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Abstracts

SESSION 1. POMPE DISEASE: CLINICAL, DIAGNOSTIC AND GENETIC ASPECTS

S1.1 Introductory notes to Pompe disease and aims of the Meeting

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A disease is considered rare when it has a prevalence in the general population below a given threshold, i.e., when few people are affected. The European Union defines this threshold to 0.05% of the population, i.e. 1:2000 inhabitants, and Italy adheres to this definition. The definition "rare", however, rather than to simply stigmatize the epidemiology of certain diseases, has long labeled disorders considered to represent an insurmountable frontier to the possibility to find a therapy for every human disease, despite the detailed knowledge on their pathogenesis and etiology. In the course of the years devoted to the research of therapies for rare disease, one main factor of frustration has been the finding that promising results obtained in "in vitro models" by traditional biochemistry and pharmacology methodologies were usually not replicable in human beings. The pharmaceutical industry has therefore traditionally manifested scarce interest in rare diseases. The inability to provide therapy to patients affected by a rare disease has limited the interest of practitioners on this topic. Rare disease are, therefore, generally under-diagnosed and technologies and expertise necessary to diagnose them are only available in a few university and hospital specialized centers even in the most advanced nations. Treatment is, therefore, restricted to treat the symptoms, in the large majority of patients with rare diseases. A turning point in a positive direction to the efforts of researchers came by applying molecular biology and recombinant DNA technologies to drugs development. This has rendered possible to produce species-specific molecules capable to effectively replace "in vivo" native molecules not correctly working in specific diseases. One relevant result of the application of these advanced methodologies has been represented by the recombinant alpha-glucosidase (alglucosidase alpha – Myozyme) that became available for enzyme replacement therapy (ERT) of Pompe disease in the year 2000 (1).

Pompe disease (synonym: "acid maltase deficiency") having an estimated frequency varying from one in 40000 in Caucasians to one in 146000 in Australian populations is a rare pan-ethnic autosomal recessive genetic disorder. It is a lysosomal storage disease classified as type II glycogenosis being caused by mutations in the gene encoding the acid α-glucosidase (GAA), located on 17q25.2-q25.3. Acidic α-glucosidase (α-GA) is a glycoprotein enzyme which degrades glycogen to glucose within the lysosomes. Shortage of α-GA activity in Pompe disease hampers the lysosomal degradation of glycogen that progressively accumulates inside the lysosome. These latter become unusually large and fuse to form wide spaces that eventually occupy a substantial part of the cellular volume and are recognizable as intracytoplasmic glycogen storing vacuoles at microscopy. The ensuing cellular pathology predominantly affects muscle fibers displacing their myofibrils and ultimately leading to skeletal muscle weakness, but also other tissues (particularly cardiac and smooth muscle cells) and organs show vacuolation of their cells cytoplasm. The resulting clinical spectrum ranges from the classical infantile form presenting soon after birth, that is characterized by hypertrophic cardiomyopathy and marked muscle weakness, and leads to death usually before the first year of age, to a milder form characterized by gradually progressing miopathy and respiratory insufficiency with either juvenile or adult onset. These latter lead progressively to varying degrees of disability and are associated to reduced life expectancy on average. The different disease phenotypes correlates with the levels of residual α-GA activity in muscle; less than 3% of normal enzyme activity is found in severe infantile cases and residual levels ranging 3 - 30% of normal are found in less severe late onset forms (2).

Several published studies support the effectiveness of ERT with alglucosidase alpha in inducing significant improvement of motor and heart functions and dramatic extension of survival time in infants with the classic form of Pompe disease (3). Although the effects of long-term therapy are still unknown and a marked variability in the individual response to the drug is undeniable, these encouraging data make advisable starting ERT with alglucosidase alpha as soon as possible both in affected infants and symptomatic adults. Follow-up of patients with late-onset Pompe disease should be continued for several years to assess the full efficacy of treatment. In view of the high cost of ERT, it is also advisable to perform a careful long term observation of untreated pre- and mildly-symptomatic patients to identify, if possible, markers that allow prediction of the clinical evolution. This in order to distinguish patients needing ERT treatment from patients who can maintain autonomy and a good quality of life being supported from exercise therapy, diet, and assisted ventilation when adequate.

The diagnosis of the classic infantile form of Pompe disease is made, usually, early and relatively easily because, due to the marked severity of the symptoms of the disease yet at it onset, the little patients are immediately admitted to pediatric intensive care centers where physicians are well trained to recognize the disease. Conversely, the diagnosis of late-onset forms is complicated by the rarity of the condition and the heterogeneity of the clinical manifestations, which vary with respect to organ involvement, age at onset, and severity. Symptoms are often unspecific especially at onset and they may remain mild

even for decades so that neither the patient nor the doctor consider to deepen diagnostic procedures.

