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難治性疾患等政策研究事業（難治性疾患政策研究事業）

乳児特発性僧帽弁腱索断裂の病態解明と
治療法の確立に関する総合的研究

平成26年度 総括・分担研究報告書

研究代表者 白石 公

国立循環器病研究センター小児循環器部

平成27年3月

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「乳児特発性僧帽弁腱索断裂の病態解明と

治療法の確立に関する総合的研究」

研究代表者 白石 公

国立循環器病研究センター 小児循環器部

[背景] 乳児特発性僧帽弁腱索断裂とは、生来健全な乳児に突然の急性呼吸循環不全が発症し、診断と早期の外科治療が遅れると死に至る疾患である。ほとんどが日本人で、生後4-6ヶ月に発症が集中するという特徴を持つ。基礎疾患として川崎病、抗SSA抗体、弁の粘液変成、ウイルス心内膜炎等などが示唆されるが詳細は不明である。乳児特発性僧帽弁腱索断裂の病因および臨床経過および臨床検査所見を詳細に調査し、本疾患の早期診断および的確な内科的および外科的治療法を早急に確立する。

[対象と方法] 乳児特発性僧帽弁腱索断裂と診断された乳児。発症年齢、基礎疾患の有無、発症様式、血液生化学所見、画像所見、手術所見、病理組織所見、予後、転帰などについて調査。サンプルが得られた症例では、全血および血清サンプルの凍結保存、尿、弁、咽頭拭い液からのウイルス分離、弁置換を行った症例では弁組織の凍結保存やホルマリン固定病理組織標本の免疫組織科学的検討を行い、腱索断裂のメカニズムを解明研究する。

[結果] 平成22年度より行った全国調査から、過去16年間に発症した95例について臨床所見を要約。発症は生後4~6ヶ月に集中し(85%)、やや男児に多く(53:42)、春から夏の頻度が高かった(66%)。全体的に近年増加傾向にある。基礎疾患として、川崎病10例、抗SSA抗体陽性2例、細菌性心内膜炎1例が認められた。CRPの上昇は軽度で、外科治療は弁形成が52例(55%)、人工弁置換が26例(27%)に行われた。死亡例は8例(8.4%)で、中枢神経系後遺症は10例(11%)認められた。これらの結果は、2014年9月に米国心臓協会(American Heart Association)の公式雑誌(Circulation. 2014;130:1053-1061)に論文として掲載された。また、本年度は血液からウイルスが分離された症例はなく、凍結された弁および腱索組織が得られなかったに

で、来年度以降にこれらの検索を押し進め、病因解明と治療法の確立に役立てる。
[結論] 今回の研究で病因および病態がかなり明らかになったので、今後研究を継続して、早期発見および的確な治療法を早急に確立する。また基礎研究と疫学調査を継続して行い、病因解明に向けた努力を行う。生来健康な乳児に突然発症する本疾患を重篤な合併症を残すことなく的確に診断治療することは、小児の保健・医療・福祉の向上に不可欠である。

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A. 研究目的

生来健康である乳児に、数日の感冒様症状に引き続き突然に僧帽弁の腱索が断裂し、急速に呼吸循環不全に陥る疾患が存在する。本疾患は原因が不明で、過去の報告例のほとんどが日本人であるという特徴をもつ。発症早期に的確に診断され、専門施設で適切な外科治療がなされないと、急性左心不全により短期間に死に至る。また外科手術により救命し得た場合も人工弁置換術を余儀なくされるもしくは神経学的後遺症を残すなど、子どもたちの生涯にわたる重篤な続発症をきたす。しかしながら本疾患は国内外の小児科の教科書に独立した疾患として記載されておらず、多くの小児科医は本疾患の存在を認識していない。またその急激な臨床経過の特徴から、過去の死亡例は「乳児突然死症候群」と統計処理された可能性があり、実際の発症はさらに多いと考えられる。これまでの我々の調査の結果、僧帽弁腱索が断裂する原因として、ウイルス感染（心内膜心筋炎）、母体から移行した血中自己抗体（抗SSA抗体）、川崎病（回復期以降）、細菌性心内膜炎などが明らかになっており、これら何らかの感染症や免疫学的異常が僧帽弁腱索断裂の引き金になると考えられているが、各々の病態の詳細は不明である。また最近数年間、国内での症例報告が増加しており、早期の実態調査、早期発見の啓蒙、診断治療方針の確立が急務である。

本疾患の全国実態調査をこれまでに行った調査を発展させて継続的に行うことで、発症頻度、発症状況、危険因子などを明らかにする。また、診断基準や治療に関するガイドラインを確立し、情報を広く全国の小児科医に伝達する

ことにより、早期診断や早期治療が可能にして、死亡例や重篤な合併症を大きく減らすことができる。

B. 研究方法

1. 平成22, 25年度の全国調査で得られた臨床情報を土台として、班会議で議論を重ね、早期診断および適切な内科的・外科的治療に必要な現時点での診断基準を作成する。その情報は日本小児科学会、日本小児循環器学会、日本循環器学会、日本心臓血管外科学会などを通じて、できるだけ早く全国の小児科医のみならず循環器内科医や心臓血管外科医にも伝達する。
2. 本疾患の継続的な全国実態調査を、本研究班員のみならず日本小児循環器学会評議員会を利用して行い、患者の詳細な臨床情報を分析するとともに、国立循環器病研究センター予防健診部において、流行性、地域性、栄養や予防接種との関連などの疾患のリスクおよび予後因子などの疫学研究を実施する。
3. 更に今後新たに発症する症例において、前向きに血液サンプル、弁置換を行った症例では弁組織の凍結保存や病理組織標本を収集し、ウイルスゲノムの解析、免疫組織学的検討、分子生物学的検索を加え、腱索断裂のメカニズムの解明研究を展開する。具体的には、発症時の患者血液を用いて、IL-1 β , IL-6, IL-10, TNF α などの炎症性サイトカイン、ブドウ球菌や溶連菌由来のスーパー抗原、血液中のリンパ球分画、抗核抗体、

