Table 4 The percentages of institutes that had criteria for each disorder.

Abnormal ganglia	
IG	46/69 (67%)
HG	
Congenital HG	55/69 (80%)
Acquired HG	19/69 (28%)
IND	34/69 (49%)
Normal ganglia	
MMIHS	47/69 (68%)
SD	42/69 (61%)
IASA	21/69 (30%)
CIIP	57/69 (83%)

CIIP = chronic idiopathic intestinal pseudo-obstruction; HG = hypoganglionosis; IASA = internal anal sphincter achalasia; IG = immaturity of ganglia; IND = intestinal neuronal dysplasia; MMIHS = megacystis microcolon intestinal hypoperistalsis syndrome; SD = segmental dilatation.

46/57 (81%); abnormality of urinary tract, 13/57 (23%); dilatation of intestine in radiography 9/57, (16%); positive rectospincteric reflex, 8/57 (14%); intermittent or recurrent symptoms, 6/57 (11%); and normal AchE staining, 6/57 (11%). For the diagnosis of IG, immunohistochemical studies using Bcl-2 antibody were performed and shown to be effective in a few institutes (Figure 3).

The survival rates of each entity for which the follow-up data were available are shown in Table 5. Three entities, congenital HG, MMIHS, and CIIP, showed poor survival rate, compared with those of the other five entities. These three entities required long-term nutritional support, including parenteral and enteral nutrition (Table 6). In particular, outcome is extremely poor in MMIHS.

4. Discussion

Almost all Japanese cases (~ 98%) of ADHD in 10 years were collected in this nationwide survey. However, the number of cases in each institute was very small, and actually more than half of the institutes (53 institutes) had three cases or fewer. Therefore nation-wide survey is considered to be important.

Okamoto and Toyosaka[5] published a multicenter study of ADHD in the Japanese literature in 1994. They classified ADHD into two categories based on pathology: (1) abnormal histology including IG, HG, hypogenesis, and IND; and (2) normal histology, including CIIP[6] and MMIHS. We followed the classification of Okamoto and Toyosaka[5] in order to compare our results to those of their survey. In addition to Okamoto and Toyosaka's[5] classification, SD and IASA are included in this study, referring to the literature.[1,3]

The presence of immaturity and HG was confirmed and published by Taguchi et al.[7] We proposed there were two types of HG, namely congenital and acquired.[7] *Hypogenesis* is considered to be the initial histological finding of congenital HG at neonatal period. *The 4th International Symposium on Hirschsprung's disease and related neurocristopathies* discussed that diagnosis of HG was difficult and the presence of HG was questionable.[8] However, our

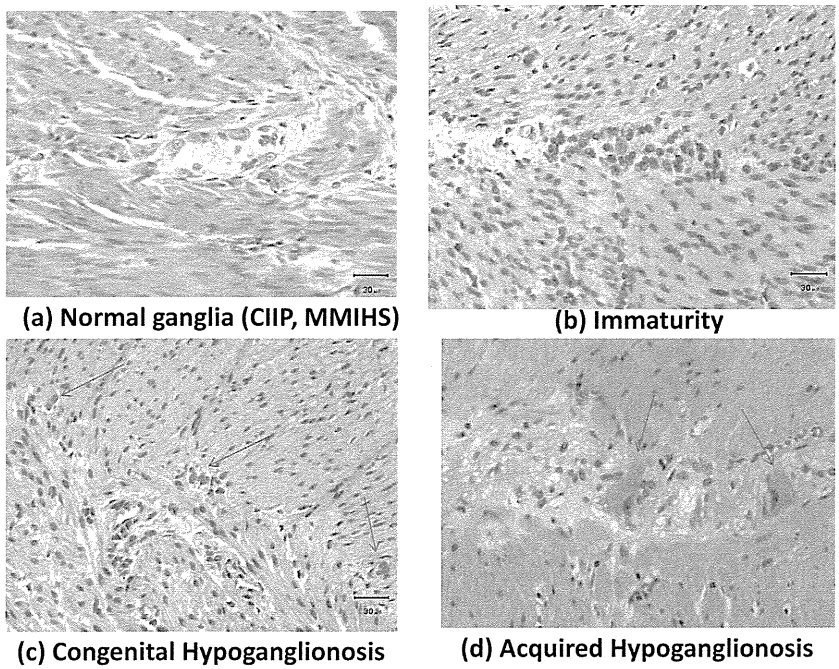

Figure 2 Typical pathology of allied disorders of Hirschsprung's disease (ADHD) in hematoxylin–eosin staining. (A) Normal ganglia (megacystis microcolon intestinal hypoperistalsis syndrome, MMIHS; chronic idiopathic intestinal pseudo-obstruction, CIIP; segmental dilatation). (B) Immaturity of ganglia. (C) Congenital hypoganglionosis. Arrows indicate small ganglion cells. (D) Acquired hypoganglionosis. Arrows indicate degenerated ganglion cells.

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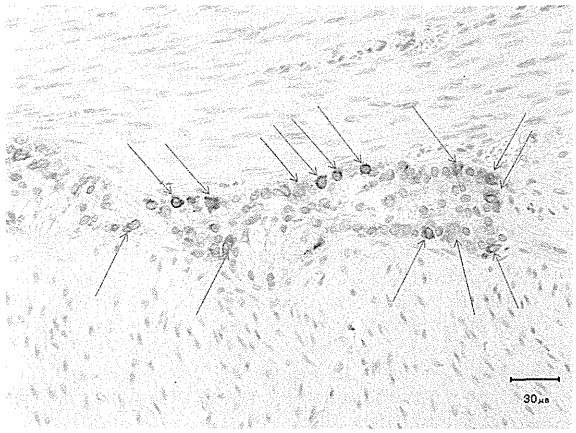

Figure 3 Bcl-2 immunostaining for immaturity of ganglia (2-day-old boy). Mature ganglion cells (blue arrows) show weekly positive, while immature ganglion cells (red arrows) show strongly positive in Bcl-2 immunostaining. Glial cells are not stained. Therefore, this staining is considered to be able to distinguish mature ganglion cells, immature ganglion cells, and glial cells.

study shows that two types of HG do exist and congenital HG is one of the two main disorders of ADHD in Japan.

The 4th International Symposium on Hirschsprung's disease and related neurocristopathies discussed IND and reported as follows[8]: (1) almost all the participants believe that IND does exist; (2) some believe in presently defined diagnostic criteria, whereas others suggest that these diagnostic criteria are not reliable enough; and (3) some participants question if IND is a truly separate entity or an acquired secondary phenomenon related to long-standing constipation or chronic obstruction. Therefore, we decided to include IND as one of ADHD.

The concept of chronic intestinal pseudo-obstruction (CIPO) including myopathy, neuropathy, collagenopathy (desmosis or fibrosis), and idiopathic.[9] Some CIPO patients are reported to be adult onset.[10] However, most myopathy and neuropathy types of CIPO cannot be diagnosed by conventional HE and AChE staining. Furthermore, abnormalities of Cajal cells shown by c-kit immunostaining were reported in some cases of CIIP.[11] Therefore, so far, we decided to treat CIIP as a disorder that shows recurrent or persistent functional intestinal obstruction with normal histology by conventional staining by HE and AchE. Because the diagnosis of Hirschsprung's disease is generally obtained by HE and AchE staining in the most institutes of Japan, the criteria of ADHD are recommended to be based on the conventional histology so far. MMIHS has been considered to be the severe form of CIIP. However, MMIHS can be distinguished from CIIP by clinical characteristics.[12,13]

The entity of SD was proposed by Swenson and Rathauser in 1959.[14] The symptoms and signs of SD, especially sigmoid type of SD, resemble those of Hirschsprung's disease. Therefore, SD is included in ADHD in this study.

The entity of IASA has been considered to be synonymous of ultrashort-segment aganglionosis, which shows normal AchE staining but lacks rectoanal reflex.[15] This entity was discussed in *The 4th International Symposium on Hirschsprung's disease and related neurocristopathies* and was reported to exist.[8] Therefore, we decided that IASA is included in ADHD.

The numbers of cases in each disorder are summarized and compared with Okamoto and Toyosaka's[5] study in Table 2. The distributions of each disorder are similar in these two studies. The numbers of patients as well as the answer rates of criteria were very small in acquired HG and IASA. The rarity of disease is considered to make criteria difficult.

For definitive pathological diagnosis of ADHD, immnunohistochemical staining has been reported to be useful using neuronal and muscular markers, such as: Bcl-2 for immature neurons; CD56 for the size of enteric ganglia; synaptophysin for neuromuscular innervation: S-100 protein for Schwann cells; c-kit for interstitial cells of Cajal; and smooth muscle actin for myopathy.[16] The diagnosis of IG was easily obtained in several of our cases using Bcl-2 immunostaining (Figure 2).

In conclusion, almost all Japanese cases of ADHD for 10 years were collected in this study. Congenital HG and CIIP showed relatively high incidence, whereas acquired HG and IASA were extremely rare. Criteria of each institute were consisted with clinical signs, symptoms, and conventional histological examinations including AchE staining. Congenital HG, MMIHS, and CIIP showed poor survival rate. Further collection of precise data of each case is required to make guidelines for criteria and treatment strategies for ADHD.

Table 5 Survival rate of allied disorders of Hirschsprung's disease.

