リンパ管腫症/ゴーハム病

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【概要】

1．概要

中枢神経系を除く、骨や胸部（肺、縦隔、心臓）、腹部（腹腔内、脾臓）、皮膚、皮下組織など全身臓器にびまん性に異常に拡張したリンパ管組織が浸潤する原因不明の希少性難治性疾患である。小児、若年者に多く発症するが先天性と考えられている。症状や予後は様々であるが、胸部に病変を認める場合は予後不良である。骨溶解を起こすゴーハム病も、骨病変だけでなく同様の内臓病変を持つ場合があるため、類縁疾患と考えられ、現時点では１つの疾患としてとらえられている。病理学的には不規則に拡張したリンパ管が同定されるが、内皮細胞のMIB-1は陰性で腫瘍性の増殖は無い。また鑑別上問題となるリンパ管奇形（リンパ管腫）は多くの場合病変の範囲拡大や離れた部位の新たな出現はなく、一方でリンパ管腫症は多発性・びまん性（多臓器に及ぶ、リンパ液貯留や周囲の組織に浸潤傾向があるなど）である。なおリンパ管腫症/ゴーハム病は、びまん性リンパ管腫症、ゴーハム・スタウト症候群、大量骨溶解症と呼ばれることもある。

2．原因

原因は不明である。遺伝性は認められていない。

3．症状

症状は病変の浸潤部位による。

a) 胸水（胸腔内に液体が貯留）、乳び胸、心嚢水、縦隔浸潤、肺浸潤により、息切れ、咳、喘鳴、呼吸苦、慢性呼吸不全、心タンポナーデ、心不全を起こす。胸部単純エックス線写真、CTで（両側肺に）びまん性に広がる肥厚した間質陰影や縦隔影拡大、胸水貯留、胸膜肥厚、心嚢水を認める。多くは致命的で、特に小児例は予後不良である。

b) 骨溶解、骨欠損による疼痛や病的骨折、四肢短縮、病変周囲の浮腫、脊椎神経の障害などを起こす。頭蓋骨が溶解し、髄液漏や髄膜炎、脳神経麻痺などを起こす場合もある。単純X線写真にて骨皮質の菲薄化や欠損、骨内の多発性骨溶解病変などを認める。

c) 腹水（腹腔内に液体が貯留）や脾臓内および他の腹腔内臓器に多発性の嚢胞性リンパ管腫（リンパ管奇形）病変を認める。また皮膚、軟部組織のリンパ浮腫、リンパ漏や、血小板減少、血液凝固異常（フィブリノーゲン低下、FDP、D-dimer上昇）なども起こす。

4．治療法

局所病変のコントロール目的に外科的切除が行われるが、全身性、びまん性であるため、根治は困難である。胸部病変に対して胸腔穿刺、胸膜癒着術、胸管結紮術、腹部病変に対しては腹腔穿刺、脾臓摘出などの外科的治療を行う。病変部位によっては放射線治療を行うこともあるが、小児例が多く推奨されない。手術困難な病変に対しては、ステロイド、インターフェロンα、プロプラノロール、化学療法（ビンクリスチン）などが試されるが治療効果は限られる。

5．予後

乳び胸などの胸部病変を持つと生命予後は不良である。また病変が多臓器に渡り、様々な症状を引き起こし、慢性呼吸不全や運動機能障害などの永続的な障害を残す場合が多い。多くの症例が長期間に渡って診療が必要であり、治癒率は極めて低い。

【要件の判定に必要な事項】

- 患者数
  約100人（研究班全国調査より推定）
- 発病の機構
  不明（リンパ管の発生異常と考えられている。
- 効果的な治療方法
  未確立（根本的治療はなく、対症療法が主である。）
- 長期の療養
  必要（治癒しないため、永続的な診療が必要である。）
- 診断基準
  あり（学会で承認された診断基準あり。）
- 重症度分類
  modified Rankin Scale（mRS）、食事・栄養、呼吸のそれぞれの評価スケールを用いて、いずれかが３以上を対象とする。

【情報提供元】

「難治性血管腫・血管奇形・リンパ管腫・リンパ管腫症および関連疾患についての調査研究班」
研究代表者　聖マリアンナ医科大学放射線医学講座　病院教授　三村秀文
「リンパ管腫症の全国症例数把握及び診断・治療法の開発に関する研究班」
研究代表者　岐阜大学大学院医学系研究科小児病態学　助教　小関道夫

＜リンパ管腫症・ゴーハム病診断基準＞

リンパ管腫症・ゴーハム病の診断は、（I）脈管奇形診断基準に加えて、後述する(II)細分類診断基準を追加して行なう。鑑別疾患は除外する。

（I）脈管奇形（血管奇形およびリンパ管奇形）診断基準
軟部・体表などの血管あるいはリンパ管の異常な拡張・吻合・集簇など、構造の異常から成る病変で、理学的所見、画像診断あるいは病理組織にてこれを認めるもの。
本疾患には静脈奇形（海綿状血管腫）、動静脈奇形、リンパ管奇形（リンパ管腫）、リンパ管腫症・ゴーハム病、毛細血管奇形（単純性血管腫・ポートワイン母斑）および混合型脈管奇形（混合型血管奇形）が含まれる。

鑑別診断
１．血管あるいはリンパ管を構成する細胞等に腫瘍性の増殖がある疾患
例）乳児血管腫（イチゴ状血管腫）、血管肉腫など
２．明らかな後天性病変
例）静脈瘤、リンパ浮腫、外傷性・医原性動静脈瘻、動脈瘤など

（II）細分類　リンパ管腫症/ゴーハム病診断基準

下記（1）のa)～c)のうち一つ以上の主要所見を満たし、（2）の病理所見を認めた場合に診断とする。病理検査が困難な症例は、a)～c)のうち一つ以上の主要所見を満たし、臨床的に除外疾患を全て否定できる場合に限り、診断可能とする。

（1）主要所見
a) 骨皮質もしくは髄質が局在性もしくは散在性に溶解（全身骨に起こりうる）。
b) 肺、縦隔、心臓など胸腔内臓器にびまん性にリンパ管腫様病変、またはリンパ液貯留。
c）肝臓、脾臓など腹腔内臓器にびまん性にリンパ管腫様病変、または腹腔内にリンパ液貯留。

(2) 病理学的所見
組織学的には、リンパ管内皮によって裏打ちされた不規則に拡張したリンパ管組織よりなり、一部に紡錘形細胞の集簇を認めることがある。腫瘍性の増殖は認めない。

特記事項
・除外疾患：リンパ脈管筋腫症などの他のリンパ管疾患や悪性新生物による溶骨性疾患、遺伝性先端骨溶解症、特発性多中心性溶骨性腎症、遺伝性溶骨症候群などの先天性骨溶解疾患（皮膚、皮下軟部組織、脾臓単独のリンパ管腫症は、医療費助成の対象としない。）。
・リンパ管奇形（リンパ管腫）が明らかに多発もしくは浸潤拡大傾向を示す場合には、リンパ管腫症と診断する。

＜重症度分類＞

リンパ管腫症・ゴーハム病の重症度分類

modified Rankin Scale（mRS）、食事・栄養、呼吸のそれぞれの評価スケールを用いて、いずれかが３以上を対象とする。

日本版modified Rankin Scale (mRS) 判定基準書		
modified Rankin Scale		参考にすべき点
0_	まったく症候がない	自覚症状および他覚徴候がともにない状態である
1_	症候はあっても明らかな障害はない： 日常の勤めや活動は行える	自覚症状および他覚徴候はあるが、発症以前から行っていた仕事や活動に制限はない状態である
2_	軽度の障害： 発症以前の活動がすべて行えるわけではないが、自分の身の回りのことは介助なしに行える	発症以前から行っていた仕事や活動に制限はあるが、日常生活は自立している状態である
3_	中等度の障害： 何らかの介助を必要とするが、歩行は介助なしに行える	買い物や公共交通機関を利用した外出などには介助を必要とするが、通常歩行、食事、身だしなみの維持、トイレなどには介助を必要としない状態である
4_	中等度から重度の障害： 歩行や身体的要求には介助が必要である	通常歩行、食事、身だしなみの維持、トイレなどには介助を必要とするが、持続的な介護は必要としない状態である
5_	重度の障害： 寝たきり、失禁状態、常に介護と見守りを必要とする	常に誰かの介助を必要とする状態である
6_	死亡	

