RCT を開始した。今後，北米や南米，オーストラリアの一部施設もこの研究への共同参加を予定している。そのプロトコールは次稿に詳述されているため省略するが，大きく分けて 2 つの臨床試験で構成されている。すなわち，プライマリアウトカムを患児の生命予後においた重症例に対する臨床試験と，患児の出生後の肺機能においた中等症例に対する臨床試験である。各臨床試験への適応は単胎，本症単独，左側例に加え，肺低形成の重症度によって判定されるが，肺低形成の重症度判定において O/E LHR がもっとも重視されている点が特徴といえる。例えば，重症例の臨床試験では O/E LHR＜25％のみで適応とされ，肝脱出の有無は問われない。

IV. わが国における胎児治療の適応症例数と問題点

わが国では，2012 年 10 月現在まで FETO による胎児治療は行われていないが，今まさに国内でも FETO が開始されようとしている。FETO の導入期にあたるわが国では，参加要件を満たす限定された施設が TOTAL trial に参加して，統一プロトコールのもとに開始することが望ましい。当面は単一の施設へ症例を集中するため，胎児治療の候補症例を全国から拾い上げて集約化するシステムの構築が必要となる。

その際，症例の発見時期が重要となる。例えば TOTAL trial の重症例臨床試験では，在胎 29 週 5 日までに適応を判断する必要がある。しかし，実際にわが国のどこかで候補症例が発見された場合，臨床試験の情報提供を受けて希望した母体が中央施設に紹介され，中央施設での精査と臨床試験参加のインフォームドコンセント取得を経て適応が最終決定される。各段階に要する時間を想定すれば，遅くとも在胎 27 週ごろまでには発見されていることが望ましい。

わが国における胎児治療の適応を考える場合，2008 年に国内 5 施設により行われた多施設共同研究が一つの参考になる。本研究は出生前診断された本症単独例 117 例（2002～2007 年）についての後方視的コホート観察研究として行われた[10]。生後 90 日の生存率は 79％（92/117 例）であり，酸素，人工呼吸，経管栄養，肺血管拡張薬投与などの在宅治療を必要とせずに退院できた「合併症なき退院」の割合は 63％（74/117 例）であった[10]。すなわち，25 例が生後 90 日以内に死亡し，以降に死亡した症例と，合併症を有したまま退院した症例を加えると，計 43 例は「合併症なき退院」ができなかった。しかしこのうち，在胎 27 週以前に診断されていた症例は半数以下の 17 例にとどまる。胎児治療の適応範囲を合併症を有したまま退院する症例にまで広げるとしても，わが国の出生前診断時期が諸外国に比べて遅いことが，胎児治療推進の妨げとなっていることがわかる。

同様のことは，2011 年にわが国で実施された本症の全国調査[11]からもいえる。全国調査には国内の 72 施設が参加し，本症の 614 例（2006～2010 年）が集計された。日本小児外科学会が行っている 5 年ごとの新生児外科統計における年間症例数（約 180 例）から類推すると，本調査ではわが国の半数を超える症例が調査されたものと推測された。過去 5 年間の 614 例中，本症単独例は 520 例（85％）であり，そのうち出生前診断された症例は 364 例（70％）であった。これらの症例の出生前診断週数の分布を示した（**図**）。63 例（黒）が生後 90 日以内に死亡し，45 例（灰色）が生後 90 日以降に死亡したか，合併症を有したまま退院した。在胎 27 週以前に発見された症例（点線より早期）が FETO の適応になりうると仮定すれば，死亡例のみを適応とした場合 32 例となり，合併症を有して退院した例を含めても 54 例であった。国内の約半数例が調査できたと仮定すると，わが国における胎児治療の候補症例数は，死亡例を適応とした場合年間 14 例，合併症を有して退院する例を含めても年間 22 例と概算される。胎児治療の候補症例のうち全例が中央施設への搬送や胎児治療を希望するとは考え難く，さらに RCT の振り分けにより約半数には FETO が実施されないことも考えれば，わが国で実際に施行される FETO の症例数は自ずと限定されてくる。今後，胎児スクリーニングを整備して，より早期に本症を発見しない限り，症例数の増加は見込めないと思われる。

しかし一方で，診断時期が早ければ早いほど適応症例が増加するかといえば，若干疑問が残る。

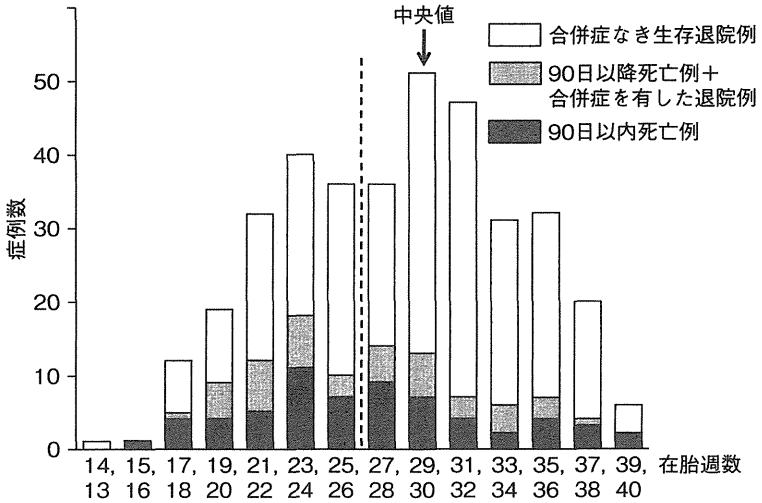

図　新生児横隔膜ヘルニア全国調査（2011年）における本症単独症例の出生前診断時期と予後との関係（臼井ら[11]，2012）

わが国では，在胎22週未満の妊婦には，母体理由による人工妊娠中絶が法的に認められている。出生後治療だけで救命可能と見込まれる症例であっても，ときに人工妊娠中絶が選択されている現状を考えれば，在胎22週以前の早期診断例の増加は，かえって本症の胎児治療適応例を減少させる可能性もはらんでいる。

V．わが国における胎児治療の適応基準と問題点

わが国のFETO導入期に，TOTAL trialに参加する施設が統一プロトコールのもとでFETOを実施する際には，胎児治療の適応基準で戸惑うことはなかろう。しかし，本来リスクを伴う治療の適応の決定は，各施設や地域，あるいは国におけるその時代の治療実態や治療成績などと治療効果を比較したうえで行うべきであろう。TOTAL trialのような国際的な多施設共同研究の終了後は，治療実態や治療成績の異なる地域や国で，共通の適応基準を堅持する意味合いは乏しい。したがって，将来的にはわが国の治療実態に即した，わが国独自の適応基準が必要になると思われる。

前述の共同研究の結果，Kitanoら[12]は，本症左側例の胃の位置に関する新たな分類を提唱し，重症度予測における胃の位置の重要性を述べている。肝脱出の有無と胃の位置の組合せから，肝脱出を伴わないGroup I，肝脱出を伴い胃の位置がGrade 0～2のGroup II，肝脱出を伴い胃の位置がGrade 3のGroup IIIに分けると，「合併症なき退院」が可能であった割合はそれぞれ87%，47%，10%であった[12]。このGroup IIIをもって胎児治療の適応とするという意見もある[13]。いずれにしても手技の習熟を必要とする計測を行うことなく，高リスク症例を簡便に判定できる意義は大きく，FETOの候補症例を拾い上げるための一次スクリーニングとしても応用可能であろう。

また同研究では，肝脱出とL/T比を組合わせて出生前診断例のリスクを層別化することも試みられている[14]（表）。もっとも重症なC群では，90日生存率が35%，「合併症なき退院」の割合が5%ときわめて予後不良であったのみならず，さまざまなパラメータが治療の困難さを示していた[14]。わが国でFETOが本症の治療法の選択肢の一つとして確立されれば，この群のような重症度をもつ症例が胎児治療の適応になるのかもしれない。

TOTAL trialにみられるように，肺低形成の国際的な評価法はO/E LHRが一般的となりつつある。O/E LHRはL/T比と指標としての類似性が強いため，両者に強い一次相関があると推測される。今後両者を比較して相互に換算する方法を，早急に検討する必要がある。

表　先天性横隔膜ヘルニアの出生前診断例におけるリスク層別化分類別にみた症例の重症度比較

リスク分類	Group A	Group B	Group C	
判定基準[注1)]	肝脱出（−）かつ L/T 比≧0.08	肝脱出（−）かつ L/T 比<0.08, 肝脱出（+）かつ L/T 比≧0.08	肝脱出（+）かつ L/T 比<0.08	
症例数	n=48	n=35	n=20	p
動脈管左右優位（%）[注2)]	39.1（n=46）	36.4（n=33）	0.0（n=18）	0.007
動脈管右左優位（%）[注2)]	37.0（n=46）	51.5（n=33）	72.2（n=18）	0.036
PGE_1 の使用率（%）	14.6	40.0	70.0	<0.001
NO 吸入療法の施行率（%）	70.8	94.3	95.0	0.005
ECMO の施行率（%）	2.1	14.3	40.0	<0.001
NO 吸入療法期間（日）¶	8（5〜12）*	11（7〜19）†	34（22〜40）‡	<0.001
人工呼吸期間（日）¶	14（9〜28）*	30（21〜48）†	545（30〜747）‡	<0.001
酸素投与期間（日）¶	23（15〜38）*	43（37〜73）†	555（529〜748）‡	<0.001
入院期間（日）¶	48（39〜69）*	73（56〜108）	162（95〜545）‡	<0.001
手術不能例（%）	0.0	11.4	35.0	<0.001
75%以上の横隔膜欠損例（%）	17.8（n=45）*	81.5（n=27）*	100.0（n=11）*	<0.001
パッチ閉鎖手術例（%）	20.8（n=48）	71.0（n=31）	92.3（n=13）	<0.001
90 日生存率（%）	100.0	80.0	35.0	<0.001
生存退院率（%）	100.0	74.3	20.0	<0.001
合併症なき退院率（%）	95.8	60.0	5.0	<0.001

