Prevalence of four Lysosomal Storage Diseases in primary care in Italy

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A strong culture on primary care medicine is pivotal to strengthen General Practitioners' (GPs) ability to improve the health of individuals, families, and communities. Nowadays, primary care data sources are largely used to conduct real-life studies to answer several research questions and improve clinical practice. The primary care setting is indeed representative of general population and allows powerful analyses to identify associations between uncommon exposures and rare events. Along this line, the use primary care databases allow clinical researchers and GPs to develop and validate prediction scores with which clinicians, given the patients' features, may assess the risk of developing certain diseases and/or raising the suspect of hidden or unrecognized morbidities. In this context, several conditions which are usually perceived as specialists' competence only, might be investigated using GPs' data. Thus, we propose this paper to underline how GPs may have a crucial role to raise clinical suspect of rare diseases such as Lysosomal Storage Diseases (LSDs). We provided prevalence estimates for four LSDs, namely Gaucher disease, Fabry disease, Pompe disease and mucopolysaccharidosis (MPS) using the Health Search Database of the Italian College of General Practitioners and Primary Care.

Summary. Objectives. Lysosomal Storage Diseases (LSDs) are not easily recognized in primary care. However, General Practitioners (GPs) may have a crucial role to raise clinical suspect of LSD. We therefore aimed to provide prevalence estimates for four LSDs, namely Gaucher disease, Fabry disease, Pompe disease and mucopolysaccharidosis (MPS), in 2013 in Italy. **Methods.** We used a primary care database (HS IMS Health LPD) to extract data regarding all patients with a diagnosis of Gaucher disease, Fabry disease, Pompe disease or MPS, as of December, 31, 2013. **Results.** The standardized prevalence estimates were 2.32 (95% CI: 1.45-3.59) per 100,000 patients for MPS, 2.16 (95% CI: 1.28-3.32) per 100,000 for Fabry disease, 0.89 (95% CI: 0.39-1.71) per 100,000 for Gaucher disease and 0.77 (95% CI: 0.32-1.61) per 100,000 for Pompe disease. **Conclusions.** The overall prevalence estimates of MPS and Fabry disease were in accordance with the incidence rates reported in newborn screening programmes, whereas, Gaucher and Pompe diseases resulted underestimated in the HS IMS Health LPD. Significant gender differences in prevalence estimates for all four LSDs in the HS IMS Health LPD were observed.

Introduction

Lysosomal Storage Diseases (LSDs) are a group of more than 40 genetic metabolic diseases, usually autosomal recessively inherited, in which the impaired cell function derives from the intra-lysosomal accumulation of metabolic products in multiple tissues and organs, as a result of mutations in proteins critical for lysosomal functions. Given their complex and heterogeneous clinical phenotypes, LSDs diagnosis and management represent a challenge for General Practitioners (GPs) [1]. Gaucher disease, Fabry disease, Pompe disease and mucopolysaccharidosis (MPS) are among the most common LSDs, whose early diagnosis is crucial since effective treatments are available.

Gaucher disease is an autosomal recessive inborn error of glycosphingolipid metabolism due to a deficiency of the lysosomal enzyme glucocerebrosidase. The subsequent intra-lysosomal storage of glucosylceramide in the reticulo-endothelial system in bone marrow, spleen and liver, causes bone abnormalities, anaemia, thrombocytopenia, and hepatosplenomegaly, that characterize type 1 Gaucher disease. Its incidence has been reported to be as high as at 1/40,000 births [2-4]. Several approved treatments for Gaucher disease, among which enzyme replacement therapy, that specifically reduce glucosylceramide storage and reliably reverse/alleviate most manifestations, have been available for more than two decades [5-7].

Fabry disease is an X-linked disease caused by deficient alpha-galactosidase A activity. Men may present with neuronopathic pain, gastrointestinal disturbances, angiokeratoma, and hypoidrosis and, later on,

progressive renal dysfunction, hypertrophic cardiomyopathy and stroke. Heterozygous women may have disease manifestations due to skewed X-chromosome inactivation. The classic phenotype of Fabry disease has an estimated incidence of approximately 1/50,000 males; atypical later-onset phenotypes may be much more common [8]. Enzyme replacement therapy has been available since 2001 [9 10], and it has been proven to be effective in slowing disease progression, especially if started at a young age [11].

Pompe disease is an autosomal recessively inherited disorder of glycogen metabolism caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase. Its main clinical features are skeletal and cardiac muscle myopathy, ultimately leading to myogenic respiratory failure and hypertrophic cardiomyopathy. The phenotype varies according to the age of onset [12-14]. Its estimated incidence is of 1/50,000 newborns. Enzyme replacement therapy, available since 2006, is currently the only approved treatment for Pompe disease which has improved overall survival in infants and has resulted in disease course stabilization in patients with late-onset disease.

Mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders caused by the deficiency of lysosomal enzymes required to break down glycosaminoglycans. The accumulation of glycosaminoglycans in multiple tissues may cause coarse facial features, skeletal deformities, mental retardation, visual and/or hearing impairment, recurrent upper respiratory infections, cardiomyopathy with valvular involvement, inguinal and umbilical hernias, and hepatosplenomegaly. The overall estimated incidence of MPS in western countries ranges from 3.4 to 4.5/100,000 live births [15]. Enzyme replacement therapy is available for types I, II, IVa and VI.

In this context, the role of the primary care physicians might be extremely relevant. In fact, a timely recognition of the disorder, a prompt referral to specialist for treatment, an adequate coordination of multidisciplinary care and the support to patient in the management of the disease can maximise the benefits of therapies and make a substantial difference in the clinical outcomes [16 17]. Some authors recently pointed to the need to raise the General Practitioners' awareness of rare diseases, as the level of knowledge is still inadequate [18]. The availability and communication of reliable epidemiological data about these conditions can help raising clinicians' awareness of the problems and improve the quality and effectiveness of health care delivery [16]. However, even if some incidence data derived from newborn screening programs are available, the exact prevalence of these conditions in the general population is difficult to ascertain. From a bibliographic study of the epidemiology of rare diseases in Europe, which is currently being conducted by the *European Organisation for Rare Diseases* in partnership with Orphanet [19], a low level of consistency between studies and a poor documentation for methods used to assess the prevalence were reported. With the present study, we aimed to provide improved prevalence estimates for four aforementioned conditions in the Italian population, using data from a large national GP database.

Materials and methods

Data source

Information was obtained from the *Health Search IMS Health Longitudinal Patient Database* (HS IMS Health LPD), an Italian general practice database in place since 1998 comprising data from computer-based patient records registered by a selected group of GPs, uniformly distributed throughout the whole national territory. GPs voluntarily agreed to contribute to the general practice database and to attend specific training courses for data entry. Patient demographic details included in HS IMS Health LPD are linked through the use of an encrypted patient code with medical records (diagnoses, tests and tests results, procedures, hospital admissions), drug prescriptions information, lifestyle information (alcohol, BMI, smoking habit), and date of death. Diseases are classified according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). To be considered for participation in epidemiological studies, GPs must meet up-to-standard quality criteria pertaining to the levels of coding, prevalence of well-known diseases, mortality rates, and years of recording [20]. Quality and consistency of data collected in the database were well demonstrated through several studies in which the retrieved information was compared with current data sources or findings from national surveys [21-25].

At the beginning of the present study, 700 GPs homogeneously distributed across Italy, covering a patient population of 1,222,595, reached the up-to standard quality criteria. The study was based on the records collected by these GPs.

Study population

Data regarding all active patients aged 15 years or older, as of December 31, 2013, were extracted from the database. Diagnoses were identified using the respective ICD-9-CM codes and to the physicians' free-text notes. Extraction of the following ICD-9-CM codes was performed: 271.0 (Pompe disease), 272.7 (Fabry disease and Gaucher disease) and 277.5 (MPS). To differentiate between Fabry and Gaucher disease, we coupled the code with keywords "Fabry" or "Gaucher" as inserted by GPs.

Data analyses

Crude prevalence estimates were calculated identifying the number of active patients (currently alive) in the GPs' lists at the index date (December 31, 2013) as denominator. To assess the prevalence of the four selected LSDs in Italy, the crude frequencies by gender and age observed in the population subgroups were adjusted to the same age subgroups in the Italian population, available in the Demographic Tables provided by the *Italian National Institute of Statistics* (http://demo.istat.it/index_e.html), according to the direct standardization method.

Results

Results are shown in Figure 1 and in Table I. Out of a target population of 923,464 patients, the diseases with the highest prevalence in the HS IMS Health LPD were MPS (n = 21) and Fabry disease (n = 20). The crude prevalence estimates for MPS and for Fabry disease in the population were 2.27 and 2.17 per 100,000 inhabitants, respectively and the standardized prevalence values were 2.32 per

FIGURE 1.

Crude prevalence (x 100,000) of Gaucher disease, Pompe disease, Fabry disease or mucopolysaccharidosis in the Health Search Database, as of January 1, 2013.

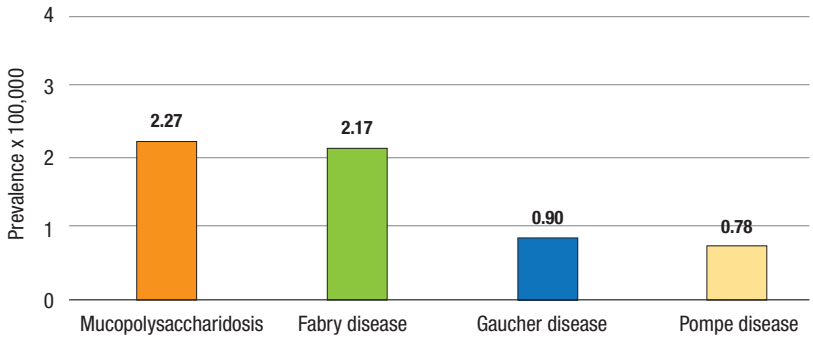

TABLE 1.

