Case Report

Hunter syndrome with hyperthyroidism: a 16-month follow-up case report

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Mucopolysaccharidosis (MPS) is a rare genetic disorder caused by a deficiency in the activity of lysosomal enzymes required for glycosaminoglycan (GAG) degradation. An accumulation of GAG in many organs results in progressive cellular damage, and clinically results in joint stiffness, airway and cardiac as well as, mental and hearing impairments. Incidence of MPS was reportedly 2.04 per 100,000 live births, but varies depending on type and region. In Taiwan, MPS type II was the most prevalent MPS, with an incidence of 1.07 per 100,000 live births.[1] MPS is generally inherited in an autosomal recessive pattern, with the exception of MPS II, which is X-linked recessive.[2] There are seven types of MPS (MPS I, II, III, IV, VI, VII, and IX), based on enzyme deficits.[3] The types of MPS with their enzyme deficiencies are listed in **Table** 1.

Mucopolysaccharidosis shows wide clinical heterogenity, and is, therefore, difficult to diagnose. Skeletal involvement in MPS include coarse face, loss of joint range of motion, restricted mobility, and slowed growth leading to short stature. Other signs and symptoms include vision and hearing loss, recurrent respiratory infections, obstructive sleep apnea, hepatosplenomegaly, umbilical and inguinal hernia, hydrocephalus, spinal cord compression, and cognitive impairment.[2,4] Patients with suspected MPS should have urinary GAG laboratory testing and enzyme activity assays in tissue (blood or fibroblasts). Urinary elevation of GAG, as compared with GAG levels expected in age-matched normal subjects,

is the first diagnostic approach. The definitive specific diagnosis for MPS is based on enzyme activity assays from cultured fibroblasts, leukocytes, plasma, or serum.[2,5,6] The MPS patients require multidiciplinary subspeciality management, including ENT, orthopedics, cardiology, pulmonary, growth and development, and physiotherapy. Specific treatments for MPS are hematopoietic stem cell transplantation (HSCT) and enzyme-replacement therapy (ERT) with recombinant human enzymes for MPS I, II, and VI.[3,6,7,8] Life expectancies in MPS may vary among types, but generally are markedly reduced. Patients with MPS III and VII and severe forms of MPS I and MPS II have mental retardation. Patients with MPS II usually survive until only the second decade of life, with respiratory failure as the leading cause of death (56%), followed by cardiac failure (18%).[9,10] **[Paediatr Indones. 2018;58:317-22; doi: http://dx.doi.org/10.14238/pi58.6.2018.317-22]**

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Table 1. The types of MPS

Type	Enzyme deficiency	GAGdeposits	Gen loci
I (Hurler, Hurler Scheie, Scheie syndrome)	α-L iduronidase (IDUA)	Heparan sulphate, dermatan sulphate	4p 16.3
II (Hunter syndrome)	iduronate-2-sulphatase (I2S)	Heparan sulphate, dermatan sulphate	Xq28
III (Sanfilippo syndrome)	A: heparan N-sulphatase B: N-acetyl- α-glucosaminidase C: acetyl-CoA α-glucosaminidase D: N-acetylglucosamine 6-sulphatase	Heparan sulphate	A: 17q25.3 B: 17q21 C: 8p11.1 D: 12q14
IV (Morquio syndrome)	A: N- acetylgalactosamine 6- sulphatate sulphatase B: β-galactosidase	A: Keratan sulphate, chondroitin sulphate B: Keratan sulphate	A: 16q24.3 B: 3p21.33
VI (Maroteaux-Lamy syndrome)	N-acetylgalactosamine 4-sulphatase	Dermatan sulphate, chondroitin sulphate	5q11-q13
VII (Sly syndrome)	β-glucoronidase	Dermatan sulphate, chondroitin sulphate, heparan sulphate	7q21.11
IX (Natowicz syndrome)	Hyalurinidase	Hyaluronan	3p21.3-p2 12

