) and in Japan (*one that affects fewer than 50,000 patients in Japan, or about 1 in 2500 people*).² It is interesting to note that epidemiological data on rare disorders are rapidly changing with the new screening technology presently available. Indeed, in this Special issue of the journal, Cecchi *et al.* points out that new epidemiological data based on newborn screening showed that the prevalence of Anderson-Fabry disease (AFD) is higher than previously reported.³⁻⁵

The *umbrella* rare disease includes genetic syndromes, inherited metabolic diseases (inborn error or metabolism) and neuromuscular disorders with various organ involvement and phenotypic expression. In most cases, a multidisciplinary approach is required in the diagnosis and management of the diseases. The diagnosis is generally difficult and is often delayed, since the clinical characteristics of the disease are not well recognized by most of the clinicians. However, in the last few years, attention is growing due to the interest for innovative therapeutical approaches. Lysosomal storage disorders (LSD), *i.e.* a group of disorders characterized by various enzymatic deficits regulating the metabolism of glycogen, mucopolysaccharides and sphingolipids, is a classical example. For a long time, these disorders have been frustrating for clinicians and a *death sentence* for patients, while in the last 20 years the discovery of new

therapies (*i.e.* enzyme replacement therapy, ERT) has given the opportunity to clinicians to change the natural history of LSD. The cardiologist is one of the specialists involved in LSD management. Indeed, myocardial involvement (cardiomyopathy) is a typical feature of Pompe disease and AFD, while valvular degeneration is typically present in patients with mucopolysaccharidoses⁶ and, sometimes, in patients with Gaucher disease.⁷ Early diagnosis is one of the key points for an efficacious ERT, and this is a fundamental message for any specialist involved in the management of these disorders. The knowledge and early clinical recognition of the classical clinical features of the disease (*red flags*) are essential for the diagnosis. ERT in patients with early symptoms and initial organ disease, such as microalbuminuria and neuropathic pain, seem to be effective in AFD.³ A presentation with severe muscle involvement (*floppy baby*) and progressive cardiomyopathy in the newborn should immediately arise the suspect of a metabolic disorder, potentially treatable, as Pompe disease. The presence of conduction abnormalities at electrocardiogram and macroglossia represents cardiac and non-cardiac *red flags*, respectively.⁸ It is important to remember that some of the red flags are *age-related*, as proteinuria and cardiomyopathy in AFD (rarely present in young patients).³

In this issue of *Cardiogenetics*, we aimed to describe the genetic basis, the multidisciplinary diagnosis and the management of the principal LSD. To this purpose, we invited a group of specialists for each disease to describe their day-by-day clinical experience with LSD, and their experience to co-operate as a *network*. In the near future new therapeutic approaches are about to happen (gene therapy chaperones, etc.),^{9,10} but the main secret for the diagnosis and management remains in the three key words: *early, multidisciplinary, network*.

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Key words: lysosomal storage disorders, diagnosis and management.

Received for publication: 8 February 2013.

Accepted for publication: 11 February 2013.

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Cardiogenetics 2013; 3(s1):e1
doi:10.4081/cardiogenetics.2013.s1.e1

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