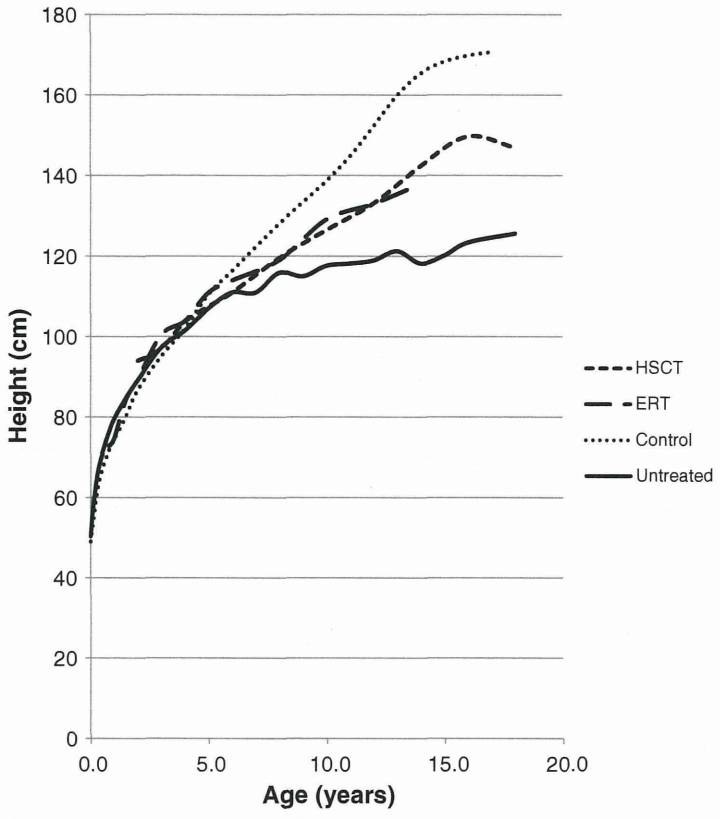

Fig. 1. Mean height for MPS II patients undergoing ERT or HSCT. Dotted line shows the mean heights for normal healthy controls. Solid line shows the mean height for untreated patients.

3.3. Body weight

Patients younger than 8 years old appeared to be heavier than age-matched controls, with or without ERT- or HSCT-treatment (Fig. 2). Weight gain in ERT-treated patients younger than 10 years of age was not significantly different to that in untreated patients (Table 2, Fig. 2). After the age of 10, weight gain slows in untreated patients and weight is significantly lower in 12 year old patients compared to the age-matched treated patients (Table 2).

Similarly, HSCT-treated patients were not significantly heavier than untreated patients up to 10 years of age and older, HSCT-treated patients were heavier than age-matched controls (Table 2). The two 18-year-old HSCT-treated patients were not as heavy as the 16 years old, but the significance of this change for just 2 patients is not clear. Increases in body weight for ERT- and HSCT-treated patients were similar (Table 2, Fig. 2).

3.4. BMI

BMI of untreated patients with MPS II is significantly higher than that of controls (Fig. 3). BMI was significantly lower in ERT-treated patients in the 10 year age group and in HSCT-treated patient in the 16 year age group compared to age-matched untreated patients, but were not significantly different in other age-groups (Table 3, Fig. 3).

3.5. Case reports

3.5.1. Sibling cases

There were 4 sibling pair cases included in our study, one of which gave enough data to compare growth charts. One patient with a severe form was treated with HSCT at 2 years of age. His height and