*p<0.05 A vs B, †p<0.05 B vs C, ‡<0.05 C vs A, ¶中央値（四分位範囲）

注1) 出生前の画像診断で胸郭の 1/3 以上肝が脱出しているものを肝脱出（+）とした。胸郭の 1/3 に満たない脱出や，手術時に初めて肝脱出が判明した症例は肝脱出（−）とした。

注2) 出生後 24 時間以内に判定した。

（Usui ら[14]，2011 より引用，一部改変）

全国調査から明らかとなったもう一つの問題点は，出生前診断された 442 例中 LHR が計測されていた症例は 57%（240/422 例），L/T 比が計測されていた症例が 55%（231/422 例）と 6 割にも満たなかった[11]点である。Kitano の分類[12]など，どの施設でも簡便にリスクを判別できる方法を含め，肺低形成の正しい評価方法を広く啓蒙する必要がある。

最後に，わが国では本症に対して FETO とは全くコンセプトの異なる内科的胎児治療として，低形成に陥った本症胎児の左心室を母体酸素投与によって育成するという発想に立つ新しい胎児治療の試みも開始されつつある[15]。今後の研究成果に期待したい。

おわりに

いよいよわが国でも，TOTAL trial に参加した形で FETO が開始されようとしている。もしこの RCT で本症に対する胎児治療の有効性が明らかとなれば，わが国でも本格的に FETO が本症の治療手段の選択肢の一つとなる。来たるべき日に備え，わが国の多数の施設が互いに協力しあい，本症の胎児治療を推進できるシステムを構築すべきであると思われた。

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シンポジウム13「先天性横隔膜ヘルニア診療の施設間差異とそれぞれの質向上を目指して」

新生児横隔膜ヘルニア全国調査からみた治療方針の収束化と施設間差異

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Key words
Congenital diaphragmatic hernia
Nationwide survey
Treatment strategy
Variance investigation

はじめに

わが国における新生児横隔膜ヘルニア(以下本症)の治療成績は, gentle ventilationを中心とした呼吸管理の普及とともに, 近年急速に向上しつつある. しかし, わが国における本症の治療方針が, 施設間でどの程度収束化し, またどの程度異なっているかは明らかでない. そこで, わが国の主要施設における本症の治療成績と, 治療方針の施設間差異を明らかにし, 今後本症の治療を標準化するに向かっての足がかりとすることを目的に本研究を行った.

対象と方法

平成23年度厚生労働科学研究費補助金・難治性疾患克服研究事業として, 日本小児外科学会認定施設・教育関連施設および総合周産期母子医療センター159施設に対して, 新生児横隔膜ヘルニアに関する全国実態調査が実施された(承認番号11017). 各症例についての二次調査は, 上記のうち72施設の協力を得て614例に対して行われた. そこで本研究では, 二次調査が実施された72施設中, 2006年1月1日から2010年12月31日までの5年間に, 10例以上の症例を治療した経験のある施設を対象として解析を行った.

全国調査では, 一次調査として各施設の治療方針に関するアンケート調査を実施した. また, 二次調査として症例調査票を用いて各症例に対する診断, 治療, 転帰に関する調査を実施した. 本研究では, 対象となる施設名を匿名化したうえで, 一次調査および二次調査から得られた各施設における治療方針と治療成績を比較検討した.

結果

2006年から2010年までの5年間に10例以上本症の治療経験のある施設は, 72施設中22施設であった. そのうち最も症例数の多かった施設は43症例, 最も少なかった施設は10症例であった. 全症例の転帰を比較すると, 生存率には35%から100%までの開きがあった(図1).

各施設の症例背景を見ると, 出生前診断率は32%から100%まで大きな差があった. また, 横隔膜ヘルニア単独(以下Isolated)症例の割合も, 64%から100%までの開きがあった(表1). 施設間の重症度は, 全国実態調査の解析結果[1]に基づき, Apgar Score1分値が4以下であった症例数の割合, 出生後24時間以内の最も低値であったOxygenation Indexが8.0以上であった症例数の割合, 出生前診断例における肝脱出症例の割合を用いて比較した. 重症度は単一の指標のみでは評価できないものの, Apgar Score1分値≦4の割合では9%～77%, 24時間以内最良Oxygenation Index ≧

図1 施設別の症例数と転帰の比較
*:施設の仮名は, 横隔膜ヘルニア単独(Isolated)症例の生存率が高い施設順にアルファベットで表した.

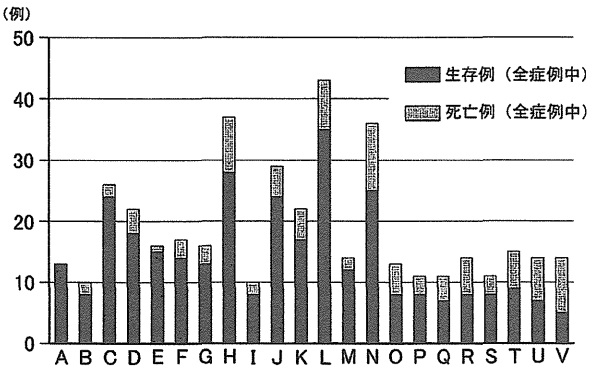

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表1　施設別の症例背景と重症度，呼吸・循環管理方針の比較

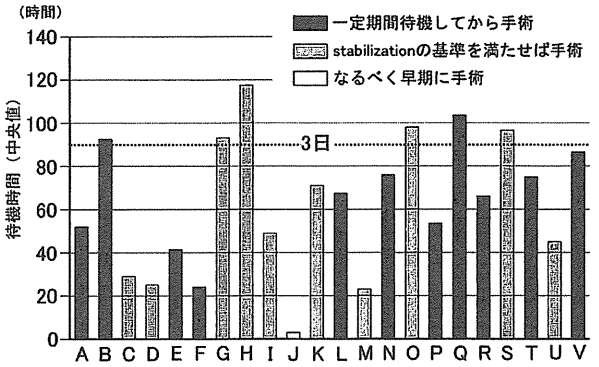
施設仮名	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	平均
症例数（5年間）	13	10	26	22	16	17	16	37	10	29	22	43	14	36	13	11	11	14	11	15	14	14	
症例の背景（症例数の割合）																							
出生前診断率（%）	70	50	73	96	75	82	81	81	80	97	32	95	50	86	77	63	100	79	63	80	79	86	79
Isolated症例（%）	100	80	92	77	100	88	75	81	90	90	77	98	86	69	77	91	82	79	100	80	71	64	85
重症度（症例数の割合）																							
Apgar Score（1）≦4（%）	54	30	48	64	63	29	73	57	38	31	60	59	31	42	63	9	73	79	36	77	NA	71	52
24hr最良OI*≧8.0（%）	33	60	5	11	8	42	27	38	0	43	45	17	46	23	71	60	33	60	36	46	NA	46	32
肝脱出症例の割合（%）	22	25	6	29	8	14	25	33	0	29	NA	49	14	47	22	NA	40	20	43	36	0	18	29
出生前診断例の治療方針（症例数の割合）																							
帝王切開の割合（%）	100	100	90	27	100	86	46	84	100	71	100	39	43	84	100	100	55	100	57	92	100	58	73
胎児麻酔の割合（%）	44	40	56	0	100	14	0	17	0	0	0	0	0	0	70	0	54	54	14	75	82	8	23
呼吸・循環管理																							
主たる管理診療科**	新	新	新	外	麻	外	外	新	麻	麻	外	新	新	外	外	新	新	新	新	外	循	新	
容認最高Pre $PaCO_2$（mmHg）	45	45	45	65	45	55	65	55	65	65	55	45	55	55	55	55	55	55	55	55	55	65	NA
容認最低Pre PaO_2（mmHg）	85	65	85	75	100	NA	65	65	75	65	60	75	65	65	NA	85	65	65	75	NA	65	60	NA
容認最低Pre SpO_2（%）	90	90	90	90	90	80	80	90	90	90	80	90	95	80	90	95	80	90	70	80	80	80	NA
NO使用施行例（%）	31	56	86	68	63	88	81	68	70	86	64	84	71	61	54	64	73	71	18	33	86	57	64
ECMO施行症例（%）	0	0	4	3	25	11	0	21	0	0	18	0	28	8	0	0	0	0	18	13	35	0	9

注）施設の仮名は，横隔膜ヘルニア単独（Isolated）症例の生存率が高い施設順にアルファベットで表した．

*：24hr最良OI：生後24時間以内に示した最も低値のOxygenation Index．**：新：新生児科，外：小児外科，麻：麻酔科，循：循環器科，NA：有効データなし