The diagnosis of Pompe disease requires the knowledge of the clinical presentation which is highly variable with respect to age at onset, disease severity, organ involvement, and clinical course. This wide clinical variability results from genetic heterogeneity, and more than 200 different mutations of the GAA gene have been reported. Clinical evaluation of suspected Pompe patients should be followed by laboratory evaluation, including blood tests creatine kinase, aspartate aminotranferase, alanine aminotransferase, lactate dehydrogenase), EMG, sensory-motor-nerve conduction studies, muscle biopsy (histological, histochemical and biochemical studies), cardiological and respiratory assessments, and skeletal muscle Magnetic Resonance Imaging studies. Finally, the diagnosis must be definitely confirmed by evaluation of α-GA enzyme activity in skeletal muscle tissues or skin fibroblasts and molecular analysis of GAA gene.

Management of Pompe disease requires a multidisciplinary approach given by a team which should include several specialists such as neonatologists, pediatricians, neuromuscular specialists, neurologists, cardiologists, pulmonologists, biochemical geneticists, genetic counselors, intensivists, physical therapists, respiratory therapists, metabolic dieticians, orthopedists, radiologists, occupational therapists, otolaryngologists, audiologists, speech therapists, and psychologists, who will be capable of addressing the different manifestations of the condition. It is important to consider that both the patients and their families need psychological support to tolerate the psycho-social distress related to living with a chronic illness and, mostly, to deal with the personal, emotional and relational consequences arising from the awareness that the disease of the family is a hereditary one. Fundamental in Pompe disease is also, as in other chronically disabling diseases that affect children, adolescent and adults, to train healthy family members and caregivers to help the patients in the execution of their daily activities in the better way with respect to the individual residual abilities.

In October 2006, a group of leading Italian Pompe disease experts held a round table meeting to review, from a multidisciplinary point of view, new development in glicogenosis type II. Best practice and unmet needs regarding the recognition, evaluation, and surveillance of disease associated morbidities, as well as therapeutic strategies, enzyme replacement therapy with alglucosidase alpha, and other adjunctive therapies, to optimize patient outcomes have been identified. One main conclusion of this meeting was that because of the complexity of the clinical picture of these patients it is warranted that primary care providers and other specialists who might be involved in their care become aware of the disease (4). Following this meeting the Italian Study Group for Glycogenosis has been constituted within the Italian Association of Myology, with the aim between others to promote the awareness of Pompe disease between the specialists working at University and Hospital medical Centers and the practitioners in all regions in Italy. The constitution of territorial networks of medical specialists, nurses, caregivers and Pompe patients Family associations is also promoted.

Epidemiological assessments indicates that in south Italy the late-onset forms of Pompe disease are largely under-diagnosed. In fact, with an estimated frequency of one in 56000 in Caucasian populations late-onset cases should be about 100 in the $6x10^3$ inhabitants of the Campania, but after a recognition at all the Centers specialized for neuromuscular diseases of this region, in June 2011, at the time of the present Meeting, less than 10 genetically proofed patients result to be followed up.

With these premises the team of neuromuscular disorders specialists at the Department of Neurology directed by professor Giuseppe Di Iorio, together with the team of Cardiomyology and Medical Genetics, directed by professor Giovanni Nigro and professor Luisa Politano of the Second University of Naples, have organized the meeting "A network for Pompe disease treatment. Genetic Myopathy of children and adults" held in Naples, Italy, on June the 13th, 2011. Specific aims of the meeting were:

- to perform a comprehensive review from a multidisciplinary point of view on basic knowledge and new developments on clinic, diagnosis and management of Pompe disease;
- to discuss personal experiences with the management of Pompe disease between experts in clinical and laboratory diagnosis, treatment, and management, including, cardiac, respiratory, gastrointestinal/nutritional, muscoloskeletal, neurological, supportive and rehabilitative care, anaesthesiology, general medicine, psychosocial, issues.

The meeting addressed to University and Hospital doctors, practitioners and doctors in training in all branches potentially involved in diagnosis, therapy and management of Pompe patients had more than 100 registered participants.

The Meeting will benefit of the contributions of speakers of international scientific level, such as Corrado Angelini, from the University of Padua, who first described along with Engel AG, variable levels of α-GA in muscle and leukocytes of patients with Pompe disease, Antonio Toscano, from the University of Messina, Coordinator of the Italian Group for the Study of Glycogenosis, who will report on the Italian guidelines and the activities of the Italian centers for the treatment of Pompe disease, Generoso Andria, from the University of Naples, Coordinator of the Reference Center for Rare Diseases of the Campania region, who first treated with alglucosidase alpha an Italian patient with classic infantile Pompe disease and will speake about the role of the pediatrician in the infantile form of Pompe disease. Furthermore, all important topics in clinics, diagnosis and treatment of Pompe disease, such as the therapeutic strategies alternatives to ERT, will be discussed by several experts from the universities and some hospitals of Naples and the Campania region.

References

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