Abnormal ganglia	**Survival rate**
IG	28/28 (100%)
HG	
Congenital HG	70/90 (78%)
Acquired HG	8/8 (100%)
IND	11/11 (100%)
Normal ganglia	
MMIHS	10/19 (53%)
SD	27/27 (100%)
IASA	3/3 (100%)
CIIP	50/56 (89%)

CIIP = chronic idiopathic intestinal pseudo-obstruction; HG = hypoganglionosis; IASA = internal anal sphincter achalasia; IG = immaturity of ganglia; IND = intestinal neuronal dysplasia; MMIHS = megacystis microcolon intestinal hypoperistalsis syndrome; SD = segmental dilatation.

Table 6 Dietary status of three poor entities.

	Survival rate	Normal diet in survivors	Normal diet in all cases
Congenital HG	70/90 (78%)	42/69 (60%)	42/89 (48%)
CIIP	50/56 (89%)	13/50 (26%)	13/56 (23%)
MMIHS	10/19 (53%)	1/10 (10%)	1/19 (5%)

CIIP = chronic idiopathic intestinal pseudo-obstruction; HG = hypoganglionosis; MMIHS = megacystis microcolon intestinal hypoperistalsis syndrome.

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特集　周産期救急の初期対応：そのポイントとピットフォール　胎児・新生児編

新生児編　疾患：いかに的確に対応するか

出生前診断された仙尾部奇形腫に対する治療戦略

宗崎 良太*,**　木下 義晶*　永田 公二*　橋爪　誠**　田口 智章*

はじめに

仙尾部奇形腫(Sacrococcygeal teratoma：SCT)は，40,000出生に1例の割合で発生するといわれている[1]。尾骨の先端にある多分化能を有する細胞(Hensen's node)より，発生すると考えられている。その形態による分類であるAltman分類が広く用いられており，殿部より外方へ突出する形態を示すAltman Ⅰ型から，完全に骨盤腔内しか存在しないAltmanⅣ型まで四つに分類されている(図1)[2]。クラリーノ3徴(直腸肛門奇形，仙骨奇形，仙骨前腫瘤)のように合併奇形を伴うこともあるものの，その頻度は低い[3,4]。

近年，胎児超音波検査・胎児MRI検査の発達に伴い，出生前診断される症例が増えている。そのような出生前診断される巨大なSCT，とりわけ充実性腫瘤においては，腫瘍が急速に増大し，高心拍出性の心不全から胎児水腫に至る症例が存在することが知られている。また，母体内または分娩時に被膜破綻により，腫瘍外への出血を起こし出血性ショックをひき起こすものもある(図2)[7]。また，摘出手術の際も，腫瘍からの出血コントロールが困難となる症例もあり，術前にAltman分類や充実性であるかどうかなどにより，適切な手術術式を選択する必要がある。

今回，出生前診断されたSCTについて，当科における治療方針について述べる。

そうざき りょうた，きのした よしあき，ながた こうじ，はしづめ まこと，たぐち ともあき
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出生前

Usuiら[5]が，我が国の出生前診断されたSCTについて報告しているが，近年，その症例数は増加している。出生前診断されたSCTの妊娠管理の考え方については，以前は，極力妊娠を継続し胎児の成熟に努めるべきで，早期娩出，早期治療の適応はないと考えられていた。しかしUsuiらの報告では，我が国では，出生週数が妊娠28週未満の症例においては死亡率が60%，28～31週は38.5%，32～36週は11.1%，37週以降は0%あった。この結果から我々は，妊娠28週以降に出生した症例の予後は比較的良好で，32週以降は死亡率がさらに下がっていたことから考えると，心不全徴候や胎児水腫の徴候が認められる可能性の高い，充実性で腫瘍径の大きい，riskの高い症例においては，心不全徴候，腫瘍出血などの徴候を認めた場合，妊娠28週以降は積極的に娩出へ向かうのがよいと考えている。

このUsuiらの研究を基に発表された，厚生労働科学研究費補助金 難治性疾患克服研究事業の一つとして行われた胎児仙尾部奇形腫の実態把握・治療指針作成に関する研究においての胎児仙尾部奇形治療指針のフローチャートをご紹介する(図3)[6]。また，娩出方法であるが，経腟娩出では娩出の際に腫瘍により分娩停止となるものや，被膜が破綻し出血するリスクがあり，当科では帝王切開で分娩している。実際，Usuiらのデータによると，80%以上の症例が帝王切開で娩出されている。

出生後

出生後搬送が必要な場合は，皮膚をかぶってい

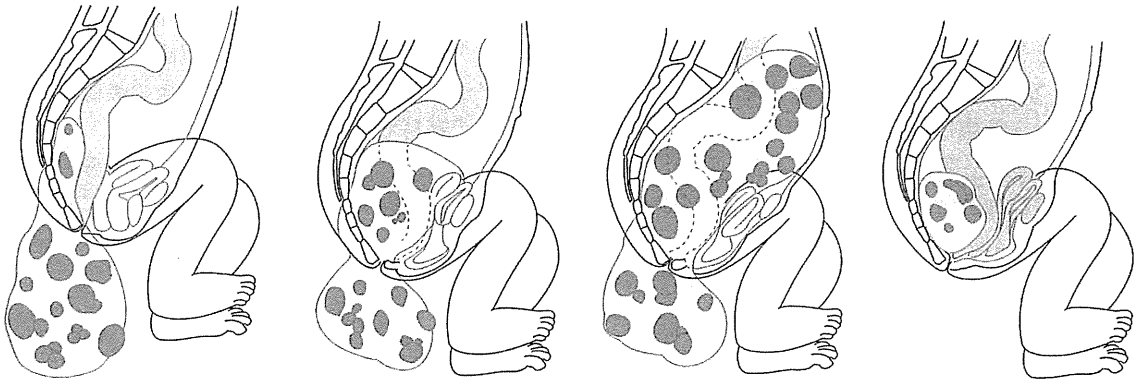

図1　Altman分類（Altmanら，1974より引用一部改変）[2]
TypeⅠ：腫瘍の大部分が骨盤外成分，TypeⅡ：骨盤腔内への進展を伴うものの骨盤外成分のほうが大きいもの，TypeⅢ：骨盤内・腹腔内成分のほうが大きいもの，TypeⅣ：骨盤内・腹腔内成分のみで骨盤外の発育を認めない

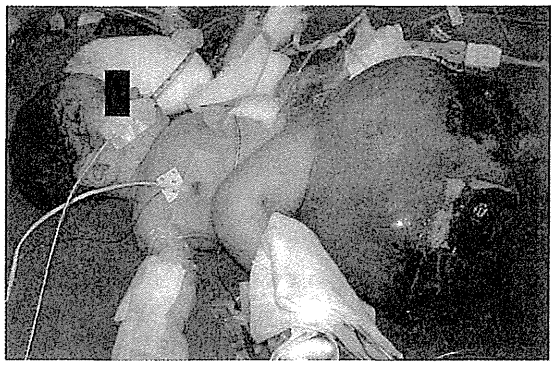

図2　被膜破綻を認めた巨大な充実性仙尾部奇形腫（宗崎ら，2007）[7]

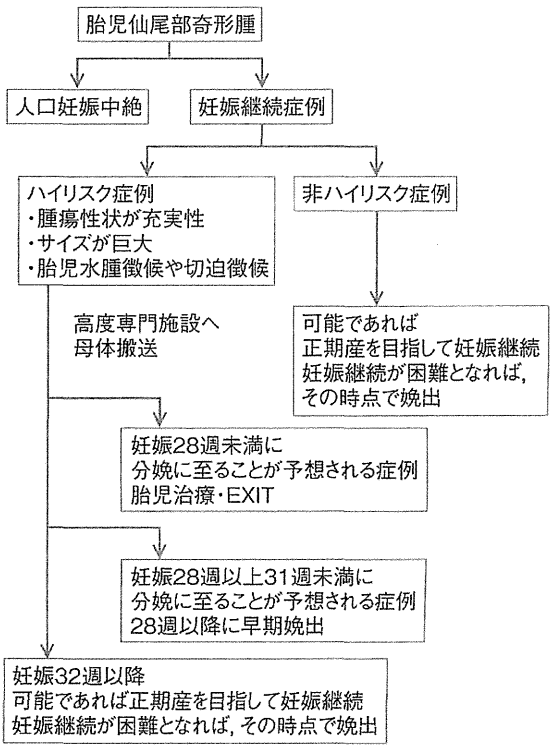

図3　胎児診断されたSCTの治療フローチャート（厚生労働科学研究費補助金難治性疾患克服事業，2012より引用一部改変）[6]

ない腫瘤の際は，低体温や脱水を防ぐために被覆が必須と思われる。腫瘍を乾燥ガーゼで覆い，さらに全身をアルミホイルで覆い，クベースに収容し体温保持に努めつつ搬送する。腫瘤を覆う際に生食ガーゼを用いると低体温を悪化させる可能性があり，乾燥ガーゼのほうがよいものと思われる。出生時にすでに被膜破綻および出血を認めた症例は，タコシール®やネオベール®とボルヒール®を散布し十分止血を行ってから搬送する必要がある。ただ，通常はAltman Ⅰ型であっても腫瘍が皮膚をかぶっていることも多く，そのような皮膚に覆われた症例では，搬送の必要がなければ，我々は余計な被覆は行っていない。重要な点としては出生後に腫瘍内に出血や溶血を起こし，腫瘍が急速に増大，凝固障害や播種性血管内凝固（DIC）が急速に進行する症例がある。そのため，被膜破綻がなくとも，腫瘍サイズの変化には十分注意して

