ライソゾーム病マススクリーニングのための検査体制のあり方

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1. はじめに

近年，一部のライソゾーム病に対する酵素補充療法が開発され普及し，いままでに多くの患者の治療成績が積み重ねられ，早期治療がより良い効果をもたらすことが確認された．兄弟例など，発病以前に診断され治療が行われた症例では，特に良い効果が認められている．しかし，早期治療のために早期診断が必要であるものの，ライソゾーム病の早期診断は，経験の多い医師でも難しい．発症前の診断は，家族例以外では不可能である．そこで，新生児マススクリーニングの考えが浮上し，方法の研究が始まり，より正確で簡便，低価格な方法が検討されている．各地でパイロットスタディが行われ，満足できるデータが得られつつあるが，全国普及は足踏み状態と言える．

将来，ライソゾーム病の新生児マススクリーニングを普及させるために，どのような取り組みが必要かを現在酵素補充療法が行われている疾患を中心に考察する．

2. 検査材料と検査方法

検査材料は，現行の新生児マススクリーニングと同じ血液ろ紙を用いることに対する異論はないと思われる．検査方法は，現在は蛍光基質を用いての酵素活性，あるいは特殊な合成基質で質量分析計を用いての酵素活性を測定する方法が主流であり，測定方法や測定機器についての改良，開発が行われている．ムコ多糖症においては，異常代謝産物の検出という方法も研究されているが，対象外疾患のピックアップのリスクが懸念されている．手間やコストおよび方法の欠点については，いずれは解決できるものと考えられる．

3. 対象疾患

新生児マススクリーニングを行うことが勧められる疾患は，効果的な治療法があり，早期（発症前）の治療がより優れた効果を持つものである．現在酵素補充療法が可能である6疾患について，以下に考察する．すでにパイロットスタディが進行しているのは，ポンペ病，ファブリー病，ムコ多糖症I型，II型である．

(1) ゴーシェ病

現在，パイロットスタディが行われている施設はない．ゴーシェ病は，I型，II型，III型と3つの臨床型があり，それぞれで状況は異なる．I型（非神経型）は，貧血，血小板減少，脾腫といった造血器症状と骨壊死などの骨症状がある．前者については，症状が出てから治療を開始しても治癒させることができる．骨症状は重篤にならないうちに治療すれば回復可能である．新生児マススクリーニングが予後を歴然と左右するということは少ないと想像される．造血器症状に神経症状を伴う神経型（II型，III型）について考えると，発症前に酵素補充療法を行ったとしても改善は望めない．酵素投与に加え神経症

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状の発現前にアンブロキソール[1]を投与すれば，緩徐に神経症状が現れるIII型について，良い効果が期待できると推測される．現在，III型に対する医師主導の臨床治験も進められている．スクリーニング陽性者に遺伝子診断を行い，正確に神経型，非神経型の病型診断ができれば，ゴーシェ病の新生児マススクリーニングは大きな意味があると考える．さらに，アンブロキソールがゴーシェ病の治療薬として承認されることが期待される．

(2) ポンペ病

ポンペ病においても早期乳児型から成人型まで幅広い臨床型が存在する．いくつかの施設でスクリーニングのパイロットスタディが行われているが，新生児マススクリーニングが最も奏功するのは早期乳児型である．早期乳児型は，無治療では3か月までに筋力低下と心肥大が起こり，18か月までにほぼ全例が死亡する．台湾ではすでに新生児マススクリーニングが行われており[2]，症状が出る前に酵素補充療法を開始した患者では，ほぼ正常の発達を遂げることができている．これに対し，症状が発現してからの治療では予後の改善は明らかであるものの，人工換気を必要とするなどADLは低い．

他方，遅発型について言えば，例えば成人期になって症状がでる場合に，乳児期からの酵素補充療法が必要であるとは考えにくい．従って，ポンペ病についても陽性者に対し遺伝子診断によって臨床病型を確定できるようにすることが重要である．さらに，日本人においては酵素活性の低下はあるものの病気にはならないpseudodeficiencyと呼ばれる遺伝子多型が高頻度にある[3]．我々の新生児スクリーニングのパイロットスタディからも人口の約3％にpseudodeficiency alleleをホモに持つ人がいることが分かっている[4]．このことからも，陽性者に対する遺伝子解析は必須のものと思われる．

