Molecular Genetics and Metabolism 121 (2017) 227–240

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Epidemiology of mucopolysaccharidoses☆

Shaukat A. Khan [a,1], Hira Peracha [a,1], Diana Ballhausen [b,1], Alfred Wiesbauer [c,1], Marianne Rohrbach [d,1], Matthias Gautschi [e], Robert W. Mason [a], Roberto Giugliani [f], Yasuyuki Suzuki [g], Kenji E. Orii [h], Tadao Orii [h], Shunji Tomatsu [a,h,i,*]

[a] Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE, United States
[b] Centre for Molecular Diseases, Service for Genetic Medicine, University Hospital Lausanne, Switzerland
[c] Institute of Social and Preventive Medicine, University of Bern, Switzerland
[d] Division of Metabolism and Children's Research Centre (CRC), University Children's Hospital, Zurich, Switzerland
[e] Division of Endocrinology, Diabetology and Metabolism, University Children's Hospital, University Institute of Clinical Chemistry, Inselspital, University of Bern, Bern, Switzerland
[f] Medical Genetics Service, HCPA, Dep. Genetics, UFRGS, and INAGEMP, Porto Alegre, Brazil
[g] Medical Education Development Center, Gifu University
[h] Department of Pediatrics, Gifu University, Gifu, Japan
[i] Department of Pediatrics, Thomas Jefferson University, Philadelphia, PA, United States

ARTICLE INFO

Article history:
Received 21 March 2017
Received in revised form 22 May 2017
Accepted 22 May 2017
Available online 26 May 2017

Keywords:
Mucopolysaccharidoses
Incidence
Prevalence
Epidemiology
Japan
Switzerland

ABSTRACT

The aim of this study was to obtain data about the epidemiology of the different types of mucopolysaccharidoses in Japan and Switzerland and to compare with similar data from other countries.

Data for Japan was collected between 1982 and 2009, and 467 cases with MPS were identified. The combined birth prevalence was 1.53 per 100,000 live births. The highest birth prevalence was 0.84 for MPS II, accounting for 55% of all MPS. MPS I, III, and IV accounted for 15, 16, and 10%, respectively. MPS VI and VII were more rare and accounted for 1.7 and 1.3%, respectively.

A retrospective epidemiological data collection was performed in Switzerland between 1975 and 2008 (34 years), and 41 living MPS patients were identified. The combined birth prevalence was 1.56 per 100,000 live births. The highest birth prevalence was 0.46 for MPS II, accounting for 29% of all MPS. MPS I, III, and IV accounted for 12, 24, and 24%, respectively. As seen in the Japanese population, MPS VI and VII were more rare and accounted for 7.3 and 2.4%, respectively.

The high birth prevalence of MPS II in Japan was comparable to that seen in other East Asian countries where this MPS accounted for approximately 50% of all forms of MPS. Birth prevalence was also similar in some European countries (Germany, Northern Ireland, Portugal and the Netherlands) although the prevalence of other forms

Abbreviations: MPS, mucopolysaccharidosis; GAG, glycosaminoglycang; CS, chondroitin sulfate; DS, dermatan sulfate; HS, heparan sulfate; KS, keratan sulfate; ECM, extracellular matrix; IDUA, α-L-iduronidase; I2S, iduronate-2-sulfatse; SGHS, heparan-N-sulfatase; NAGLU, α-N-acetylglucosaminidase; HGSNAT, α-glucosaminidase acetyltransferase; GNS, N-acetyl-glucosamine 6-sulfatase; GALNS, N-acetylgalactosamine-6-sulfate sulfatase; GLB, 1β-galactosidase; G4S, N-acetylgalactosamine-4-sulfatse; GUSB, β-D-glucuronidase; LDS, lysosomal storage disease; MSD, multiple sulfates deficiency; DBS, dried blood spot; NBS, newborn screening; C6S, chondroitin 6 sulfate; C4S, chondroitin 4 sulfate; IDS, iduronate-2-sulfatase; SGSH, heparan-N-sulfatase; ARSB, arylsulfatase B; HYAL 1-3, hyaluronidase 1-3; HA, hyaluronan; DMB, dimethylmethylene blue.