管理を行い，増大傾向を認めた場合は，迅速に切除術を行う必要がある。

また，SCTに対する画像診断であるが，SCTは充実性から嚢胞性までさまざまな形態をとるが，SCTを嚢胞性，嚢胞優位，充実優位，充実性の四つに分類した場合，その頻度は，それぞれ，26.7%，36.0%，29.1%，8.1%と嚢胞成分が多い形態を示すものが多いと報告している[5]。また，Altman分類についても，Ⅰ型が57.1%と最も多く，Ⅱ型31.0%，Ⅲ型5.9%，Ⅳ型5.9%という頻度であった[5]。このことから，出生前診断されるSCTは体外へ突出する嚢胞性腫瘤の形態をとるものが多いといえる。

そのような形態から，SCTの鑑別診断としては，髄膜瘤，リンパ管腫，血管腫，骨盤部神経芽腫などが上がると考えられるが，SCTは尾骨先端から発生するため，腫瘍と尾骨は必ず接している。また，脊髄髄膜瘤は二分脊椎などの異常を伴うことが多いため，脊椎の異常がないことや，充実成分があるものについては，脂肪成分の有無や石灰化の有無により鑑別が可能と思われる。また，我々は状況が許す症例では超音波検査に加えて，造影CTやMRI検査を行っている。腫瘍の性状や腹腔内成分の大きさ，石灰化の有無を確認し，仙尾部奇形腫の診断をより確かにすることはもちろんであるが，後述する栄養血管である正中仙骨動脈の有無を確認し，手術術式を決定するためにも極めて有用である。

手術術式

手術については，全身状態として待機可能であれば，前述のように造影CTを撮影した後に手術を行う。手術術式としては，仙骨式アプローチ，腹会陰式アプローチ，腹仙骨式アプローチがある。主に，AltmanⅠ型やⅡ型の腹腔内成分の小さいものに対しては仙骨式アプローチが行われる。腹会陰式アプローチ，腹仙骨式アプローチは，腹腔内成分の大きいAltmanⅡ型，Ⅲ型，Ⅳ型に対して行われる。いずれも下腹部横切開で開腹して，後腹膜を切開し正中仙骨動脈を同定，結紮切離する。その後腫瘤の周囲を剝離した後，殿部の操作に移る。腹会陰式アプローチに比較して，腹仙骨式アプローチは開腹操作を行い閉腹した後にジャックナイフ位として腫瘤を摘出するため手術時間がかかるが，一般的に肛門挙筋の確認，直腸の確認が容易であるといわれている。

我々は，巨大な充実性腫瘤で腹腔内成分の大きいAltmanⅡ型，Ⅲ型，Ⅳ型に対しては，腹会陰式アプローチで行っている。腹会陰式アプローチで行う理由としては，腫瘍の栄養血管は正中仙骨動脈のみではなく内腸骨動脈から分枝するものもあり，文献的には，正中仙骨動脈を結紮した上であらかじめ大動脈や内腸骨動脈をテーピングしておき，切除を行った報告もある。また，我々は，術中腫瘍内の壊死物質の流入によると思われる急激な高K血症をきたした症例も経験している。その際は，大動脈と下大静脈を用手的に圧迫し，可及的に腫瘍を切除し救命し得た[7]。よって当科では，充実性で巨大なものは仰臥位で開腹したまま腫瘍切除を行っている。また，術中に大量出血から心臓マッサージが必要となる症例も多数報告されており，その点でも仰臥位のまま手術が行えることは，大きな利点である。また，会陰式アプローチに比較して仙骨式アプローチのほうが肛門括約筋や直腸の視野が優れている点については，我々は患児の両足も含めて消毒し清潔野とし，視野に応じて両足ごと動かすことで，肛門挙筋や直腸の確認を容易にしている。

特に胎児水腫に陥って緊急で娩出した症例については，組織が非常に脆弱で易出血性のため，出血コントロールは容易ではない。我々は十分な止血と手術時間の短縮のためLigaSure™ Small Jawを用いているが，それでも出血コントロールに難渋するため，前述したように，胎児水腫が完成する前に娩出するかが非常に重要であると考えている。

晩期合併症

また，SCTにおける晩期的な問題点としては，その悪性再発と，排便障害や排尿障害，下肢の運動障害といった合併症の問題がある。Yonedaら[8]が報告しているが，出生前診断された84症例のSCTにおいて，出生直後に切除された標本で卵黄嚢腫瘍であった症例は1例も認めなかった。しか

し，その後，6例が再発し，6例中4例が卵黄嚢腫瘍として再発していたと報告している。また再発時期としては生後16カ月以下で，しかも全摘出できたと考えられた症例においても悪性再発を認めている。このことから，初回手術で全摘できたと考えられた症例においても，再発の有無を考え血清AFPや画像検査による定期的なフォローが必要であると考えられる。

また，排便・排尿障害，下肢の運動障害については，その頻度は，Leeら[9]の報告では，生存したSCT症例の中で排便障害を15%，排尿障害を5%，下肢の運動障害を5%認めたと報告している。よってその発生頻度は意外に高く，生存症例においてもQOLを大きく損なっている。それらの合併症の原因としては，骨盤腔内へ進展する巨大な腫瘍の症例において多いことがいわれているが，今度は巨大な充実性のSCTにおいては，救命することはもちろんであるが，合併症を防ぐことも，重要であると考えられる。

おわりに

胎児期に診断されたSCTの救命においては，その娩出時期はもちろんであるが，腫瘍の性状やAltman分類に基づいた手術術式の決定，術中の予期しない出血への対策などさまざまな要因が影響を与える。また，晩期合併症の問題や，その悪性化の問題など，術後フォローアップについても重要な点がある。それらについて十分な理解に基づいた，SCTに対する治療が重要であると考えられる。

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Molecular
Gastrointestinal

小児消化管疾患の遺伝子異常（とくにヒルシュスプルング病とその類縁疾患に関して）

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KEY WORDS

小児機能的消化管障害（FGID），遺伝子異常，遺伝子導入，ヒルシュスプルング病（H病），ヒルシュスプルング病類縁疾患（H類縁）

SUMMARY

消化管疾患は，機能的消化管障害（FGID）と器質的消化管障害に大別される．小児期に発症するFGIDとしては，機能性ディスペプシア（FD），過敏性腸症候群（IBS）などが代表的であり，器質的消化管障害としては，ヒルシュスプルング病（H病）とその類縁疾患（H類縁）が代表的である．FGIDと遺伝子異常の関与として，FDと*SCN10A*遺伝子多型，IBSと*SLC6A4*遺伝子多型（*5-HTTLPR*）の発現頻度低下があがる．H病と遺伝子異常としては，*GDNF*，*Ret*，*GFRα1*，*Phox2b*，*ED3*，*EDNRB*，*Sox10*，*ECE 1*など，複数の遺伝子異常がその病因と考えられている．H類縁では，腸管神経節細胞僅少症（Hypo）と*Hlx1*，intestinal neuronal dysplasia（IND）と*Ncx/Hox11L.1*，慢性特発性偽性腸閉塞症（CIIP）と*c-kit*などが近年遺伝子異常として報告されており，今後も新たな知見が得られる可能性がある．本稿では小児消化管疾患と遺伝子異常について，H病とその類縁疾患を中心に概説する．

はじめに

消化管疾患は，機能的消化管障害（functional gastrointestinal disorders：FGID）と器質的消化管障害に大別される．前者は器質的生化学的に説明のできない種々の慢性反復性消化器症状を6ヵ月以上前から認め，最近3ヵ月間に一定頻度以上症状発現を呈するものと定義され[1]，後者は消化器症状の原因に病理組織学的もしくは解剖学的な異常を有するものと定義されている．小児期に発症するFGIDとしては，周期性嘔吐症（cyclic vomiting syndrome：CVS），機能性ディスペプシア（functional dyspepsia：FD），過敏性腸症候群（irritable bowel syndrome：IBS）などが代表的であり，器質的消化管障害としては，ヒルシュスプルング病（Hirschsprung's disease：H病）とその類縁疾患（H類縁）が代表的である．本稿は，これら疾患の遺伝子異常について，とくにH病とその類縁疾患を中心に概説する．

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表❶ 新生児・乳幼児期における機能的消化管障害の分類

1	Infant regurgitation
2	Infant rumination syndrome
3	Cyclic vomiting syndrome
4	Infant colic
5	Functional diarrhea
6	Infant dyschezia
7	Functional constipation

(Hyman PE *et al*, 2006[4]より改変引用)

表❷ 小児・思春期における機能的消化管障害の分類

1. Vomiting and aerophagia
   - 1a. Adolescent rumination syndrome
   - 1b. Cyclic vomiting syndrome
   - 1c. Aerophagia
2. Abdominal pain-related FGIDs
   - 2a. Functional dyspepsia
   - 2b. Irritable bowel syndrome
   - 2c. Abdominal migraine
   - 2d. Childhood functional abdominal pain
     - 2d1. childhood functional abdominal pain syndrome
3. Constipation and incontinence
   - 3a. Functional constipation
   - 3b. Nonretentive fecal incontinence

(Rasquin A *et al*, 2006[5]より改変引用)

機能的消化管障害と遺伝子異常

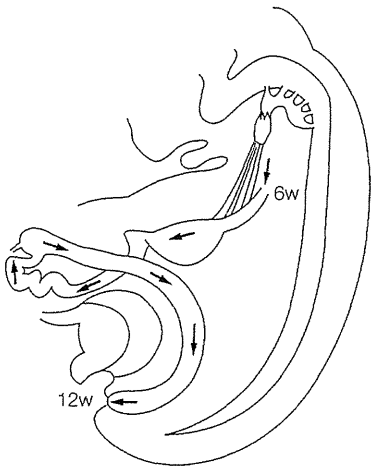
FGIDの分類であるRome分類は，1990年にIBSのコンセンサスの発表としてはじまり[2]，Rome Ⅱを経て[3]，2006年にRome Ⅲ[1]として現在広く用いられている．Rome Ⅲでは，小児領域を「新生児・乳幼児期」[4]と「小児・思春期」[5]に分離している．