(3) ファブリー病

すでに，多くの施設で新生児スクリーニングのパイロットスタディが行われている[5]．このスクリーニングには2つの意義があると考える．ひとつは，早期診断という本来の意義である．ファブリー病は症状が比較的非特異的であるため，早期の診断が難しい．小児期より症状が認められていたにもかかわらず，多くの患者は20年近くたってから診断されており，診断時にはすでに不可逆的な臓器障害が起こっていることが考えられる．スクリーニングにて早期診断され無症状である小児に対して定期的な健診を行い，酵素補充療法の導入時期を決めなければいけない．もうひとつの意義は，子供の診断がきっかけで親や血縁者の診断・治療に結びつくものである．家系内に多数の患者が見つかることがよくあるため，きちんとした遺伝カウンセリングが求められる．また，ファブリー病のスクリーニングにおいても高頻度のpseudodeficiencyを認めている[5]．

(4) ムコ多糖症Ⅰ型，Ⅱ型，Ⅵ型

現在，新生児マススクリーニングのパイロットスタディが行われているのは，ムコ多糖症Ⅰ型とⅡ型について我々の大阪市立大学と東京都予防医学協会との共同研究によるもののみである．日本における患者頻度は，Ⅱ型が最も多く，次いでⅠ型で，Ⅵ型はまれである．しかし，早期治療が最も奏功すると想像されるのは，脳の障害を伴わないⅥ型である．Ⅰ型，Ⅱ型では，脳障害を伴う重症型と伴わない軽症型がある．いずれにおいても早期の治療がより良い治療効果をもたらす．確定診断されれば，直ちに酵素補充療法を開始することが勧められるが，脳障害を伴う病型に対しては，早期の造血幹細胞移植が勧められる[6]．スクリーニングで酵素診断された乳児に対しては，確定診断のための代謝産物の分析（尿中ムコ多糖）と重症度の判定のための遺伝子診断が必須である．とくに，Ⅱ型においては，ポンペ病と同様にpseudodeficiencyが高頻度に存在する[7]ので注意を要する．

(5) その他のライソゾーム病

米国の一部の州においてクラッベ病の新生児マススクリーニングが行われている．クラッベ病の治療法は早期の造血幹細胞移植しかなく，新生児マススクリーニングには賛否両論がある[8]．

4．検査体制・診療体制のあり方と今後

ライソゾーム病の原因治療ができるようになってからまだ日は浅く，新生児期からの治療がどれほどの予後の改善をもたらすかは明らかではないが，症状が進行する前の治療が望ましいことは言うまでもない．しかしながら，兄弟例の治療経験などから，症状発現前に治療を開始してもゴーシェ病I型を除き，ゆっくりではあるが症状は進行する．すなわち，フェニルケトン尿症や甲状腺機能低下症のような治療結果ではない．さらに，最近ではライソゾーム病の領域における治療法の研究，開発は著しい速さで進んでおり，新しい臨床治験が次々に出てきていることから，症状に即した適切な治療法の選択が求められる．他方，ライソゾーム病の場合，現在のところ代謝産物による疾患のスクリーニングが難しく，酵素活性による方法が中心である．この場合，前述のようなpseudodeficiencyの問題がある．

先天代謝異常症のスクリーニングにおいては，陽性者の確定診断および治療法の選択と治療の導入のそれぞれの段階において専門家の的確な判断を必要とする．ライソゾーム病では特に臨床型の幅が広く，確定診断および発症前の疾患説明，遺伝カウンセリングには，専門的な経験を必要とする．X連鎖性遺伝のファブリー病やムコ多糖症II型では，新生児の診断がきっかけで家族・家系内に患者や保因者の存在が明らかになることから，特に専門的な遺伝カウンセリングが求められる．治療法の選択においても，遺伝子診断を行うことが必須となるため，遺伝カウンセリングは欠かせない．ライソゾーム病の治療は歴史が新しいうえ，必ずしも完治が望めるものではない．さらに，現在普及している酵素補充療法や造血幹細胞移植は，飲み薬や食事療法に比べ負担が大きい．そのうえ，同じ疾患でも病状により異なる治療法が選択されることもあるし，すぐに治療を始めないこともある．陽性者への満足で適切な説明のためには，ある程度以上の治療経験が必要である．