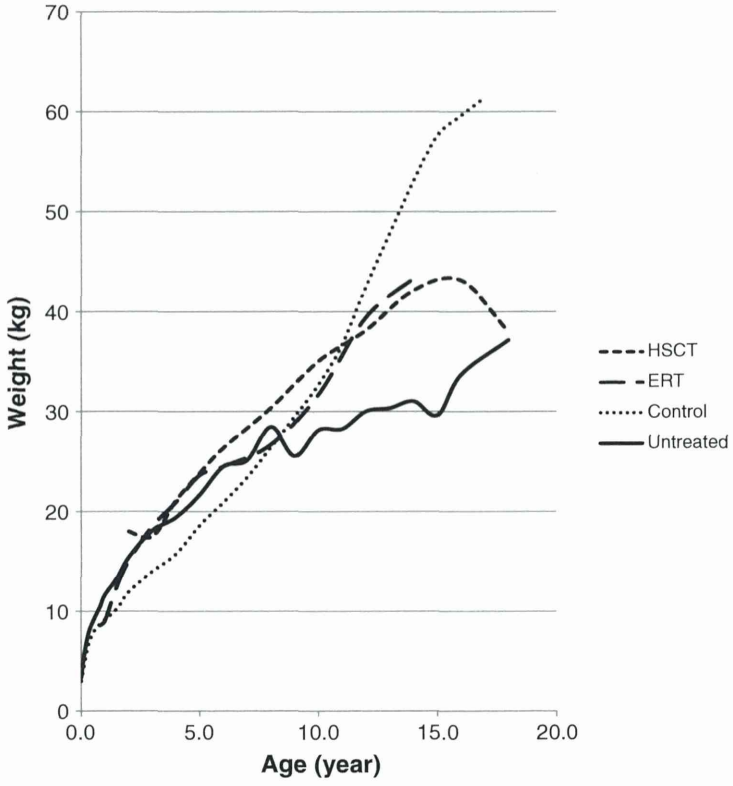

Fig. 2. Mean weight for MPS II patients undergoing ERT or HSCT. Dotted line shows the mean weights for normal healthy controls. Solid line shows the mean height for untreated patients.

body weight were 89 cm and 12.8 kg at the time of treatment. He was followed up to 16 years of age when his height and weight was 154.0 cm and 47.0 kg. A sibling of this patient with a similar severe form was also treated with HSCT, but at 5.4 years of age. At 18 years of age he reached a height and weight of 149.0 cm and 40.0 kg. The patient treated at the age of 2 was approximately 8.0 cm taller and 5.8 kg heavier than his sibling at ages 6 to 16.

Table 2
Weight of patients with MPS II undergoing therapy.

	HSCT (kg)		*t*-Test to untreated group		ERT (kg)		*t*-Test to untreated group		*t*-Test between two treatment groups
Age (years)	n	Mean	SD	p	n	Mean	SD	p	p
9.5 months					1	8.56			
1 y					1	9.04			
1.5 y					4	12.45	1.33	0.29	
2 y	1	18.00			4	15.05	1.34	0.64	
3 y	1	17.50			5	18.53	2.08	0.68	
4 y	5	21.10	2.79	0.27	6	20.94	1.48	0.08	0.91
5 y	8	23.84	3.83	0.19	5	23.63	2.03	0.12	0.90
6 y	12	26.35	6.42	0.39	8	24.51	3.76	1.00	0.43
8 y	10	30.36	7.45	0.53	11	26.68	2.41	0.39	0.16
10 y	9	35.04	9.72	0.07	7	31.70	5.13	0.15	0.39
12 y	9	38.13	8.50	0.02	7	39.41	9.61	0.04	0.79
14 y	6	42.12	8.01	0.02	1	43.30	–	–	
16 y	4	43.13	5.07	0.03					
18 y	2	38.00	–	–					