新生児・乳幼児期にみられるFGIDを表❶[4]にまとめた．CVSを除く6疾患に関しては検索しえたかぎりでは明らかな遺伝子異常の関与は認められなかったため，CVSに関して述べる．CVSは1年で1～70回（平均12回）の嘔吐を，定期的もしくは孤発性に認め，発症は1日のうちでおもに朝もしくは夜，嘔吐は消失傾向となる一方で，嘔気はシリーズが終了するまでつづくが，無症状期は一切症状を認めないという特徴を有する．CVSはその80%は環境因子が原因であるといわれているが，thymidine phosphorylase（TP）遺伝子の機能喪失型変異が遺伝学的原因である消化器症状を主徴とするミトコンドリア胃腸脳筋症もCVS同様に反復性嘔吐を呈することがあり[6]，治療難渋例においてはその鑑別疾患として留意すべきと思われる．

つぎに，小児・思春期にみられるFGIDを表❷[5]にまとめた．これら疾患のなかで，遺伝子学的関与が示唆されているFDおよびIBSに関して述べる．FDの診断基準[5]は，① 持続性もしくは反復性の上腹部正中の痛みもしくは不快感，② 排便によって症状が改善せず，便回数や便性の変化で発症し，IBSを除外したもの，③ 症状を説明できる炎症性疾患，解剖学的，内分泌的，悪性疾患がないものとされ，少なくとも2ヵ月以上の経過で週に1回以上基準を満たすものとされている．有病率は，約3.5～27%といわれ，その発症には消化管運動障害や心理社会的要因のほかに遺伝子学的要因として，*SCN10A*遺伝子多型の関与を示唆する報告がある[7]．また，IBSの診断基準[5]は，① 腹痛まではいかない腹部不快感もしくは以下の所見のうち2つ以上を25%で満たす腹痛を有するもの（a．排便により軽快する，b．排便回数の変化により発症する，c．便性の変化により発症する），② 症状を説明できる炎症性疾患，解剖学的，内分泌的，悪性疾患がないもの，であり，少なくとも2ヵ月以上の経過で週に1回以上基準を満たすものとされている．遺伝学的にはIBSの家族内発症に関する報告[8]，遺伝子学的には，セロトニントランスポーター（SERT）遺伝子である*SLC6A4*の遺伝子多型（*5-HTTLPR*）の発現頻度がIBS患者で低いとの報告がある[9]．

H病にかかわる遺伝子異常

H病は，通常腸管に存在する神経節細胞が先天的に欠如する疾患であり，その病因は，cranio-caudal migrationの途絶[10]であり，胎生6～12週における神経堤から発生した神経節細胞の移動が障害され，無神経節腸管となると考えられている（図❶）．その原因遺伝子としては，異なる2系統の細胞間シグナル伝達系（GDNF/Ret系およびED3/EDNRB系）で考えられ，そのほかにもGDNF/Ret系の*PHOX2B*やED3/EDNRB系の



図❶ cranio-caudal migration の途絶が H 病の原因といわれている
胎生 6～12 週の時期の神経堤から発生した神経節細胞の移動が障害され，無神経節腸管となる．
(Okamoto E *et al*, 1967[10] より改変引用)

SOX10 などが遺伝子変異として報告され[11~19]，これら遺伝子の異常では腸管神経節細胞の migtration がなされないことが知られている（**表❸**）．

1）GDNF/RET 系

H 病患者の多くで変異が認められ，最も関連性が深いとされている遺伝子が *Ret* 遺伝子である．Ret はグリア細胞由来神経栄養因子（glial cell line-derived neutrophic factor：GDNF）をはじめ，neurturin（NTN），artemin（ART），persephin（PSP）の 4 種類のリガンドファミリーによって活性化される膜貫通型蛋白であり，これらリガンドが細胞表面に存在する 4 種のリガンド結合蛋白である GFRα1-4 に結合し複合体を形成し，Ret を活性型に変換させている[20]．なかでも H 病の原因といわれているシグナル伝達系は**図❷**に示すように，GDNF-GFRα1-RET 系であり，いずれの遺伝子変異でも H 病に類似した病態になることがマウスで確認されている[13~15]．

2）ED3/EDNRB 系

エンドセリンは血管内皮細胞が産生する 21 アミノ酸からなるきわめて強力な血管収縮ペプチドであり，エンドセリンにはエンドセリン 1，2，3（ED1，ED2，ED3）が，エンドセリン受容体には A（endothelin receptor type A：EDNRA）および B（endothelin receptor type B：EDNRB）がある．これらエンドセリンのうち，ED3 は消化管において優位に機能し，EDNRB への親和性が高いといわれている[16)21)]．H 病の症例解析によると，約 5% で *ED3* 遺伝子の変異を，約 3～7% で *EDNRB* 遺伝子の変異を認めていると報告がある[21]．ED3 はその前駆体（preproED3）がプロテアーゼのフリンによって切断され中間体の big endothelin 3 になり，edothelin converting enzyme 1（ECE 1）によって活性型の ED3 となり，SOX10 が発現を制御している EDNRB に作用する（**図❸**）．このシグナル系に関連する遺伝子として，EDNRB の発現を制御するといわれている *SOX10* 遺伝子[19]や，上記 *ECE 1* 遺伝子があがる．SOX10 遺伝子変異は，H 病に目や皮膚の色素異常を伴う Waardenburg-Hirschsprung 症候群の原因として，また ECE 1 遺伝子変異例は少数の H 病症例において報告がある[18]．

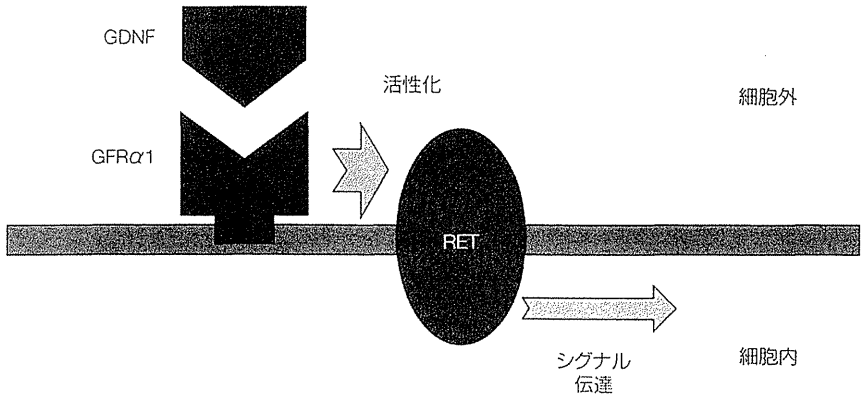
表❸ H 病および H 類縁の原因もしくは関連が示唆されている遺伝子

H 病		H 類縁		
		Hypo	IND	CIIP
GDNF/Ret	ED3/EDNRB			
GDNF	*ED3*	*GDNF*	*Ncx/Hox11L.1*	*c-kit*
Ret	*EDNRB*	*Ret*		
GFRα1	*Sox10*	*EDNRB*		
Phox2b	*ECE 1*	*Hlx1*		

Hypo：腸管神経節細胞僅少症，IND：intestinal neuronal dysplasia，CIIP：慢性特発性偽性腸閉塞症．

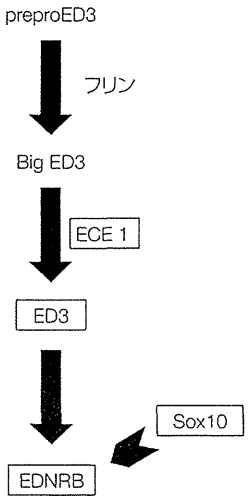
H 類縁にかかわる遺伝子異常

H 類縁は，神経節細胞が存在するにもかかわらず H 病に類似した腸管蠕動不全を呈する疾患の総称である．疾患の希少性[22]から，その病因はいまだ十分に解明されていないが，近年徐々に遺伝子異常の関与が示唆されている（**表❸**）．H 類縁のなかで最も症例数の多い腸管神経節細胞僅少症（hypoganglionosis：Hypo）は，腸管筋間神経叢の神経節細胞が減少し，神経線維網の未発達が



図❷ GDNF-GFRα1-RET 系のシェーマ
リガンドである GDNF が，結合蛋白である GFRα1 と結合することで，Ret を活性型に変換させる．

(Rosenthal A, 1999[20] より改変引用)



図❸ ED3/EDNRB 系のシグナル伝達機構
preproED3 がフリンによって big endothelin 3 になり，edothelin converting enzyme 1 (ECE 1) によって活性型の ED3 となり，SOX10 が発現を制御している EDNRB に作用する．

その病理組織学的病態である[23]．遺伝子異常に関しての報告はいまだ少ないが，近年 *Ret* 遺伝子の変異の報告[24]や EDNRB の発現量低下の報告[25][26]，*Hlx1* 遺伝子変異[27]がなされている．

