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Current diagnosis and management of mucopolysaccharidosis VI in the Asia-Pacific region

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ABSTRACT

Introduction: Mucopolysaccharidosis (MPS) type VI (Maroteaux–Lamy syndrome) is a clinically heterogeneous lysosomal storage disorder. It presents significant diagnostic and treatment challenges due to the rarity of the disease and complexity of the phenotype. As information about MPS VI in Asia-Pacific countries is limited, a survey was conducted to assess current practices for diagnosis and management of MPS VI in this region. The participants were selected based on their experience in diagnosing and managing MPS patients.

Methods: The survey comprised 29 structured quantitative or qualitative questions. Follow-up consultations were undertaken to discuss the data further.

Results: Thirteen physicians from eight countries or regions (Australia, China, Hong Kong, Japan, Malaysia, Philippines, Taiwan and Thailand) were surveyed. At the time of the survey twenty-two patients with MPS VI were directly treated by the respondents and most (~80%) had rapidly progressing disease. A wide range of medical specialists are involved in managing patients with MPS VI, the most common being orthopedic surgeons, pediatricians and geneticists. The availability/accessibility of diagnostic tools, therapies and national insurance coverage vary greatly across the countries/regions and, in some cases, between different regions within the same country. Currently, there are national MPS management groups in Australia and Japan. Australia, Taiwan and Hong Kong have local guidelines for managing MPS and local MPS registries are available in Australia, Taiwan, and Japan.

Conclusions: This survey highlights differences in the diagnosis and management of MPS VI between Asia-Pacific countries/regions. Important barriers to advancing the identification, understanding and treatment of MPS VI include the paucity of epidemiological information, limited access to laboratory diagnostics and therapies, low disease awareness, and a lack of monitoring and treatment guidelines. There is a clear need to facilitate communications between physicians and establish regional or national disease registries, a multidisciplinary referral network, and a centralized diagnostic and management framework.

Abbreviations: ARSB, arylsulfatase B gene; ASB, arylsulfatase B; BMT, bone marrow transplantation; DBS, dry blood spot; dx, diagnosis; ERT, enzyme replacement therapy; GAG, glycosaminoglycan; HSCT, hematopoietic stem cell transplantation; LSDP, Life Saving Drugs Program; MDAC, Mucopolysaccharidosis Disease Advisory Committee; MPS, mucopolysaccharidoses; NK, not known; NA, not applicable; SCC, spinal cord compression; uGAG, urinary glycosaminoglycan.

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1. Introduction

The mucopolysaccharidoses are a heterogeneous group of lysosomal storage diseases. There are currently 11 known enzyme deficiencies that cause seven distinct mucopolysaccharidosis (MPS) disorders [1]. MPS type VI, or Maroteaux–Lamy syndrome, is an autosomal recessive lysosomal storage disorder in which mutations in the arylsulfatase B gene (*ARSB; Gene/Locus MIM #611542*) cause defects in N-acetylgalactosamine 4-sulfatase (EC 3.1.6.12), resulting in impairment of the stepwise degradation of the glycosaminoglycan (GAG) dermatan sulfate [2]. This leads to progressive intra- and extracellular accumulation of dermatan sulfate in various tissues and organs. As with other MPS disorders, MPS VI is a clinically heterogeneous condition, and due to the complexity of the disease phenotype it often presents considerable diagnostic challenges to clinicians. Diagnosis of MPS VI occurs through a combination of clinical findings and laboratory test results. Clinical findings for patients with rapidly progressing MPS VI typically include impaired growth, coarse facial features, dysostosis multiplex, restriction of joint movement, flexion contractures, impaired vision and/or hearing, nerve entrapment syndromes such as carpal tunnel syndrome and spinal cord compression (SCC), organomegaly, umbilical and/or inguinal hernias, reduced pulmonary function, and cardiac valve disease. Onset usually occurs before 2 or 3 years of age [3,4]. Without treatment, most of these patients die in their second or third decade of life. Patients with attenuated disease live longer and tend to have close to normal height. Facial or skeletal changes may be absent or mild. Although symptoms appear later in these patients, usually in adolescence or early adulthood [5,6], they ultimately develop severe morbidity or life-threatening symptoms such as cardiopulmonary diseases, hip dysplasia, impaired vision and SCC.