図2　施設別の術前待機の方針と実際の待機時間（中央値）の比較

*：施設の仮名は，横隔膜ヘルニア単独（Isolated）症例の生存率が高い施設順にアルファベットで表した．



8.0の割合では0%～71%，肝脱出症例の割合では0%～47%と施設によって重症例の占める割合に偏りが認められた．

出生前診断例に対する治療方針も，施設間で異なっていた．帝王切開分娩については，全例施行していた施設が9施設と多かったが，経腟分娩を原則とするため帝王切開症例の割合が50%未満であった施設も4施設あった．全出生前診断例における帝王切開の施行率は73%であった．一方胎児麻酔については，高率に行っていた施設は比較的少なく，9施設で全く行っていなかった．全例施行していた施設は1施設のみで，全出生前診断例における胎児麻酔の施行率は23%に留まっていた（表1）．

呼吸・循環管理には，施設間で収束化が認められるとともに，差異も認められた．呼吸・循環管理を主として担当している診療科は，11施設が新生児科であり，それに続き7施設が小児外科，3施設が麻酔科であった（表1）．全施設が「原則としてgentle ventilationの考え方に基づき呼吸管理を行っている」と回答した．また，「大いに」（18施設）と「ある程度」（4施設）を合わせると，全施設が「心臓超音波検査を治療方針決定の参考にしている」と回答した．しかし，人工呼吸管理上，容認できるpre $PaCO_2$の最高値には45mmHgから65mmHgまで，容認できるpre PaO_2の最低値には60mmHgから100mmHgまでの開きが認められた（表1）．また，NO吸入療法も使用頻度に施設間の差がみられた．重症例が比較的多かった施設Aや施設S，施設TではNO吸入療法の使用頻度が低かったのに対し，重症例が比較的少なかった施設Cや施設Iでは，逆に使用頻度が高かった．ECMOについても，重症度に関係なく使用頻度に施設間差異が認められた．最も症例が多かった施設Lを含めた11施設は1例もECMOを行っていなかったが，症例数が2番目に多かった施設Hを含めた4施設は20%以上の症例に対してECMOを施行していた．

全症例に対するECMOの施行率は9%であった（表1）．

術前待機の方針や実際に待機した時間についても，施設間で差が認められた．一定期間待機してから手術する方針の施設が11施設，期間に関係なく一定のstabilizationの基準を満たせば手術する方針の施設が10施設であった．なるべく早期に手術するとした施設は1施設のみであった．しかし，一定期間待機する施設と，stabilizationの基準を満たせば手術する施設を比較すると，実際に待機した時間の中央値に明らかな差は認められなかった．Isolated症例における生存率との関連性を見ると，比較的早期に手術している施設の生存率がやや高い傾向が認められた（図2）．

退院までに認められた合併症については，気胸では0%から42%，乳糜胸水では0%から37%，胃食道逆流症では0%から50%と，発症率に施設間差異が認められた．Isolated症例の生存率が低かった施設に，気胸の発症率が高い傾向が認められた（表2）．全症例の生存率は36%から88%，Isolated症例の生存率は57%から100%と大きな開きが認められたが，同時に各施設の重症度も異なっていたため，生存率のみで単純に施設間の治療成績は比較できなかった．しかし，生存率が低かった一部の施設では救命しうる症例を失っている可能性も考えられた（表2）．

考案

出生前診断症例の割合やIsolated症例の割合は，施設間で大きな差異が認められた．その一つの原因は，各施設のおかれた地理的あるいは社会的条件に起因するのではないかと推測された．人口密集地では，産科が出生前診断や胎児治療に力を入れている施設に自ずと出生前診断症例，しかも肝脱出例などの重症例が選択的に集約される可能性がある．一方，産科が充実していない施設では，出生後の診断例が診療の主体となる．また，地方にあって広範囲の地域を単一施設でカバーしている場合には，症例背景が偏るバイアスはかかりにくい状況にあると推測される．

重症度についても同様で，近年では出生前の段階で，ある程度の重症度予測が可能になったことから，都市部では自然に重症例の集約化が起こっている可能性が考えられる．症例数の多かった施設の中でも，施設H，施設L，施設Nなどは，重症例の占める割合が相対的に高く，地域の中核施設として重症例が集約されていることが推測される．一方，同じように症例数の多かった施設C，施設Eなどでは，比較的軽症例が集まる傾向にあったと考えられた．各地域における施設の役割が少しずつ異なるために，施設の治療成績を比較する場合には，重症例が占める割合も考慮する必要があると考えられた．

出生前診断例に対する帝王切開分娩や胎児麻酔の実施などの周産期管理の方針は，施設間での違いが大き

表2　施設別の退院までの合併症発症と治療成績の比較

施設仮名	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	平均
症例数（5年間）	13	10	26	22	16	17	16	37	10	29	22	43	14	36	13	11	11	14	11	15	14	14	
退院までの合併症の発症（症例数の割合）																							
気胸（%）	8	0	4	15	18	0	13	5	20	10	9	14	7	16	23	18	18	35	18	7	27	42	14
乳糜胸水（%）	8	37	19	15	0	0	25	35	0	24	22	11	7	25	8	18	0	0	18	0	0	7	15
胃食道逆流症（%）	38	12	8	16	6	29	13	41	50	24	28	12	29	14	23	9	9	0	0	8	10	0	18
治療成績（症例数の割合）																							
無病退院*（全症例）（%）	85	70	77	73	88	59	44	51	80	69	64	70	71	58	62	64	64	57	73	40	43	36	63
生存率（全症例）（%）	100	80	92	82	94	82	81	76	80	83	77	81	86	69	62	73	64	57	73	60	50	35	76
無病退院*（Isolated）（%）	84	88	83	88	88	67	58	63	89	77	77	71	67	76	80	70	78	73	73	50	50	56	73
生存率（Isolated）（%）	100	100	96	94	94	93	92	90	89	89	88	83	83	80	80	80	78	73	73	67	60	57	85

注）施設の仮名は，横隔膜ヘルニア単独（Isolated）症例の生存率が高い施設順にアルファベットで表した．
*：無病退院：酸素投与，気管切開，人工呼吸，経管栄養，肺高血圧内服治療薬投与などの在宅治療を要さない状態での退院

かった．これらの管理方針が治療成績に及ぼす影響については，未だに結論が出ておらず，今後ランダム比較試験などを通じて，治療法の有効性を検証すべき課題の一つと思われた．

呼吸管理の方針については，gentle ventilationの考え方が広く普及し，治療方針が収束化していた．しかし，同じgentle ventilationといっても，人工呼吸管理における血液ガスの目標値は，施設間でばらつきが認められた．治療成績の良くない施設の一部には，低酸素血症をやや容認し過ぎる傾向があった．循環管理の方針については，心臓超音波検査の重視という点で収束化していた．しかし，治療成績の良くない施設の一部には，NO吸入療法に対して比較的消極的な傾向があると考えられた．ECMOは，重症度とは関係なく，施設によって使用頻度に差があり，ECMO導入の適応が施設毎に異なっていると考えられた．

術前待機の方針は，「一定期間待機後の手術」と「一定のstabilization後の手術」が大半を占めた．しかし，実際の待機時間は，両者でほとんど差がなく，中央値は生後3日未満であった施設が多数を占めた．欧米などにおけるいわゆる「待機手術」例に比べて，わが国では比較的早期に手術が行われる傾向があると考えられた．適正な手術時期も，今後ランダム比較試験などを通じて検証すべき課題の一つと考えられた．

術後退院までに発症する合併症として気胸，乳糜胸水，胃食道逆流症を比較したが，これらの発症率も施設による差が大きかった．このような合併症の発症要因は，手術手技とも関連が深いと考えられ，発症率の高い施設は，自施設の手術手技を再検討するべきであると思われた．特に気胸の発生率の高さは，一部の施設において生存率を下げる要因になっていることが推測された．

結語

わが国における本症の治療方針は，gentle ventilationの普及と心臓超音波検査の重視という点で収束化が認められた．しかし，出生前診断例の周産期管理や術前待機時間などについては，未だに施設による治療方針の差が認められた．治療成績は概ね良好であったが，一部に救命の可能性がありながら失われている症例があるのではないかと思われた．本研究によって，今後本症の治療を標準化するに当たって，検討すべき課題が明らかとなった．

[謝辞]

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文　献

1) 臼井規朗，田口智章，永田公二．新生児横隔膜ヘルニアの重症度別治療指針の作成に関する研究．平成23年厚生労働科学研究費補助金（難治性疾患克服研究事業）新生児横隔膜ヘルニアの重症度別治療指針の作成に関する研究．総括・分担研究報告書．臼井規朗編．pp1-28，2012

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Original Article

Effect of hospital volume on the mortality of congenital diaphragmatic hernia in Japan

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Abstract ***Background***: During the last decade, new supportive modalities and new therapeutic strategies to treat congenital diaphragmatic hernia (CDH) have been introduced. In Japan, the large number of hospitals prevents centralizing infants with CDH in tertiary centers. The aim of this study was to evaluate the correlations between the number of CDH patients, survival rates, and the current strategies employed to treat CDH at the individual hospitals.