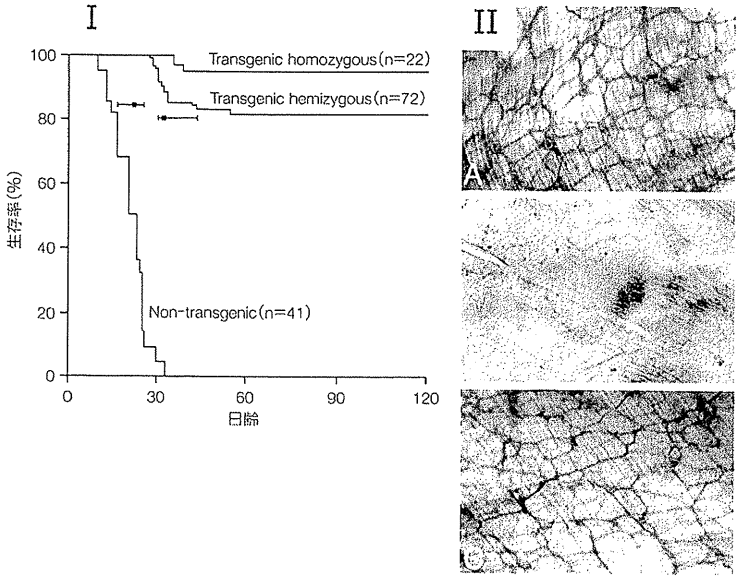
また，そのほかに遺伝子異常が指摘されている H 類縁として，intestinal neuronal dysplasia (IND) や慢性特発性偽性腸閉塞症 (chronic idiopathic intestinal pseudo-obstruction：CIIP) がある．IND の罹患腸管の粘膜下神経叢は giant ganglia と称され，成熟過程の神経節細胞が 1 つの神経叢に 9 個以上存在することがその病理組織学的特徴である[28]．IND の原因遺伝子として *Ncx/Hox11L.1* が知られており，欠損マウスは腸管神経の未熟性や腸管蠕動不全の病態解明に用いられている[29][30]．CIIP の原因遺伝子として現在，*c-kit* 遺伝子が考えられ，*c-kit* 遺伝子の変異マウスでは消化管児童運動能の低下が認められている[31][32]．

H 病に対する遺伝子導入の試み

原因遺伝子の解明には，これまで述べてきたような原因遺伝子欠損モデル動物の解析だけでなく，そのモデル動物に欠損した遺伝子を導入させることで現症の改善につながるかどうかを解析する方法もある．Rice ら[33]と Gariepy ら[34]は，いずれも EDNRB 欠損モデル動物に対し，dopamine-β-hydroxylase (DβH) を導入することで *EDNRB* 遺伝子発現をさせた．Gariepy ら[34]は腸管筋間神経叢における神経線維網が未発達で生後 20 日程度で巨大結腸で死亡する EDNRB 欠損モデル動物の予後を DβH を導入することで劇的に改善させ，腸管神経線維網が野生型と遜色ない状態に改善したと報告した(図❹)．

おわりに

小児消化管疾患に関する遺伝子異常について，機能的



図❹ EDNRB 欠損モデル動物に対する DβH 導入の効果

（Ⅰ）Non-transgenic 群は，日齢 30 日程で全例死亡する一方で，Transgenic hemizygous 群の生存率は劇的に改善している．（Ⅱ）A は wild type，B は EDNRB 欠損動物．C は遺伝子導入 EDNRB 欠損動物における遠位結腸の筋間神経叢のアセチルコリンエステラーゼ陽性神経線維網を示す．A に比較し，B は著明な未熟性を示すが，C は A 同等の神経線維網の発達を示している．
（Gariepy CE, 1998[34] より改変引用）

および器質的障害に分け，とくに H 病および H 類縁に関して概説した．これら遺伝子異常の究明が各疾患の病態解明につながり，一人でも多くの難病に苦しむ子ども達の救いになればと考える．また，H 病に関して，現行の外科的手術に加え，今後新規治療法として種々の再生医療[35]，さまざまな課題はあるものの遺伝子導入などが知見の幅を広げ，H 病の根絶に向かうものとなれば幸いである．

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趣味はバスケットボールと映画鑑賞.
好きな言葉は「千里の道も一歩から」.

Pediatr Blood Cancer

Clinical Features and Prognosis of Generalized Lymphatic Anomaly, Kaposiform Lymphangiomatosis, and Gorham–Stout Disease

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Background. Complex lymphatic anomalies are intractable lymphatic disorders, including generalized lymphatic anomaly (GLA), Gorham–Stout disease (GSD), and kaposiform lymphangiomatosis (KLA). The etiology of these diseases remains unknown and diagnosis is confused by their similar clinical findings. This study aimed to clarify the differences in clinical features and prognosis among GLA, KLA, and GSD, in Japanese patients. ***Procedure.*** Clinical features, radiological and pathological findings, treatment, and prognosis of patients were obtained from a questionnaire sent to 39 Japanese hospitals. We divided the patients into three groups according to radiological findings of bone lesions and pathology. Differences in clinical findings and prognosis were analyzed. ***Results.*** Eighty-five patients were registered: 35 GLA, 9 KLA, and 41 GSD. Disease onset was more common in the first two decades of life (69 cases). In GSD, osteolytic lesions were progressive and consecutive. In GLA and KLA, 18 patients had osteolytic lesions that were multifocal and nonprogressive osteolysis. Thoracic symptoms, splenic involvement, and ascites were more frequent in GLA and KLA than in GSD. Hemorrhagic pericardial and pleural effusions were more frequent in KLA than GLA. GSD had a significantly favorable outcome compared with combined GLA and KLA ($P = 0.0005$). KLA had a significantly poorer outcome than GLA ($P = 0.0268$). ***Conclusions.*** This survey revealed the clinical features and prognosis of patients with GLA, KLA, and GSD. Early diagnosis and treatment of KLA are crucial because KLA has high mortality. Further prospective studies to risk-stratify complex lymphatic anomalies and optimize management for KLA are urgently needed. Pediatr Blood Cancer © 2016 Wiley Periodicals, Inc.

Key words: complex lymphatic anomaly; generalized lymphatic anomaly; Gorham–Stout disease; kaposiform lymphangiomatosis; lymphatic malformation; osteolysis

INTRODUCTION

Complex lymphatic anomaly is a recently proposed disease category of intractable lymphatic disorders, including generalized lymphatic anomaly (GLA) and Gorham–Stout disease (GSD).[1] The current literature is confined to case reports and several small series because of the low incidence of these diseases. The clinical features and mortality rate of the patients remain unknown. In some patients, proper diagnosis is difficult because the clinical findings are overlapping.

GLA is characterized by diffuse or multicentric proliferation of dilated lymphatic vessels resembling common lymphatic malformation (LM). The International Society for the Study of Vascular Anomalies (ISSVA) has recently suggested replacing the term "lymphangiomatosis" with GLA. This is because the suffix "oma" implies neoplastic proliferation.[2] GLA may present at birth but may also occur in children and young adults. It has a variable presentation and can affect several different sites including bone, liver, spleen, mediastinum, lungs, and soft tissues. The clinical course is directly related to the affected sites and extent of the disease.[3] Thoracic involvement may be associated with poor prognosis compared with cases with soft tissue or bone involvement.[4]

GSD is a rare disease characterized by osteolysis in bony segments, with localized proliferation of lymphatic or vascular channels in areas adjacent to the affected bone.[5] Several bones may become involved and these undergo progressive destruction and resorption. Areas commonly affected by GSD include ribs, cranium, clavicle, and cervical spine.[6] Pain and swelling in the affected area may occur. While GSD mainly involves the skeletal system, it can also involve the viscera, and clinical findings of GSD and GLA closely overlap.[7] Lala et al. have reported that patients with GLA and GSD displayed differences in the radiological findings of their bone lesions; GLA patients have lytic areas confined to the medullary cavity, whereas GSD patients have progressive osteolysis resulting in the loss of cortical bone.[6] Although these diseases are known as different conditions, affected bones from both groups of patients show abnormal lymphatic channels and appear histologically similar. Further study of GLA and GSD will help delineate the clinical,

Additional Supporting Information may be found in the online version of this article.

Abbreviations: CT, computed tomography; GLA, generalized lymphatic anomaly; GSD, Gorham–Stout disease; ISSVA, International Society for the Study of Vascular Anomalies; KLA, kaposiform lymphangiomatosis; LM, lymphatic malformation; MRI, magnetic resonance imaging

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Conflict of interest: Nothing to declare.

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histological, and genetic similarities and differences between these two rare diseases.

Kaposiform lymphangiomatosis (KLA) has recently been distinguished as a novel subtype of GLA with foci of spindle endothelial cells amid a background of malformed lymphatic channels.[8] All cases of KLA involve multiple organs with a predilection for the thoracic cavity, causing pleural effusion that commonly leads to respiratory distress and dyspnea.

The etiology of these diseases is poorly understood and it is likely that the diseases represent a clinical spectrum of lymphatic pathological processes. However, recent studies about this spectrum of lymphatic diseases have suggested differences in the clinical characteristics of these complex lymphatic anomalies. The purposes of the present study were to investigate the clinical features of patients with these diseases, and to clarify the differences among the diseases and their prognoses.

METHODS

Ethical Approval, Organization, Questionnaire, and Data Collection

The Institutional Review Board of Gifu University Graduate School of Medicine approved this study. To elucidate the clinical characteristics of GLA and GSD, we conducted a nationwide, questionnaire-based survey in Japan under the auspices of the Japanese Ministry of Health, Labour and Welfare Research Program into Intractable Diseases Research Grants. The first set of questionnaires was sent to 520 Japanese hospitals with pediatric departments. The first questionnaire queried how many patients with GLA and GSD the target hospitals had between 2000 and 2013. We did not ask about KLA because it was not a known disease at the start of the study. The second set of questionnaires, which focused on clinical information such as age at onset and diagnosis, family history, perinatal history, symptoms, lesion site, radiographic and pathological findings, treatment, complications, clinical course, and outcome of patients, was sent to their attending physicians. Additionally, we requested that the authors, who had reported GLA and GSD in the literature in the past 10 years, complete the second questionnaire. To avoid reporting duplicate data, we identified overlapping patients by date of birth, sex, home village, and time of diagnosis.