日本脳卒中学会版

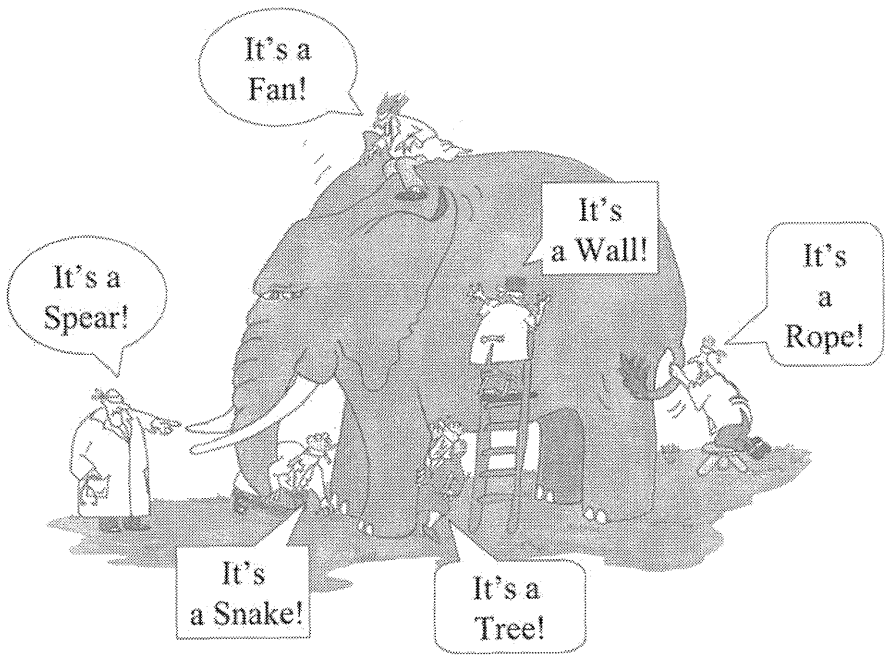
食事・栄養 (N)
0. 症候なし。
1. 時にむせる、食事動作がぎこちないなどの症候があるが、社会生活・日常生活に支障ない。
2. 食物形態の工夫や、食事時の道具の工夫を必要とする。
3. 食事・栄養摂取に何らかの介助を要する。
4. 補助的な非経口的栄養摂取（経管栄養、中心静脈栄養など）を必要とする。
5. 全面的に非経口的栄養摂取に依存している。

呼吸 (R)
0. 症候なし。

1. 肺活量の低下などの所見はあるが、社会生活・日常生活に支障ない。
2. 呼吸障害のために軽度の息切れなどの症状がある。
3. 呼吸症状が睡眠の妨げになる、あるいは着替えなどの日常生活動作で息切れが生じる。
4. 喀痰の吸引あるいは間欠的な換気補助装置使用が必要。
5. 気管切開あるいは継続的な換気補助装置使用が必要。

※診断基準及び重症度分類の適応における留意事項

１．病名診断に用いる臨床症状、検査所見等に関して、診断基準上に特段の規定がない場合には、いずれの時期のものを用いても差し支えない（ただし、当該疾病の経過を示す臨床症状等であって、確認可能なものに限る）。
２．治療開始後における重症度分類については、適切な医学的管理の下で治療が行われている状態で、直近６ヵ月間で最も悪い状態を医師が判断することとする。
３．なお、症状の程度が上記の重症度分類等で一定以上に該当しない者であるが、高額な医療を継続することが必要な者については、医療費助成の対象とする。


It's a Fan!
It's a Spear!
It's a Wall!
It's a Rope!
It's a Snake!
It's a Tree!

III. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Terui K, Nagata K, Ito M, Yamoto M, Shiraishi M, Taguchi T, Hayakawa M, Okuyama H, Yoshida H, Masumoto K, Kanamori Y, Goishi K, Urushihara N, Kawataki M, Inamura N, Kimura O, Okazaki T, Toyoshima K, Usui N.	Surgical approaches for neonatal congenital diaphragmatic hernia: a systematic review and meta-analysis.	Pediatr Surg Int.	31(10)	891-897	2015
Terui K, Nagata K, Hayakawa M, Okuyama H, Goishi K, Yokoi A, Tazuke Y, Takayasu H, Yoshida H, Usui N.	Growth Assessment and the Risk of Growth Retardation in Congenital Diaphragmatic Hernia: A Long-Term Follow-Up Study from the Japanese Congenital Diaphragmatic Hernia Study Group.	Eur J Pediatr Surg.	26(1)	60-66	2016
Nagata K, Usui N, Terui K, Takayasu H, Goishi K, Hayakawa M, Tazuke Y, Yokoi A, Okuyama H, Taguchi T.	Risk Factors for the Recurrence of the Congenital Diaphragmatic Hernia-Report from the Long-Term Follow-Up Study of Japanese CDH Study Group	Eur J Pediatr Surg.	25(1)	9-14	2015
Inamura N, Usui N, Okuyama H, Nagata K, Kanamori Y, Fujino Y, Takahashi S, Hayakawa M, Taguchi T.	Extracorporeal membrane oxygenation for congenital diaphragmatic hernia in Japan.	Pediatr Int.	57(4)	682-686	2015
Kuroda T, Nishijima E, Maeda K, Fuchimoto Y, Hirobe S, Tazuke Y, Watanabe T, Usui N.	Clinical features of congenital cystic lung diseases; a report on a nationwide multicenter study in Japan.	Eur J Pediatr Surg	26(1)	91-95	2016
Morita K, Yokoi A, Bitoh Y, Fukuzawa H, Okata Y, Iwade T, Endo K, Takemoto J, Tamaki A, Maeda K.	Severe acquired subglottic stenosis in children: analysis of clinical features and surgical outcomes based on the range of stenosis.	Pediatr Surg Int.	31(10)	943-947	2015
Ozeki M, Hori T, Kanda K, Kawamoto N, Ibuka T, Miyazaki T, Fukao T.	Everolimus for primary intestinal lymphangiectasia with protein-losing enteropathy.	Pediatrics	E-Pub	DOI: 10.1542/peds.2015-2562	2016
Nozawa A, Ozeki M, Kuze B, Asano T, Matsuoka K, Fukao T.	Gorham-Stout Disease of the Skull Base with Hearing Loss: Dramatic Recovery and Anti-Angiogenic Therapy.	Pediatr Blood Cancer	E-Pub	DOI: 10.1002/pbc.25886	2016
Ozeki M, Fujino A, Matsuoka K, Nosaka S, Kuroda T, Fukao T.	Clinical Features and Prognosis of Generalized Lymphatic Anomaly, Kaposiform Lymphangiomatosis and Gorham-Stout Disease.	Pediatr Blood Cancer	E-Pub	DOI: 10.1002/pbc.25914	2016

Matsumoto H, Ozeki M, Hori T, Kanda K, Kawamoto N, Nagano A, Azuma E, Miyazaki T, Fukao T.	Successful Everolimus Treatment of Kaposiform Hemangioendothelioma with Kasabach-Merritt Phenomenon: Clinical Efficacy and Adverse Effects of mTOR Inhibitor Therapy.	J Pediatr Hematol Oncol	E-Pub		2016
臼井規朗、中畠賢吾、銭谷昌弘、奈良啓悟、上野豪久、上原秀一郎、大植孝治、松岡健太郎.	先天性嚢胞性肺疾患における胎児超音波検査所見の再検討.	日本小児放射線学会雑誌	31	34-39	2015
藤野明浩、小関道夫、上野　滋、岩中　督、木下義晶、野坂俊夫、松岡健太郎、森川康英、黒田達夫.	リンパ管腫とリンパ管腫症・ゴーハム病の成人例の実際	小児外科	47	775-782	2015

IV. 研究成果の刊行物・別刷

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ORIGINAL ARTICLE

Surgical approaches for neonatal congenital diaphragmatic hernia: a systematic review and meta-analysis

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Abstract

Purpose The optimal surgical approach for neonatal congenital diaphragmatic hernia (CDH) remains unclear. We conducted a systematic review and meta-analysis of the effectiveness of endoscopic surgery (ES) for neonatal CDH.