The Case

A boy aged 7 years and 10 months was a referral case to Sardjito Hospital, Yogyakarta, who was diagnosed with hyperthyroidism and global developmental delay in April 2013, due to tachycardia, chronic diarrhea, regressed motor ability, and cognitive impairment. Thyroid function test showed FT4 elevation (70 pmol) and low TSH (0.064 μIU/mL). After 1 year of propylthiouracil (PTU) treatment, the patient became euthyroid (FT4: 0.89 pmol and TSH 0.79 μIU/mL) so medication was stopped. The patient returned to Sardjito Hospital on May 2014 with restlessness, inability to sleep for two days, and diarrhea (three times/day). Physical examination showed manifestations of mucopolysaccharidosis, i.e., coarse face, short stature, hepatosplenomegaly, joint stiffness, and cognitive imparment. His coarse face is shown in **Figure 1**. The patient was diagnosed with hyperthyroidism (relapsed), intellectual disability, and suspected MPS. Laboratory results for thyroid function were FT4 1.56 μIU/mL and TSH 0.207 μIU/mL. Radiological examinations were done to evaluate for adenoid hypertrophy, joint stiffness, cardiomegaly, and vertebral deformities. This patient had adenoid hypertrophy (**Figure 1**), joint stiffness (**Figure 2**), and claw hands (**Figure 3**, **Figure 4**). Echocardiography revealed mild-moderate aortic insufficiency and mitral

insufficiency. The patient also had profound bilateral distal neural hearing loss. Urinary GAG and enzyme activity assays were performed at the University of Taiwan Laboratory. Urinary GAG analysis showed

Figure 1. Patient with coarse facial features
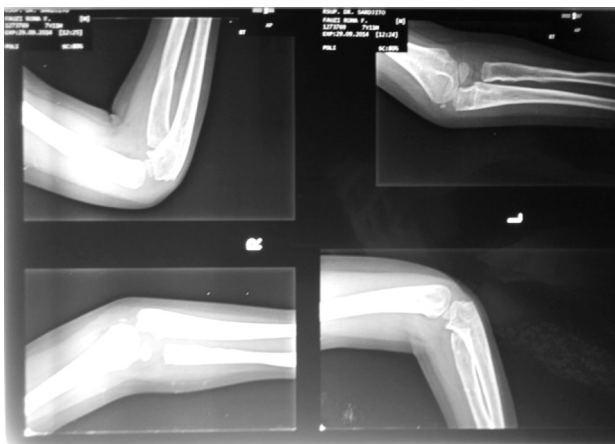
Figure 2. X-rays revealing adenoid hypertrophy
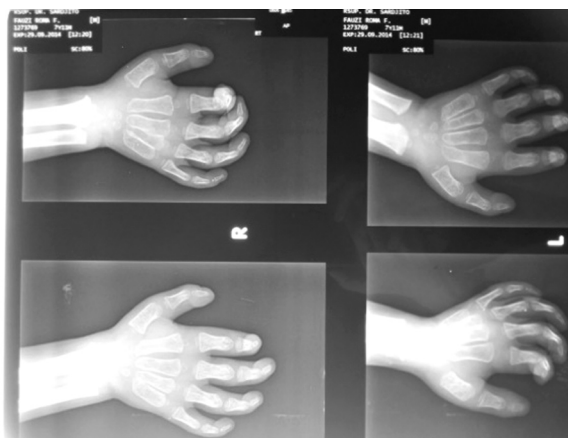

Figure 3. X-rays of the elbow joint

Figure 4. X-rays indicating claw hand

was low plasma α-iduronate sulphatase activity, but normal activity in his leukocytes. The enzyme activity results are listed in **Table 2** and **Table 3**. The final diagnosis for this patient was MPS type II (Hunter syndrome), hyperthyroidism, mild-moderate aortic insufficiency, mitral insufficiency, intellectual disability, and profound bilateral distal neural hearing loss. The patient received palliative therapy for MPS. He also received propylthiouracyl for hyperthyroidism, ACE-I for cardiac insufficiency, and physiotherapy. Psychosocial testing performed by a psychologist revealed that this 7-year-old patient had a mental age below 2 years, communication skill of a 3-month-old,