抗 DNA 抗体、抗 SSA 抗体、抗 SSB 抗体、心筋心内膜炎を引き起こすウイルス分離とウイルス抗体価、薬剤投与がある場合はリンパ球幼弱試験などを調べ、基礎疾患を明らかにするとともに、腱索組織の破壊に至る病理組織学的、免疫組織学的メカニズムを明らかにする。得られる新鮮な腱索組織を用いて、血管新生因子である VEGF、弁や腱索組織に含まれ膠原線維や弾性線維の remodeling に関与する matrix metalloproteinases、抗核抗体、抗 DNA 抗体、抗 SSA 抗体、抗 SSB 抗体、などの免疫組織化学を行う。免疫組織学的研究の一部は、文部省科学研究費基盤(C)「乳児特発性僧帽弁腱索断裂の病因に関する基礎的研究」(主任：白石 公)により現在実施中である。これらの基礎研究は平成 25 年度より実施展開し、3 年後の平成 27 年度末までには病因と断裂のメカニズムを明らかにする予定である。

4. 更なる臨床情報の収集および基礎研究の結果に基づき、病因に基づいた新たな薬物治療法や的確な外科手術療法を開発し提言する。研究開始 5 年後の平成 29 年度末には、病因解明と治療法を確立させ、世界に情報を発信する予定である。具体的には、以上の研究により腱索断裂にいたる分子細胞生物学的なメカニズムがある程度明らかになれば、TNF α や NF κ B などの炎症メディエーター、MMP-9 などによる弁組織の構造破壊を引き起こすシグナルを抑制することを目的に、班会議で薬剤の種類とプロトコルを定めた上で、新たに発症する症例に対

して、ガンマグロブリン大量療法、ステロイドパルス療法、TNF α 抗体などの実施を考慮する。平成 22 年度の全国調査では、腱索修復術後も炎症が持続し、手術後数日後に新たな腱索断裂が進行し、再手術による人工弁置換術を余儀なくされた症例が多数認められたため、抗炎症療法は術後の腱索断裂の進行を予防することに役立つ可能性が高い。

5. 今回の研究では平成 26 年度において約 10 例において血液や摘出組織の集約が可能と考えている。以降も同様に病因研究に寄与するサンプル収集を行う。

以上、乳児僧帽弁腱索断裂の臨床情報の集積と分析、独立した重症難治疾患としての認知及び啓蒙活動、血液や摘出腱索組織を用いた基礎的研究、早期診断と適切な内科的外科的治療、発症抑制に向けた新しい治療法の確立などを研究の最終目標とする。

C. 研究結果

本疾患は生後 4~6 ヶ月の乳児に好発する。ただし母親由来の SSA 抗体陽性患者では生後 1~2 ヶ月以内に発症することがある。数日の発熱、咳嗽、嘔吐などの感冒様の前駆症状に続き、突然に僧帽弁腱索が断裂する。重度の僧帽弁閉鎖不全により心拍出量の低下および著しい肺うっ血をきたし、短時間に多呼吸、陥没呼吸、呼吸困難、顔面蒼白、頻脈、ショック状態に陥る。少数で三尖弁の腱索断裂を合併することがある。複数の腱索が断裂すると、人工弁置換術を余儀なくされることがある。術後に別の腱索次々と断裂し、数日後に人工弁置換が必要とな

る症例も散見される。乳児時期に人工弁置換を行った場合は、生涯にわたる抗凝固剤の内服が必要であるとともに、再弁置換もしくは再々弁置換術が必要となる。また女兒では成人期に達した際、抗凝固薬の内服は妊娠や出産において大きな障害となる。

通常、胸骨左縁第 III 肋間から心尖部にかけて収縮期逆流性心雑音が聴取される。心雑音の指摘のない乳児が急速に呼吸循環不全に陥り、新たな心雑音が聴取された場合には、本疾患を疑う。ただし急性左心不全による肺水腫のため、肺野に全体に湿性ラ音が聴取されて心雑音が聴き取りにくい場合があるので注意が必要である。また急速な経過のために心拡大が顕著でなく、心疾患として認識されず、肺炎と初期診断する可能性があるので注意を要する。

典型的な症例を 1 例示す。図 1 は生後 4 ヶ月の乳児に発症した僧帽弁腱索断裂である。2 日間の発熱の後、顔面蒼白のショック症状を呈した。二次救急病院での初期診断は肺炎であったが、心雑音に気づかれて心エコーを行ったところ、重度の僧帽弁逸脱および僧帽弁腱索断裂に気付かれ、三次救急病院に搬送された。強心利尿薬による内科的治療で循環不全が改善できなかったため、速やかに外科手術が執り行われた。搬送当初、ショック状態で人工呼吸を必要とし、速やかに外科手術が行われ、人工腱索による腱索修復と僧帽弁縫縮術が行われた。術後経過は順調で、軽度の僧帽弁閉鎖不全を遺残するのみで、現在外来で内服治療もなく良好に経過している。