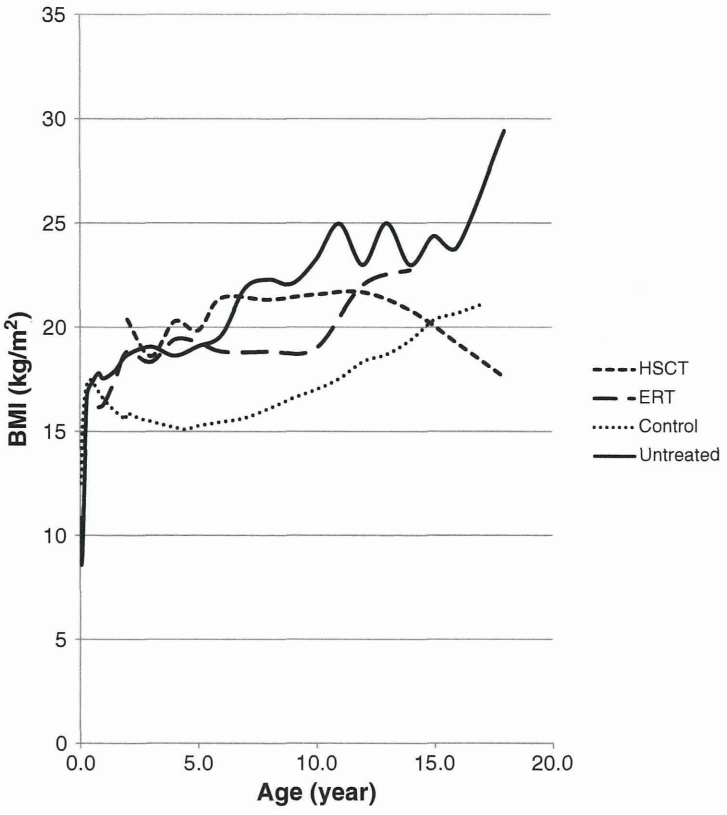

Fig. 3. Mean BMI for MPS II patients undergoing ERT or HSCT. Dotted line shows the mean BMI for normal healthy controls. Solid line shows the mean height for untreated patients.

3.5.2. Combined therapies

Six patients were initially treated with ERT before being treated with HSCT. The mean time difference between start of ERT and start of HSCT was 2.08 ± 0.93 years. ERT was discontinued immediately or

Table 3
BMI of patients with MPS II undergoing therapy.

	HSCT (kg/m^2)		*t*-Test to untreated group		ERT (kg/m^2)		*t*-Test to untreated group		*t*-Test between two treatment groups
Age (years)	n	Mean	SD	p	n	Mean	SD	p	p
9.5 months					1	16.15			
1 y					1	16.29			
1.5 y					4	17.49	0.41	0.15	
2 y	1	20.37			4	18.83	1.07	0.80	
3 y	1	18.60			5	18.33	0.36	0.05	
4 y	4	20.27	3.87	0.46	6	19.40	0.95	0.19	0.69
5 y	8	19.84	2.87	0.53	5	19.27	1.73	0.85	0.66
6 y	12	21.40	4.98	0.28	8	18.83	2.09	0.43	0.13
8 y	9	21.32	5.56	0.70	11	18.83	1.42	0.06	0.22
10 y	8	21.56	6.26	0.51	7	18.99	2.70	<0.01	0.32
12 y	9	21.68	4.96	0.56	7	22.02	3.23	0.62	0.87
14 y	6	20.81	3.98	0.39	1	22.74	–	–	
16 y	4	19.20	1.66	0.04					
18 y	2	17.57	–	–					

2–3 months later after treatment with HSCT. From the limited data from these patients it is not clear that there is any difference in growth characteristics between single or combined therapies.

4. Discussion

In this study, we evaluated the overall growth of patients with MPS II treated with ERT and/or HSCT, when treatment started at or before 8 years of age. Our study has demonstrated 1) that both ERT and HSCT provide a significant positive impact on the growth of patients with MPS II, and 2) that there is no significant difference in growth impact between patients treated with either ERT or HSCT from 4 to 12 years of age. These findings indicate that both treatments are equally effective at improving the overall growth in patients with MPS II.

Although one would predict that the more rigorous treatment in the HSCT-treated group, that includes chemotherapy and radiation, impairs growth, the gain in height and weight of these patients was comparable to that of the ERT-treated patients (Table 1, Fig. 1). In both treatment groups, patients showed initial overgrowth in height, when compared to the healthy control subjects. By 14 years of age, the mean heights of ERT- and HSCT-treated patients were lower than those in the healthy control group (Fig. 1). These findings show that the growth in either treatment is still not restored to that of the age-matched control group, although both treatment groups improved height significantly, when compared to untreated patients.

The overgrowth in weight of young children with MPS II compared to healthy control subjects was not reduced by either treatment. This is not unexpected as most measurements in this age range were from patients who were just beginning treatment. It is not clear whether this overgrowth could be reduced if patients were treated at an earlier age or if this overgrowth is of significance in disease progression. It was noteworthy that although the mean weight of ERT-treated patients fell below that of the healthy control subjects after 8 years of age, the mean weight of ERT-treated patients was not more than one SD below the mean weight in the age-matched control subjects (Fig. 2). Both treatment groups also showed increased body weights compared to untreated patients. Thus improved weight is a clear marker of treatment effect.