検査方法や治療方法の発展に伴い，ライソゾーム病の新生児マススクリーニングは実現の方向に向かっていくと想像される．ライソゾーム病の新生児マススクリーニングが始められる時には，いくつかの専門病院を拠点病院として，確定診断，遺伝カウンセリング，定期的なフォローアップ検査を行う体制の整備が必要であろう．先天代謝異常症はそれぞれの疾患が希少難病であることから，先天代謝異常学会は患者の登録体制を整備しようと始めている．マススクリーニング学会とも相まって，スクリーニングで診断された患者の登録も充実していくべきと考える．

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Letter to the Editor

The complete type of pachydermoperiostosis: A novel nonsense mutation p.E141* of the *SLCO2A1* gene

Pachydermoperiostosis (PDP), or primary hypertrophic osteoarthropathy (PHO: MIM: 167100), is a rare genetic disease affecting both skin and bones. The major diagnostic criteria include finger clubbing, periostosis, pachydermia, and cutis verticis gyrata (CVG). Additional symptoms, including sebaceous hyperplasia, hyperhidrosis, and arthropathy have been reported [1,2].

A homozygous mutation in *HPGD*, which encodes 15-hydroxyprostaglandin dehydrogenase (15-PGDH), leads to PHO and PDP [3]. However, PHO and PDP are genetically heterogeneous. Whole exome analysis of PDP in Japanese, Chinese, Caucasian, and other populations has revealed homozygous mutations in the solute carrier organic anion transporter family member 2A1 (*SLCO2A1*) gene, encoding prostaglandin transporter (PGT) [4–6]. Increased tissue levels of prostaglandin E2 (PGE2) resulting from defective degradation contribute to the pathogenesis of PHO and PDP. A genetic defect in either *SLCO2A1* or *HPGD* can cause PHO and PDP. These observations enabled us to categorize the disease into two types: (1) PHOAR1, MIM: 259100, caused by *HPGD* deficiency, and (2) PHOAR2, MIM: 614441, caused by *SLCO2A1* deficiency. Whereas the male to female ratio is approximately 1 for PHOAR1, no female patients have presented with the typical skin and bone manifestations of PHOAR2 [7]. We previously reported a female *SLCO2A1*-deficient PDP patient with minimal pachydermia [8].

We herein report four cases of complete type of pachydermoperiostosis carrying five different *SLCO2A1* mutations including a novel mutation.

PDP was diagnosed according to established clinical and radiological criteria [1]. Individuals participating in the study provided written informed consent. This study was approved by the ethics committee of the National Center for Child Health and Development and Keio University School of Medicine. Serum and urinary levels of PGE2 were measured as described elsewhere [4]. Isolation of genomic DNA, amplification, sequencing, and screening for mutations of the *SLCO2A1* and *HPGD* genes have been described elsewhere [4].

We screened four PDP patients for *SLCO2A1* and *HPGD* mutations. Clinical features, gene mutations, and serum and urine levels of PGE2 are summarized in Table 1. The study population comprised of only men (age range, 19–25 years). No participant had a family history of PDP, and all had non-consanguineous parents. Their medical histories have been provided in the Supplementary data.

All four patients were compound heterozygous for *SLCO2A1* mutations (Table 1). We identified five different mutations, of which c.421G>T/p.E141* was novel (Fig. 1, and Supplementary Fig. 3). No *HPGD* mutation was found.

Table 1
Summary of clinical phenotype, *SLCO2A1* mutations, and PGE2.