Methods A systematic literature search was conducted using MEDLINE and the Cochrane Library. Studies that compared surgical approaches for neonatal CDH were selected. Mortality and recurrence of herniation were analyzed as primary endpoints. Each study was evaluated following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.

Results Eight observational studies comparing ES and open surgery (OS) met the criteria. As compared with the OS group, the ES group showed both a significantly lower mortality rate [risk ratio (RR) 0.18, 95 % confidence interval (CI) 0.09–0.38, $p < 0.0001$] and a significantly higher recurrence rate (RR 3.10, 95 % CI 1.95–4.88, $p < 0.00001$). However, serious selection bias was seen in seven of the eight studies—because the indication of ES had been determined intentionally, the ES groups may have included less severe cases.

Conclusion Although the evidence was insufficient, ES was clearly associated with more recurrence than was OS. Therefore, ES should not be the routine treatment for every neonate. It is crucially important to select suitable cases for ES.

Keywords Congenital diaphragmatic hernia · Video-assisted thoracic surgery · Minimally invasive surgical

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procedures · Conversion to open surgery, reoperation, meta-analysis

Introduction

Congenital diaphragmatic hernia (CDH) is a malformation characterized by a defect of the posterolateral diaphragm, intrathoracic herniation of abdominal viscera, and varying degrees of pulmonary hypoplasia and pulmonary hypertension [1]. Although survival in cases of CDH has improved during the past decades, the treatment of severe cases remains challenging, and a considerable number of survivors experience long-term morbidity [2, 3].

The initial treatment for CDH comprises surgical repair of the diaphragmatic defect and perioperative intensive care. Surgeries are commonly planned after stabilization of the patient's general condition. Traditionally, open surgery (OS) has been performed, mostly via laparotomy. However, endoscopic surgery (ES) (including laparoscopic and thoracoscopic surgeries) has become increasingly common since the mid-1990s. ES is recognized to be useful for late childhood CDH [4]. However, late childhood CDH appears to differ from neonatal CDH in several respects, especially in cases with early onset or prenatal diagnosis. In addition to their small body sizes, neonates with CDH often have unstable respiratory and circulatory dynamics. Therefore, the application of thoracoscopic surgery to neonatal CDH should be considered carefully.

In order to integrate the evidence from recent studies, we conducted a systematic review and meta-analysis of the effectiveness of ES for neonatal CDH.

Materials and methods

Electronic data sources and search planning

Systematic searches of English-language articles were conducted by using MEDLINE and the Cochrane Library, including all records dated from their first entries to March 2015. When searching MEDLINE, we used the term "congenital diaphragmatic hernia," as well as terms related to surgical methods, including "laparotomy," "transabdomi*," "abdomi*," "thoracotomy," "transthoracic*," "open," "laparoscop*," "thoracoscop*," "minimally invasive," and "minimal access." The term "congenital diaphragmatic hernia" was used when searching the Cochrane Library. The articles were screened according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (Fig. 1).

Selection criteria for included trials

To be included in this meta-analysis, each study had to fulfill the following criteria: (1) the article type was not a review, case report, or letter; (2) all candidates were neonates; and (3) ES and OS were compared. ES included laparoscopic and thoracoscopic surgery, while OS included open abdominal surgery and open chest surgery. There were no exclusions based on patient numbers or duration of follow-up.

Data abstraction from included trials

Two individual authors extracted data from each selected study. The following items were collected: (1) authors' names and year of publication, (2) title of the published study, (3) journal in which the study was published, (4) country and year of the study, (5) whether the study was single-center or multicenter, (6) whether the study had a prospective or retrospective design, (7) testing sample size, (8) patient age, (9) whether consecutive patients were included, (10) surgical approaches in both arms of the trial, (11) method of assigning patients to the two groups, (12) number of patients receiving each surgical approach, (13) number of patients who failed the allocated treatment (conversion to OS), (14) postoperative follow-up period, (15) number of postoperative deaths, and (16) number of patients who developed recurrence. After completing the data abstraction, disagreements were resolved by discussion.

Statistical analysis

Risk ratios (RRs) and 95 % confidential intervals (CIs) were determined using RevMan 5.3 software, which is provided by the Cochrane Collaboration (http://tech.cochrane.org/revman/download; Oxford, England). The random-effects model was used to estimate the combined outcomes [5]. Heterogeneity was assessed using the χ^2 test, and was quantified using I^2. I^2 less than 30 % was considered to reflect low heterogeneity [6]. Forest plots were used to display results graphically. The square around the estimate indicates the accuracy of the estimation (sample size), and the horizontal line represents the 95 % CI. When a statistically significant difference was observed between the groups, the number needed to cause harm (NNH) was calculated.

Assessing quality of evidence

The quality of evidence for each outcome was evaluated based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [7]. In the

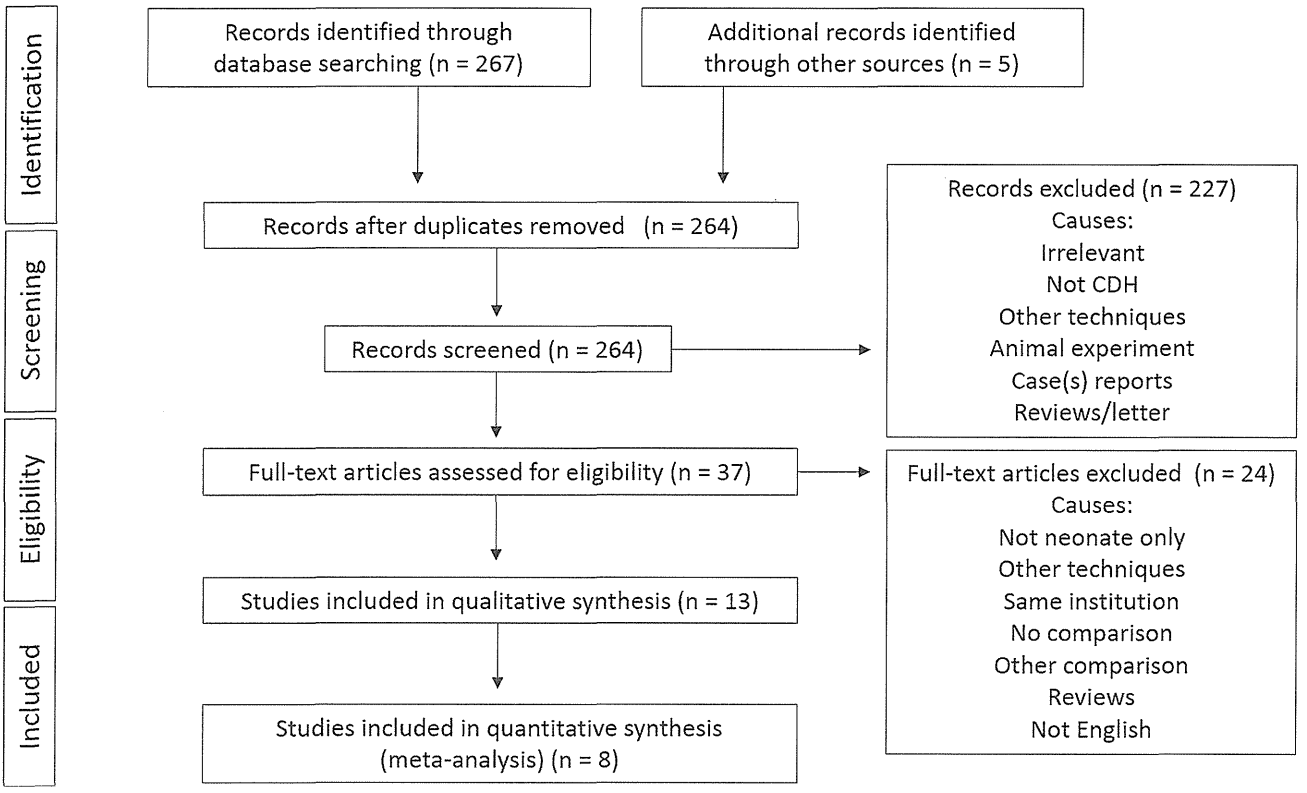

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart

GRADE system, the quality of evidence is rated as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), or very low (any estimate of effect is very uncertain). The analyses were performed using GRADEpro software version 3.6 (http://tech.cochrane.org/revman/gradepro), as also provided by the Cochrane Collaboration.