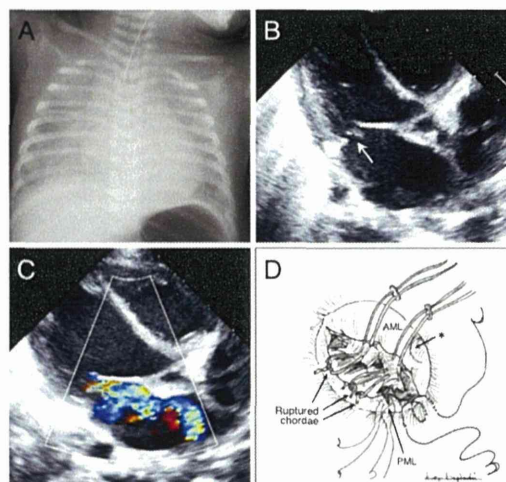


図 1：生後 4 ヶ月の乳児に発症した僧帽弁腱索断裂 (A:胸部 Xp 所見、B:断層心エコー所見、C:ドプラー断層所見、D:手術所見)

全国調査の結果、過去 16 年間に発症した 95 例の臨床データを得た。発症は生後 4～6 ヶ月に集中した(85%，図 2)。性別では、やや男児に多かった(図 3)。季節別では、春から夏の頻度が高かった(66%，図 4)。

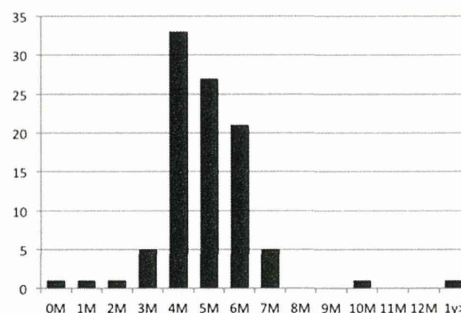


図 2：発症月例の分布

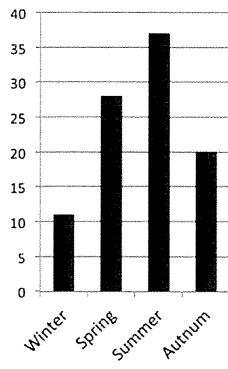
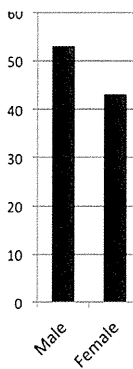


図3：男女分布 図4：発症の季節分布

基礎疾患として、川崎病10例、抗SSA抗体陽性は調べた12例中2例に、細菌性心内膜炎1例が認められた（表1）。

Table 1. Clinical Characteristics of the 95 Patients

Clinical Findings	
Age at onset (months)	5 (4-6)*
Body weight at onset (kg)	6.83 (6.14-7.51)*
Gestational weeks	39 (38-40)*
Body weight at birth (kg)	2.97 (2.70-3.28)*
History of Kawasaki disease	10 cases; Acute and convalescent stage (day ≤ 30), 3 cases Beyond convalescent stage (day > 30), 7 cases
Anti-SSA antibody-positive (12 cases examined)	2 cases; 0 and 5 mo
Prodromal symptoms	88 cases; fever 37, cough 16, vomit 14, others 21
Cardiogenic shock after initial prodromes	2 (1-7)*

*Data are presented as median (interquartile range).

表1：95例の臨床所見

血液生化学所見では、急性循環不全によるショックから白血球数は中等度の増加（全国調査での中央値 15,440/uL）がみられるが、一般にCRPは軽度の上昇に留まる（中央値 1.60mg/dL）。トランスアミナーゼ値は心不全の強い症例では上昇するが多くの場合は正常範囲で（AST, ALT 中央値 44, 21(IU/L)）、心筋逸脱酵素、とくにCPK-MB や心筋トロポニン T の上昇は見られない。ほとんどの症例でBNP値は高度に上昇

する（中央値 1,450pg/mL）（表2）。

胸部X線所見では、急速に心不全が進行するために心拡大は軽度（心胸郭比中央値 56%）にとどまるが、多くの症例（75%）において両肺野にうっ血像が認められる（図1）。一部の僧帽弁閉鎖不全の経過が長い症例では心拡大が明らかとなる。心電図では特徴的な所見は少なく、急性左心不全による左胸部誘導でT波の平定化や陰転が見られることがある。僧帽弁腱索断裂の診断は、断層心エコー検査で確定可能である。左室長軸断面および心尖部四腔断面像において、僧帽弁尖の逸脱および翻転、断裂により遊離した腱索、ドプラー断層で大量の僧帽弁逆流シグナルが確認できる。僧帽弁閉鎖不全の程度は、全国調査では高度70例（73%）、中等度22例（23%）、軽度4例（4%）であった。しかしながら、急性心不全のために左室腔の拡大は明らかでなく（左室拡張末期径 z value 中央値 1.47）、左室短縮率は高度な僧帽弁閉鎖不全のため軽度亢進する（中央値 0.41）。全国調査では、断層心エコーで特徴的な所見として乳頭筋頂部の腱索付着部位にエコー輝度の亢進が8例（8.4%）に認められた。粘液変性と考えられる僧帽弁尖の有意な肥厚は9例（9.5%）に認められた。全国調査では僧帽弁前尖の断裂が28例、後尖の断裂が33例、両者の断裂が22例に認められた。まれに三尖弁の腱索断裂を伴う症例も存在し（6例）、心不全が重篤になるので注意が必要である。