Methods: Eighty-three hospitals with 674 CDH cases were analyzed using questionnaires. We classified the hospitals into three groups according to the number of CDH patients treated: Group 1 (G1; more than 21 patients), Group 2 (G2; 11–20 patients), and Group 3 (G3; fewer than 10 patients).

Results: The median number of CDH patients in G1, G2, and G3 were 28, 14, and 4, respectively. The overall survival rate was 74.5%. When only the isolated CDH cases with a prenatal diagnosis were included, the overall survival rate was 79.3%. The survival rate of isolated CDH cases with a prenatal diagnosis was significantly higher in G1 than that in G2 or G3 (87.2% vs 75.2% vs 74.3%; $P < 0.001$). There were no differences in perinatal therapeutic strategies among the three groups.

Conclusions: We concluded that it might therefore be important to centralize infants with CDH, especially those with isolated CDH with a prenatal diagnosis, to tertiary centers in Japan in order to improve the survival rates.

Key words centralization, congenital diaphragmatic hernia, mortality, nationwide survey, prenatal diagnosis.

Congenital diaphragmatic hernia (CDH) occurs in approximately 1 in 2500–5000 live births.[1–3] Infants with CDH experience severe respiratory failure due to pulmonary hypoplasia and pulmonary hypertension of the newborn (PPHN). During the last decade, new supportive modalities and new therapeutic strategies, such as inhalation of nitric oxide (iNO), extracorporeal membrane oxygenation (ECMO), high-frequency oscillation ventilation (HFOV), and gentle ventilation strategies with permissive hypercapnia, have been introduced. Such medical advances have improved mortality and morbidity in infants with CDH.

In Japan, the large number of hospitals for neonatal surgery makes centralizing infants with CDH in tertiary centers difficult. Therefore, it is speculated that the therapeutic strategies used to treat CDH might not be standardized and might vary among institutions. The use of different strategies to treat CDH might affect the outcome of the disease. Additionally, recent reports have demonstrated a correlation between outcome and hospital volume in the treatment of CDH[4] as well as a correlation with neonatal intensive care.[5] Because a nationwide survey of CDH has not been conducted in Japan, the effects of the hospital-volume–outcome correlation and the effects of different therapeutic strategies used with CDH patients in Japan remain unexplored. The aim of this study was to evaluate the correlations among the number of CDH patients, survival rates, and the current strategies employed at individual hospitals.

Methods

This study was approved by the ethics committees at Nagoya University Hospital, Osaka University Graduate School of Medicine, the National Center for Child Health and Development, the Hyogo College of Medicine, Osaka Medical Center, the Research Institute for Maternal and Child Health, and the Graduate School of Medical Sciences, Kyushu University.

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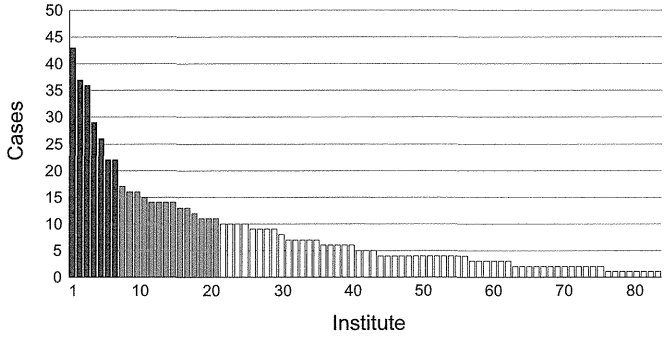

Fig. 1 Number of congenital diaphragmatic hernia cases at the individual hospitals. The black bar, gray bar, and white bar indicate Group 1, Group 2, and Group 3, respectively.

We distributed a questionnaire to 159 educational hospitals for pediatric surgery and/or tertiary perinatal care centers. The study participants included infants with CDH born between 2006 and 2010. In total, 109 institutes responded. The collection rate was 68.6%. Twenty-six institutes had no cases with CDH. Ultimately, 83 institutes with 674 CDH cases were analyzed.

The questionnaire included items regarding the number of patients, the type of CDH (isolated or non-isolated CDH), the number of survivors, the timing of diagnosis (prenatal or postnatal), the delivery mode, and neonatal therapeutic strategies.

Isolated CDH was defined as a case without the occurrence of any life-threatening major anomalies. Survival was defined as "survival to discharge." Vaginal delivery included both spontaneous delivery and induction delivery. Neonatal therapeutic strategies included choosing a ventilator mode, applying the policy of gentle ventilation with permissive hypercapnia, using tolerable levels of blood gas parameters, administering sedation during acute phases, using specific modalities to treat PPHN (iNO, ECMO), and choosing the timing of surgical repair. We classified the hospitals into three groups according to the number of CDH patients treated: Group 1 (G1; more than 21 patients), Group 2 (G2; 11–20 patients), and Group 3 (G3; fewer than 10 patients).

Data were analyzed by using SPSS version 19.0 (SPSS, Chicago, IL, USA). The statistical analysis was performed using the χ^2-test, Fisher's exact test for categorized factors, and a logistic regression analysis. Bonferroni's correction was used as a post-hoc test. A P-value < 0.05 was considered to be significant. The numerical data represent the medians (range).

Results

The number of hospitals in G1, G2, and G3 were 7, 14, and 62, respectively. Total number of CDH patients was 674. The median (range) numbers of CDH patients in G1, G2, and G3 were 29 (22–43), 14 (11–17), and 4 (1–10), respectively. The median (range) number of the CDH patients at the individual hospitals

Table 1 Survival rates

	Total	Group 1	Group 2	Group 3
Total cases				
Overall				
n/N	502/674 (74.5%)	171/215 (79.5%)	134/191 (70.2%)†	197/268 (73.5%)
OR (95%CI)		1.00	0.605 (0.384–0.952)	0.714 (0.465–1.096)
Isolated cases				
n/N	473/572 (82.6%)	159/181 (87.8%)	126/160 (78.8%)‡	188/231 (81.4%)
OR (95%CI)		1.00	0.513 (0.286–0.920)	0.605 (0.347–1.054)
Non-isolated cases				
n/n	29/102 (28.4%)	12/34 (35.3%)	8/31 (25.8%)	9/37 (34.3%)
OR (95%CI)		1.00	0.638 (0.219–1.857)	0.589 (0.211–1.649)
Cases with prenatal diagnosis				
Overall				
n/N	337/483 (69.8%)	139/178 (78.1%)	93/144 (64.6%)§	105/161 (65.2%)¶
OR (95%CI)		1.00	0.512 (0.313–0.837)	0.526 (0.325–0.851)
Isolated cases				
n/N	318/401 (79.3%)	129/148 (87.2%)	88/117 (75.2%)††	101/136 (74.3%)‡‡
OR (95%CI)		1.00	0.447 (0.236–0.847)	0.425 (0.230–0.787)
Non-isolated cases				
n/n	19/82 (23.2%)	10/30 (33.3%)	5/27 (18.5%)	4/25 (16.0%)
OR (95%CI)		1.00	0.210 (0.133–1.559)	0.149 (0.103–1.414)
Cases with postnatal diagnosis				
Overall				
n/N	165/191 (86.4%)	32/37 (86.5%)	41/47 (87.2%)	92/107 (86.0%)
OR (95%CI)		1.00	1.068 (0.299–3.816)	0.958 (0.322–2.848)
Isolated cases				
n/N	155/171 (90.6%)	30/33 (90.9%)	38/43 (88.4%)	87/95 (91.6%)
OR (95%CI)		1.00	0.760 (0.168–3.468)	1.087 (0.271–4.367)
Non-isolated cases				
n/N	10/20 (50.0%)	2/4 (50.0%)	3/4 (75.0%)	5/12 (41.7%)
OR (95%CI)		1.00	3.000 (0.150–59.890)	0.714 (0.074–6.922)

†$P = 0.030$. ‡$P = 0.023$. §$P = 0.008$. $P = 0.009$. ††$P = 0.013$. ‡‡$P = 0.007$.