Table 2. Enzyme activity assays in the patient's plasma

Enzymes	Results	Normal values
4B: β-galactosidase	9.31	10.22 ± 5.03 nmol/mg prot/30min
2: α-iduronate sulfatase	0.76	496.3 ± 165.7 nmol/mg prot/4 hrs
3B : α-hexoaminidase	721.08	320.4 ± 131.3 nmol/mg prot/17 hrs

Table 3. Enzyme activity assays in the patient's leuk ocytes

Enzymes	Results	Normal values
1-α-iduronidase	26.24	41.8 ± 15.9 nmol/mg prot/hrs
2-α-iduronate sulfatase		28.8 ± 11.3 nmol/mg prot/4 hrs
3A-heparan sulphamidase		4.6 ± 2.2 nmol/mg prot/24 hrs
3B-α-hexoaminidase		17.2 ± 6.4 nmol/mg prot/17 hrs
3C-acetyl-CoA: a-glucosaminide N acetytransferase	2.32	7.5 ± 2.2 nmol/mg prot/17 hrs
3D-N-acetylglucosamine-6-sulphate sulphatase		7.76 ± 5.15 nmol/mg prot/24 hrs
4A-galactose-6-sulphate sulphatase	177.72	158.9 ± 82.8 nmol/mg prot/17 hrs
4B-β-galactosidase	93.57	93.85 ± 28.75 nmol/mg prot/30min
4MLD: arylsulfatase A	76.53	76.6 ± 29.9 nmol/mg prot/hrs
6: arylsulfatase B	85.76	92.3 ± 49.6 nmol/mg prot/hrs
7: β-glucuronidase	72.58	110.3 ± 32.4 nmol/mg prot/hrs

elevated GAG of 685.57 mg GAG/g creatinine, in comparison with the age-matched value of 35.74 (10.77-77.50) mg of GAG/g creatinine. There

daily activity skill of a 10-month-old, social skill of a 2-month-old, and motor skill of an 8-month-old.

We followed up this patient for 16 months to see the natural history of MPS with hyperthyroidism and its complications, including growth, physical performance, cardiac involvement, and sleep disturbance. This patient demonstrated a flat pattern of growth, with no significant increase in weight and height. On the initial examination, the patient's weight was 20.0 kg and height was 103.0 cm. Upon monthly follow-up visits, his body weight was stable at 20.0 kg, i.e., between -3 SD and -2 SD weight-for-age, according to the 2006 WHO Child Growth Standards.[11] At the end of follow-up, the patient's height was 105.0 cm, an increase of 2 cm. However, it was still below -3SD, according to the *2006 WHO Child Growth Standards* for 8-year-old boys. His BMI was normal.

Cardiac involvement included worsening valvular insufficiency, with aortic insufficiency developing from mild-moderate to moderate, and mitral insufficiency progressing from mild to moderate, although the patient routinely consumed an angiotensin converting enzyme inhibitor (ACEI) for 4 months. There were no signs or symptoms of heart failure in this patient. However, towards the end of his life, he received diuretics for suspected heart failure. The first respiratory problem was obstructive sleep apnea syndrome (OSAS) caused by adenoid hypertrophy, which resulted in sleep complications. However, his family refused an adenotonsillectomy due to worries of anaesthetic complications. This patient did not suffer from pneumonia until his last follow-up visit. After having a cough for 5 days, the patient was hospitalized for pneumonia. His condition worsened with seizures without fever that occurred on the 1st day of hospitalization. He required intubation. The patient was never extubated because of excessive saliva production. The patient also suffered from heart failure, and unfortunately he died at the age of 9 years, with respiratory failure as the cause of death after 30 days of hospitalization.

The patient's quality of life was measured with *PedsQL version 4.0* for parental perception. His scores were 25 for initial and final monitoring, indicating that he had physical, social, and emotional problems. The lack of difference between the initial and final score indicated that his quality of life neither improved nor worsened. *The Pediatric Symptoms Checklist* was also performed, with a score above 28 (score=38), i.e., appropriate for psychological impairment.