The time lag between the start of treatment and its effect on growth could be due to the avascular region of the growth plate, causing the infused or expressed enzyme to have poor access. Even if either of the treatments is able to quickly reduce GAG levels in urine, blood, and visceral organs, it may take more time to correct pathology in bone lesions.

The youngest patient treated with HSCT was 2 years of age, and he reached a height of 154 cm at 16 years of age, showing the most growth among any HSCT- or ERT-treated patients in our study. A sibling of this patient was treated with HSCT at 5.4 years of age, and was on average 8 cm shorter and 5.8 kg lighter than his brother at the same age between 6 and 16 years. This unique case indicates that early intervention with HSCT may provide a major benefit for patients. The mean age at which patients were treated with HSCT in this study was 4.68 years of age. The limited number of patients did not enable a statistical analysis of potential benefit of early treatment, but it is likely that early diagnosis and treatment of patients with HSCT will have a larger impact on growth. Accumulation of more data on growth charts of patients treated with HSCT at a younger age will help to clarify the potential benefit of early treatment on growth and development.

It is of interest that the more significant differences between treated and untreated patients were in height rather than in weight. The less significant changes in body weight resulted in the fact that the BMI of patients remains still higher during treatment compared to normal controls (Table 3, Fig. 3). Increased BMI with age is a hallmark of untreated patients with MPS II (Fig. 3). A high BMI might stem from an overall lower activity in daily life for patients, with or without treatment. In clinical trials, ERT-treated patients showed a significant increase in the 6-minute walk test (6MWT) [20–22], but this may not have an effect on the daily activity of patients receiving treatment. We recommend that physicians should consider the effect of overweight or obesity to the general health and activity of daily life in patients with Hunter syndrome during the course of treatment and encourage increased activity. More data is required to determine whether treatment can reduce BMI as the children approach adulthood.

In this study, we could not determine whether one treatment was more effective than the other, based on growth charts. Although the diagnosis of phenotype (severe or attenuated) is classified by CNS involvement [6], growth charts for patients with severe or attenuated phenotypes are similar [19]. This is consistent with the observation that patients respond equally to treatment with ERT, regardless of CNS involvement or

puberty status [11]. This study had several limitations that impact interpretation. One limitation is the restricted number of patients in each treatment group. Comparisons between the two therapies could not be achieved at all ages, although statistical analysis of patients between 4 and 12 years of age showed no significant difference in effect on growth.

A second limitation is that the starting age of treatment varies in clinical practice. Schulze-Frenking et al. showed that patients who had begun treatment with ERT before 10 years of age had larger improvements in growth than patients who had started treatment after 10 years of age [17]. Therefore, we focused on patients who started therapy before 8 years of age. The mean age at the start of treatment with ERT (4.5 ± 2.4 years) was similar to the mean age at the start of treatment with HSCT (4.7 ± 1.6 years). The limited range of treatment start dates did not allow a detailed analysis of effect of age at treatment on growth even though the staring age is predicted to provide a substantial impact on growth.

A third limitation of our study is that the data collected was from patients from one ethnic background. While this data allows for an accurate tool to track the progression of the disease and any treatments given to Japanese patients, it may not accurately reflect the growth in other ethnicities.

Another limitation is that the accuracy of body length measurements might vary due to contractures, an inability to stand erect, and lack of investigator cooperation in performing the measurements that could skew measurements, particularly for younger patients.

It has been reported that combined treatment with ERT and HSCT has an additive effective in reducing GAG concentrations in kidney, heart, and lung in an MPS II mouse model [23]. Six patients in our study had been given ERT for 2.08 ± 0.93 years before HSCT, but ERT continued only for a short time after HSCT. Consequently, we could not determine whether there was any additive effect of prior or overlapping ERT treatment on the growth.