Case	P1	P2	P3	P4
Current age (years)	19	21	20	20
Onset age (years)	15	16	14	14
Gender	M	M	M	M
Clinical subtype	Complete	Complete	Complete	Complete
HPGD	ND	ND	ND	ND
SLCO2A1 allele 1	c.940+1 G>A p.R288Gfs*7	c.1807C>T p.R603*	c.940+1 G>A p.R288Gfs*7	c.940+1 G>A p.R288Gfs*7
SLCO2A1 allele 2	c.1279_1290del12 p.E427_P430del	c.754C>T p.R252*	c.421G>T p.E141*	c.1807C>T p.R603*
Serum PGE2 (pg/ml)[a]	337	127	256	NA
Urinary PGE2 (pg/ml)	264	895	3688	NA
Triad				
Digital clubbing	+	+	+	+
Periostosis	+	+	+	+
Pachydermia	+	+	+	+
Cutis verticis gyrata	+	+	+	+
Skin				
Palmar and plantar hyperhidrosis	+	+	+	–
Acne	+	+	+	+
Seborhoea and eczema	+	–	+	+
Skeletal				
History of bone fractures	–	–	+	–
Swelling of large joints	+	+	+	+
Painful joints on exercise	–	+	–	+
Hydrarthrosis	+	+	+	+

All patients except for P4 had no history of peptic ulcers and anemia. M: male, ND: (tested but) not detected, NA: not available, +: positive, –: negative or unknown.
[a] normal range: 25–200 pg/ml.

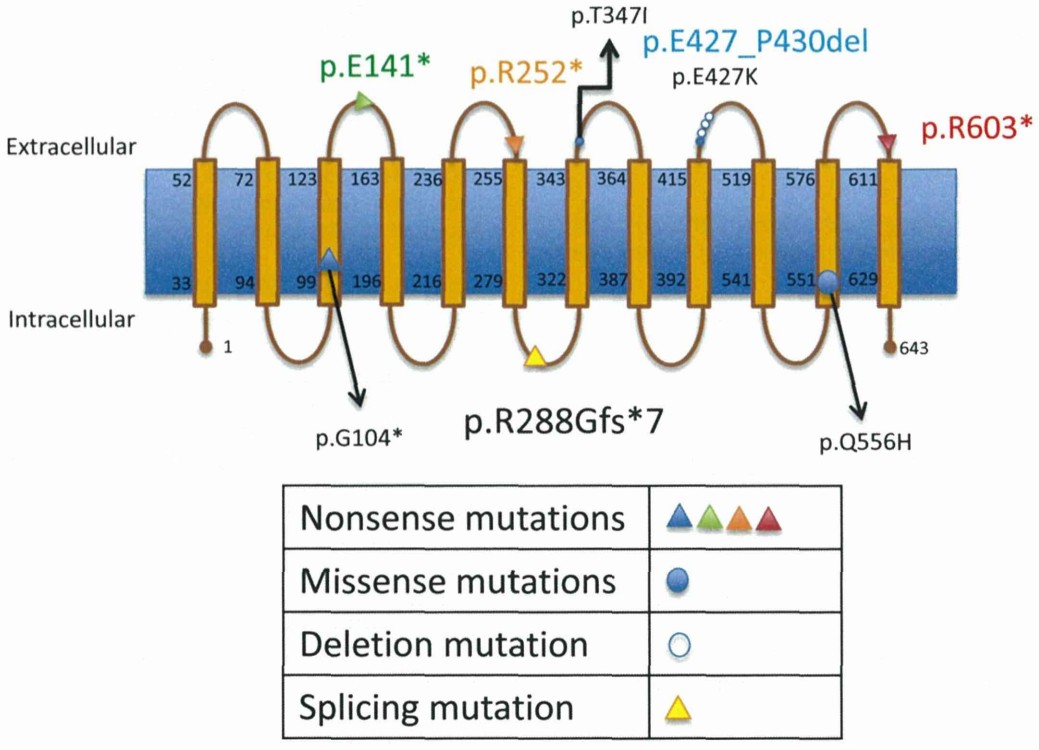

Fig. 1. Schematic representation of the prostaglandin transporter protein. The positions of the mutations of the *SLCO2A1* gene in Japanese patients with pachydermoperiostosis are depicted [4,8]. The green arrowhead indicates the position of the novel nonsense mutation p.E141* in this study.

