Sanfilippo disease (mucopolysaccharidosis type III): Early diagnosis and treatment
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EIGHT
GENERAL DISCUSSION AND FUTURE PERSPECTIVES
FUTURE TREATMENT OF SANFILIPPO DISEASE: CHANGING THE PHENOTYPE?

Over the last decades much has been learned about the pathophysiology and the clinical course of Sanfilippo disease as well as about potential treatments options. However, much still needs to be done to achieve optimal treatment and care for Sanfilippo patients. Drugs that are currently studied for treatment of Sanfilippo syndrome are either specific for the type of Sanfilippo (A t/m D; intrathecal enzyme replacement therapy or chaperone therapy) or are aimed at pathophysiological mechanisms involved in all subtypes (substrate inhibition therapy and therapies aimed at diminishing the inflammatory processes in the brain). However, in view of the complex pathophysiology of brain disease in Sanfilippo, it may be argued that treatment for Sanfilippo disease should always be a multidrug approach, at least in symptomatic patients.

Finally, the contribution of reference centers of expertise for Sanfilippo disease is essential to continuously improve the quality of care for patients and families by facilitating diagnosis, defining the therapeutic and psychological goals of treatment as well as providing tailor made support for patients and their families.

In this chapter I will briefly discuss those issues that, to my opinion, need to be high on the agenda for research on Sanfilippo.

BIOMARKERS, BIOCHEMICAL ABNORMALITIES, AND SURROGATE MARKERS OF DISEASE

Heparan sulfate (HS) in plasma and urinary glycosaminoglycans (GAGs) show a remarkably good correlation with disease severity in Sanfilippo patients. Since we performed a cross-sectional study, longitudinal data need be obtained in order to identify the true prognostic value of these biomarkers. For assessment of treatment efficacy, the use of CSF biomarkers, such as HS in CSF, Macrophage Inflammatory Protein 1α (MIP-1 α) 1, and phosphorylated tau (P-tau) 2 may prove to be essential. However, to obtain more information on potential CNS biomarkers, natural history studies in the different types of Sanfilippo disease, and in patients with different phenotypes at different stages of the disease, urgently need to be done. For type IIA, such a study is ongoing (HGT-SAN-053, NCT01047306) and the first results from this study are expected soon. Preferably, data on the natural course of Sanfilippo disease and on biomarker profiles should be available before the start of new therapeutic trials. Furthermore, these studies need to be longitudinally, collecting CSF and plasma and serum samples at different time points, e.g. every 6 or 12 months, in combination with clinical data.

TREATMENT: NOT-ONE-DRUG-WILL-FIT-ALL!

Given the complex pathophysiology of the CNS disease in Sanfilippo disease it is likely that treatment of patients diagnosed on the basis of clinical signs and symptoms will require combination therapy. As the process of neurodegeneration has already been initiated
in symptomatic patients and as this is characterized by secondary events including neuro-inflammation \(^3\), the use of small molecules with anti-inflammatory properties in combination with drugs preventing ongoing accumulation of HS may improve treatment efficacy. Anti-inflammatory drugs for Sanfilippo disease may include corticosteroids and NSAIDs. Indeed, one study in MPS IIIA mice showed that treatment with acetylsalicylic acid ameliorated brain pathology \(^4\). It may well be that a combination of two different treatment modalities, such as substrate inhibition therapy, e.g. isoflavone therapy, with enzyme replacement therapy (i.e. intrathecal ERT) may lead to greater efficacy with a more rapid reduction of stored HS.

In addition, some therapies will only be an option in a subset of patients. For instance, chaperone therapy, aimed at protecting synthesized enzymes with significant residual enzyme activity from rapid degradation by the cellular quality control mechanisms because of abnormal folding, will only be effective in patients with certain missense mutations \(^5,6\). In addition, it is likely that different chemical chaperones need to be developed for the different MPS III subtypes. For this reason, it is important to genotype all newly diagnosed Sanfilippo patients and to test the consequences of the different mutations at the cellular level.