☆ Molecular genetics and metabolism.Conflict of interest: All the authors contributed to the original article and had no conflict of interest with any other party. Shaukat A. Khan, Hira Peracha, Alfred Wiesbauer, Tadao Orii, Roberto Giugliani, Matthias Gautschi, Marianne Rohrbach, Diana Ballhausen and Shunji Tomatsu declare that they have no conflict of interests.Contributions to the project: Shaukat A. Khan is an expert in molecular biology and biochemistry. He has over 10 years of experience in MPS field from basic science to the development of therapy. He has contributed to the concept and planning of the article, collection of previous articles and data, and reporting of the work described.Hira Peracha is the primary author of this article and expert in biology. She has contributed to the planning, data analysis, and reporting of the work described.Alfred Wiesbauer is the primary author of this article. He has a child affected with MPS IVA. He entered the data of the Swiss LSD patients in a database (Swiss registry for LSD patients) and analyzed them in the context of a master thesis in public health. He has thus contributed to the data collection, and reporting of the work described.Marianne Rohrbach is a pediatrician and geneticist specialized in LSD. She has 14 years' experience in LSD and works at the University Children's Hospital in Zürich, one of the three Swiss centers for inborn errors of metabolism, where she diagnosed MPS patients and collected data. She is a mentor of Alfred Wiesbauer and contributed to the concept, planning, data analysis and reporting of the Swiss registry for LSD patients.Diana Ballhausen is a pediatrician specialized in LSD. She first worked during 6 years in Zurich and now since 11 years in Lausanne where she diagnosed and followed a couple of the Swiss MPS patients. She is also responsible for the molecular diagnosis of MPS patients in Switzerland.Matthias Gautschi is a pediatrician specialized in LSD and works since a couple of years at University Children's Hospital in Bern where he diagnosed MPS patients and collected and analyzed the data of his patients.Robert W. Mason has contributed to data analysis, and reporting of the work described.Roberto Giugliani has diagnosed a large number of MPS patients in Brazil and contributed to data analysis, and reporting of the work described.Tadao Orii is a medical doctor with 50 years of clinical and research experiences in MPS. He diagnosed over 500 MPS patients in his career in Japan. He published over 150 articles and chapter books in this field. He has contributed to the planning, data analysis, and reporting of the work described.Shunji Tomatsu is a Principal Investigator and has 30 years of clinical and research experience in MPS, publishing over 150 articles in this field. He has contributed to the concept of the project, planning, analysis of data, and reporting of the work described in the article.

* Corresponding author at: Department of Biomedical Research, Nemours/Alfred I. duPont Hospital for Children, 1600 Rockland Rd., Wilmington, DE 19899-0269, United States.
E-mail addresses: stomatsu@nemours.org, stomatsu@gifu-u.ac.jp (S. Tomatsu).

[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.ymgme.2017.05.016

of MPS is also reported to be higher in these countries. Birth prevalence of MPS II in Switzerland and other European countries is comparatively lower. The birth prevalence of MPS III and IV in Switzerland is higher than in Japan but comparable to that in most other European countries. Moreover, the birth prevalence of MPS VI and VII was very low in both, Switzerland and Japan. Overall, the frequency of MPS varies for each population due to differences in ethnic backgrounds and/or founder effects that affect the birth prevalence of each type of MPS, as seen for other rare genetic diseases. Methods for identification of MPS patients are not uniform across all countries, and consequently, if patients are not identified, recorded prevalence rates will be aberrantly low.

1. Introduction

1.1. Mucopolysaccharidoses

The Mucopolysaccharidoses (MPS) are a group of inherited metabolic diseases caused by the deficiency of enzymes required to degrade glycosaminoglycans (GAGs) in the lysosome. GAGs are sulfated polysaccharides comprising repeating disaccharides, uronic acid (or galactose) and hexosamines including chondroitin sulfate (CS), dermatan sulfate (DS), heparan sulfate (HS), and keratan sulfate (KS). Hyaluronan is an exception in the GAG family because it is a non-sulfated polysaccharide. Lysosomal enzymes are crucial for stepwise degradation of GAGs to provide a normal function of tissues and extracellular matrix (ECM). The deficiency of one or more lysosomal enzyme(s) results in accumulation of undegraded GAGs causing cell, tissue, and organ dysfunction. Accumulated GAGs of various tissues and their ECM are secreted into the blood circulation and then excreted in urine. MPS are autosomal recessive disorders except for MPS II that is X-linked.

1.2. Types of MPS

Seven types of MPS are categorized based on lack or defect in one of eleven specific lysosomal enzymes and are described as MPS I through MPS IX (excluding MPS V and VIII, which are no longer used). Clinical features vary with the type of MPS and clinical severity of the disease.