Table 2 Ventilator care

	Total (n = 83)	Group 1 (n = 7)	Group 2 (n = 14)	Group 3 (n = 62)	P-value
Ventilator mode					0.963
HFOV	67 (80.7%)	6 (85.7%)	11 (78.6%)	50 (80.6%)	
Decision depending on the situation	6 (7.2%)	1 (14.3%)	1 (7.1%)	4 (6.5%)	
SIMV	5 (6.0%)	0 (0.0%)	1 (7.1%)	4 (6.5%)	
No treatment principle	2 (2.4%)	0 (0.0%)	0 (0.0%)	2 (3.2%)	
No response	3 (3.6%)	0 (0.0%)	1 (7.1%)	2 (3.2%)	
Gentle ventilation					0.819
Applying to all cases	69 (83.1%)	7 (100%)	13 (92.9%)	49 (79.0%)	
Decision depending on the situation	4 (4.8%)	0 (100%)	0 (0.0%)	4 (6.5%)	
Not applied	2 (2.4%)	0 (0.0%)	0 (0.0%)	2 (3.2%)	
No treatment principle	4 (4.8%)	0 (0.0%)	0 (0.0%)	4 (6.5%)	
No response	4 (4.8%)	0 (0.0%)	1 (7.1%)	3 (4.8%)	
Tolerable level of pre-ductal PCO_2					0.891
<40 mmHg	5 (6.0%)	0 (0.0%)	0 (0.0%)	5 (8.1%)	
40 mmHg–50 mmHg	17 (20.5%)	2 (28.6%)	3 (21.4%)	12 (19.4%)	
50 mmHg–60 mmHg	36 (43.3%)	3 (42.9%)	8 (57.1%)	25 (40.3%)	
60 mmHg–70 mmHg	15 (18.1%)	2 (28.6%)	2 (14.3%)	11 (17.7%)	
≥70 mmHg	3 (3.6%)	0 (0.0%)	0 (0.0%)	3 (4.8%)	
No response	7 (8.4%)	0 (0.0%)	1 (7.1%)	6 (9.7%)	
Tolerable level of pre-ductal PO_2					0.745
<60 mmHg	10 (12.0%)	1 (14.3%)	2 (14.3%)	7 (11.3%)	
60 mmHg–70 mmHg	25 (30.1%)	3 (42.9%)	5 (35.7%)	17 (27.4%)	
70 mmHg–80 mmHg	10 (12.0%)	2 (28.6%)	1 (7.1%)	7 (11.3%)	
80 mmHg–90 mmHg	12 (14.5%)	1 (14.3%)	1 (7.1%)	10 (16.1%)	
90 mmHg–100 mmHg	7 (8.4%)	0 (0.0%)	0 (0.0%)	7 (11.3%)	
≥100 mmHg	5 (6.0%)	0 (0.0%)	1 (7.1%)	4 (6.5%)	
No response	14 (16.9%)	0 (0.0%)	4 (28.6%)	10 (16.1%)	
Tolerable level of pre-ductal SpO_2					0.533
<80%	2 (2.4%)	0 (0.0%)	1 (7.1%)	1 (1.6%)	
80–90%	22 (24.5%)	2 (28.6%)	5 (35.7%)	15 (24.2%)	
90–95%	34 (41.0%)	5 (71.4%)	6 (42.9%)	23 (56.5%)	
95–100%	19 (22.9%)	0 (0.0%)	1 (7.1%)	18 (29.0%)	
100%	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	
No response	5 (6.0%)	0 (0.0%)	1 (7.1%)	4 (6.5%)	
Tolerable level of pH					0.445
<7.25	7 (8.4%)	0 (0.0%)	1 (7.1%)	6 (9.7%)	
7.25–7.30	18 (21.7%)	1 (14.3%)	3 (21.4%)	14 (22.6%)	
7.30–7.35	38 (45.8%)	4 (57.1%)	8 (57.1%)	26 (41.9%)	
7.35–7.40	11 (13.3%)	1 (14.3%)	0 (0.0%)	10 (16.1%)	
7.40–7.45	2 (2.4%)	0 (0.0%)	0 (0.0%)	2 (3.2%)	
≥7.45	2 (2.4%)	1 (14.3%)	1 (7.1%)	0 (0.0%)	
No response	5 (6.0%)	0 (0.0%)	1 (7.1%)	4 (6.5%)	

SIMV, synchronized intermittent mandatory ventilation; HFOV, high-frequency oscillation ventilation.

was 5 (1–43). The mode value of the CDH patients at the individual hospitals was 4 (Fig. 1).

Timing of diagnosis

The rates of prenatal diagnosis in G1, G2, and G3 were 82.8%, 75.4%, and 60.1%, respectively. The rate of prenatal diagnosis in G3 was significantly lower than that in both G1 and G2 (G1 vs G3, $P < 0.001$; G2 vs G3, $P = 0.003$).

Survival rate

The survival rates are shown in Table 1. The overall survival rates for all cases, the cases with a prenatal diagnosis, and the cases with a postnatal diagnosis were 74.5%, 69.8%, and 86.4%, respectively. The overall survival rate for the cases with a prenatal diagnosis was significantly lower than that among the cases with a postnatal diagnosis ($P < 0.001$).

In all cases, the survival rates in G1, G2, and G3 were 79.5%, 70.2%, and 73.5%, respectively. If the cases were restricted to those with isolated CDH, the survival rate was 82.6%. Compared among the three groups, the survival rates in G1, G2, and G3 were 87.8%, 78.8%, and 81.4%, respectively. The survival rate in G1 was significantly higher compared with that in G2 ($P = 0.023$).

When only the cases of CDH with a prenatal diagnosis were included, the survival rate was significantly higher in G1 than that in G2 or G3 (78.1% vs 64.6% vs 65.2%, G1 vs G2, $P = 0.008$; OR: 0.512 [95%CI: 0.313–0.837], G1 vs G3, $P = 0.009$; OR: 0.526 [95%CI: 0.325–0.851]). If the cases were restricted to

Table 3 Sedation treatments used during acute management

	Total (n = 83)	Group 1 (n = 7)	Group 2 (n = 14)	Group 3 (n = 62)	P-value
Analgesia/sedative agents					0.842
Yes	82 (98.8%)	7 (100%)	14 (100%)	61 (98.4%)	
No	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	
Muscle relaxant					0.373
Yes	72 (86.7%)	7 (100%)	13 (92.9%)	52 (83.9%)	
No	1 (13.3%)	0 (0.0%)	1 (7.1%)	10 (16.1%)	
Degree of sedation level					0.752
Movability acceptable	30 (36.1%)	3 (42.9%)	5 (35.7%)	22 (35.4%)	
Movability unacceptable	48 (57.8%)	4 (57.1%)	9 (64.3%)	35 (56.5%)	
Other	5 (6.0%)	0 (0.0%)	0 (0.0%)	5 (8.1%)	
Mode of muscle relaxant administration					0.797
Administration as necessary	17 (23.6%)	2 (28.6%)	4 (30.8%)	11 (21.2%)	
Continuous infusion	52 (72.2%)	5 (71.4%)	9 (69.2%)	38 (73.1%)	
Other	3 (4.2%)	0 (0.0%)	0 (0.0%)	3 (5.7%)	

those with isolated CDH with a prenatal diagnosis, the overall survival rate was 79.3%. The survival rates of isolated CDH with a prenatal diagnosis in G1, G2, and G3 were 87.2%, 75.2%, and 74.3%, respectively. The survival rate in G1 was significantly higher than that in G2 or G3 (G1 vs G2, P = 0.013; OR: 0.447 [95%CI: 0.236–0.847], G1 vs G3, P = 0.007; OR: 0.425 [95%CI: 0.230–0.787]).

Delivery mode

There were no differences in policies regarding the delivery mode used among the three groups. An elective cesarean section was the first-line treatment at almost all of the hospitals (G1, 42.9%; G2, 71.4%; G3, 71.0%; P = 0.535).

Ventilator strategies

HFOV was widely used and the infants were managed in accordance with the policy of gentle ventilation with permissive hypercapnia in most of the hospitals in G1, G2, and G3. Overall, there was variability in the tolerable levels of blood gas parameters. There were no differences in the tolerable level of blood gas parameters among the three groups. The highest percentage for the tolerable levels of preductal $PaCO_2$, preductal PaO_2, preductal SpO_2, and preductal pH were as follows: 50–60 mmHg, 60–70 mmHg, 90–95%, and 7.30–7.35, respectively (Table 2).

Sedation

In most of the hospitals in G1, G2, and G3, analgesia, sedative agents, and muscle relaxants were widely used. In approximately half of all the hospitals, the infants with CDH were cared for without body movements. Muscle relaxants were administered by continuous infusion in most of the hospitals. The strategies of sedation were the same among the three groups (Table 3).

Specific treatments of PPHN

Most of the hospitals in Japan were able to treat infants with PPHN using iNO, independent of hospital volume (G1, 100%; G2, 100%; G3, 90.3%; P = 0.901). On the other hand, ECMO tended to be available only in the high-volume hospitals (G1, 85.7%; G2, 78.6%; G3, 46.8%; P = 0.073).

Timing of surgical repair

The timing of surgical closure of the diaphragmatic defect was not different among the groups. In most of the hospitals, surgery was performed after stabilization of the respiratory and circulatory conditions. Regarding the postnatal day of surgical repair, surgery was performed within 4 postnatal days in most of the hospitals. In almost all of the hospitals in G1, surgery was performed within 2 postnatal days (Table 4).

Table 4 Timing of surgical repair

	Total (n = 83)	Group 1 (n = 7)	Group 2 (n = 14)	Group 3 (n = 62)	P-value
Timing of surgical repair					0.818
Early operation	4 (4.8%)	1 (14.3%)	0 (0.0%)	3 (4.8%)	
Decision depending on the situation	34 (41.0%)	4 (57.1%)	5 (35.7%)	25 (40.3%)	
After stabilization	41 (49.4%)	2 (28.6%)	8 (57.1%)	31 (50.0%)	
No treatment principle	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	
No response	3 (3.6%)	0 (0.0%)	1 (7.1%)	2 (3.2%)	
Postnatal day of surgical repair					0.139
Day 0	2 (2.4%)	1 (14.3%)	0 (0.0%)	1 (1.6%)	
Day 1–2	31 (37.3%)	4 (57.1%)	5 (35.7%)	22 (35.5%)	
Day 3–4	37 (44.6%)	1 (14.3%)	6 (42.9%)	30 (48.4%)	
Day 5–7	5 (6.0%)	1 (14.3%)	0 (0.0%)	4 (6.5%)	
Day 8–	1 (1.2%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	
No response	7 (8.4%)	0 (0.0%)	2 (14.3%)	5 (8.1%)	

Difference in strategies by physicians of different specialties

In 54 institutes, neonatologists treat CDH infants. In five institutes, pediatric surgeons collaborate with neonatologists. Therefore, neonatologists were involved in CDH treatments in 59 institutes. On the other hand, in 24 institutes, the attending doctors did not belong to the department of neonatology. The attending physicians were pediatric surgeons, pediatric cardiologists, anesthesiologists, obstetricians and from other specialties. The strategies of CDH treatments employed by neonatologists versus non-neonatologists (data not shown) were not different. The survival rates for the infants treated by neonatologists versus those treated by non-neonatologists (74.8% vs 74.0%; $P = 0.87$) were not different.