Outcomes

Mortality and recurrence of herniation were analyzed as primary endpoints. The ES group included the patients who initially underwent ES and were later converted to OS.

Results

Study selection

Of 264 search results, 226 studies were excluded based on titles and abstracts. After screening the remaining 38 studies based on their full texts, 14 studies were included in the qualitative synthesis [8–21]. Furthermore, eight observational studies [14–21] published between 2009 and 2013 were included in the quantitative synthesis (Fig. 1). There were seven single-center studies [14–18, 20, 21] and one study that used the database of the Congenital Diaphragmatic Hernia Study Group (CDHSG) from January 1995 to January 2010 [19].

Description of included studies

There were five systematic reviews [8–12], including the Interventional Procedure Guidance by the National Institute for Health and Clinical Excellence [9]. Of these systematic reviews, four included both neonates and infants/childhood cases [9–12], while only one systematic review was specific to neonates [8]. However, this neonate-specific systematic review included only three studies; the five newly reported studies were not included. Although there was one randomized controlled trial (RCT) [13], the investigated outcome was intraoperative condition, rather than prognosis. Therefore, we excluded the RCT from the quantitative synthesis.

The eight observational studies were included in a quantitative synthesis [14–21]. The eight studies included a total of 4698 patients, of whom 288 belonged to ES groups

and 4410 belonged to OS groups. In seven of the studies, ES only included thoracoscopic surgery [14–18, 20, 21]. In the other study, the ES group included 151 cases, of which 125 (82.8 %) were treated by a thoracoscopic approach and the remainder were treated by a laparoscopic approach [19]. The characteristics of the included studies are presented in Table 1. All of the surgeries were performed during the neonatal period. The overall rates of patch usage were 34.0 % in the ES group and 51.5 % in the OS group. The median rate of conversion in each facility was 25.1 % (3.4–40.0 %), and the overall rate of conversion was 10.7 %. Reasons for conversion to OS included technical problems and unstable cardiorespiratory dynamics during surgery. Across five of the studies, the mean duration of follow-up varied from 1.2 to 37 months; however, the duration of follow-up was not described in the remaining three studies.

Methodological quality of included studies

As assessed on the GRADE scale, the quality of evidence was very low for all outcomes (Fig. 2). There was very serious risk of bias due to inappropriate patient selection, unequal follow-up durations, and the absence of controlling for confounding. Particularly, selection bias cannot to be ignored; patients who underwent ES were selected by their surgeons or according to facility criteria in six of the studies [16–21]. Therefore, the ES groups potentially included milder cases, as compared with the OS groups. In Cho et al.'s study, the ES group was not selected intentionally. Instead, historical controls were used—OSs performed in 2001–2004 were compared with ESs performed in 2001–2007. However, the therapeutic strategy also changed in 2004, and the mortality rates before and after 2004 were 21.4 and 6.9 %, respectively [14]. Thus, this difference was regarded as an indication of serious performance bias. Gourlay et al. used the control (OS) cases, as matched by congenital heart defects, extracorporeal membrane oxygenation (ECMO) use, ventilatory peak inspiratory pressure, and oxygenation index on the day of the operation [15].

There was also substantial imprecision because of the broad confidence intervals in all studies, except for the database study [19]. Regarding the outcome of recurrence, strong associations (RR >2.0) were seen in seven studies [14, 15, 17–21]. Furthermore, plausible forms of confounding would be expected to decrease the effect, because the higher recurrence rate was observed in the ES group, which is assumed to have included many mild cases.

Mortality

No heterogeneity was observed among the included studies ($\tau^2 = 0.00$, $\chi^2 = 1.32$, $\gamma = 5$, $p = 0.93$; $I^2 = 0$ %). The incidence of overall mortality was higher in the OS group than in the ES group (RR = 0.18; 95 % CI 0.09–0.38; $z = 4.48$; $p < 0.00001$; Fig. 3). The NNH was 6.7 for mortality.

Recurrence

No heterogeneity was observed among the included studies ($\tau^2 = 0.00$, $\chi^2 = 2.76$, $\gamma = 7$, $p = 0.91$; $I^2 = 0$ %). The

Table 1 Characteristics of the included studies

References	Surgery	No.	Age at operation (days)	Patch use (%)	Conversion to OS (%)	Follow-up (months)
Cho et al. [14]	ES	29	ns	52	3	1.2
	OS	28	ns	43	–	8.1
Gourlay et al. [15]	ES	20	ns	20	5	14.5
	OS	18	ns	44	–	37.0
Keijzer et al. [16]	ES	23	3.0	35	26	ns
	OS	23	4.1	20	–	ns
McHoney et al. [17]	ES	13	12.5	46	39	15
	OS	35	11.7	34	–	31
Gander et al. [18]	ES	26	3	46	35	14
	OS	19	4	84	–	14
Tsao et al. [19]	ES	151	5.4	33	ns	ns
	OS	4239	6.9	52	–	ns
Nam et al. [20]	ES	16	4.6	25	13	35.6
	OS	34	4.3	15	–	
Tanaka et al. [21]	ES	10	ns	0	40	ns
	OS	14	ns	ns	–	ns

ES endoscopic surgery, *OS* open surgery, *ns* not stated

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MIS	OS	Relative (95% CI)	Absolute		
Mortality												
7	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	6/275 (2.2%)	748/4375 (17.1%)	RR 0.18 (0.09 to 0.38)	140 fewer per 1000 (from 106 fewer to 156 fewer)	⊕OOO VERY LOW	CRITICAL
Recurrence												
8	observational studies	very serious[2]	no serious inconsistency	serious[4]	serious[3]	strong association[5] reduced effect for RR >> 1 or RR << 1[6]	33/257 (12.8%)	122/4415 (2.8%)	RR 3.10 (1.95 to 4.94)	58029 more per 1,000,000 (from 26251 more to 108874 more)	⊕OOO VERY LOW	CRITICAL

[1] Including 8 case-control studies

[2] Due to selection bias, unequable follow-up duration, and without controlling for confounding.

[3] Due to wide range of confidence interval in all the studies but one using the database.

[4] Cases with conversion to OS were allocated into ES group.

[5] RR>2.0 in 7 studies.

[6] In 7 studies, the rates of recurrence were higher in selected mild cases.