Table 2. Laboratory Findings of the 95 Patients

Examinations	On Admission	At Discharge	P Value
WBC (/uL)	15 440 (11 990–21 650)	9160 (7330–11 100)	<0.0001
Hb (g/dL)	10.2 (8.9–11.1)	11.8 (10.9–13.0)	<0.0001
PLT (×10 ⁹ /uL)	501 (338–600)	368 (302–439)	0.0003
CRP (mg/dL)	1.60 (1.97–3.15)	0.11 (0.16–0.31)	<0.0001
AST (IU/L)	44 (30–105)	36 (29–44)	0.0003
ALT (IU/L)	21 (13–135)	22 (16–36)	0.0160
LDH (IU/L)	421(267–763)	332 (264–484)	0.0046
CPK (IU/L)	119 (77–247)	76 (45–123)	0.0002
CPK-MB (IU/L)	27 (12–91)	31 (20–42)	0.0749
BNP (pg/mL)	1,450 (839–2545)	72 (32–114)	0.0007
cTnT (n=22, ng/mL)	0.027 (0–0.132)	—	—

Data are presented as median (interquartile range). ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic protein; CPK, creatine phosphokinase; CRP, C reactive protein; cTnT, cardiac troponin T; Hb, hemoglobin; LDH, lactate dehydrogenase; MB, myocardial band; PLT, platelets; and WBC, white blood cells.

表2：95例の血液生化学所見

生来健康で心雑音が指摘されたことがない生後4～6ヶ月の乳児に、数日の感冒要症状に引き続き、突然の多呼吸、陥没呼吸、顔面蒼白、ショック症状がみられ、聴診で収縮期の逆流性心雑音が聴取された場合、本疾患を疑う。断層心エコーにより診断がつき次第、可及的に乳児の開心術が行える小児循環器専門施設に紹介する。必要な治療としては、診断がつき次第まず呼吸循環動態の改善に努める。全身蒼白のショック状態で呼吸困難が強い場合には、鎮静下に気管内挿管による人工呼吸管理を行い、動脈ラインおよび中心静脈ラインの確保による集中治療管理を開始し、アシドーシスの補正、強心薬の持続静脈投与、利尿薬の静脈内投与により、左心不全および肺うっ血の改善を試みる。診断がついた後も、内科的治療により経過観察している間に次々と新たな腱索が断裂する可能性があるため、これらの集中治療によっても呼吸管理および循環動態が維持できない場合は、時期を逃さず外科手術に踏み切ることが重要である。

手術は一般に人工腱索を用いた僧帽弁腱索形成術を行う。僧帽弁輪が拡大した症例では弁輪縫縮術も併用する。ただし複数の腱索が断裂した症例や、断裂が前尖と後尖の広範囲にわたり、人工腱索だけでは修復不可能と判断される場合は、機械弁置換術を行う。好発年齢である生後4～6ヶ月の乳児では、通常16mmの機械弁を挿入する。

今回の調査では、外科治療は、最終的に腱索形成もしくは弁輪縫縮が52例(55%)、機械弁置換が26例(27%)に行われた。死亡例は8例(8.4%)であった。中枢神経系後遺症は10例(11%)認められた。全体では35例(40%)が何らかの後遺症/続発症を残し、本疾患の罹病率は極めて高い。(図5)。

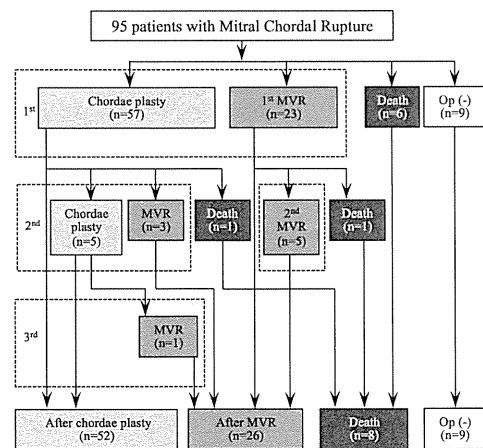


図5：95例の外科的治療内容

腱索の病理組織(21例)では、単核球を主体(とする心内膜下の炎症細胞浸潤が18例(64%)に認められた。多核白血球の浸潤はごく少数のみ認められた。断裂部位は線維性組織で置換され癒着化していた。粘液様変成が11例(39%)に認められた。急性炎症のマーカーであるテネイシンCは腱索全体にわたり陽性であった。

(図6)。免疫組織科学では、浸潤した単核球は、CD3 陽性Tリンパ球およびCD68 陽性マクロファージであった。剖検のえられた2症例では、他の内臓臓器に腱索と同様な炎症所見は認められなかった。

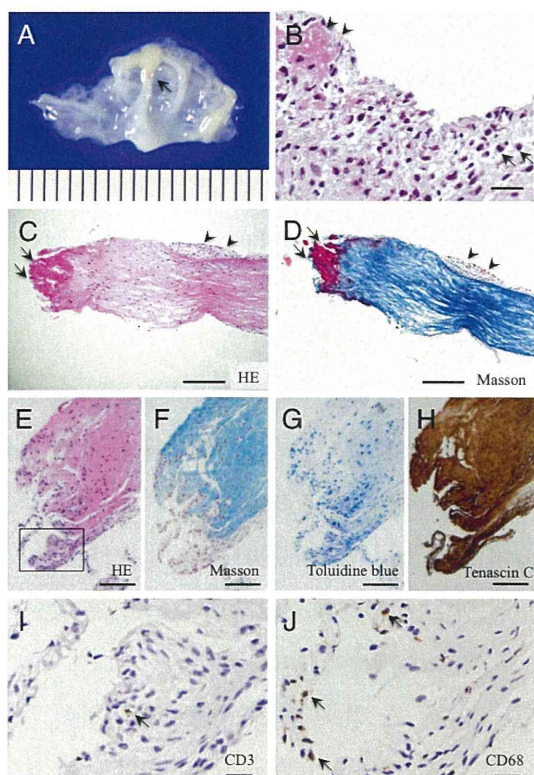


図6：断裂した腱索の病理組織所見

D. 考察

本疾患の原因は現時点では明らかではないが、今回の研究から、川崎病の回復期、母親由来の抗 SSA 抗体、僧帽弁および腱索組織の粘液変成、ウイルス感染などが引き金になって発症することが明らかになった。