MPS VI is an extremely rare disorder and data on the prevalence of MPS VI in the Asia-Pacific region are limited. Current knowledge about the epidemiology of MPS VI is therefore restricted to reports that describe the birth incidence of the disorder or single center studies. The results from observational studies suggest that the prevalence of MPS VI may be highly variable among different populations and geographic regions [7–9]. The global incidence of MPS VI based on countries ranges from 1 in 238,095 and 1 in 1,505,160 live births [4]. About 1100 individuals may be affected in the developed world [10]. A retrospective survey in Australia reported 18 patients with MPS VI for the period from 1980 to 1996. These data translate to an incidence of 1 per 248,000 live births [11]. An epidemiological study in Western Australia for the period from 1969 to 1996 estimated an incidence of approximately 1 in 320,589 live births for MPS VI [12]. MPS VI accounted for around 9–10.4% of total MPS diseases in Australia. The reported incidence in Taiwan is 1 per 708,589 live births (7% of all MPS births) between 1984 and 2004 [13]. A retrospective study conducted by the Korean Pediatric Society identified 131 patients with MPS between 1991 and 2000, with 69 MPS II, 22 MPS I, 11 MPS III, one MPS IV, one MPS VI and 27 unclassified [14]. In a single center study in Malaysia, of 40 suspected patients, 17 were diagnosed with MPS and one patient was diagnosed with MPS VI [15]. In a single center report from Shanghai, China in 2009, of 47 MPS cases (28 MPS II, 12 MPS IVA and 7 MPS I) no patients were diagnosed with MPS VI [16]. In terms of MPS subtypes, MPS III is the most common in Australia [11,12], whereas in South Korea [14,17], Malaysia [15], Taiwan [13], Japan and China, MPS II appears to be the most prevalent.

The management of patients with MPS VI was traditionally limited to physical and occupational therapy, symptom-based medications, surgical interventions involving orthopedic, otorhinolaryngological, ophthalmological, cardiac and neurosurgical interventions, and hematopoietic stem cell (HSCT) or bone marrow transplantation (BMT) [3]. However, treatment with HSCT or BMT has been limited by the high procedure-related morbidity and mortality risk and the difficulty of finding HLA-matched donors [18,19]. With the advent of disease-specific enzyme replacement therapy (ERT) with the human recombinant ASB galsulfase (Naglazyme®), more patients with MPS VI are now treated effectively and safely, thereby improving health and quality of life [20,21]. However, there are a number of factors that have a major influence on clinicians' approaches to MPS VI such as the rarity of MPS VI and subsequently low awareness of the disease, wide regional variations in national healthcare systems, the availability of testing facilities for the confirmation of diagnosis, differences in, or lack of, regulations regarding rare diseases and orphan drugs, and disparities in affluence both within and between countries. These factors are likely to influence approaches to diagnosis and management of MPS VI.

Therefore, a survey and literature search to assess current MPS VI diagnosis and treatment patterns in the Asia-Pacific region was conducted to identify knowledge gaps and unmet needs that should be addressed, as well as opportunities for research on topics of particular relevance in the region.

2. Methods

2.1. Survey questionnaire and follow-up interviews

The survey was designed in consultation with pediatricians and clinical geneticists in the Asia-Pacific region and with the Mudskipper Business Consulting (Shanghai) Limited. Invitation letters outlining the rationale for conducting the survey were distributed to 15 pediatricians in October 2010 together with the accompanying questionnaire. The participants were selected based on their experience in diagnosing and managing MPS patients. The questionnaire was a quantitative and qualitative survey comprising 29 structured questions that could be completed electronically in approximately 30 minutes once they had accessed all the necessary data. Respondents were required to classify their primary workplace (academic institution/university; government general hospital; regional/ community hospital; private general hospital/private practice or another healthcare setup). The survey was divided into four distinct sections: (1) country-specific information; (2) general diagnosis, treatment and follow-up; (3) available laboratory tests; and (4) the physicians' general opinions about the diagnosis and management of MPS VI in their countries and the Asia-Pacific region. Table 1 shows the particular questions asked in each of the sections. Although many questions could be answered by choosing the appropriate answer, all questions allowed for detailed answers. Each section was followed by a question to assess the respondents' perceived accuracy for his/her answers in that particular section.

In addition, each respondent was asked a post-hoc question regarding the assessment and management of SCC. Spinal cord compression is a potentially serious complication of MPS VI resulting in debilitating muscle weakness or paralysis. However, early diagnosis by means of MRI can identify clinical features suggestive of SCC and treatment, to prevent or forestall SCC, can be initiated early on [22]. From our survey responses it was clear that patients generally undergo a skeletal survey at diagnosis, and we wanted to assess whether MRI for the detection of SCC is done routinely or as a result of abnormal results during the skeletal survey. The question regarding the assessment and management of SCC was therefore posed.

We also provided an opportunity for further discussion of the data by means of follow-up e-mails, telephonic contact or face-to-face meetings. The survey was divided into four distinct sections: (1) country-specific information; (2) general diagnosis, treatment and follow-up; (3) available laboratory tests; and (4) the physicians' general opinions about the diagnosis and management of MPS VI in their countries and the Asia-Pacific region. The study was completed in April 2012.

2.2. Analysis

Collection and analysis of the survey information was done by the Mudskipper Business Consulting (Shanghai) Limited.