Discussion

This study is the first Japanese nationwide survey of infants with CDH and demonstrates the current state of CDH care in Japan. The overall survival rate of all cases was 74.5%. The survival rate of cases with a postnatal diagnosis was significantly higher than that of cases with a prenatal diagnosis. The survival rate of cases with a prenatal diagnosis was dependent on hospital volume. In particular, the survival rate of isolated cases with a prenatal diagnosis in G1 was significantly higher than that in G2 or G3.

A systematic review of CDH, which included 763 patients from 13 reports, showed that the overall survival rate and the survival rate of infants with isolated CDH were 79% (range: 69–93%) and 85% (range: 78–96%), respectively.[6] In this study, the overall survival rate and the survival rate of infants with isolated CDH were 74.5% and 82.7%, respectively. The survival rate of CDH infants in Japan was compatible with that of other countries. Focusing on the cases with a prenatal diagnosis, both the overall survival rate and the isolated CDH survival rate were significantly associated with the hospital volume in this study. The dependency of the survival rates on the hospital volume was not clear. One possibility is the habituation to care for critical newborns. The care and handling of critical patients are very important factors in neonatal medicine and they might affect the patients' outcome. The infants with CDH, especially prenatally diagnosed cases, are critical and can easily develop into PPHN. The medical staff members in large-volume hospitals (G1) are generally used to dealing with CDH. This might be the reason for the low mortality of isolated CDH with a prenatal diagnosis in G1. The prenatal diagnosis makes it possible to plan the optimal time and place of delivery. Neonatal transport is associated with an increased mortality.[7] Therefore, in order to increase the survival rates, maternal cases with a prenatal diagnosis should be referred to tertiary centers.

In prenatally diagnosed CDH, the best delivery mode remains unknown. While the delivery mode is not associated with the outcome of prenatally diagnosed CDH,[8] recent data suggest that cesarean sections increase survival rates[9] or increase survival without ECMO.[10] In Japan, elective cesarean sections were the first-line choice in most of the hospitals. The reason for this might be that the number of medical staff was not adequate to care for such critical patients on holidays and/or night shifts.

The most important ventilator strategy for treating CDH is avoiding ventilator-induced lung injury (VILI). To avoid and minimize VILI, gentle ventilation with permissive hypercapnia[11,12] and early conversion to HFOV have been used.[13,14] Although the majority of Japanese hospitals applied gentle ventilation with permissive hypercapnia, the tolerable levels of blood gas parameters varied widely. In actuality, infants with CDH were not always treated with gentle ventilation. Originally, the gentle ventilation strategy reported by Wung included the use of respiratory treatments without muscular relaxants, as well as the use of permissive hypercapnia.[12] The systematic review revealed that the infants with CDH received light sedation, and muscle relaxants tended to be used less frequently.[6] In our study, both analgesia and muscle relaxants were widely used in most of the hospitals. A pulmonary hypertensive crisis can be triggered by handling the infants or from nursing care provided at bedside. To prevent pulmonary vasospasms secondary to these procedures, most Japanese neonatologists/pediatric surgeons might therefore choose to keep such patients paralyzed using analgesia and muscle relaxants.

Most infants with CDH suffer from PPHN. iNO is one of the treatments used for severe respiratory failure and/or PPHN. Although there is little evidence for the effectiveness of iNO for CDH, iNO has nevertheless been widely used to treat CDH infants.[15,16] In this study, iNO was found to be widely available in Japanese neonatal intensive care units. One report from Japan showed that the combination of iNO and early operations improved the outcome and reduced the need for ECMO.[17] With the widespread dissemination of gentle ventilation techniques, the use of ECMO has decreased in some centers.[14] ECMO was used in only 7.4% of CDH infants in a Canadian study.[18] Although treatment with iNO and HFOV reduced the need for ECMO, it did not reduce mortality in infants with PPHN.[19] The systematic review showed that preoperative mortalities were reduced in ECMO centers.[1] The Congenital Diaphragmatic Hernia Study Group demonstrated that ECMO significantly improved survival rates in CDH neonates with a high risk of mortality.[20] In this study, ECMO tended to be more available in the hospitals in G1; however, a statistically significant difference was not seen ($P = 0.073$). In order to treat infants with critical CDH, ECMO should therefore be provided in tertiary centers.

In about half of the hospitals that participated in this study, infants with CDH were operated on after stabilization. The role of the timing of surgery in influencing outcomes of CDH is widely debated and the published reports provide controversial results. Some centers delay surgery until physiologic stabilization has occurred, while others prefer to perform surgery immediately after birth.[21] Rozmariek proposed that the outcome of patients with CDH depends more on the degree of physiologic derangement than on the timing of surgery.[22] Sometimes surgery might worsen or trigger bouts of PPHN. The optimization of hemodynamic and respiratory parameters might improve the outcome.

Some centers described their protocols for treating CDH and the possible beneficial effects of these protocols.[23–25] In these studies, the outcome for infants who received standardized

treatment was favorable compared with that for infants who did not receive standardized treatment. In our study, the ventilation strategies, such as the use of tolerable levels of blood gas parameters, used among the centers varied widely. Multicenter collaboration and the establishment of successful protocols are essential for improving outcomes in patients with CDH.[26]

A few reports have demonstrated the existence of a hospital-volume–patient-outcome correlation for CDH.[4,27] The Canadian Pediatric Surgery Network reported a volume–outcome correlation for infants with CDH. They classified hospitals into high-volume (≥12 cases/22 months) and low-volume (<12 cases/22 months) groups according to the number of patients treated. The high-volume hospitals had a significantly higher survival rate (90% vs 77%).[27] A recent study using the Pediatric Health Information System in the USA reported a correlation between hospital volume and outcome. In their study, 2203 infants with CDH from 37 children's hospitals were divided into three groups according to the number of CDH cases at each individual hospital.[4] Hospital volume was categorized as being low (≤6 cases/year), medium (6–10 cases/year), or high (≥10 cases/year). The results showed that the high-volume and medium-volume centers had significantly lower mortality rates compared with the low-volume centers. In this study, we divided hospitals into three groups according to the number of patients treated. There are too many hospitals in Japan to centralize infants with CDH. Even in G1, the median (range) number of patients was 29 (22–43) during 5 years. Although individual hospitals had a small number of CDH infants, the survival rate of the infants with prenatally diagnosed CDH was dependent on hospital volume. Therefore, we suggest that, at a minimum, the cases with a prenatal diagnosis should be referred to tertiary centers.

This study employed a retrospective survey using a questionnaire and was not designed to compare the outcomes that resulted from the management strategies. Judging from the birth prevalence of CDH,[1–3] the number of patients in our survey corresponded to approximately half of the estimated cases for that period. Consequently, the results of this study accurately describe the current status of infants with CDH in Japan. This study will therefore provide useful information for prenatal counseling of parents and for cross-national research.

The perinatal management strategies used to treat CDH were the same for the three groups of institutions divided based on the number of cases treated. The survival rate was dependent on hospital volume, particularly in cases with a prenatal diagnosis. We concluded that it might be important to centralize the infants with CDH in tertiary centers in Japan in order to improve survival rates.

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Original Article

Prognostic factors of congenital diaphragmatic hernia accompanied by cardiovascular malformation

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Abstract ***Background***: Congenital diaphragmatic hernia is associated with cardiovascular malformation. Many prognostic factors have been identified for isolated congenital diaphragmatic hernia; however, reports of concurrent congenital diaphragmatic hernia and cardiovascular malformation in infants are limited. This study evaluated congenital diaphragmatic hernia associated with cardiovascular malformation in infants. Factors associated with prognosis for patients were also identified.

Methods: This retrospective cohort study was based on a Japanese survey of congenital diaphragmatic hernia patients between 2006 and 2010. Frequency and outcome of cardiovascular malformation among infants with congenital diaphragmatic hernia were examined. Severity of congenital diaphragmatic hernia and cardiovascular malformation were compared as predictors of mortality and morbidity.

Results: Cardiovascular malformation was identified in 76 (12.3%) of 614 infants with congenital diaphragmatic hernia. Mild cardiovascular malformation was detected in 19 (33.9%) and severe cardiovascular malformation in 37 (66.1%). Their overall survival rate at discharge was 46.4%, and the survival rate without morbidity was 23.2%. Mortality and morbidity at discharge were more strongly associated with severity of cardiovascular malformation (adjusted OR 7.69, 95%CI 1.96–30.27; adjusted OR 7.93, 95%CI 1.76–35.79, respectively) than with severity of congenital diaphragmatic hernia.