Fig. 2 Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evidence profile. The quality of evidence was low for both mortality and recurrence

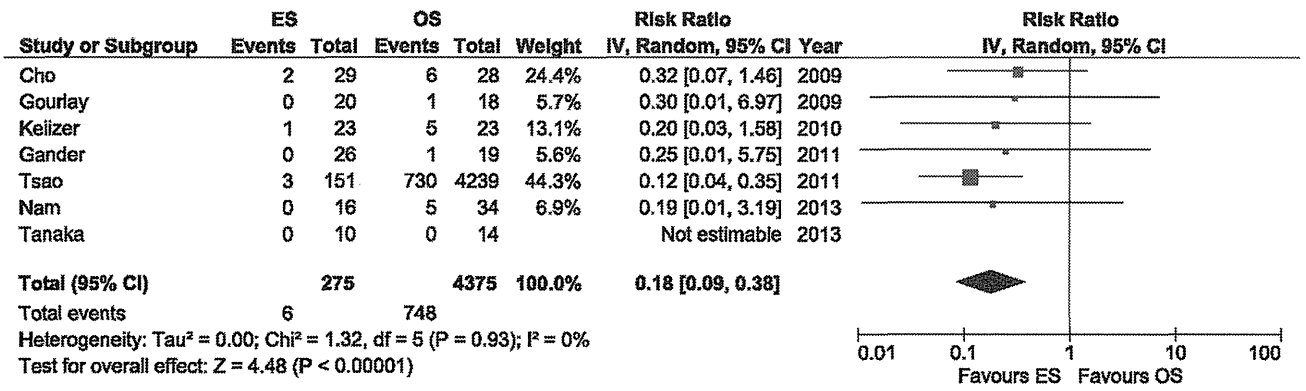

Fig. 3 Forest plot of mortality rates, comparing endoscopic surgery with open surgery

risk of recurrence was higher in the ES group than in the OS group (RR = 3.10; 95 % CI 1.95–4.94; $z = 4.78$; $p < 0.00001$; Fig. 4). NNH of recurrence was 10.0.

Discussion

The present systematic review was designed to establish the optimal surgical approaches for neonatal CDH. Although some systematic reviews regarding CDH have been published previously, this is currently the most up-to-date review that is specific to neonatal CDH. As compared with the previous report on this subject [8], this review includes five additional studies. Furthermore, the present review is the first to rate the quality of evidence according to the GRADE system, which has been broadly accepted.

In regard to the outcome of death, mortality in the ES group was significantly lower than that in the OS group. However, the quality of evidence was "very low," mainly as a product of selection bias. As noted previously, ES was selected intentionally, and it is likely that the ES group included a larger share of cases that were less severe. Therefore, the low mortality in the ES group could not be taken at face value, and it was impossible to draw a definitive conclusion concerning mortality.

In regard to recurrence, the rate of recurrence was significantly higher in the ES group than in the OS group. The quality of evidence was "very low," mainly as a product of the selection bias discussed above. However, unlike the mortality outcome, the recurrence rate was higher in the ES group. Since the ES group was expected to include less severe cases, the effect size may have been decreased by

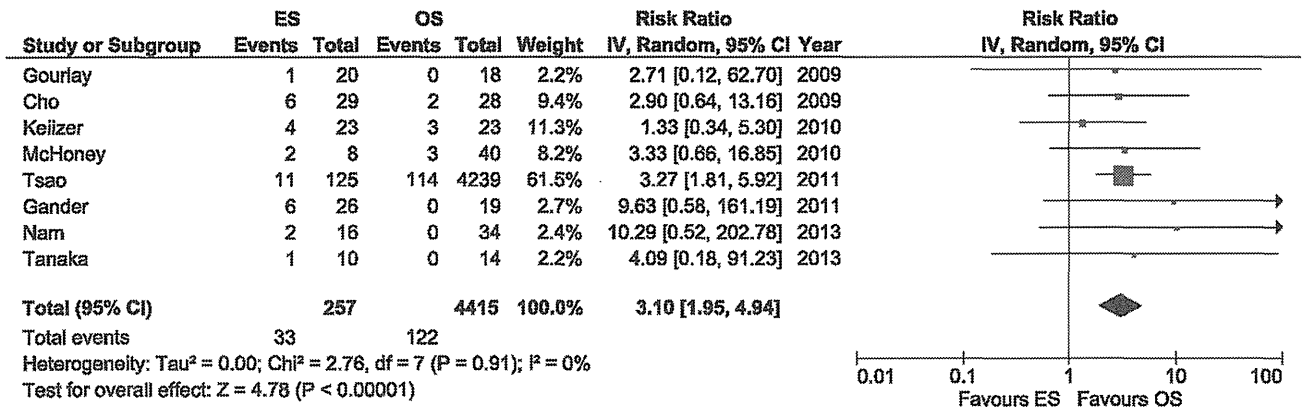

Fig. 4 Forest plot of recurrence rates, comparing endoscopic surgery with open surgery

this confounding. Furthermore, the relative risk was high (RR = 3.10) and the influence was considered to be relatively large.

To estimate the rate of recurrence in an appropriate manner, the rate of conversion to OS should also be considered. Among the seven observational studies that clearly described completion rates, only one study presented the recurrence rate in the ES group by counting the completed cases [17]. In the other six studies, the calculation of recurrence rates in the ES group included cases with conversion to OS [14–16, 18–21]. Therefore, the recurrence rate in the ES group could have been underestimated.

The presumed advantages of ES for CDH are good cosmetics for the wounds, as well as reduced intra- and post-operative surgical stresses. Early recovery from surgical stresses often reduces the duration of postoperative mechanical ventilation and the overall length of stay [15]. Furthermore, the longitudinal incidences of subsequent scoliosis and chest deformity may also be reduced [18, 22]. On the other hand, ES was clearly associated with a higher recurrence rate than OS in our study. Additionally, the RCT that compared surgical approaches for CDH showed that thoracoscopic repair of CDH is associated with severe intraoperative hypercapnia and acidosis [13]. This unstable status during thoracoscopic surgery probably resulted from CO_2 insufflation into the thorax [23]. Little information is available regarding the cost-effectiveness; Gourlay et al. reported the adjusted total hospital charges of both approaches did not have significant difference [15].

Considering the advantages and disadvantages that have been described above, we concluded that ES should not be the routine treatment for every neonate. The previous systematic reviews also noted high rates of recurrence, but their conclusions were controversial. The first systematic review that was specific to neonatal CDH did not refer to clear strategies, but instead emphasized the importance of further studies, including a prospective registry followed by RCTs. Vijfhuize et al. concluded that ES potentially had beneficial effects on postoperative recovery in a selected population, and that the higher recurrence rate would be overcome by technical developments [10]. The other two systematic reviews concluded that the potential morbidity associated with ES should be carefully considered [9, 12]. Despite these controversies, the previous reviews agreed that it is crucially important to select cases that are suitable for ES. However, the optimal criteria for ES in neonatal CDH remain unclear. Various criteria have been adopted in individual studies: no iNO [13, 20, 21], no ECMO [13, 15, 20], low FiO_2 setting (40–50 %) [13, 14], low airway pressure (mean airway pressure <13 mmHg [14], maximum inspiratory pressure <26 cmH_2O [15]), no vasopressor [13, 14], infants who do not have very low birth weights [13], no cardiac malformation [13], pre-ductal SaO_2 >90 % [14], oxygenation index <5 [15], no costal malformation [20], no respiratory distress after birth [17], and stable vital signs in the lateral position for 2 h [14] or 10 min [21]. The development of a consensus is a topic for future discussion.

It is useful to consider the characteristics of CDH patients with recurrence when thinking about the selection criteria for ES. In a recent systematic review that included neonatal and infantile CDH, the recurrence rate was shown to be higher after ES with patch repair (odds ratio 4.29, 95 % CI 2.13–8.67, $p < 0.0001$) than after ES with primary closure (odds ratio 2.05, 95 % CI 0.77–5.45, $p < 0.15$) [12]. The authors strongly recommended converting to OS if a patch was required during ES. Vijfhuize et al. presented a decision algorithm for ES, and excluded cases with diaphragmatic agenesis and/or liver up, as well as cases with unstable respiratory and circulatory dynamics [10]. Although the use of a patch seemed to be a risk factor for recurrence in ES, patch use is difficult to predict. In actuality, the rates of patch use among operative cases were 51.0 % in CDHSG [19] and 37.8 % in the Japanese CDH Study Group [24]. To establish definitive criteria for ES, further studies are needed.