SLCO2A1 mutation screening of Patient (P) 1 revealed compound heterozygous mutations c.940 + 1 G > A and c.1279_1290del12; the heterozygous mutation c.940 + 1 G > A was located in the splice donor site of intron 7, which resulted in the loss of exon 7 and a truncation of PGT [4]. The heterozygous c.1279_1290del12 mutation in exon 9 resulted in the deletion of four amino acids at positions 427–430 (p.427_430del). The proband's mother was heterozygous for c.1279_1290del12 (Supplementary Fig. 1F).

P2 was compound heterozygous for c.1807C > T in exon 13, and c.754C > T in exon 6 introduced a stop codon at position 603 (p.R603*) and 252 (p.R252*), respectively [8,9]. The proband's family was not available (Supplementary Fig. 2E).

P3 was compound heterozygous for c.940 + 1 G > A and c.421G > T; the heterozygous mutation c.421G > T in exon 4 introduced a stop codon at position 141 (p.E141*). This mutation probably decreases PGT function. The proband's mother was heterozygous for c.940 + 1 G > A (Supplementary Fig. 3E).

P4 was compound heterozygous for c.940 + 1 G > A and c.754C > T as found in P1 and P2. The proband's family was not available (Supplementary Fig. 4E).

It is unlikely that the serum level of PGE2 is useful for differential diagnosis of the disease, as the serum level of P2 was within normal limits. By contrast, the urinary level of PGE2 appeared to be associated with the disease, but we did not correct the measurement value by the urinary concentration of creatinine, which was not available in this study (Table 1).

We diagnosed P1 as complete PDP because of the CVG. The *SLCO2A1* mutations (c.940 + 1 G > A and c.1279_1290del12) were identical to those of P1 in our previous report (Sasaki's P1) [4]. Magnetic resonance imaging (MRI) showed vertex scalp folds in Sasaki's P1, indicating CVG (unpublished observation). We thus diagnosed a conversion from the incomplete type to the complete type. This relatively mild phenotype of CVG observed in these two patients can be explained by assuming that the four-amino-acid deletion mutant protein p.E427_P430del has partial PGT activity as discussed in our previous report [4]. Seifert et al. [9] observed that patients with homozygous *SLCO2A1* mutations developed manifestations of PHO later than patients with *HPGD* mutations. Similar to PDP, symptoms began with clubbing of the distal phalanges during puberty, followed by pachydermia shortly after puberty. However, patients with homozygous *SLCO2A1* mutations showed more arthritis, joint involvement, and pachydermia than those with homozygous or compound heterozygous *HPGD* mutations. In this regard, clinical diagnosis of the type of PDP should be tentative in early childhood. Based on the *SLCO2A1* gene mutations in Japanese patients found in this study, the diagnosis may change after puberty, as seen in P1.

Except for P1, who had an atypical phenotype, three of four patients in the present study carried the *SLCO2A1* mutation, which resulted in a premature stop codon (p.R603*; p.R252*; p.E141*). Quantitative PCR revealed a significant reduction of the *SLCO2A1* mRNA level in cultured fibroblasts obtained from the patient carrying the mutation p.R252*, suggesting nonsense-mediated decay [9]. It has not been reported whether the novel mutation p.E141* and the recently discovered mutation p.R603* affect the *SLCO2A1* mRNA level. Further analyses are necessary whether these mutations introduce a truncation or deficiency of PGT leading to more severe phenotypes of PDP.

In conclusion, we found five different *SLCO2A1* mutations including a new mutation p.E141* in the complete type of pachydermoperiostosis.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jdermsci.2014.05.008.