Finally, patients at different stages of the disease will probably benefit from different medication or combinations of medication. For instance, if patients are detected very early in their disease, e.g. by sib-screening or by newborn screening (NBS), monotherapy with intrathecal ERT or gene therapy may be sufficient to prevent the onset of the cascade of neuropathologic events causing the neurodegeneration, while patients with more advanced disease may need additional therapies such as anti-inflammatory agents.

NEWBORN SCREENING

In 2007, the national newborn screening (NBS) program in the Netherlands was expanded from 3 to 17 disorders, including 14 metabolic diseases. The World Health Organization’s Wilson and Jungner screening criteria \(^7\), especially on the subject of treatability, was used as a basis for decision making on inclusion in the NBS panel by a committee of the Dutch Health Council. Participation in this voluntary screening program is almost 100% (99.8% in 2007; www.rivm.nl). Sanfilippo disease was not considered for inclusion in the NBS program, because of lack of a disease modifying treatment. However, a strong impulse for research on Sanfilippo disease was generated after disease modifying treatment became available for other lysosomal storage disorders (LSDs). Intravenous enzyme replacement therapy (ERT) is now available for Gaucher disease, Pompe disease and Fabry disease and the mucopolysaccharidoses (MPSs) types I, II and VI \(^8\), and is under investigation for MPS IV. Because of the increased research-focus on Sanfilippo disease and the improved knowledge on the pathophysiological mechanisms involved, it seems reasonable to assume that, an effective disease modifying treatment will be developed and approved for Sanfilippo disease. Therefore, potential approaches for NBS for this disorder should be studied, as pre-symptomatic diagnosis will be the key to successful treatment.
Although Sanfilippo disease should still be regarded as an ‘untreatable’ condition; there is a lot to achieve with programs of prevention by family planning and by early support for the affected individuals and their families. Benefits of NBS include an early diagnosis which enables earlier access to supportive interventions, and informed reproductive choices for parents and extended family members. Furthermore, families often undergo a lengthy ‘diagnostic odyssey’ before the right diagnosis is finally made. Improper diagnosis could hamper the appropriate care of the patient, and may have significant psychological impact on the parents and other family members. Moreover, early diagnosis may have direct benefit for the patient by enabling participation at a very early age in clinical trials, as pre-symptomatic or early symptomatic treatment is likely to be associated with a better clinical outcome.

CENTERS OF EXCELLENCE FOR SANFILIPPO DISEASE

Patients with a confirmed diagnosis of Sanfilippo disease should be promptly referred to a specialized center of excellence and referral, as parents and caregivers may easily become overwhelmed with the demands of care, and symptomatic treatment options should be discussed at an early stage of the disease. The child may need to be seen by multiple specialists, including specialists in cardiology, neurodevelopment, ophthalmology, orthopedics, otorhinolaryngology, psychiatry and pulmonology. In addition, supportive services such as physiotherapy, occupational therapy, audiology and behavioral therapy are usually required. The managing metabolic pediatrician may also guide the family when seeking out additional support through patient/family support organizations. A multi-disciplinary team with expert knowledge on Sanfilippo disease is the best approach for securing optimal care.

A center of excellence for Sanfilippo disease should combine easy access to optimal patient care with clinical research aimed at improvement of both symptomatic as well as disease modifying therapy. In addition, close collaboration with other (international) centers for Sanfilippo disease is a prerequisite to remain updated on ongoing research and new treatment options. Finally, to continuously improve the quality of care and research, a Sanfilippo center of excellence should be subject to regular and rigorous quality control, which can best be done by external, preferably international, visitation.

For day-to-day management of symptoms, direct medical care in case of urgent medical needs and for overseeing local supportive care, a Sanfilippo expert center should work closely with local hospitals (paediatricians or internists) and institutes for mentally challenged individuals (physicians for the mentally handicapped), thus establishing a shared services system.

Indeed, the Dutch patient and family support organization for inborn errors of metabolism (VKS, Adults, Children and Metabolic Disorders) recently published a roadmap for care and follow up for Sanfilippo disease (www.stofwisselingsziekten.nl) in which the need for a Sanfilippo expert center is underpinned.
REFERENCES