In conclusion, evidence for the effectiveness of ES in CDH neonates remains insufficient. As derived in the present study, the best available evidence showed that ES had an unclear effect on mortality in neonatal CDH, and that the recurrence rate in the ES group was clearly higher than that in the OS group. Therefore, ES should not be the routine treatment for every neonate. It is crucially important to select suitable cases for ES, but the details of this selection remain a topic for future discussion.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. van den Hout L, Sluiter I, Gischler S, De Klein A, Rottier R, Ijsselstijn H, Reiss I, Tibboel D (2009) Can we improve outcome of congenital diaphragmatic hernia? Pediatr Surg Int 25:733–743. doi:10.1007/s00383-009-2425-8
2. Nagata K, Usui N, Kanamori Y, Takahashi S, Hayakawa M, Okuyama H, Inamura N, Fujino Y, Taguchi T (2013) The current profile and outcome of congenital diaphragmatic hernia: a nationwide survey in Japan. J Pediatr Surg 48:738–744. doi:10.1016/j.jpedsurg.2012.12.017
3. Peetsold MG, Heij HA, Kneepkens CM, Nagelkerke AF, Huisman J, Gemke RJ (2009) The long-term follow-up of patients with a congenital diaphragmatic hernia: a broad spectrum of morbidity. Pediatr Surg Int 25:1–17. doi:10.1007/s00383-008-2257-y
4. Morini F, Bagolan P (2012) Surgical techniques in congenital diaphragmatic hernia. Eur J Pediatr Surg 22:355–363. doi:10.1055/s-0032-1329411
5. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188. doi:10.1016/0197-2456(86)90046-2
6. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21:1539–1558. doi:10.1002/sim.1186
7. Atkins D, Best D, Briss PA et al (2004) Grading quality of evidence and strength of recommendations. BMJ 328:1490. doi:10.1136/bmj.328.7454.1490
8. Lansdale N, Alam S, Losty PD, Jesudason EC (2010) Neonatal endosurgical congenital diaphragmatic hernia repair: a systematic review and meta-analysis. Ann Surg 252:20–26. doi:10.1097/SLA.0b013e3181dca0e8
9. NICE interventional procedure guidance [IPG379] (2011) Thoracoscopic repair of congenital diaphragmatic hernia in neonates. https://www.nice.org.uk/guidance/ipg379. Accessed 6 Mar 2015
10. Vijfhuize S, Deden AC, Costerus SA, Sloots CE, Wijnen RM (2012) Minimal access surgery for repair of congenital diaphragmatic hernia: is it advantageous?—an open review. Eur J Pediatr Surg 22:364–373. doi:10.1055/s-0032-1329532
11. Dingemann C, Ure B, Dingemann J (2014) Thoracoscopic procedures in pediatric surgery: what is the evidence? Eur J Pediatr Surg 24:14–19. doi:10.1055/s-0033-1350060
12. Chan E, Wayne C, Nasr A (2014) Minimally invasive versus open repair of Bochdalek hernia: a meta-analysis. J Pediatr Surg 49:694–699. doi:10.1016/j.jpedsurg.2014.02.049
13. Bishay M, Giacomello L, Retrosi G et al (2013) Hypercapnia and acidosis during open and thoracoscopic repair of congenital diaphragmatic hernia and esophageal atresia: results of a pilot randomized controlled trial. Ann Surg 258:895–900. doi:10.1097/SLA.0b013e31828fab55
14. Cho SD, Krishnaswami S, Mckee JC, Zallen G, Silen ML, Bliss DW (2009) Analysis of 29 consecutive thoracoscopic repairs of congenital diaphragmatic hernia in neonates compared to historical controls. J Pediatr Surg 44:80–86. doi:10.1016/j.jpedsurg.2008.10.013
15. Gourlay DM, Cassidy LD, Sato TT, Lal DR, Arca MJ (2009) Beyond feasibility: a comparison of newborns undergoing thoracoscopic and open repair of congenital diaphragmatic hernias. J Pediatr Surg 44:1702–1727. doi:10.1016/j.jpedsurg.2008.11.030
16. Keijzer R, van de Ven C, Vlot J, Sloots C, Madern G, Tibboel D, Bax K (2010) Thoracoscopic repair in congenital diaphragmatic hernia: patching is safe and reduces the recurrence rate. J Pediatr Surg 45:953–957. doi:10.1016/j.jpedsurg.2010.02.017
17. McHoney M, Giacomello L, Nah SA, De Coppi P, Kiely EM, Curry JI, Drake DP, Eaton S, Pierro A (2010) Thoracoscopic repair of congenital diaphragmatic hernia: intraoperative ventilation and recurrence. J Pediatr Surg 45:355–359. doi:10.1016/j.jpedsurg.2009.10.072
18. Gander JW, Fisher JC, Gross ER, Reichstein AR, Cowles RA, Aspelund G, Stolar CJ, Kuenzler KA (2011) Early recurrence of congenital diaphragmatic hernia is higher after thoracoscopic than open repair: a single institutional study. J Pediatr Surg 46:1303–1308. doi:10.1016/j.jpedsurg.2010.11.048
19. Tsao K, Lally PA, Lally KP, Congenital Diaphragmatic Hernia Study Group (2011) Minimally invasive repair of congenital diaphragmatic hernia. J Pediatr Surg 46:1158–1164. doi:10.1016/j.jpedsurg.2011.03.050
20. Nam SH, Cho MJ, Kim DY, Kim SC (2013) Shifting from laparotomy to thoracoscopic repair of congenital diaphragmatic hernia in neonates: early experience. World J Surg 37:2711–2716. doi:10.1007/s00268-013-2189-0
21. Tanaka T, Okazaki T, Fukatsu Y, Okawada M, Koga H, Miyano G, Ogasawara Y, Lane GJ, Yamataka A (2013) Surgical intervention for congenital diaphragmatic hernia: open versus thoracoscopic surgery. Pediatr Surg Int 29:1183–1186. doi:10.1007/s00383-013-3382-9
22. Lao OB, Crouthamel MR, Goldin AB, Sawin RS, Waldhausen JH, Kim SS (2010) Thoracoscopic repair of congenital diaphragmatic hernia in infancy. J Laparoendosc Adv Surg Tech A 20:271–276. doi:10.1089/lap.2009.0150
23. Kalfa N, Allal H, Raux O et al (2007) Multicentric assessment of the safety of neonatal videosurgery. Surg Endosc 21:303–308. doi:10.1007/s00464-006-0044-1
24. Nagata K, Usui N, Terui K, Takayasu H, Goishi K, Hayakawa M, Tazuke Y, Yokoi A, Okuyama H, Taguchi T (2015) Risk factors for the recurrence of the congenital diaphragmatic hernia-report from the long-term follow-up study of Japanese CDH study group. Eur J Pediatr Surg 25:9–14. doi:10.1055/s-0034-1395486

Growth Assessment and the Risk of Growth Retardation in Congenital Diaphragmatic Hernia: A Long-Term Follow-Up Study from the Japanese Congenital Diaphragmatic Hernia Study Group

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Abstract

Introduction Little information exists about the physical growth of patients with congenital diaphragmatic hernia (CDH). This study aimed to assess the growth of patients with CDH during long follow-up periods, and to identify growth retardation (GR) risk factors.

Patients and Methods A multicenter retrospective observational study was conducted in 2013. Of the 228 patients with CDH born between 2006 and 2010, 182 (79.8%) survived to discharge, and 174 cases were included in the study. Body weights and heights were measured at 1.5, 3, and 6 years of age. GR was defined as a Z-score relating to the weight or height of < -2.0. Cases with GR at 1.5, 3, or 6 years of age comprised the GR group. The clinical variables of the GR and non-GR groups were compared using univariate analysis. Multiple logistic regression analyses were conducted successively on the factors that were significant at $p < 0.01$ in the univariate analysis and had low correlations with other factors ($r < 0.7$). The numerical data were

Keywords
- congenital diaphragmatic hernia
- growth
- long-term care
- nutrition assessment
- birth weight

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divided into two groups based on a cutoff value that was calculated from a receiver operating characteristic curve.