川崎病が10症例において病歴があり、川崎病による心内膜炎が僧帽弁尖や腱索組織に波及して、細胞浸潤から線維化、瘢痕化をきたし

て腱索断裂に導いた可能性がある。今後川崎病は、僧帽弁腱索断裂の一因として認識しておく必要がある。

母親由来の抗 SSA 抗体は、症例数は2例であるとはいえ見逃すことのできない原因であると考えられる。抗 SSA 抗体は、胎盤を通過して、胎児の心筋細胞、とくに刺激伝導系細胞に結合してアポトーシスから炎症細胞の浸潤をきたし、抗 SSA 抗体陽性の母親の約1%に完全房室ブロックを起こす。詳細は明らかではないが、同様な機序で心内膜細胞にも結合して胎児期に炎症を引き起こし、腱索部分が瘢痕化して、出生後のある特定の時期に断裂することが想定される。しかしこの機序に関するエビデンスはないので、今後 SSA 抗体と胎児心内膜組織、弁組織、腱索組織を用いた *in vitro* の実験が必要になる。一部の症例で僧帽弁乳頭筋頂部の腱索への移行部にエコー輝度の高い所見が認められた。非特異的所見であり、echogenic intracardiac focus (EIF)と区別されなければならないが、今後症例を重ねて、これらの所見を抗 SSA 抗体陽性の母親から生まれた児に対する腱索断裂の早期診断につなげてゆく必要がある。

弁および腱索組織の粘液様変成も比較的高率(39%)に求められた。元々弁および腱索に脆弱性のある児に何らかの炎症もしくは物理的要因が加わり発症した可能性が示唆される。

直接的なエビデンスは現時点でないが、CRPが上昇しないこと、腱索組織から単核球を主体とする炎症細胞浸潤が高率(69%)に見られたこと、感冒様の症状が高率(88例)に認められたこと、母親からのIgG抗体が低下する生後4

ヶ月を筆頭に、生後4ヶ月をヶ月に高率に発症する、季節的に春から夏に多発する、これは心筋炎を引き起こすエンテロ系ウイルスの好発時期に一致するが、これらの所見から、何らかのウイルス感染が腱索に炎症を引き起こし断裂に導いた可能性が高く示唆された。今後患者の血液、尿、心臓のサンプル（弁置換を行った症例）からウイルス分離やウイルスゲノムの検索を行う必要がある。残念ながら本年度は血液のウイルス分離を2例で行ったが、いずれも陰性であった。

E. 結論

弁形成もしくは弁置換により外科手術が成功すれば、左室の収縮機能は比較的短期間に改善する。また症例によっては、腱索形成術後に別の腱索が新たに断裂することがあり、術後も断層心エコーおよびドプラー断層により僧帽弁閉鎖不全の増悪に十分留意する必要がある。ショック状態で搬送された症例では、低血圧もしくは低酸素による中枢神経系障害を合併することがあるので、術直後より頭部エコー検査や頭部CT検査を実施して、脳浮腫や頭蓋内出血などの中枢神経系障害の出現に留意する。

死亡例が8名（8.4%）、人工弁置換症例が27例（27.3%）、呼吸循環不全に伴い発症した中枢神経系後遺症が10例（10.5%）に認められ、生来健康な乳児に発症する急性疾患として見逃すことのできない疾患である。病因を明らかにし適切な治療法を確立することが急務である。

F. 健康危険

情報

該当なし

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Acute Rupture of Chordae Tendineae of the Mitral Valve in Infants

A Nationwide Survey in Japan Exploring a New Syndrome

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Background—Recently, infant cases of acute heart failure attributable to rupture of the mitral chordae tendineae have been reported. However, little is known about the pathogenesis and clinical course of this condition.

Methods and Results—Ninety-five children with rupture of mitral chordae tendineae were identified in nationwide surveys of Japan diagnosed from 1995 to 2013. The clinical manifestations, management strategies, and prognosis were investigated. Eighty-one (85%) patients were between 4 and 6 months (median, 5 months) of age. In 63 (66%) patients, rupture occurred during the spring or summer. The underlying conditions before rupture included Kawasaki disease (10 cases), maternally derived anti-SSA antibodies (2 cases), and infective endocarditis (1 case). Surgery was performed in 80 patients (94 operations), and the final operations included plasty of mitral chordae in 52 cases and mechanical valve replacement in 26 cases. The histopathologic examinations of the mitral valves and chordae (n=28) revealed inflammatory reactions with predominant mononuclear cell infiltration in 18 cases (64%) and increased fibrous and myxoid tissue in 11 cases (39%), suggesting that nonbacterial infectious or autoimmune endocarditis and myxoid changes are involved in the pathogenesis. Eight patients (8.4%) died before (n=6) and shortly after (n=2) the operation, and significant neurological complications persisted in 10 cases (11%).

Conclusions—Acute heart failure attributable to rupture of the mitral chordae tendineae in infants is a unique disease resulting from diverse causes. This condition should be recognized as a significant cardiovascular disorder that may cause sudden onset of cardiogenic shock and death in infants. (*Circulation*. 2014;130:1053-1061.)