Conclusions: The prognosis for infants with both congenital diaphragmatic hernia and cardiovascular malformation remains poor. Severity of cardiovascular malformation is a more important predictive factor for mortality and morbidity than severity of congenital diaphragmatic hernia.

Key words cardiac anomaly, diaphragmatic hernia, liver herniation, prognostic factor.

In recent years, outcomes in patients with isolated congenital diaphragmatic hernia (CDH) have markedly improved because of advances in perinatal management. Some studies have reported overall survival and intact survival rates exceeding 80% and 60%, respectively.[1–3] However, CDH is also known to be associated with other congenital malformations. Cardiovascular malformation (CVM) is found in 10–20% of infants with CDH.[4,5] Some reports have shown higher mortality rates in infants with both CDH and CVM than in those with CDH alone.[6,7]

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Many prognostic factors, such as liver herniation, lung-to-head ratio, Apgar score, and pulmonary artery size, have been previously evaluated for their association with isolated CDH. These factors are important for counseling of parents or management in the perinatal period.[8–12] However, in infants with both CDH and CVM, the association of the severity of these conditions with mortality and morbidity remains uncertain. This study evaluated the incidence and outcome of CDH associated with CVM and factors influencing the prognosis for infants with CDH and CVM were also examined.

Methods

This study was approved by the ethics committees of the National Center for Child Health and Development, Nagoya University Hospital, Osaka University Graduate School of Medicine, Hyogo College of Medicine, Osaka Medical Center and Research

Institute for Maternal and Child Health, Osaka University Hospital and Graduate School of Medical Sciences, and Kyushu University. A questionnaire was distributed to the departments of pediatric surgery and/or tertiary perinatal care centers of 159 educational hospitals. The survey inquired about infants with CDH born between 2006 and 2010. Of the 159 institutes invited to participate, 109 (68.8%) responded to the questionnaire. Of these, 26 institutes reported no CDH cases and 11 refused to participate in the survey, although some cases of CDH were treated at these institutes. Thus, the final sample included 72 institutes in which 614 CDH cases were treated during the study period.

Data from the CDH survey were combined with data from a nationwide survey conducted in Japan. All infants described as having cardiac defects were selected for review. Infants with patent foramen ovale, atrial septal defects, patent ductus arteriosus, and hemodynamically insignificant vascular malformation (including right aortic arch) were excluded from the review. The incidence of CVM among infants with CDH identified in the hospital survey was examined.

Factors influencing mortality and morbidity in infants with both CDH and CVM were assessed using multivariate analysis. Infants with trisomy 13 or trisomy 18 and those who received palliative care after birth were excluded from the analysis of prognostic factors. Severe CVM was defined as hemodynamically significant heart disease requiring surgical intervention. Severe CDH was defined as liver herniation. In infants with more than two CVM, the anomaly most likely to affect outcome was adopted. In addition, survival without morbidity was defined as no need for respiratory support, including oxygen supplementation, tube feeding, parenteral nutritional support, or vasodilation.[3]

All data were analyzed using the statistical software program Stat Flex for Windows version 6.0 (Artec, Osaka, Japan). Univariate analysis was performed to identify differences between survivors and non-survivors and differences between infants with and without morbidity at discharge or death. The χ^2-test, Fisher's exact test, the 2-sample test, and the Mann–Whitney nonparametric test were selected as appropriate. Multiple logistic regression analysis was performed to evaluate the association of CDH and CVM severity with mortality and morbidity. Mortality was defined as death during hospitalization. Statistical significance was set at $P < 0.05$.

Results

CVM was identified in 76 of the 614 (12.3%) infants. Life-limiting genetic defects were identified in 14 infants (trisomy 13, $n = 4$; trisomy 18, $n = 10$). Palliative care for severe CVM, trisomy 21, heterotaxia, or tracheal stenosis was administered in six cases, and full intervention was required in 56 cases. Mild CVM was detected in 19 (33.9%) of these 56 infants and severe CVM in 37 (66.1%) (Fig. 1).

Details of the 76 infants with CVM are provided in Table 1. Ventricular septal defect (VSD) was identified in four of the infants with trisomy 13 or trisomy 18, three infants with tetralogy of Fallot (TOF) and double-outlet right ventricle (DORV) with right ventricular outflow tract obstruction (RVOTO), and four

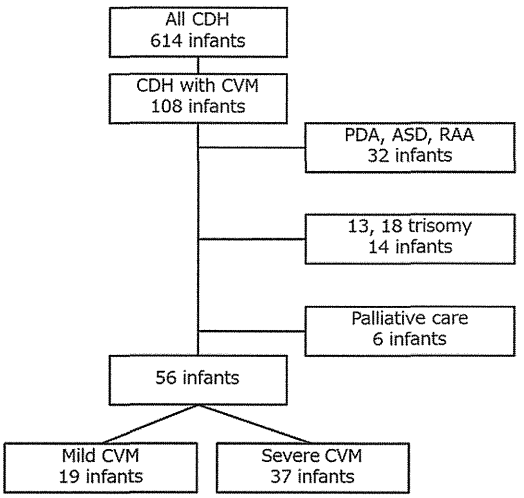

Fig. 1 Diagram summarizing the study population. ASD, atrial septal defect; CHD, congenital diaphragmatic hernia; CVM, cardiovascular malformation; PDA, patent ductus arteriosus; RAA, right aortic arch.

infants with DORV without RVOTO. The majority of infants with mild CVM had VSD ($n = 14$, 73.7%).

The overall survival rate at discharge of the infants with CVM who required full intervention was 46.4% (26/56). This rate for those with mild CVM and severe CVM was 77.8% (14/18) and 31.6% (12/38), respectively. The overall usage rate of extracorporeal membrane oxygenation (ECMO) and nitric oxide inhalation (iNO) were 8.9% (5/56) and 71.4% (40/56), respectively. On the other hand, the overall survival rate without morbidity at discharge was 23.2% (13/56). For those with mild and severe CVM, this rate was 50.0% (9/18) and 10.5% (4/38), respectively. Morbidities at discharge included use of supplemental oxygen ($n = 10$), tube feeding ($n = 6$), and vasodilation ($n = 4$). No ventilation, tracheostomy, or total parenteral nutrition was required at discharge for any of the patients.

Univariate analysis revealed that severe CVM was found significantly more frequently in non-survivors than in survivors (86.7% vs 46.2%, $P = 0.001$). However, no significant difference between survivors and non-survivors was observed for the other variables (including liver herniation, which was used to represent severity of CDH) (Table 2). Severe CVM was significantly more frequent in infants with morbidity at discharge or in non-survivors than in survivors without morbidity at discharge (79.1% vs 30.8%, $P = 0.001$) (Table 3). The adjusted OR for mortality in infants with CDH associated with CVM was 7.69 (95%CI 2.00–30.27) for infants with severe CVM and 0.49 (95%CI 0.12–1.91) for those with liver herniation. Morbidity in infants with CDH associated with CVM was calculated as 7.93 (95%CI 1.76–35.79) for those with severe CVM and 0.82 (95%CI 0.15–4.63) for those with liver herniation (Table 4).

In a subgroup analysis, the survival rate of infants with VSD was 72.2% (13/18); however, that of infants with the other CVM was <50%. No infants with hypoplastic left heart syndrome (HLHS) survived. In contrast, the intact survival rate in infants

Table 1 Types of cardiac defects observed in patients with CDH and CVM

n	13, 18 trisomy	Palliative care	Full intervention		Overall CVM
			Severe CVM	Mild CVM	
	14	6	37	19	76
VSD	4	2	5	14	25 (32.9%)
TOF or DORV with RVOTO	3	–	8	1	12 (15.8%)
DORV without RVOTO	4	–	4	–	8 (10.5%)
CoA or IAA	1	–	4	3	8 (10.5%)
HLHS	–	1	6	–	7 (9.2%)
SV	1	2	4		7 (9.2%)
PS or PA	–	–	1	1	2 (2.6%)
AVSD	1	–	1	–	2 (2.6%)
TAPVR	–	–	1	–	1 (1.3%)
TGA	–	–	1	–	1 (1.3%)
Truncus arteriosus	–	1	–	–	1 (1.3%)
TA	–	–	1	–	1 (1.3%)
TV dysplasia	–	–	1	–	1 (1.3%)

AVSD, atrioventricular septal defect; CDH, congenital diaphragmatic hernia; CoA, coarctation of the aorta; CVM, cardiovascular malformation; DORV, double-outlet right ventricle; HLHS, hypoplastic left heart syndrome; IAA, interruption of the aortic arch; PA, pulmonary atresia; PS, pulmonary stenosis; RVOTO, right ventricular tract obstruction; SV, single ventricle; TA, tricuspid valve atresia; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; TV, tricuspid valve; VSD, ventricular septal defect.

with VSD was 38.9% (7/18). The intact survival rate in infants with other CVM was very low (Table 5).

Discussion

Results of this report showed that CVM was concurrent with CDH in 12% of infants included in this study during this period. Ninety percent of infants with CVM (except those with trisomy 13 and trisomy 18) underwent full intervention. Despite this intervention, overall and intact survival rates at discharge were extremely poor (46% and 23%, respectively). VSD was the most common cardiac defect, and left-sided heart disease and conotruncal anomalies, such as TOF and DORV, were also common. Severe CVM was more closely associated with mortality and morbidity at discharge than liver herniation, which represented severe CDH in this study. The survival rate of infants with VSD was about 70%; however, less than 50% of infants with other types of CVM survived. In addition, even infants with VSD had low intact survival rate.