It has been proposed that HSCT provides a limited effect or no impact to improve the clinical features of MPS II, with a high mortality rate (Table 4). Therefore, HSCT should not have been considered as the first treatment option for MPS II. Recent long-term follow-up studies on MPS I, II, III, IVA, VI, and VII patients treated with HSCT allowed the therapeutic efficacy of HSCT to be re-assessed. Recent data indicate that HSCT does show improvement in brain and bone involvement, while conventional ERT did not provide effectiveness in brain and heart valves [18,24,25, personal communications with Dr. Chinen, Dr. Tanaka, Dr. Kato, Dr. Yabe, and Dr. K. Orii]. Results presented in this study also show that HSCT has a positive effect on growth that is indistinguishable from the effect of ERT.

A potential advantage of HSCT for treating MPS II is that marrow-derived donor macrophages can provide a continuous secreting source of enzyme and that these cells can gain access to sites throughout the body where GAGs are stored. The clinical consequence of HSCT relies on 1) the age of the patient at the time of transplantation, 2) the severity of clinical phenotype, 3) the type of donor, and 4) the course of preparative regimen. Tanaka et al. reported long-term efficacy of HSCT on urinary GAG level and improvement/attenuation of CNS and heart involvement for patients with MPS II. They concluded 1) that urinary GAG concentration was remarkably lower in HSCT-treated patients compared to age-matched untreated patients and reduced more compared to ERT-treated patients, and 2) that HSCT showed improvement or stabilization of brain MRI, activity of daily life, and heart valves, compared to ERT-treated patients [18]. Especially, more impact on therapeutic efficacy for CNS involvement was shown to the group of the patients whose clinical signs and symptoms appear after 2 years of age.

Advantages of HSCT over ERT include (Table 4); 1) one time permanent treatment if engraftment is successful, 2) active enzyme secreted from bone marrow can access many tissues including brain, bone, and heart valves, 3) continuous expression of the enzyme during the life-time of the patient, 4) improvement of cognitive function with early treatment, and 5) it is cost-effective (less than the cost of ERT for one year). Disadvantages of HSCT include 1) a chance of mortality during treatment (although the risk has been diminished substantially), 2) age limitation for a severe phenotype of patients with CNS involvement, 3) limited by patient health condition, 4) limited by expertise at medical facility, and 5) requires a rigorous regimen in hospital before and after HSCT for 2–3 months (Table 4). In early studies, the mortality rate of HSCT was approximately 20–25% [26,27]. With advanced techniques and earlier introduction of HSCT, the survival rate after treatment of MPS II improved to 88.5% during the period from 1990 to 2003 [18]. All eighteen patients with MPS treated by HSCT since 2000 have survived (personal communication with Dr. Yabe, Tokai University). Thus, HSCT is much safer than before, although survival rates could still depend upon the institution and expertise of their staff.

Overall, we propose that HSCT should be considered as a therapeutic option for MPS II, depending on a careful consideration of the risk/benefit ratio. Prospective investigation for improvement or attenuation of CNS involvement is required in order to fully evaluate the impact of HSCT compared with ERT.

One of the reasons why the mortality rate of HSCT was high during initial attempts in 1980–1990 is that patients who underwent HSCT were already at an advanced or even a terminal stage of disease progression. It will not always be suitable for patients with advanced stage disease to complete the rigorous regimen of HSCT. However, with the advanced technology and awareness of the disease, early diagnosis is becoming more feasible, and, therefore, patients with MPS II can receive HSCT when their health condition is favorable at an early stage.

Several models of newborn screening (NBS) for MPS are now under development [28–32]. Once NBS is established leading to diagnosis of asymptomatic patients, a tailor-made therapeutic approach for the individual patient with MPS can be devised by a well-trained multi-disciplinary team (Fig. 4). Cell therapy including HSCT and/or ex-vivo gene therapy should be one of the primary choices as a permanent therapy. ERT could also contribute to the short-term care to keep patients in a better condition before and after cell therapy. A careful long-term assessment of HSCT, ERT or combination therapy should be made to determine the ultimate guideline of treatment.

In conclusion, we have evaluated an impact on growth in patients with MPS II treated by ERT and/or HSCT. ERT and HSCT provide a comparable impact on growth, indicating that HSCT can be a recommended option at an early stage in MPS II considering effectiveness towards brain or heart involvement.