Data Curation, Review of Pathological and Radiological Examinations, and Diagnosis

We categorized collected patients into GLA, KLA, and GSD according to pathological and radiological examinations. Exclusion criteria included diagnosis of other lymphatic diseases, for example, localized common LM lesions without extensive involvement, central conductive lymphatic anomaly, and lymphedema, or insufficient data. The pathological examinations were reviewed retrospectively. We defined as KLA foci of spindle endothelial cells amid a background of malformed lymphatic channels.[8] As noted previously, the key features of GSD are osteolysis and disappearing bone.[9] To diagnose GSD, the radiological findings of all patients were reviewed. Thus, only patients with evidence of cortical loss and/or progressive bone resorption were categorized as having GSD.[6] Patients with evidence of lytic bone confined to the medullary cavity or without bone lesions were diagnosed with GLA. Clinical data of these patients were carefully reviewed by two pediatric specialists (T.H. and K.K.). Pathological examinations were reviewed independently by a pediatric pathologist (K.M.). Imaging examinations were reviewed independently by a pediatric radiologist (S.N.). In cases of diagnostic discrepancy, a final decision was reached by consensus.

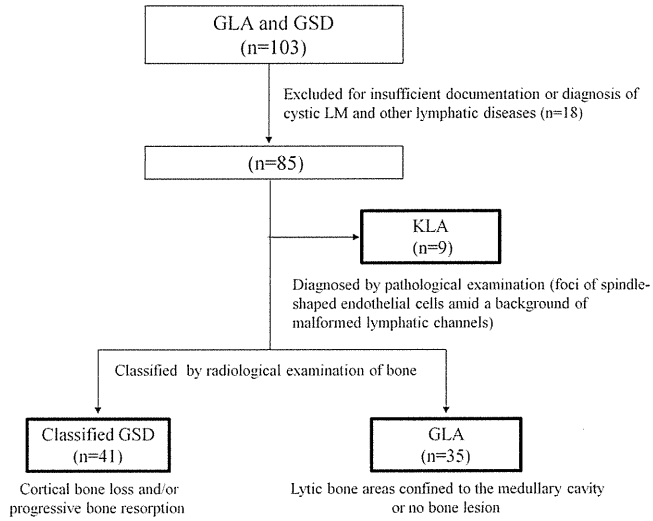

Fig. 1. Diagnostic charts of GLA, KLA, and GSD. GLA, generalized lymphatic anomaly; GSD, Gorham–Stout disease; KLA, kaposiform lymphangiomatosis.

Data Analysis

Because of the similarity between GLA and KLA, the findings including the number and distribution of bones involved in these two groups combined were initially compared with GSD, and then specific differences between GLA and KLA were sought. Prognosis as measured by overall survival was compared in the same way.

Statistical analysis was performed with GraphPad Prism version 6. Descriptive statistical methods (median and standard deviation), Wilcoxon's rank sum test for comparison of age, the number of bones involved, duration from symptom onset to diagnosis and follow-up period, and Fisher's exact test for two-group comparison, were used for the statistical analyses. Overall survival was analyzed from the date of onset by the product–sum method of Kaplan–Meier. The differences in survival times between the combined GLA and KLA group and GSD group, or GLA group and KLA group, were compared with the log-rank test. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Patients and General Characteristics at Study Entry

A total of 420 responses (80.7% response rate) were received to the first set of questionnaires. A second questionnaire was then sent to 39 institutions, asking for information regarding clinical features, treatments, and outcomes for each patient. One hundred and three patients were diagnosed with GLA and GSD.

Eighteen cases were excluded because of insufficient documentation or diagnosis of other lymphatic diseases. Therefore, 85 patients were included in our study. Pathological examination was available in 71 patients (83.5%). It was not available in 14 patients because of the following reasons: examination was not performed (n = 6), pathological specimens were already disposed or for internal hospital use only (n = 4), or we could not obtain the cooperation of the primary doctor (n = 4). We categorized these patients into GLA or GSD according to pathological diagnosis in the survey center and radiological examinations. The number of patients with GSD, GLA, and KLA was 41, 35, and 9, respectively (Fig. 1). Among 44 patients with GLA and KLA, 39 (88.6%) underwent pathological examination for confirmation of diagnosis. Two patients did not undergo pathological examination because they died from rapid progression of respiratory failure. These two patients also had severe thrombocytopenia and coagulation disorder at clinical diagnosis. Another three patients without pathological examination were all infants (0, 7, and 12 months old) and their diagnosis was made by radiological examination alone.

The clinical characteristics of the patients are shown in Supplemental Table I. No family and perinatal history was evident for any of these patients. There was no significant difference in the male-to-female ratio among the three groups of patients. The median age of all patients at the time of data collection was 19.0 years (range: 1.3–70 years). The median ages of the GLA, KLA, and GSD groups were 18.0 (range: 1.3–70), 10.0 (range: 1.5–18.5), and 21.9 (range: 1.5–64.7) years, respectively. Age of onset ranged from infancy to adulthood (mean: 12.0, range: 0–63 years) but disease was more common in the first two decades of life (69/85, 81.2%), and 18 patients were aged <1 year, most of whom (12 infants) had GLA. The duration between onset and diagnosis in the three groups did not differ significantly. However, the duration in the KLA patients tended to be shorter than in other groups.

Characteristics of Affected Areas

Bone lesions, being a diagnostic criterion, were present in all patients diagnosed with GSD, but were also present in 40.9% (18 of 44) of GLA or KLA patients (Supplemental Table II). Osteolysis was the most common finding. The typical bone resorption in GSD is shown in Figures 2A, 2C, and 2D. In GLA and KLA, 16 of 44 (36.4%) patients had osteolysis, which was characterized by multiple lytic changes (Figs. 3A–3C). There were no significant radiological differences in the bone lesions between GLA and KLA. In GSD, pathological fracture was more frequent. A greater number of bones were involved in GLA or KLA than in GSD (Supplemental Table III). The spine was the most common site of osseous changes in all patients, and the spine lesions were identified more often in GLA or KLA than GSD (Fig. 3C). In GSD, 19 patients (54.3%) had bone lesions in any of the four limbs (14 femur, four humerus, nine lower leg, and two tarsal bone). With regard to skeletal axis of the osteolytic lesion, the axial skeleton (skull, spine, and ribs) was affected in 16 of the 18 patients with GLA or KLA. However, the appendicular skeleton (scapula, clavicle, pelvis, ilium, and four limbs) was only affected in six patients. An infiltrative soft tissue abnormality adjacent to the area of osseous involvement was identified more often in GSD than GLA or KLA ($P \leq 0.001$).

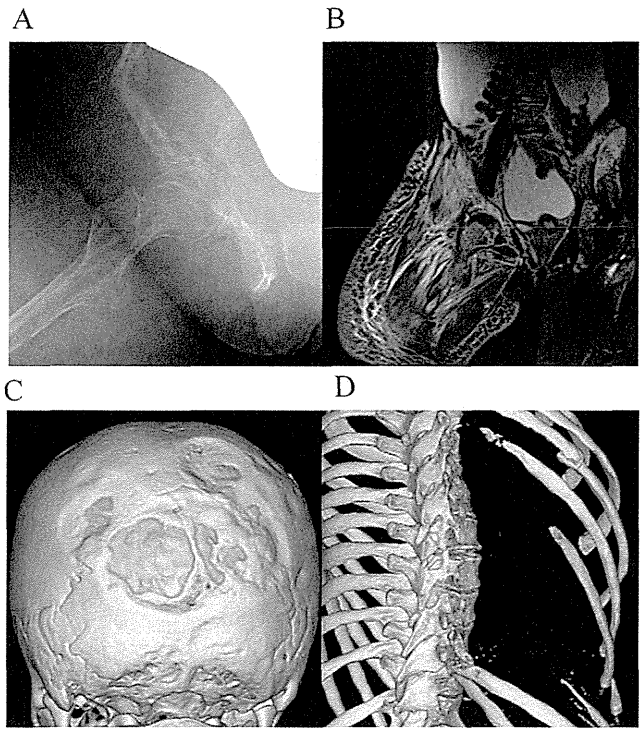

Fig. 2. Radiological findings of patients with GSD. (**A** and **B**) Thirteen-year-old female with GSD involving right lower extremity, right pelvis, spine, abdomen, and right thorax. (**A**) Plain radiograph of the right pelvis shows osteolysis at the proximal femoral shaft as well as the pelvic bone. (**B**) Coronal fat suppressed in T2-weighted image of the pelvis demonstrates extensive high signal intensity in the soft tissue surrounding the femur as well as subcutaneous fat tissue. Involved right pelvis shows high signal intensity secondary to osteolysis. Also visible is a large amount of ascites. (**C**) Nine-year-old male with GSD involving the occipital and temporal bones. Posterior view of 3D CT imaging shows almost complete resorption of the occipital bone. (**D**) Thirteen-year-old female with GSD involving the ribs. Right oblique posterior view of 3D CT shows multiple osteolysis and fracture of the posterior portion of the right 5–10 ribs. CT, computed tomography; GSD, Gorham–Stout disease (GSD).