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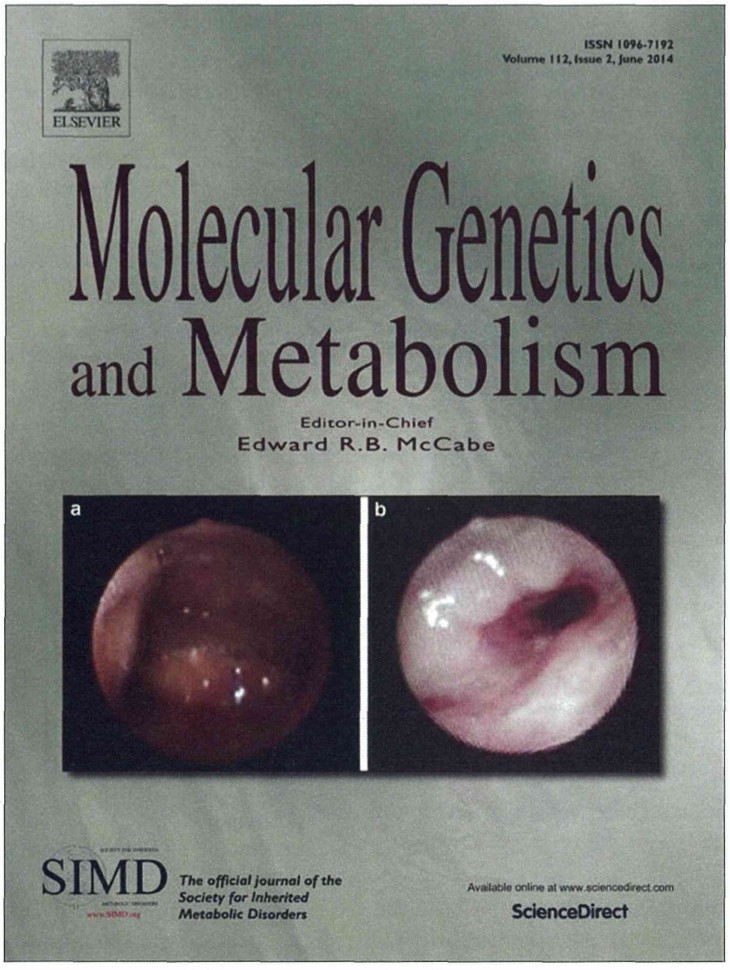
Letter to the Editor

The natural trait of the curvature of human hair is correlated with bending of the hair follicle and hair bulb by a structural disparity in the root sheath

The shape of human hair is one of the most distinguishable characteristics among various populations and commonly classified according to geographic regions and ethnic differences. Two hypotheses have been proposed as key determinants of human hair shape based on morphological features. One proposes that hair shape is determined solely by the shape of the hair follicle (HF) [1], straight hair being generated from straight cylindrical HFs whereas highly curled hair is produced by curved HFs. The second hypothesis proposes that hair shape is programmed by the hair bulb (HB) based on results from organ culture, suggesting that an asymmetric differentiation and proliferation of each follicular layer beginning in the HB and mechanical stress on the concave side of the HB are closely related to the formation of hair shape [2].



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CT and endoscopic evaluation of larynx and trachea in mucopolysaccharidoses

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ABSTRACT

Background: Mucopolysaccharidoses (MPSs) are lysosomal storage disorders caused by lysosomal enzyme deficiencies that result in systemic accumulation of glycosaminoglycans (GAGs). Accumulation of GAGs in the upper airway can lead to respiratory failure. The aim of this study was to investigate changes of the airway by flexible endoscopy and CT.

Methods: Thirty-five patients aging from 2 to 16 years (mean: 9.2 ± 4.4 years) participated in this study. The majority had MPS I (n = 5) or MPS II (n = 25). The shape of the trachea and the cross-sectional trachea surface area (TSA) was determined at the Th1 and Th2 levels. Airway obstruction was evaluated from endoscopic findings and classified into 3 grades (Grades 0, 1, and 2). Forty-five patients in the control group who underwent tracheal CT for other conditions were retrospectively selected from the database.