Key Words: heart failure ■ mitral regurgitation ■ pathology, surgical ■ pediatrics

Acute massive mitral regurgitation attributable to rupture of the chordae tendineae is a serious condition in which the patient experiences the sudden onset of circulatory and respiratory failure.¹⁻³ This disease generally occurs in older children, adolescents, and adults, and the underlying conditions are diverse^{2,3}; for example, myxomatous change of the mitral valve,³ systemic connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome,^{2,4,5} infectious endocarditis,^{2,6,7} rheumatic fever,^{2,3,8,9} hypertension,^{10,11} labor and delivery,¹² blunt chest trauma,^{2,13} and abnormalities of mitral apparatus such as single papillary muscle or double orifice mitral valve.^{14,15}

Clinical Perspective on p 1061

Until recently, rupture of the mitral chordae tendineae was thought to be rare in young children. However, several child cases without congenital malformations of mitral valve apparatus have been reported in Japan, with the majority of cases, interestingly, being in infants.¹⁶⁻²² According to the literature, the prognosis of affected patients is, in general, unsatisfactory, as a number of patients were treated with mechanical valve replacement and several patients died of cardiogenic shock.^{19,20} To make matters worse, the clinical entities and criteria of the disease have not been described in any textbook

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of pediatrics or pediatric cardiology. Consequently, pediatricians, and even pediatric cardiologists, do not know much about the disease.

To elucidate the cause, clinical manifestations, appropriate medical and surgical treatment, and prognosis of the disease, we conducted a nationwide retrospective survey of acute rupture of the chordae tendineae of the mitral valve in children in Japan. Although the cases reported here are limited to Japanese infants, this disease does occur in other countries. Some patients may have gone unnoticed after dying or being misdiagnosed with other conditions such as sudden infant death syndrome. Therefore, acute rupture of the mitral chordae tendineae in infants is a new syndrome and should be recognized as a significant cardiovascular disorder that may cause sudden onset of cardiogenic shock and death.

Methods

Study Patients

This study is a retrospective cohort study of acute rupture of the mitral chordae tendineae in children occurring between July 1995 and August 2013. A primary questionnaire was sent to 532 clinical training hospitals approved by the Japanese Society of Pediatrics, requesting information on cases of children (under 15 years of age) with rupture of the mitral chordae between 1995 and 2013. Two hundred fifty-two hospitals (56.3%) responded to the first questionnaire, and 64 (12.0%) hospitals gave affirmative responses to such cases. The second questionnaire was forwarded to the 64 institutes, inquiring about clinical manifestations, medical and surgical treatments, and prognoses of patients. Ninety-five cases were investigated in the study. Seventeen cases previously reported^{17,19,20,22} were included in this nationwide survey. The diagnosis of Kawasaki disease was conducted by Board Certified Pediatricians of each hospital according to the diagnostic guidelines for Kawasaki disease.^{23,24} The institutional review committee of National Cerebral and Cardiovascular Center approved the study.

Pathological Diagnosis and Immunohistochemistry

A pathologist at the National Cerebral and Cardiovascular Center examined the actual specimens in 13 of 28 cases, whereas the study group relied on written documents and microphotographs of the specimens in the 15 remaining cases reported by board-certified pathologists at each institute. The immunohistochemistry procedures for tenascin C (mouse monoclonal, clone: 4F10TT, dilution 1:1000; Immuno-Biological Laboratories Inc), CD3 (rabbit polyclonal, dilution 1:10; Dako Japan Inc), and CD68 (mouse monoclonal, clone: KP-1, dilution 1:1,000; Dako Japan Co Ltd) were performed on formalin-fixed, paraffin-embedded chordal sections using an established method. All the immunohistochemical studies were performed in the department of pathology, National Cerebral and Cardiovascular Center.

Statistical Analysis

The data of the patients are presented as the median with interquartile range values for continuous demographic variables and laboratory findings. The Wilcoxon signed rank test was used to compare the laboratory data obtained at the onset of symptoms and discharge from the hospital because of the skewed nature of distribution. For the rate of pulmonary congestion, the McNemar test was conducted. Cumulative event-free survival curves were estimated using the Kaplan-Meier method. Cox proportional hazards models were used to identify factors associated with the time to aortic valve replacement and time to death. Hazard ratios and 95% confidence intervals (CIs) were also estimated. *P* value of <0.05 was considered to be statistically significant.

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Results

Clinical Features of the 95 Patients

A typical case of acute rupture of the mitral chordae tendineae is shown in Figure 1. A 4-month-old female infant without a history of significant illnesses exhibited the sudden onset of a cyanosis and dyspnea after 2 days of fever. The initial diagnosis was pneumonia (Figure 1A); however, severe mitral regurgitation and rupture of the chordae tendineae were diagnosed in secondary and tertiary hospitals, respectively (Figure 1B and 1C). Surgical repair using artificial chordae was performed in association with mitral annuloplasty (Figure 1D). The intraoperative findings demonstrated that 4 chordae tendineae on the posterior leaflet were lacerated. After surgery, severe regurgitation successfully reduced to a trivial level.

The clinical characteristics of 95 patients are shown in Table 1 and Figure 2. There were 52 males and 43 females (Figure 2A), and ages ranged from 21 days to 16 months after birth (median, 5 months). The majority of patients were infants: 81 patients (85%) were between 4 to 6 months of age (Figure 2C), with body weight of 6.83 kg. Patients were born at 39 gestational weeks (median), with a body weight of 2.97 kg. Apgar score at 1 minute after birth was 9 (interquartile range, 8–10), indicating that perinatal asphyxia with myocardial ischemia was not an underlying condition of rupture.