Results The GR group comprised 35 cases (22.7%). The rates of GR at 1.5, 3, and 6 years of age were 19.5 (26/133), 14.4 (16/111), and 13.5% (5/37), respectively. The body weight Z-scores improved in cases with GR between the ages of 1.5 and 3 years ($p = 0.036$). As the patients aged, the wasting type of GR decreased in frequency (31, 0, and 0% at 1.5, 3, and 6 years of age, respectively) and the stunting type of GR increased in frequency (27, 31, and 100% at 1.5, 3, and 6 years of age, respectively). The univariate analysis showed that birth weight and height, liver-up, large defect size of the diaphragm, use of nitric oxide, patch repair, long hospital stay, home oxygen treatment (HOT), and vasodilator administration at discharge were significant risk factors of GR. The multivariate analysis determined that a birth weight of < 2,698 g (odds ratio [OR] = 5.5, 95% confidence interval [CI] = 2.1–16.8, $p < 0.001$) and HOT (OR = 5.8, 95%CI = 1.6–23.8, $p = 0.007$) were significant risk factors for GR.

Conclusion GR was observed in 22.7% of the CDH survivors. Body weight improved between 1.5 and 3 years of age in the GR cases, but some patients developed chronic malnutrition via acute malnutrition. Low birth weight and the need for HOT were GR risk factors. Aggressive management of acute malnutrition may improve the growth of patients with CDH.

Introduction

The overall survival of congenital diaphragmatic hernia (CDH) patients has improved over the past two decades. However, a significant number of survivors suffer from a variety of morbidities, including developmental delays, growth retardation (GR), bronchopulmonary dysplasia (BPD), gastroesophageal reflux, and hearing loss. Therefore, agreement about the importance of long-term follow-up for CDH survivors is unanimous.[1] Physical growth is the important parameter to assess during follow-up, because it accurately reflects a patient's nutritional status and the severity of the morbidity. GR is also linked to impaired immune functions, inferior cognitive/academic functioning, and personality development disorders.[2]

GR has been defined using different methodologies, but the Z-score has frequently been used in recent studies, because it evaluates children's growth precisely.[3] The rates of GR in CDH, which was defined as a weight Z-score of < -2.0, were 20.8 and 8.2%, respectively,[4,5] at 1 year of age in recent single-institution studies. Both studies showed improving trends associated with growth in CDH survivors during the first year of life, but little was known about growth thereafter. Cortes et al showed that the incidence rates of GR, which was defined as a Z-score of < -2.0, were 68.8% at 1 year and 28.6% at 2 years of age, but the study's cohort comprised extremely severe CDH cases who met the criteria for fetal tracheal occlusion.[6] Jaillard et al reported that the incidence of GR, which was defined as a weight that was lower than the 5th percentile at 2 years of age, was 17.6%, but the trend over the 2-year course was not assessed.[7] Kamata et al found that 21.2, 15.2, and 12.1% of their patients had weights that were lower than the 25th percentile at 1, 2, and 3 years of age, respectively.[8] They also stated that all four of the patients who had weights that were lower than the 25th percentile at 3 years of age were within the reference range of the Waterlow classification, and this has been the only report on the classification of GR in CDH.[8] Therefore, this study's first purpose was to assess the growth of patients with CDH during long-term follow-up using the Z-score and Waterlow classification.

The pathophysiology of GR in CDH remains poorly understood, but it is considered multifactorial and involves catabolic stress during the neonatal period, gastroesophageal reflux disease, oral aversion, and an increased caloric requirement as a consequence of persistent pulmonary morbidity.[1,7,9] The severity of CDH itself, a low birth weight, low nutritional intakes, and pulmonary insufficiency have been reported as risk factors associated with GR.[5,10,11] It is important to know the factors that contribute to GR and to take specific measures to reduce the numbers of patients with GR; hence, this study's second purpose was to identify the risk factors for GR in CDH survivors, and to discuss available solutions.

Patients and Methods

Patient Selection

A multicenter retrospective observational study was conducted between September 2013 and October 2013 by the nine high-volume centers that belong to the Japanese Congenital Diaphragmatic Hernia Study Group and that declared their intention to participate in the study. This study was subsequent of a nationwide survey of neonatal CDH conducted by the Japanese Congenital Diaphragmatic Hernia Study Group in 2011.[12] Of the 228 patients, who were born with CDH between January 2006 and

December 2010 and who underwent operations at the nine participating institutions, 182 patients (79.8%) survived to discharge. Of these surviving patients, 174 were included in the present study. Patients who had chromosome abnormalities ($n = 5$) or very low birth weights ($n = 3$) were excluded from the study. The study was performed after it had received approval from Chiba University's institutional ethics committee (no. 509) and from the independent ethics committees of the eight other participating institutions.

Data Collection

Body weights and heights, which were measured when the patients were 1.5, 3, and 6 years of age during follow-up assessments, were retrieved from the patients' medical records. Only the data that were gathered when the patients were 1.5 years of age were adjusted according to gestational age. The time point defined as 1.5 years of age ranged from 1 year and 3 months to 1 year and 9 months of age. The time point defined as 3 years of age ranged from 2 years and 9 months to 3 years and 3 months of age. The time point defined as 6 years of age ranged from 5 years and 7 months to 6 years and 5 months of age. The Z-scores for weight and height were calculated according to the patient's sex, using the average values and the standard deviations for weight and height at each month of age. These values were obtained from national databases from 12,426 infants and 695,600 school children, respectively.[13,14] GR was defined as a weight or height Z-score that was < -2.0 at each time point. The patients who had GR at any of the three time points were assigned to the GR group. The details of the patients' GR were evaluated using the Waterlow classification.[15] Briefly, a percentage of the height divided by the standard height for the patient's age (H/A) and a percentage of the weight divided by the standard weight for height (W/H) were used to evaluate GR. A H/A of $< 90\%$ is defined as the stunting type of GR, which represents chronic malnutrition. A W/H of $< 80\%$ is defined as the wasting type of GR, which represents acute malnutrition.

The clinical variables of the GR and non-GR groups were compared. The following factors were assessed by reviewing the medical records: sex, gestational age, birth weight, birth height, whether the baby was small for the gestational age (SGA), the Apgar scores at 1 minute and 5 minutes, prenatal diagnoses, whether the patient was inborn or outborn, the mode of delivery, the side of the hernia, the use of inhaled nitric oxide, the use of extracorporeal membrane oxygenation, whether patch repair was undertaken during the primary operation, a surgical finding of liver-up, the size of the defect in the diaphragm, which was categorized as a defect of $< 25\%$, $\geq 25\%$ and $< 75\%$, $\geq 75\%$ and $< 100\%$, or agenesis, the length of the hospital stay, weight at discharge, vasodilator administration at discharge, home oxygen treatment (HOT), a history of surgery for ileus, a history of surgery for gastroesophageal reflux disease, the recurrence of herniation, and the duration of follow-up. SGA was defined as a birth weight that was below the 10th percentile for the gestational age using the Japanese gestational age-specific criteria for birth weight that are based on a nationwide population.[16] Variables that had high levels ($> 15\%$) of missing data were excluded from this study.

Statistical Analysis

The statistical analyses were performed using the JMP software program, version 9.02 (SAS Inc., Cary, North Carolina, United States). As continuous variables were not normally distributed, they were described as median values with an interquartile range 25th to 75th percentiles (IQR). The Wilcoxon rank-sum test and Fisher exact test were used to compare values for the univariate analyses. Multiple logistic regression analyses were conducted successively on the factors that were statistically significant at $p < 0.01$ and had low correlations with other factors ($r < 0.7$). In the multivariate analysis, the continuous data were divided into two groups according to a cutoff value that was calculated from a receiver operating characteristic curve. p Values of < 0.05 were considered statistically significant.