Compliance with ethics

The study was approved by the Institutional Review Boards (IRB) at Gifu University and at the Nemours/Alfred I. duPont Hospital for Children.

Conflict of interest

All the authors contributed to the original article and have no conflict of interest with any other party.

Contributions to the project

Pravin Patel has contributed to the planning, data analysis, and reporting of the work described.

Table 4
Advantages and disadvantages of ERT or HSCT for MPS patients.

	ERT	HSCT	References
Advantage	• Low risk of mortality • No need of a donor and can immediately be conducted. • No age limit • Not limited by health condition • Not limited by medical facility	• One time permanent treatment • Secretion of active enzyme to various tissues • Continuous expression: more physiological • Improvement of cognitive function with early treatment • Cost-effective (less than one year the expense of ERT)	• Current study • [17] • [23–25]
Disadvantage	• Continuous life-time treatment • Weekly-based treatment for 4–5 h • Little effect on brain, bone, and heart valves • Short half-life of injected enzyme • High-cost	• A chance of mortality although the risk has been reduced • Rigorous treatment regime for 2–3 months • Age limitation[a] • Limited by health condition • Limited by medical facility	Personal communications • Dr. Chinen for MPS III • Dr. Orii for MPS VII • Dr. Tanaka and Dr. Yabe for MPS II

[a] Impact on CNS involvement for patients with a severe type is limited by age and HSCT is preferred before the signs and symptoms of CNS disease appear. In this context, the age limitation could be applied to patients with a severe form.

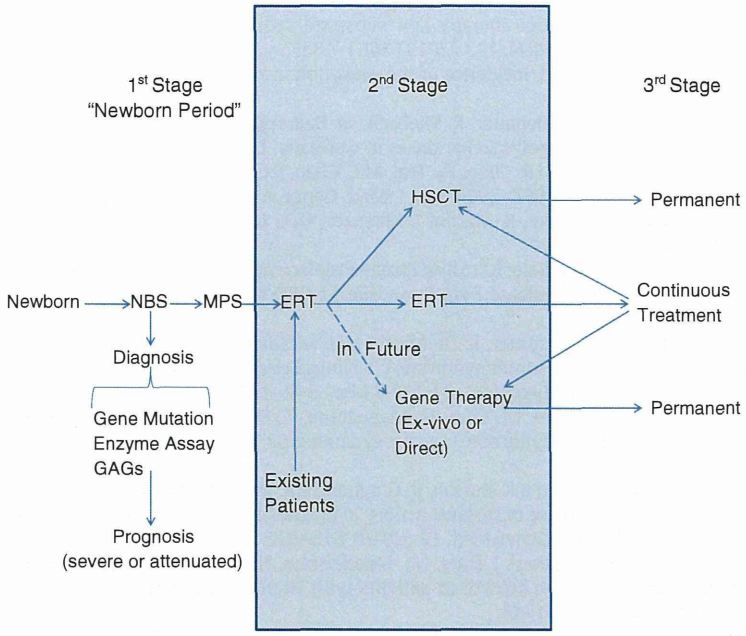

Fig. 4. Model for diagnosis and treatment of patients with MPS II. NBS: newborn screening.

Yasuyuki Suzuki is a Principal Investigator for this project and has contributed to the concept, treatment of patients, planning of the project, informed consent, analysis of data, and reporting of the work described. He and his team conducted the project and followed up on the patients.

Akemi Tanaka has contributed to the treatment of patients, data analysis, and reporting of the work described.

Hiromasa Yabe has contributed to the treatment of patients, data analysis, and reporting of the work described.

Shunichi Kato has contributed to the treatment of patients, data analysis, and reporting of the work described.

Tsutomu Shimada has contributed to the data analysis and reporting of the work described.

Kenji E. Orii has contributed to the treatment of patients and the planning, data analysis, and reporting of the work described.

Toshiyuki Fukao has contributed to the treatment of patients and the planning, data analysis, and reporting of the work described. He and his team conducted the project with Dr. Suzuki.

Tadao Orii has contributed to the planning, data analysis, and reporting of the work described.