Results: Tracheal morphology was abnormal in 50–60%, which showed a transversely collapsing narrow trachea. Tracheal deformity was severe in MPS II and MPS IV. The mean TSA of the MPS patients was 55.5 ± 29.0 mm^2 at Th1 and 61.4 ± 29.0 mm^2 at Th2, while that of the control group was 90.1 ± 41.9 mm^2 and 87.9 ± 39.3 mm^2, respectively. Respiratory distress was noted in 15 of the 35 patients, among whom 7 patients showed tracheal deformity and 7 patients had laryngeal redundancy. Three patients had no abnormalities of the larynx or trachea, so other factors such as pharyngeal stenosis or lower airway stenosis might have contributed to their respiratory distress.

Conclusion: CT and flexible endoscopy allow quantitative and morphological evaluation of airway narrowing, which is beneficial for airway management in MPS children.

1. Introduction

Mucopolysaccharidoses (MPSs) are lysosomal storage disorders caused by lysosomal enzyme deficiencies that result in the accumulation of glycosaminoglycans (GAGs) in various organs and tissues. Infiltration of GAGs into the oropharynx, joints, and connective tissues can lead to significant upper airway abnormalities, which increase the risk of anesthesia and can cause respiratory distress [1]. Narrowing of the upper airway occurs due to enlargement of the tongue and adenotonsillar hypertrophy, while MPS patients also develop a short immobile neck, thickening of the supraglottic region, and diffuse thickening of the tracheobronchial tree. In addition, respiratory distress is exacerbated by thoracic cage deformity and tracheobronchial abnormalities due to GAG deposition in the soft tissues [2,3]. It was reported that 25% of children with MPS have anatomical airway abnormalities which lead to difficulty with intubation [4]. In some cases, tracheal narrowing has been attributed to complications of endotracheal intubation or tracheotomy and there have also been many reports of sleep-disordered breathing or difficulty with anesthesia. Respiratory distress due to upper airway obstruction and tracheal stenosis is a severe problem that can result in death.

Thus, evaluation of the airway is of primary importance in children with MPS, especially before general anesthesia. Ingelmo demonstrated that performing MDCT of the airways with 3D reconstruction is useful for preoperative evaluation and planning of airway management in MPS patients [5]. However, this method is time-consuming and requires considerable expertise, so it is not suitable for airway screening at all institutions. On the other hand, flexible endoscopy can provide useful information about upper airway problems and is a safe and effective screening method for both preoperative and postoperative uses [6].

The aim of the present study was to investigate changes of the respiratory tract in children with MPS by helical CT and flexible endoscopy.

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This study represents the first multidisciplinary assessment of both the trachea and the larynx in children with MPS.

2. Materials and methods

2.1. Patients

Thirty-five MPS patients were enrolled in this study. They were aged 2–16 years (mean age: 9.2 ± 4.4 years), their mean height was 117.4 ± 19.1 cm, and their mean BMI was 19.4 ± 3.5. They included 5 patients with Hurler syndrome (MPS I), 25 patients with Hunter syndrome (MPS II), 2 patients with Sanfilippo syndrome (MPS III), 2 patients with Morquio syndrome (MPS IV), and 1 patient with Maroteaux–Lamy syndrome (MPS VI). Patients with prior tracheotomy or congenital thoracic anomalies were excluded. All of the children with MPS I, II, and IV were evaluated prior to initiation of enzyme replacement therapy or BMT.

Forty-five of the control group were retrospectively selected from a database of patients who underwent upper and lower airway CTs for possible pulmonary metastases or other conditions, and they were matched for age (mean age: 8.2 ± 4.5 years; range: 2–15 years) and stature (mean height: 124.0 ± 26.4 cm). Endoscopic evaluation and sleep studies were not performed in the control subjects.

2.2. Tracheal CT

Helical CT was performed by using a high speed CT scanner without contrast enhancement (GE, Discovery 750HD) for both groups. Contiguous 5-mm slices were obtained with the subject in the supine position. Images were obtained during breath holding in expiration as far as possible. The duration of image acquisition from neck to chest was 3 s, which meant that a stable respiratory phase could be maintained.