Thoracic lesions were the second most common, with symptoms of cough, chest pain, dyspnea, and wheezing. Some patients experienced wheezing and were misdiagnosed with asthma prior to recognition of the lymphatic disorder. Pleural effusion, mediastinal mass, and cardiac effusion were significantly more frequent in GLA and KLA than GSD ($P = 0.002$, 0.002, and 0.001, respectively). The frequency of pleural and cardiac effusion in KLA was similar to that in GLA, but mediastinal masses and hemorrhagic pericardial and pleural effusions were more frequent in KLA than GLA ($P = 0.017$ and <0.001, respectively). The other findings were heart failure, cardiac tamponade, and pulmonary infiltration and hemorrhage. In abdominal lesions, splenic involvement and ascites were more frequent in GLA and KLA than GSD ($P = 0.044$ and 0.001, respectively). However, KLA patients did not have ascites. Seven patients had cystic LM of the mesentery and retroperitoneum, in combination with ascites or invasion of the surrounding soft tissue. Skin lesions were present in 36 of 85 (42.3%) cases. Three patients

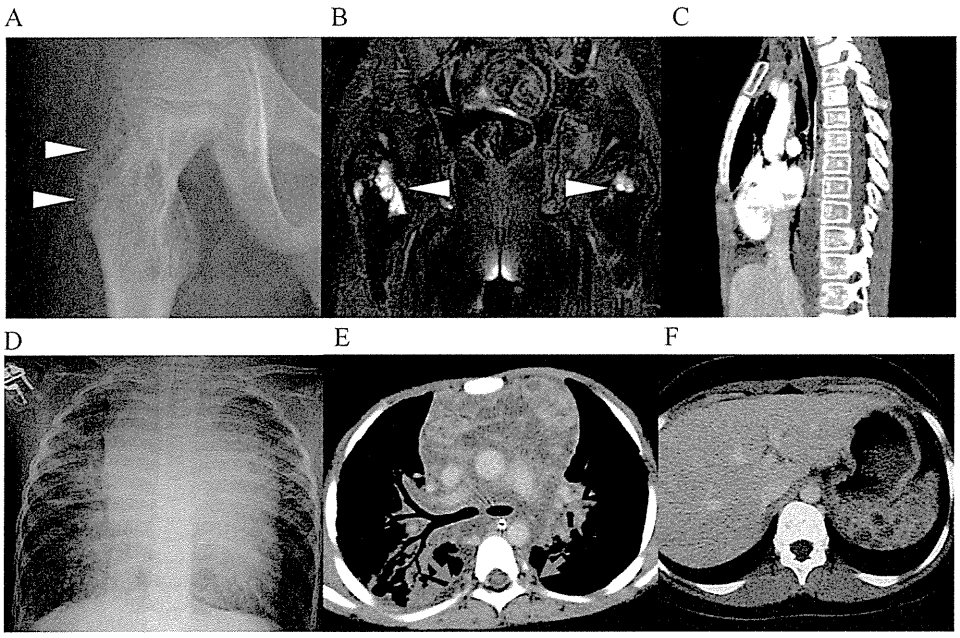

Fig. 3. Radiological findings of patients with GLA and KLA. (**A–C** and **F**) Twelve-year-old male with GLA involving bone and spleen. (**A**) Plain radiography of femoral head shows a small lytic lesion (white arrowheads). (**B**) Coronal fat suppressed, T2-weighted MRI of femoral head shows a small lytic lesion (white arrowheads). (**C**) Contrast-enhanced CT of the chest with sagittal reconstruction shows dissemination of osteolysis in the vertebrae. (**D** and **E**) Eight-year-old male with KLA involving the thoracic region. (**D**) Chest radiography shows pronounced effusion, mediastinal enlargement, and peribronchovascular infiltration extending from the hilar to the peripheral area. (**E**) Chest contrast-enhanced CT demonstrates diffuse thickening of the interlobular septa, pleural effusion in the right lung, and retroperitoneal soft tissue mass (red arrows). (**F**) An axial projection shows multiple cystic lesions in the spleen. CT, computed tomography; GLA, generalized lymphatic anomaly; KLA, kaposiform lymphangiomatosis; MRI, magnetic resonance imaging.

had subcutaneous macrocytic LMs at birth. Neurological disorders were uncommon (10/85 [11.8%]) and were associated with osteolytic lesions of the skull.

Imaging and Histopathological Examination

Bone lesions were present in 59 of 85 cases and imaging examinations of bone lesions included plain radiography (n = 59), computed tomography ([CT]; n = 59), magnetic resonance imaging ([MRI]; n = 57), and bone scintigraphy (n = 3). CT showed more definite location and number of osteolytic lesions than did plain radiography. MRI demonstrated altered signaling in bone marrow, which was hypointense on T1-weighted imaging. An infiltrative soft tissue abnormality adjacent to the area of osseous involvement was characterized by high signal intensity in T2-weighted imaging, which indicated lymphatic infiltration or accumulation of lymphatic fluid (Fig. 2B). Bone scintigraphy demonstrated increased uptake of radiotracer in the pathological fracture of one case, while there was no increased uptake in the osteolytic lesion. In thoracic lesions of typical patients with GLA or KLA, bilateral interstitial infiltrates in the lung and pericardial or pleural effusions were evident on chest radiography (Fig. 3D). Thoracic CT revealed diffuse smooth thickening of interlobular septa and bronchovascular bundles, with extensive involvement of mediastinal connective tissue and perihilar regions. The thickening and soft tissue mass of the pleura, posterior mediastinum, and anterior ribs were characteristic findings, especially in KLA (Fig. 3E). Thirty-three patients had splenic involvement, identified by CT (n = 33), MRI (n = 29), and ultrasound (n = 20). These lesions were multiple cystic lesions in most cases (Fig. 3F). On Doppler ultrasound, the lesions did not demonstrate increased vascular flow. Histopathology demonstrated anastomosing endothelium-lined spaces consistent with lymphatic vessels stained with D2-40 (Figs. 4A–4F). Although KLA was diagnosable by characteristic findings at pathological examination, there were no significant histopathological differences between GLA and GSD. Bone biopsy specimens showed dilated lymphatic lumens containing lymphatic fluid in lytic lesions; however, some specimens were not in sufficiently good condition to reconstruct their architecture for diagnosis.

Treatments

Treatment included medication, surgery, radiotherapy, and nutritional therapy. In patients with bone lesions, medical treatment included interferon-α, propranolol, bisphosphonates, and corticosteroids. When these medications were not effective, patients needed to undergo surgery or symptomatic treatment. Surgical interventions included resection of the lesion and orthopedic operations (fracture reduction or reconstruction). In some patients, surgical reconstruction undertaken to control the disease was unsuccessful because of rapid osteolysis and resorption of bone graft material. The common surgical procedures for pleural effusion were pleurocentesis, pleurodesis, and ligation of the thoracic duct. Medical therapy for thoracic lesions included corticosteroids, propranolol, interferon-α, octreotide, and mammalian target of rapamycin (mTOR) inhibitor. Sixteen patients

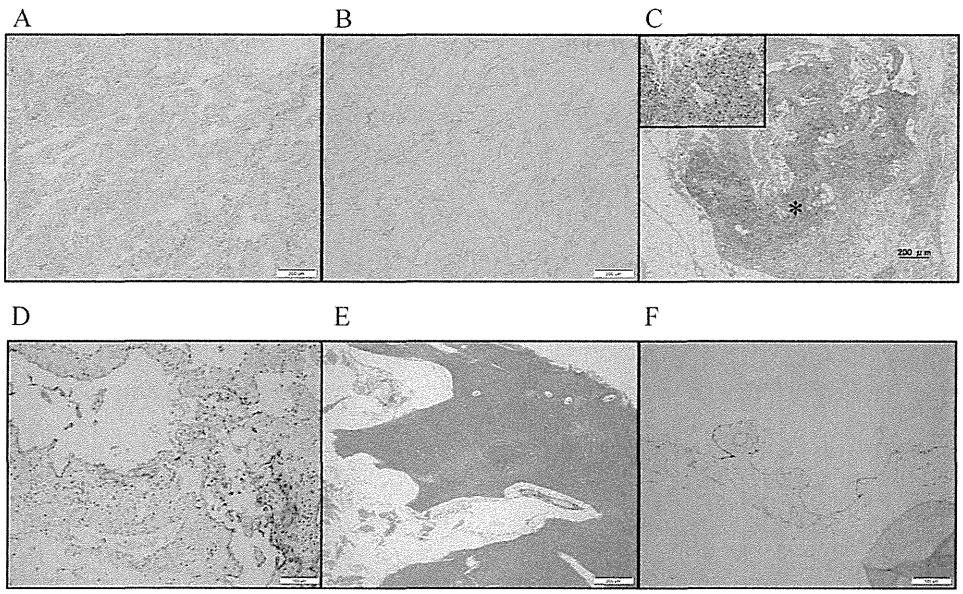

Fig. 4. Pathological findings in patients with GLA, KLA, and GSD. (**A** and **B**) Specimen of subcutaneous lesion from GLA patient. (**A**) This specimen shows proliferation of thin-walled, anastomosing lymphatic vessels lined by a single layer of endothelial cells without foci of spindle endothelial cells (bar 200 μm, hematoxylin and eosin [H&E]). (**B**) Endothelial cells were identified as lymphatic using D2-40 (bar 100 μm). (**C** and **D**) Specimen of thoracic lesion from KLA patient. (**C**) Specimen shows proliferation of thin-walled, anastomosing lymphatic vessels lined by a single layer of endothelial cells with a focus of spindle cells (*) (bar 200 μm, H&E). Spindle cells can be seen in the insert image. (**D**) Endothelial cells were identified as lymphatics using D2-40 (bar 100 μm). (**E** and **F**) Specimen of femur biopsy affected by GSD. (**E**) Typical bone structures were resorbed and replaced by thin-walled endothelium-lined capillaries of vascular or lymphatic origin (bar 200 μm, H&E). (**F**) D2-40 immunostaining delineates the endothelium of lymphatic channels (bar 100 μm, H&E). GLA, generalized lymphatic anomaly; GSD, Gorham–Stout disease; KLA, kaposiform lymphangiomatosis.