Results

Patients' Demographics

No deaths occurred during the follow-up period, and the median values of the patients' age was 4.3 (IQR, 3.4–5.9) years. Valid data relating to body size at the three time points were obtained for 154 patients, and for 133, 111, and 37 patients at 1.5, 3, and 6 years of age, respectively. Of the 154 survivors who had valid physical data, 133 cases (86.4%) were diagnosed prenatally. The right-sided herniation rate was 8.4%. The gestational age, birth weight and height were 37.9 (IQR, 37.1–38.7) weeks, 2,745 (IQR, 2,502–2964) g, and 48.4 (IQR, 46.5–49.5) cm, respectively. Of the survivors, 10.4% were determined to be SGA, and 81.3% of the patients who were SGA were low-birth-weight infants. Cases with isolated CDH accounted for 94.6% of the patients. Cases with diaphragmatic defects of $\geq 75\%$ accounted for 27.0% of the patients.

Growth Assessment

A total of 35 cases (22.7%) were assigned to the GR group. The rates of GR at 1.5, 3, and 6 years of age were 19.5 (26/133), 14.4 (16/111), and 13.5% (5/37), respectively. In the non-GR group, the median values of weight Z-scores at 1.5, 3, and 6 years of age were −0.58 (IQR, −1.35 to 0.22), −0.69 (IQR, −1.07 to 0.10), and −0.75 (IQR, −1.00 to −0.45), respectively (▸Fig. 1A), and the median values of height Z-scores at 1.5, 3, and 6 years of age were −0.43 (IQR, −0.96 to 0.44), −0.43 (IQR, −1.01 to 0.34), and −0.06 (IQR, −1.00 to 0.15), respectively (▸Fig. 1B). In the GR group, the weight Z-scores at 1.5, 3, and 6 years of age were −2.27 (IQR, −2.71 to −1.48), −1.90 (IQR, −2.13 to −1.30), and −1.88 (IQR, −1.94 to −1.81), respectively (▸Fig. 1C), and the height Z-scores at 1.5, 3, and 6 years of age were −2.33 (IQR, −2.71 to −2.12), −2.09 (IQR, −2.63 to −1.63), and −1.88 (IQR, −2.63 to −1.65), respectively (▸Fig. 1D). In the GR patients, the weight Z-score at 3 years of age was significantly higher than that at 1.5 years of age ($p = 0.036$).

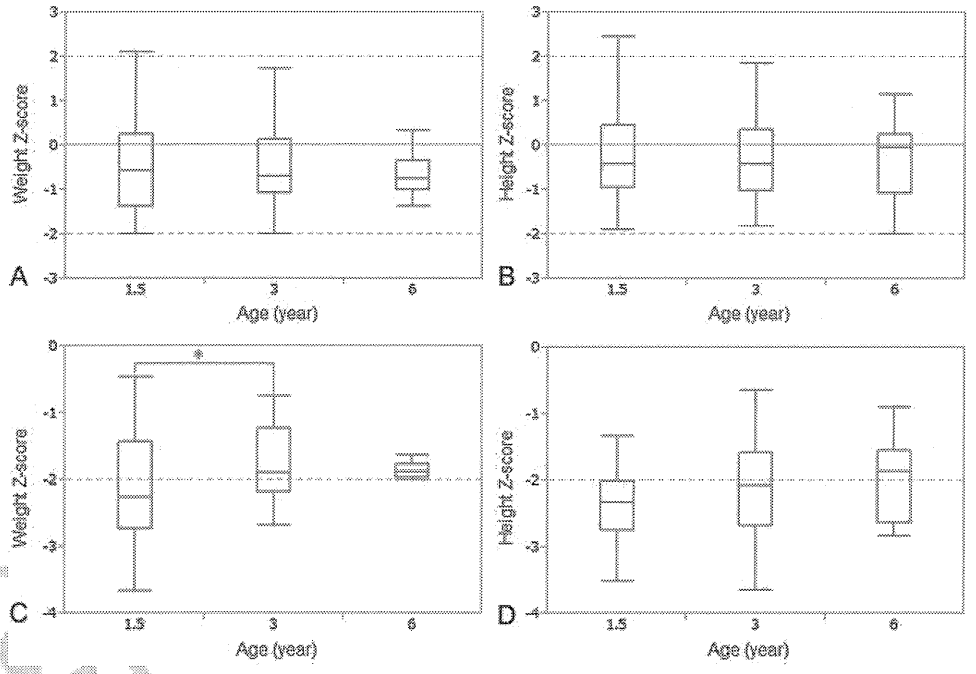

Fig. 1 Box-and-whisker plots of the Z-scores for weight and height in congenital diaphragmatic hernia survivors without growth retardation (A, B) and with growth retardation (C, D). The horizontal lines, lengths of the boxes, and whiskers represent the median values of the Z-scores, the interquartile ranges, and the ranges, respectively (*$p < 0.05$). In the patients with growth retardation, the Z-score for weight at 3 years of age was significantly higher than that at 1.5 years of age ($p = 0.036$).

►Fig. 2 illustrates the Waterlow classification of the GR cases. Among the GR cases, the rates of the stunting type of GR were 26.9, 31.3, and 100.0% at 1.5, 3, and 6 years of age, respectively. The wasting type of GR was only seen at 1.5 years of age (30.8%), and it included two cases who had both the stunting and the wasting types of GR. As the patients aged, the number of patients with the wasting type of GR declined and the stunting type of GR predominated.

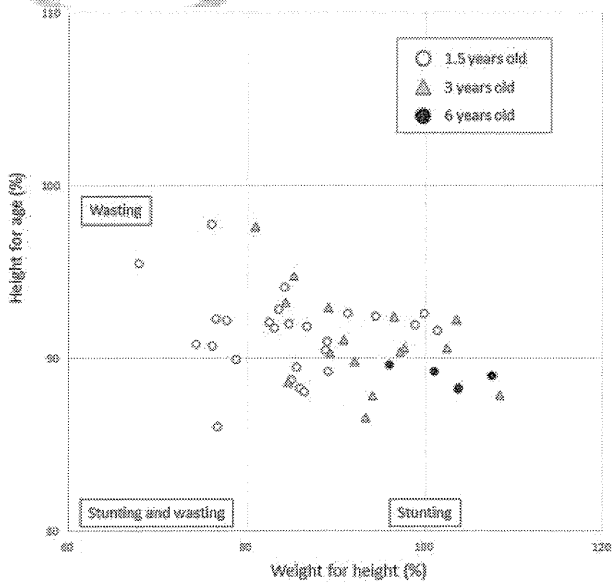

Fig. 2 The Waterlow classification of the survivors of congenital diaphragmatic hernia and growth retardation (GR). As the patients aged, the numbers of patients with the wasting type of GR decreased and the stunting type of GR became predominant.

Risks for Growth Retardation

►Table 1 showed the risk of GR in CDH patients assessed by univariate analysis. Multiple logistic regression analyses were conducted successively on the factors that were statistically significant ($p < 0.01$), which showed that a birth weight of < 2,698 g (cutoff value) (odds ratio [OR] = 5.5, 95% confidence interval [CI] = 2.1–16.8, $p < 0.001$) and HOT (OR = 5.8, 95%CI = 1.6–23.8, $p = 0.007$) were significant risk factors for GR (►Table 2). The factor of defect size of the diaphragm ≥ 75% was excluded from the multivariate analysis because of high correlation with the factor of patch repair at the primary operation ($r = 0.73$).

Discussion

This study has demonstrated that a considerable number of CDH survivors had GR during the long-term follow-up assessments, and the findings were roughly consistent with previous reports. However, the definition of GR and the timings of the evaluations were different (►Table 3). Almost none of the data from the 1980s and 1990s can be used for direct comparisons, because GR was defined as weights that were lower than the 5th percentile or the 25th percentile.[7,8,10,11,17–20] A Z-score of < − 2 was used as the definition of GR in three studies undertaken in the 2000s. Leeuwen et al reported a GR rate of 20.8% among CDH patients aged 1 year, which is similar to the rate determined in our study.[4] The GR rate was high at 68.8% at 1 year of age among