Discussion

The patient was a boy aged 7 years and 10 months at the beginning of our observation period, and was treated for hyperthyroidism. Suspected MPS was based on clinical presentation and simple investigation. The MPS is a genetic disorder that causes lysosomal enzyme deficiency, leading to a buildup of GAG metabolites in organs. A diagnosis of type II MPS can be based on increased urinary GAG levels and decreased α-iduronate sulfate enzyme activity. A patient with severe intellectual disability is reflective of a severe form of MPS type II.[2,5]

The hyperthyroidism in our patient had improved to euthyroidism following initial treatment. A number of conditions that cause hyperthyroidism in children are congenital hyperthyroidism, Graves' disease, toxic nodular thyrotoxicosis, toxic adenoma, thyroiditis, follicular carcinoma, and TSH-producing tumor of hypophysis. However, in this patient, the etiologic tracking of hyperthyroidism was not done, as the main suspected cause was MPS type II. In MPS, metabolites tend to accumulate in the thyroid gland and brain leading to endocrine disorders.[12,13] To our knowledge, there have been no reports that hyperthyroidism can occur in MPS. However, hypothyroidism is generally caused by panhypopituitarism.[12]

The joint deformity and stiffness in the patient was routinely treated by physiotherapists. Limitations and abnormalities of the bones and joints appearing in MPS require special attention, as they may result in accidents that can aggravate the condition.[7,13,14] Joint deformity correction in our patient was not undertaken because of his baseline lack of ambulation. Moreover, the risk of anesthesia was perceived to be too burdensome by the family.

Child growth is a good indicator for assessing overall child health, as it may be affected by poor nutritional intake, thyroid hormone insufficiency and growth, abnormal bone metabolism, and chronic disease.[15] According to the *2006 WHO Child Growth Standard*, our patient was severely stunted, underweight with normal weight-for-height. Similarly, a report from Taiwan noted

that the natural growth course of MPS patients is the presence of short stature, macrocephaly, weight above normal, and normal or excessive BMI.[15,16] Children with MPS appear normal at birth, but grow poorly compared to normal children. Around 90% of children presenting with MPS have height-for-age -2SD. In general, at the age of 5-10 years, the child's weight is between ± 2SD and after the age of 10, it is under 2SD.[16] Macrocephaly is found at all ages. The MPS patients in Japan aged 18 years or over have BMI above 25, indicating a tendency to obesity. The mechanism of poor growth in MPS is not widely known, but is suspected to be associated with a growth plate disturbance in the form of a decrease in the deposit matrix with decreased osteoblast function, hypertrophic chondrocytes, disorganization of growth disc structure, and GAG accumulation on growth discs. In addition to the above, GAG accumulation is also found in pituitary, thyroid, and testicular glands in children with MPS type II.[16]

Complications that appear in MPS patients include thickening of the heart valve and pneumonia. The common respiratory disorders in MPS are OSAS and recurrent respiratory infections due to airway deformity.[17] Seizures in these patients are suspected to have been induced by MPS, sepsis, or hypoxia that may occur in patients with OSAS. Without enzyme therapy, the life expectancy of patients with MPS type II reaches the age of 7-10 years. Our patient died at 9 years and 2 months of age. He had a 1-year-old sister. Although MPS type II is inherited in an X-linked fashion, the sister still had the possibility of having MPS.[5,9,19] However, we did not perform chromosome analysis of the sister due to parental refusal.

Our patient died of pneumonia. Severe type II MPS patients without enzyme replacement therapy die at the age of 13.2 ± 3.2 years, with respiratory failure (56%) and cardiac failure (18%) as the leading causes of death.[20] Such a condition is exacerbated by heart valve abnormalities. From the parents' information, the patient had delayed control for echocardiography, thus cardiac medication was not given. The condition of pregnant mothers is a barrier to bring the patient to our hospital.

Conflict of Interest

None declared.

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