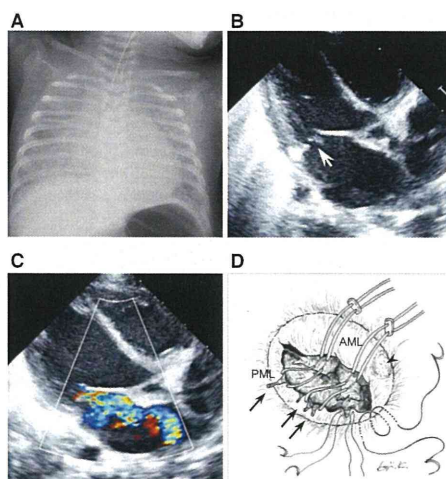


Figure 1. Case presentation of acute rupture of the mitral chordae tendineae in an infant (a 4-month-old female). **A**, A chest X-ray shows pulmonary congestion with mild cardiomegaly (cardiothoracic ratio=0.60). **B**, An echocardiogram of the left parasternal long axis view demonstrating the severely prolapsed posterior leaflet of the mitral valve (arrow). **C**, A 2-dimensional Doppler cardiogram showing severe mitral regurgitation and an enlarged left atrium. **D**, The operative record of the mitral valve and ruptured chordae tendineae. The arrows indicate ruptured chordae tendineae. The arrowhead indicates yellowish degeneration of the anterior mitral leaflet (AML). PML indicates posterior mitral leaflet.

Table 1. Clinical Characteristics of the 95 Patients

Clinical Findings	
Age at onset (months)	5 (4–6)*
Body weight at onset (kg)	6.83 (6.14–7.51)*
Gestational weeks	39 (38–40)*
Body weight at birth (kg)	2.97 (2.70–3.28)*
History of Kawasaki disease	10 cases; Acute and convalescent stage (day ≤ 30), 3 cases Beyond convalescent stage (day > 30), 7 cases
Anti-SSA antibody-positive (12 cases examined)	2 cases; 0 and 5 mo
Prodromal symptoms	88 cases; fever 37, cough 16, vomit 14, others 21
Cardiogenic shock after initial prodromes	2 (1–7)*

*Data are presented as median (interquartile range).

Diagnosis of Kawasaki disease was made in 10 patients (11%) before the onset of the rupture; acute and convalescent stage in 3 patients and beyond convalescent stage in 7 patients. The remaining 85 patients did not meet the clinical criteria for Kawasaki disease.^{23,24} In 1 patient (a 5-month-old female), Staphylococcus epidermidis endocarditis was diagnosed by positive blood culture tests and histopathologic examinations of the resected mitral valve.

Next, we analyzed seasonal epidemics of the disease (Figure 2B). The disease had a seasonal epidemic in spring and summer (65 patients, 68%). There were no sibling cases in this study. Most patients exhibited prodromal symptoms such as fever or cough 3.5 days before admission. Symptoms of cardiorespiratory shock developed 2.0 days after the onset of the prodroms. None of the 95 patients displayed any clinical symptoms of group A streptococcal

infection or clinical signs of rheumatic fever.²⁵ Clinical features of Marfan syndrome such as scoliosis, arachnodactyly, and pectus carinatum/excavatum were not found in patients. No evidence of blunt chest trauma was found in any of the patients.

Laboratory Findings

The results of the laboratory examinations are summarized in Table 2. On admission, white blood cell count increased (median, 15 440 /uL) and serum C-reactive protein concentration had a slight increase (1.60 mg/dL). However, the procalcitonin level, which is a sensitive marker of bacterial infection, remained at a normal value (0.025 ng/mL, n=4). Although the disease provoked systemic inflammatory reactions, these data suggest that bacteremia was unlikely to be a major cause of the condition.

A marked increase in the brain natriuretic protein level (1450 pg/mL) and an elevated lactate level (4.43 mg/dL, n=36) on admission indicates that the majority of patients experienced acute cardiac and circulatory failure. Serum levels of creatine kinase–myocardial band and cardiac troponin T were not significantly elevated, suggesting that prominent myocardial cell damage was not related to the disease.

Maternally derived anti-SSA antibodies, which are a well-known cause of conduction tissue disturbances and myocardial cell damage during the fetal period,^{26–28} were detected in 2 of the 12 patients examined (21 days and 5 months after birth). In these cases, no signs of complete atrioventricular block or systolic dysfunction were detected. Only elongation of the PQ interval was found in the neonate. No other antinuclear antigens, such as anti-SSB, anti-ANF, or anti-DNA, were detected in the 10 patients examined.

Because most patients were in an emergent condition, isolation of viruses and paired serum examinations for virus antibody titers were not examined. Antibody against human immunodeficiency virus, which may cause nonbacterial thrombotic endocarditis, was not detected in the 80 operated cases.

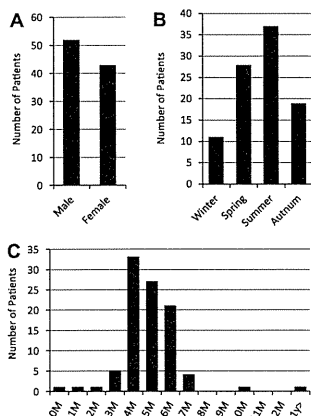


Figure 2. Clinical characteristics of acute rupture of the chordae tendineae of the mitral valve in infants. **A**, Sex differences. **B**, Seasonal differences. **C**, Age distribution of the patients.