(six with bone lesions of GSD, and 10 with thoracic lesions) underwent radiotherapy. The total doses applied and fractionation regimens varied widely among patients and lesions. Nutritional therapy (fat-restricted diet and low-fat medium chain triglyceride diet) had no effects in almost all patients.

Follow-up Period and Mortality

Follow-up was available for all patients. The mean follow-up period was 7.0 (range, 0.1–32; median, 4) years. Overall or in aggregate, mortality rate was 20% (17/85) and the cause of death was thoracic symptoms (Fig. 5A). All 29 patients (nine adults and 20 children) who lacked thoracic lesions survived. Of the 69 pediatric patients, 50 had thoracic lesions and 13 died (26%). The GSD group had a significantly more favorable outcome than the combined GLA and KLA group had ($P = 0.0005$) (Fig. 5B). In contrast, the KLA patients had a significantly poorer outcome than the GLA patients had ($P = 0.0268$) (Fig. 5C).

DISCUSSION

In this nationwide retrospective observational study, we collected data on follow-up of patients with GLA, KLA, or GSD from Japanese hospitals. This study demonstrated the frequency and features of principal symptoms, diagnostic signs, and prognosis. Our data contribute to understanding the clinical features and prognosis of these diseases.

Osteolytic lesions are important for differential diagnosis. They can be caused by several different conditions including infection, inflammation, cancer, and endocrine disorders. In our study, some cases were misdiagnosed as Langerhans cell histiocytosis and osteomyelitis before definitive diagnosis. There is no specific test or procedure to diagnose GSD definitively;[3] thus, diagnosis is based upon identification of characteristic symptoms, detailed patient history, radiological examination, and histopathological findings. Especially, radiological findings of osteolysis seem important to distinguish among GLA, KLA, and GSD. Patients with GLA and KLA displayed lytic areas confined to the medullary cavity, whereas patients with GSD showed progressive osteolysis resulting in the loss of cortical bone. GLA and KLA typically involved more bones than GSD did. The bone lesions of GSD were often progressive and sequentially infiltrative; in contrast, those of GLA and KLA were nonprogressive. However, our study also showed that there were some overlapping features and no obvious difference in bone histopathology.

KLA was recently distinguished as a novel subtype of GLA.[8,10] Although dilated malformed lymphatic channels lined by a single layer of endothelial cells are common to both GLA and KLA, the latter also has foci of patternless clusters of intra- or perilymphatic spindled cells associated with platelet microthrombi, extravasated red blood cells, hemosiderin, and some degree of fibrosis. Patients with KLA also have coagulation disorders, and hemorrhagic pericardial and pleural effusions.[8] In our study, nine patients were diagnosed pathologically with KLA from among those who were diagnosed with GLA. The multiple overlapping clinical characteristics and radiological findings of GLA have led to a hypothesis that KLA may arise from GLA. There have been no cases of

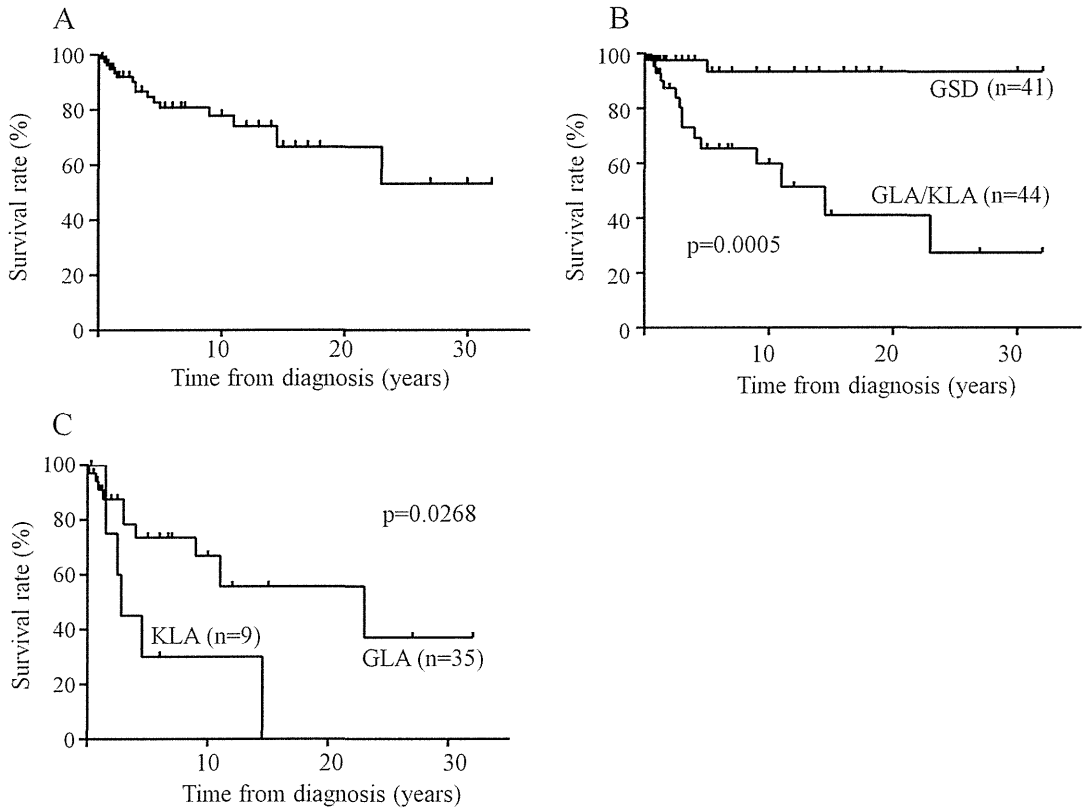

Fig. 5. Kaplan–Meier curve showing time from onset. (**A**) Overall survival of all cases (n = 85). (**B**) Overall survival in GSD group (n = 41) compared with combined GLA and KLA group (n = 44). The GSD group had a significantly more favorable outcome than the combined GLA and KLA group had ($P = 0.0005$) (**C**). Overall survival in GLA group (n = 35) compared with KLA group (n = 9). KLA group had a significantly poorer outcome than the GLA group had ($P = 0.0268$). GLA, generalized lymphatic anomaly; GSD, Gorham–Stout disease; KLA, kaposiform lymphangiomatosis.

GLA that have evolved into KLA over several months or years. However, patients with KLA had unfavorable prognosis and serious symptoms (hemorrhagic pericardial and pleural effusions). We might have to distinguish KLA from GLA or other LMs.

In patients with multifocal lesions, therapeutic options are palliative, and therapy is often aimed at reducing symptoms associated with bone lesions and chylous effusions.[11] Management of chylothorax is often the primary concern. Thoracentesis and pleural drainage are used to treat chylothorax to relieve respiratory distress. In the case of failure with such conservative treatment, thoracic duct ligation has been used to treat pleural effusion in isolated cases.[4] Radiotherapy has been used in cases in which surgery is not possible, or in combination with surgery. Several case reports have described the successful use of radiotherapy, achieving pain relief and arresting the spread of osteolysis. Positive results have been achieved with a total dose of 30–45 Gy.[11]

Patients with osteolysis have been treated with drugs that inhibit bone resorption, including bisphosphonates such as pamidronic or zoledronic acid.[12] Patients with bone or thoracic lesions have been treated with interferon-α-2b, which inhibits the formation of lymphatic vessels.[13] Other pharmaceuticals include vascular endothelial growth factor-A antibody, bevacizumab,[14] propranolol,[15] steroids, vitamin D, and calcitonin. These treatments, used alone or in combination, improve symptoms in some cases, but their effectiveness is inconsistent. A recent study suggested that the antilymphangiogenic properties of rapamycin (sirolimus; an mTOR inhibitor) and its derivatives might have therapeutic value for the prevention and treatment of malignancies.[16] In our study, there were nine patients (eight with thoracic and seven with bone lesions) who were treated with an mTOR inhibitor. Further investigation is needed to determine which treatments are effective and safe in these patients.

It is necessary to address the limitations and bias of the present study. This was a retrospective survey that was limited to general hospitals with pediatric departments and physicians who reported cases. There was also responder bias in that providers managing the most severe cases may have been more likely to report them. When we started this survey in 2013, a new classification of ISSVA had not been announced and there were no standard diagnostic criteria for complex lymphatic anomalies. Therefore, there was some possible involvement of other similar diseases. Multifocal lymphangioendotheliomatosis with thrombocytopenia, multifocal kaposiform hemangioendothelioma, and central conducting lymphatic anomalies are rare diseases, but could be misdiagnosed as GLA.[17,18] Patients diagnosed with GLA might have KLA because of a lack of characteristic findings at pathological examination. In

addition to the above limitations, it is probable that classification of vascular anomalies will be rationally modified according to advances in genetic and clinicopathological research in the future. Despite the above-mentioned limitations, this study is noteworthy because it was a large detailed survey of GLA, KLA, and GSD. We believe that sufficient data were collected to characterize the frequency of principal symptoms, diagnostic signs, and prognosis.

In conclusion, we performed a nationwide, questionnaire-based survey of complex lymphatic anomalies, GLA, GSD, and KLA, to characterize their prevalence, clinical features, radiological and pathological findings, treatment, and prognosis. This study revealed the clinical presentation and severe course of the patients, and limited current therapeutic options. Further study into the pathogenesis and a prospective study are needed for better therapy with improved outcome, especially for KLA.

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