Table 2 Clinical characteristics of survivors and non-survivors. Data are presented as mean values ± SD or median values and (Q1–Q3)

Variables	Survivors	Non-survivors	*P*
Number of infants	26	30	
GA (wk)	37.7 ± 2.0	36.9 ± 2.9	0.254
BW(g)	2259 ± 517	2447 ± 623	0.229
Apgar score at 1 min	3 (2–5)	3 (2–4)	0.172
Apgar score at 5 min	5 (3–6)	5 (3–6)	0.418
Female	13 (50.0%)	17 (56.7%)	0.618
Vaginal delivery	6 (23.1%)	4 (13.3%)	0.738
Prenatal diagnosis	20 (76.9%)	25 (83.3%)	0.547
CDH left	24 (92.3%)	27 (90.0%)	1.000
Liver herniation	8/26 (30.8%)	7/26 (26.9%)	0.760
Severe CVM	12 (46.2%)	26 (86.7%)	0.001

BW, birthweight; CDH, congenital diaphragmatic hernia; CVM, cardiovascular malformations; GA, gestational age.

In various studies, the prevalence of CVM ranges from 8 to 13 per 1000 live births.[13,14] However, a recent study suggested a much higher prevalence of CVM (50 per 1000 live births).[15] The

Table 3 Clinical characteristics of infants according to status at discharge. Data are presented as mean values ± SD or median values and (Q1–Q3)

Variables	Survival without morbidity	Survival with morbidity or death	*P*
Number of infants	13	43	
GA (wk)	37.4 ± 1.6	37.2 ± 2.7	0.787
BW(g)	2158 ± 535	2421 ± 584	0.154
Apgar score at 1 min	4 (3–6.3)	3 (2–4)	0.047
Apgar score at 5 min	5 (5–7)	5 (2.3–6)	0.068
Female	8 (61.5%)	22 (51.1%)	0.511
Vaginal delivery	1 (7.7%)	9 (20.9%)	0.424
Prenatal diagnosis	11 (84.6%)	34 (79.1%)	0.721
CDH left	12 (92.3%)	39 (90.7%)	1.000
Liver herniation	3/13 (23.1%)	12/39 (30.8%)	0.733
Severe CVM	4 (30.8%)	34 (79.1%)	0.001

BW, birthweight; CDH, congenital diaphragmatic hernia; CVM, cardiovascular malformations; GA, gestational age.

Table 4 Association of severity of CVM and CDH with status at discharge (multivariable logistic regression). Variables were adjusted for gestational age, prenatal diagnosis, and Apgar score at 1 min

Variables	Mortality		Morbidity	
	Adjusted OR	95%CI	Adjusted OR	95%CI
Severe CVM	7.69	2.00–30.27	7.93	1.76–35.79
Liver herniation	0.49	0.12–1.91	0.82	0.15–4.63

CVM, cardiovascular malformation.

Table 5 Survival rates with and without morbidity at discharge for infants with CDH according to presence and type of cardiac defect

		n	Survivors	Survivors without morbidity
CDH with CVM	Overall	56	26 (46.4%)	13 (23.2%)
	Severe	38	12 (31.6%)	4 (10.5%)
	Mild	18	14 (77.8%)	9 (50.0%)
VSD		18	13 (72.2%)	7 (38.9%)
TOF or DORV with RVOTO		9	3 (33.3%)	1 (11.1%)
DORV without RVOTO		5	2 (40.0%)	1 (20%)
CoA or IAA		7	3 (42.9%)	2 (28.6%)
HLHS		6	0	0
SV		4	2 (50%)	0
PS or PA		2	1 (50%)	1 (50%)
AVSD		1	0	0
TAPVR		1	0	0
TGA		1	1 (100%)	0
TA		1	1 (100%)	1 (100%)
TV dysplasia		1	0	0

AVSD, atrioventricular septal defect; CDH, congenital diaphragmatic hernia; CoA, coarctation of the aorta; CVM, cardiovascular malformation; DORV, double-outlet right ventricle; HLHS, hypoplastic left heart syndrome; IAA, interruption of the aortic arch; PA, pulmonary atresia; PS, pulmonary stenosis; RVOTO, right ventricular tract obstruction; SV, single ventricle; TA, tricuspid valve atresia; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; TV, tricuspid valve; VSD, ventricular septal defect.

present study detected a frequency of CVM associated with CDH of about twice as high as that in the general population. The frequency of this study (12%) was similar to that identified by the Congenital Diaphragmatic Hernia Study Group (CDHSG) (10.5%).[5] In the assessment of types of CVM, VSD was the most common in both studies (this study 32%, CDHSG study 42%). The frequency of left-sided heart disease, including HLHS, was 28% in the CDHSG study, which was higher than that identified in the present study (19.7%). Some reports have shown a lower frequency of left-sided heart disease in Asia than in Western countries. Thus, the discrepancy between our results and those of the CDHSG study may be because of differences in race.[15,16] In Japan, left-sided heart disease accounts for about 3% of all CVM, which suggests that the frequency of left-sided heart disease associated with CDH is extremely high, even in the Japanese population.[15,17]

In a study of major structural non-cardiac anomalies identified with CVM, Miller *et al.* reported a frequency of 15% for left-sided heart disease associated with all congenital anomalies. In another study, the frequency of left-sided heart disease associated with CDH was reported as 27%.[18] The higher incidence of left-sided heart disease may reflect the limited flow through the left side of the heart due to direct compression of herniated structures and decreased pulmonary blood flow caused by lung compression. In the present study, all infants with left-sided heart disease also had left-sided CDH, which supports this theory.[19,20]

In this study, numerous conotruncal anomalies, such as TOF and DORV, were observed, accounting for about 30% of all CVM. Trisomy 13 and trisomy 18 have been strongly associated with conotruncal anomalies.[21] Our sample included 14 infants with trisomy 13 and trisomy 18, half of whom had TOF or DORV. This may be one of the causes of the high frequency of conotruncal anomalies.

Many studies have reported associations between the prognosis for patients with isolated CDH and several predictors, such as lung-to-head ratio, liver herniation, low birthweight, Apgar score, pulmonary artery diameter, and best PaO_2 value.[8–12,22] This study found no association between liver herniation (used to represent severe CDH) and mortality and morbidity. However, the results indicated that severity of CVM was an independent risk factor for mortality and morbidity at discharge.

In this study, the survival rate of infants with mild CVM was about 80%, the same as that for isolated CDH (84%) in our survey.[23] On the other hand, the survival rate of infants with severe CVM was about 30% and of infants without morbidity was just 10%. This result suggests that the prognosis remains poor in infants with CDH concurrent with CVM despite improvements in outcomes in cases with isolated CDH. Furthermore, in our survey, the usage rates of ECMO and iNO in all CDH were 7.0% and 56.2%, respectively.[23] The usage rates among infants with both CDH and CVM tended to be higher than those among all CDH.

The survival rate was relatively favorable in infants with VSD (72%) but not in infants with other types of CVM (<50%). In infants with VSD, cyanosis rarely develops. However, in infants with univentricular anatomy, DORV, and pulmonary stenosis, cyanosis could develop easily even without CDH. Furthermore, in such patients, hypoxia could get worse because of presence of CDH. It may be one of the causes that infants with CDH and such types of CVM have poorer prognosis than those with VSD.

In this study, none of the six infants with HLHS survived. Termination of labor and palliative care after birth may be considered in cases associated with HLHS. Although the survival rate of infants with VSD was favorable, only 40% of infants were discharged from hospital without morbidities. This may be important information for parents of infants with this defect.

Completion of Fontan circulation is difficult for infants with CVM in whom biventricular repair is also difficult. Residual pulmonary hypertension complicates this situation. Therefore, 3- or 5-year survival rates may be lower than the survival rate at discharge used in this study. To our knowledge, no previous cases have been reported of survival in infants with cavopulmonary anastomosis and CDH. Long-term follow up in patients with these conditions is required.

This study has several limitations. First, detailed information regarding treatment was not included. This study was based on data from a retrospective national survey of infants with CDH that did not include this information. Second, severity of CVM was defined on the basis of hemodynamic significance. However, this decision may have differed between facilities, and thus, assessment of disease severity may not have been uniform. Third, the end-point of the study was at discharge; therefore, intracardiac surgery had not yet been performed in some infants. Thus, the actual mortality and morbidity rates may have been poorer than those reported in this study. Finally, the number of cases

may be insufficient for accurate evaluation of prognostic factors. The lung-to-heart ratio and pulmonary artery size are useful for assessing severity of CDH; however, data on these parameters were available for only about 20 infants included in this study. Thus, liver herniation was used as an index of CDH severity.

Despite these limitations, the results of this study demonstrate that the frequency of CVM among infants with CDH in Japan is similar to that in Western countries. Mortality and morbidity rates remain unfavorable despite improvements in perinatal management. The severity of CVM is important to the prognosis for patients who have these conditions concurrently. Further study is needed to determine factors influencing prognosis depending on the type of CVM.

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