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Diagnosis and Management of Patients with Mucopolysaccharidoses in Malaysia

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In Malaysia, diagnosis and treatment of patients with mucopolysaccharidoses (MPS) is mainly localized at Hospital Kuala Lumpur, which is the national referral center for rare diseases. To date there are 83 patients diagnosed with MPS in our center, with MPS II being the commonest. The Malaysian National Medicines Policy second edition has a specific section on the orphan drugs which includes recombinant human enzyme for enzyme replacement therapy (ERT) in MPS. So far, National Pharmaceutical Regulatory Agency Malaysia has approved recombinant human enzyme for MPS types I (Loranidase), II (idursulfase), IVA (elosulfase alfa), and VI (Galsufase). Access to Idursulfase beta (another recombinant human enzyme for MPS II) and vestronidase alfa-vjbk (MPS VII) required special authorization on named patient basic. Currently there are 25 patients receiving ERT, 70% of the funding are from Ministry of Health (MOH), the remaining 30% are from various charitable funds and humanitarian programs. Thirteen newly diagnosed patients have to queue for an additional fund. Four patients have been treated with Hematopoietic stem cell transplant. MOH has also published guidelines regarding the patient selection criteria for ERT and treatment monitoring schedule.

Keywords: Mucopolysaccharidoses, Enzyme replacement therapy

Introduction

The mucopolysaccharidoses (MPS) are a group of rare lysosomal storage disorders caused by the deficiency of enzymes required for the stepwise catabolism of glycosaminoglycans (GAGs). There are 11 clinical types of MPS, each disorder is caused by a deficiency in the activity of a single, specific lysosomal enzyme required for GAG degradation. The accumulation of fragments of partially degraded GAGs in the lysosomes results in progressive cellular dysfunction and clinical abnormalities that affect multiple organ systems. Patients with MPS have normal development initially, with abnormalities appearing in infancy or later in childhood such as coarse facial features, hepatosplenomegaly, skeletal deformities (dysostosis multiplex), joint stiffness, short stature; upper airway obstruction, recurrent ear infections, hydrocephalus, cognitive impairment, etc. All of the MPS are autosomal recessive disorders, with the exception of MPS II, which is X linked[1].

This paper described an overview of diagnosis and management of patients with MPS in Malaysia, based on the clinic database and medical records maintained at Genetics Department, Hospital Kuala Lumpur, which is the national referral center for rare genetic diseases in the country.

Diagnosis of MPS in Malaysia

Since 2005, Malaysia has been carried out in-house diagnostic testing for MPS in Institute for Medical Research, Kuala Lumpur. For any patients with suspected MPS, quantitative measurement of total urinary GAGs by a method using dimethylmethylene blue (DMB) will be done initially, followed by isolation and separation of GAGs using high resolution electrophoresis. Based on

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the GAGs high resolution electrophoresis and correlating clinical signs, selective lysosomal enzymatic assay will be then performed in leukocytes or/and plasma[2]. Molecular tests are also become available in the local genetic laboratories the last two years.

Number of Patients Diagnosed and MPS Types Distribution

A total of 83 patients (56 males, 27 females) with MPS have been diagnosed between 2003 and April 2018. Almost 40% of the patients have MPS type II (Table 1), making it the predominant MPS type in Malaysia, and same observation has been previously reported in other Asian countries such as Japan, Korea and Taiwan[3]. The distribution of other MPS types are: MPS I (13.3%), MPS III (13.3%), MPS IVA (16.9%), MPS VI (14.5%) and MPS VII (2.4%). With regard to their clinical spectrum, a vast majority of patients (73 out of 83 or 88%) manifested the severe clinical phenotype, i.e. early onset and rapidly progressing disease. Patients with attenuated clinical phenotype, i.e. slow progressing disease only represent 12% of all diagnosed patients. However, a point of note is that the prevalence of MPS with attenuated clinical phenotype may have been underestimated because the milder clinical features and less systemic disease.

Treatment of MPS In Malaysia

Disease-specific treatments for MPS include hematopoietic stem cells transplant (HSCT) and enzyme replacement therapy (ERT) with recombinant human enzyme. HSCT is treatment of choice for MPS I patients with severe phenotype and should be done before 2 years old. The use of HSCT has been reported in MPS II and MPS VI with variable success. To date, we have four MPS patients received HSCT in Malaysia: MPS I (one patient), MPS II (one patient), MPS VI (two patients).

Malaysia does not have any specific act for rare diseases or orphan drugs so far. However, The Malaysian National Medicines Policy second edition as a specific section on the orphan drugs that serves as a guideline in procurement and uses of such drugs[4,5]. To date, recombinant human enzyme for MPS types I (Loranidase), II (idursulfase), IVA (elosulfase alfa), and VI (Galsufase) has been approved for use by the National Pharmaceutical Regulatory Agency Malaysia. Loranidase and idursulfase are included in the Ministry of Health Medicines Formulary. Idursulfase beta (another recombinant human enzyme for MPS II) and vestronidase alfa-vjbk (recombinant human enzyme for MPS VII) are yet to obtain approval but can be used on named patient basic with the special authorization from Ministry of Health.

Table 2 shows the current status of the 83 patients with MPS in our center.

Ministry of Health of Malaysia has published a guideline for treatment of Lysosomal Storage Diseases by Enzyme Replacement Therapy in 2012[6]. This guideline outlines the patient selection criteria for ERT and treatment monitoring schedule. In term of funding for the ERT, nearly 70% are from Ministry of Health, the remaining 30% are from various charitable funds and humanitarian programs. Newly diagnosed patients often have to queue for an additional fund for ERT. All our MPS patients also received various multi-disciplinary supportive cares involving many medical specialties.

Conclusion

Generally, Malaysia has made significant progress in the management of MPS, but there remain key areas for substantial development opportunities. To minimise the access gap and delay of treatment, more financial resources has to be provided under

Table 1. Distribution of MPS types and clinical phenotypes of patients

MPS type	Total number of patients diagnosed	Clinical phenotype	
		Severe phenotype	Attenuated phenotype
MPS I	11	10	1
MPS II	33	25	8
MPS IIIA	5	5	0
MPS IIIB	5	5	0
MPS IIIC	1	1	0
MPS IVA	14	14	0
MPS VI	12	11	1
MPS VII	2	2	0
Total	83	73	10

Table 2. Clinical outcome and treatment status of patients

Clinical and treatment status	Number of patients
Survive and on follow up	61
-Not of ERT due to advanced disease	19
-Received hematopoietic stem cell transplant	4
-Receiving enzyme replacement therapy	25
-Waiting for enzyme replacement therapy	13
Died	15
Lost to follow up	7

national healthcare budget to meet the patients' need. Ultimately, if all healthcare providers, governance, and politicians work together to manage rare diseases including MPS, we will see an improvement of rare disease patients outcomes.

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