Patients with a diagnosis of Gaucher disease, Pompe disease, Fabry disease: crude and age-standardized prevalence estimates (x 100,000) stratified by gender.

Gaucher disease	Male	Female	Total
Crude prevalence	1.393	0.432	0.895
Standardized prevalence	1.415	0.408	0.892
95% CI			(0.386-1.706)
Pompe disease			
Crude prevalence	0.464	1.080	0.783
Standardized prevalence	0.480	1.041	0.774
95% CI			(0.315-1.610)
Fabry disease			
Crude prevalence	1.795	2.512	2.166
Standardized orevalence	1.817	2.484	2.162
95% CI			(1.280-3.320)
Mucopolysaccharidosis			
Crude prevalence	3.365	1.256	2.274
Standardized prevalence	3.429	1.271	2.315
95% CI			(1.450-3.590)

CI: Confidence Interval.

100,000 (95% Confidence Interval (CI): 1.45-3.59) and 2.16 per 100,000 (95% CI: 1.28-3.32), respectively. The crude prevalence of Gaucher (n = 8) was 0.90 per 100,000 (standardized prevalence: 0.89 per 100,000; 95% CI: 0.39-1.71) and that of Pompe disease (n = 7) 0.78 per 100,000 (standardized prevalence: 0.77; 95% CI: 0.32-1.61).

Significant gender differences were found in both crude and age-standardized prevalence rates for all LSDs. Gaucher disease and MPS were more than three folds and more than two folds more prevalent in males than in females, respectively (age-standardized prevalence for Gaucher 1.42 per 100,000 *vs* 0.41 per 100,000, for MPS 3.43 per 100,000 *vs* 1.27 per 100,000). Conversely, prevalence estimates of Pompe disease and Fabry disease were higher in females than males (age-standardized prevalence for Pompe 1.04 per 100,000 *vs* 0.48 per 100,000, for Fabry 2.48 per 100,000 *vs* 1.82 per 100,000).

Discussion

To the best of our knowledge, this is the first study concerning the epidemiological burden of LSDs in general practice. Our overall estimates of MPS and Fabry disease were in accordance with the incidence rates reported in newborn screening programmes. Whereas, Gaucher and Pompe diseases resulted underestimated in the HS IMS Health LPD. Interestingly, there were significant gender differences in prevalence estimates for all LSDs in the HS IMS Health LPD. The case of Fabry disease, which resulted more prevalent in females despite its X-linked heritability, is paradigmatic. These disparities may reflect LSDs under-diagnosis in some population groups and family clusters.

Using the direct standardization method for age and sex, considering the Italian population as standard, the crude prevalence estimates appeared to be slightly overestimated. This can be explained with the burden of disease in the younger age groups of the population, which are under-represented in the database.

The primary care role in rare diseases has not been extensively evaluated [26,27]. The scientific evidence available, however, alludes to a low level of general knowledge and awareness of rare diseases [18]. As a result, several patients might remain undiagnosed or diagnosed with delay, so limiting the effectiveness of treatment [17,28].

The GP can significantly improve treatment outcomes of these rare and potentially treatable diseases, by making a timely diagnosis, by managing the disease in a shared-care arrangement with the specialist clinicians and by assisting patients with self-help and decision-making [16]. In order to enhance the care of patients with rare diseases, a generic general practice strategy for rare diseases was proposed [16]. The increase of primary care physicians' awareness of LSDs by means of accurate epidemiological data regarding these conditions was recognized as the first step to implement such a strat-

egy. In this perspective, our study showed that LSDs are non-negligible clinical entities in primary care. However, LSDs prevalence in the general population of the HS IMS Health LPD was likely underestimated, if compared to available epidemiological data from newborn screening programmes.

The first step to a systemic general practice approach to LSDs in primary care consists in making physicians more knowledgeable of the epidemiology of these conditions in the local context. We were able to derive the crude and standardized prevalence estimates of four LSDs in Italy using data from a population-based general practice database, representative of the Italian population. "Real-life" epidemiological studies are the first step to increase awareness of these rare conditions, but more efforts should be done for a wider recognition of LSDs.

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Conflict of Interest

Francesca Carubbi received travel and speaker honoraria by Genzyme (a Sanofi company). Francesco Lapi provided consultancies in protocol preparation for epidemiological studies and data analyses for Genzyme. Claudio Cricelli provided clinical consultancies for Genzyme. Miriam Levi, Serena Pecchioli, Manuela Chelo and Fabio Nascimbeni declare that they have no conflict of interest.

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