Tracheal morphology was evaluated at the Th1 and Th2 levels, and was classified into the following 4 categories [7,8]: D-shaped (the transverse diameter is larger than the anteroposterior diameter due to collapse in the latter direction), W-shaped (an elliptical trachea with a larger anteroposterior diameter than transverse diameter due to transverse collapse), O-shaped (slight deformity with a small posterior membranous region), and normal (C-shaped with equal transverse and anteroposterior diameters) (Fig. 1). Single images obtained at the Th1 level and Th2 level were approximated with the mediastinal window in both MPS patients and controls [2], and then the selected images were digitized. Each image was traced twice using an Advantage workstation (GE, Tokyo), and the tracheal cross-sectional surface area (TSA) was calculated at the Th1 and Th2 levels.

2.3. Endoscopic evaluation

The MPS patients underwent endoscopic examination (Pentax, Tokyo, Japan) during spontaneous ventilation and images were captured with a video monitor. The airway was assessed at the level of the epiglottis, the cricoid, and the subglottic region, and findings were graded as follows (Table 1). Grade 0 was a normal airway. Grade 1 meant edema and swelling of the epiglottis or cricoid without redundant mucosa. The false vocal cords showed edema and hypertrophy, partly obscuring the true vocal cords. Grade 2 meant that the redundant mucosa of the epiglottis and cricoid caused inspiratory obstruction, while the true vocal cords were obscured due to hypertrophy of the false cords.

2.3.1. Sleep study

All MPS patients underwent overnight pulse oximetry as a screening test and polysomnography (PSG) was performed as part of the preoperative workup in some patients. Obstructive sleep apnea (OSAS) was

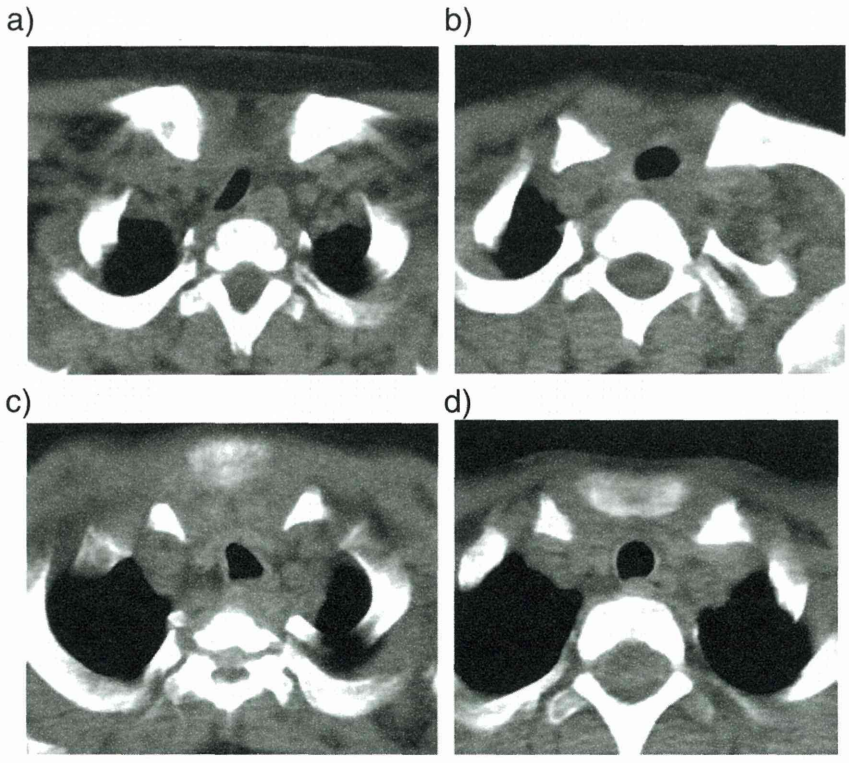

Fig. 1. Morphological change at Th2 level of the trachea. a) W type shows transverse collapse. b) D type shows antero-posterior collapse. c) O type shows deformed trachea slightly. d) Normal trachea.