1.3. MPS I (Hurler syndrome, Hurler/Scheie syndrome, Scheie syndrome)

MPS I affected individuals have traditionally been classified as having one of three MPS I syndromes (Hurler syndrome, Hurler-Scheie syndrome, or Scheie syndrome), but no easily measurable biochemical differences have been identified [1] and the clinical findings overlap. Affected individuals are best described as having either severe or attenuated MPS I, a distinction that influences therapeutic options. The greatest variability is observed in individuals with attenuated MPS I. MPS I with either severe or attenuated form has limited activity of the enzyme α-L-iduronidase (*IDUA*) that breaks down DS and HS. These GAGs remain stored in cells causing progressive damage of various tissues including bone and, in severe cases, brain. MPS I presents with a wide range of symptoms. Typical manifestations include coarse face, corneal clouding, developmental delay, mental retardation, growth retardation, contractures of the joints, kyphoscoliosis, dysostosis multiplex, hearing loss, thickening of the heart valves, hepatosplenomegaly, and umbilical and inguinal hernias. Scheie syndrome, the milder form of the disease, is characterized by a coarse face and stocky physique with normal intelligence while Hurler syndrome displays neurological symptoms such as dyslexia, thermanesthesia, and cognitive degradation. Patients with Hurler syndrome develop initial symptoms like hernias, hepatomegaly, kyphosis and developmental delay within a year and die within a decade if untreated, while Scheie syndrome patients can live >50 years [2].

1.4. MPS II (Hunter syndrome)

Like MPS I, MPS II also has both, mild and severe forms. Their clinical symptoms are very different. The severe form has features similar to Hurler syndrome, except for the lack of corneal clouding and slower progression of somatic and central nervous system involvement. The mild form is analogous to Hurler/Scheie or Scheie syndrome, with a longer life span, a slower progression of somatic deterioration, and retention of intelligence. Both forms arise from the deficiency of iduronate-2-sulfatase (I2S) that catalyzes DS and HS degradation. MPS II is inherited in an X-linked manner, resulting in mostly males being affected. However, on rare occasions, heterozygous females manifest findings of MPS II. This is thought to result from skewed inactivation of the normal paternally inherited X chromosome and expression of the maternally inherited mutated *IDS* allele [3,4].

Clinical features of MPS II usually become apparent by two to four years of age. Abnormalities may include developmental delay, mental retardation, coarsening of facial features including thickening of lips, tongue, and nostrils, dysostosis multiplex, progressive growth delay resulting in short stature, and joint stiffness associated with restriction of movements. Affected children may also have an abnormally large head (macrocephaly), a short neck, broad chest, delayed tooth eruption, hearing loss, hepatosplenomegaly, and inguinal and umbilical hernias. The life expectancy also differs in the two forms; patients with the mild form reach adulthood, while patients affected by the severe form usually die within the first two decades of life.

1.5. MPS III (Sanfilippo syndrome)

MPS III is characterized by four types; MPS IIIA, IIIB, IIIC, and IIID due to lack of heparan-N-sulfatase (*SGHS*), α-*N*-acetylglucosaminidase (*NAGLU*), α-glucosaminidase acetyltransferase (*HGSNAT*), and *N*-acetyl-glucosamine 6-sulfatase (*GNS*), respectively. A defect in any of the four enzymes compromises the degradation of HS. Phenotypic variation exists among MPS III patients but to a lesser degree than in the other MPS, possibly because very mild forms of MPS III may not be diagnosed. MPS III is characterized by severe central nervous system (CNS) degeneration and progressive developmental delay and mental retardation. It is noteworthy that MPS I, II, III and MPS VII share partial or incomplete degradation of HS that results in CNS involvement.

1.6. MPS IV (Morquio syndrome)

MPS IV is caused by the deficiency of any of two distinct enzymes, *N*-acetylgalactosamine-6-sulfate sulfatase (*GALNS*) and β-galactosidase (*GLB1*) resulting in MPS IVA and IVB. Both chondroitin-6-sulfate (C6S) and KS accumulate in MPS IVA whereas only KS accumulates in MPS IVB. Accumulation of KS (and C6S) in MPS IV directly results in impairment of cartilage and bone development leading to systemic skeletal dysplasia. MPS IV has minimal impact on cognitive function in these patients, distinguishing this from other forms of MPS. Clinical features include coarsening of facies, short neck and trunk dwarfism, fine corneal clouding, skeletal dysplasia, small teeth with thin enamel and frequent caries formation, atlantoaxial subluxation, cervical spinal cord compression, pectus carinatum, kyphoscoliosis, bilateral genu valgum, pes