Shunji Tomatsu is a Principal Investigator for this project and has contributed to the concept and planning of the project, analysis of data, and reporting of the work described. He and his team conducted the project with Dr. Suzuki.

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Overcoming the barriers to diagnosis of Morquio A syndrome

Kaustuv Bhattacharya[1], Shanti Balasubramaniam[2], Yew Sing Choy[3], Michael Fietz[4], Antony Fu[5], Dong Kyu Jin[6], Ok-Hwa Kim[7], Motomichi Kosuga[8], Young Hee Kwun[6], Anita Inwood[9], Hsiang-Yu Lin[10], Jim McGill[9], Nancy J Mendelsohn[11], Torayuki Okuyama[8], Hasri Samion[12], Adeline Tan[13], Akemi Tanaka[14], Verasak Thamkunanon[15], Teck-Hock Toh[16], Albert D Yang[17] and Shuan-Pei Lin[10*]

Abstract

Background: Morquio A syndrome is an autosomal recessive lysosomal storage disease often resulting in life-threatening complications. Early recognition and proficient diagnosis is imperative to facilitate prompt treatment and prevention of clinical complications.

Methods: Experts in Asia Pacific reviewed medical records focusing on presenting signs and symptoms leading to a diagnosis of Morquio A syndrome.

Results: Eighteen patients (77% female) had a mean (median; min, max) age of 77.1 (42.0; 0.0, 540.0) months at symptom onset, 78.9 (42.0; 4.5, 540.0) months at presentation and 113.8 (60.0; 7.0, 540.0) months at diagnosis. Orthopedic surgeons and pediatricians were most frequently consulted pre-diagnosis while clinical geneticists/metabolic specialists most frequently made the diagnosis. Delayed diagnoses were due to atypical symptoms for 5 patients (28%), while 4 patients (22%) experienced each of subtle symptoms, symptoms commonly associated with other diseases, or false-negative urine glycosaminoglycan analysis. Two patients (11%) each experienced overgrowth within the first year of life. Two patients with Morquio A syndrome (11%) were diagnosed with craniosynostosis and 1 (6%) for each of Legg-Calv-Perthes disease, Leri-Weill syndrome, and pseudoachondroplasia. Early radiographic features of Morquio A syndrome led to more efficient diagnosis.

Conclusions: Increased awareness of clinical symptomology overlapping with Morquio A syndrome is essential. Clinicians encountering patients with certain skeletal dysplasia should consider Morquio A syndrome in their differential diagnosis. Atypical or subtle symptoms should not eliminate Morquio A syndrome from the differential diagnosis, especially for patients who may have non-classical phenotype of Morquio A syndrome.

Keywords: Mucopolysaccharidosis, Morquio A syndrome, Diagnosis, Skeletal dysplasia, Asia Pacific

Background

Morquio syndrome (mucopolysaccharidosis IV, MPS IV) is a rare autosomal recessive lysosomal storage disease that includes Morquio A and Morquio B [1]. Morquio A is characterized by a deficiency of the enzyme N-acetylgalactosamine-6-sulfatase (GALNS) while Morquio B is a distinct disease characterized by a deficiency of beta-galactosidase (GLB1). The reduced GALNS activity of Morquio A results in impaired catabolism of the glycosaminoglycans (GAGs) keratan sulfate (KS) and chondroitin-6-sulfate (CS) in various tissues and organs [2,3], and leads to the multi-systemic manifestations of the disease. Common initial skeletal symptoms of Morquio A include short stature [4,5] and dysostosis multiplex [6] with abnormal gait, genu valgum, pectus carinatum and kyphoscoliosis [7,8]. Kyphosis and pectus carinatum are often present before the first year with gibbus observable before the age of two years in patients with a classical phenotype [9]. In contrast to the joint stiffness observed in other MPS subtypes, joints in Morquio A are typically hypermobile secondary to ligamentous laxity [10]. Mobility is frequently impaired for Morquio A

* Correspondence: zsplin14@gmail.com
[10]Department of Pediatrics, Mackay Memorial Hospital, No. 92, Sec. 2, Zhongshan N. Road, Taipei City 10449, Taiwan
Full list of author information is available at the end of the article