Table 2. Laboratory Findings of the 95 Patients

Examinations	On Admission	At Discharge	P Value
WBC (/uL)	15 440 (11 990–21 650)	9160 (7330–11 100)	<0.0001
Hb (g/dL)	10.2 (8.9–11.1)	11.8 (10.9–13.0)	<0.0001
PLT (x10 ⁹ /uL)	501 (338–600)	368 (302–439)	0.0003
CRP (mg/dL)	1.60 (1.97–3.15)	0.11 (0.16–0.31)	<0.0001
AST (IU/L)	44 (30–105)	36 (29–44)	0.0003
ALT (IU/L)	21 (13–135)	22 (16–36)	0.0160
LDH (IU/L)	421(267–763)	332 (264–484)	0.0046
CPK (IU/L)	119 (77–247)	76 (45–123)	0.0002
CPK-MB (U/L)	27 (12–91)	31 (20–42)	0.0749
BNP (pg/mL)	1,450 (839–2545)	72 (32–114)	0.0007
cTnT (n=22, ng/mL)	0.027 (0–0.132)	—	—

Data are presented as median (interquartile range). ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic protein; CPK, creatine phosphokinase; CRP, C reactive protein; cTnT, cardiac troponin T; Hb, hemoglobin; LDH, lactate dehydrogenase; MB, myocardial band; PLT, platelets; and WBC, white blood cells.

Chest X-Ray, ECG, and Echocardiography Findings

Although bilateral pulmonary congestion was recorded in 71 patients (75%), cardiomegaly was not evident; the median cardio-thoracic ratio in chest X-ray was 56 (51–59)%. In the majority of patients, electrocardiograms revealed nonspecific ST-T changes in the precordial leads, which had normalized by the time of discharge. No abnormal Q waves were recorded in any of the patients.

The diagnosis of rupture of the mitral chordae was confirmed on echocardiography. Fractional shortening ($[\text{left ventricular end-diastolic diameter} - \text{left ventricular end-systolic diameter}] / [\text{left ventricular end-diastolic diameter}]$) of the left ventricle on admission was seemingly high (median, 0.41; range, 0.36–0.46). Doppler echocardiography on admission showed severe mitral regurgitation in 70 patients (73%), moderate in 22 (23%), and mild in 4 (4%). To exclude the possibility that preceding chronic mitral regurgitation induced the rupture, end-diastolic diameter (body surface area indexed) z score of the left ventricle was assessed. The median value of the z score was 1.47, indicating that the rupture is an acute event. A noteworthy echocardiographic finding was the presence of high echoic lesions at the top of the mitral papillary muscle adjacent to the chordae (8 patients, 8.4%). Abnormal thickening of the mitral valve leaflets was also detected in 9 patients (9.5%). No coronary artery aneurysms or abnormal origins of the left coronary arteries were detected. Dilatation of aortic root was not detected, either.

Surgical Treatment

A total of 95 surgical operations (Figure 3) were performed on 80 patients (84%). Plasty of the mitral apparatus included reinforcement of the ruptured chordae with autologous pericardium, suture of the lacerated mitral valve leaflet, and mitral valve annuloplasty (52 patients). Twenty-six mechanical valves (16–19 mm in diameter)

were implanted. In 9 patients, mitral regurgitation deteriorated after the surgical repair, primarily as a result of newly emerged rupture of the chordae tendineae. Although mitral regurgitation remained after the surgical repair, significant mitral stenosis was noted only in 1 patient (right ventricular/left ventricular pressure=0.86), who is a candidate for mechanical valve replacement.

In 83 patients, the details of the portions of the ruptured mitral chordae were recorded in the clinical charts. Rupture in 1, 2, 3, and 4 portions was noted in 38, 33, 9, and 3 patients, respectively. Rupture of the anterior leaflets alone, the posterior leaflet alone, and both leaflets was identified in 28, 33, and 22 patients, respectively. Thickened and myxoid mitral valve leaflets were identified in 13 patients at the time of surgery. No vegetation on the mitral valve apparatus was detected.

Rupture of the chordae tendineae of the tricuspid valve was detected in 6 patients; 5 patients survived after chordae repair, and 1 patient died before undergoing surgery. In 9 patients, surgical repair was not performed because the mitral regurgitation was limited in the small area and the patients became asymptomatic after medical treatment. These patients were carefully followed up with echocardiography and medical treatment, including diuretics and angiotensin-converting enzyme inhibitors.

Histopathologic Findings

Macroscopic (Figure 4A) and histopathologic examinations (Figure 4B–4L) of the mitral chordae or valves were performed in 28 patients. In the majority of patients, mononuclear cells had infiltrated the endocardium of the mitral valve leaflets and chordae tendineae (18 patients, 64%; Figure 4B and 4C). Polymorphonuclear leukocyte infiltration was also detected in the inflammatory lesions (Figure 4C); however, the number of polymorphonuclear leukocytes was far less than that of mononuclear cells. Ruptured portions were replaced by scar formation with fibrin deposition and fibrous tissue (Figure 4E and 4F). Myxoid change of the mitral valve leaflets and chordae tendineae was detected in 11 patients (39%). Thickening of the spongiosa accompanied by infiltration of the fibrous component was also identified (Figure 4G). Immunohistochemical examinations revealed that tenascin C, a characteristic component of the extracellular matrix during embryonic development, inflammatory reactions, and tissue repair, was expressed in all layers of chordal tissue (Figure 4J). Immunohistochemical study revealed that infiltrated mononuclear cells consisted of CD3-positive T-lymphocytes (Figure 4K) and CD68-positive macrophages (Figure 4L).

In a 5-month-old female with *Staphylococcus epidermidis*-positive blood culture tests, predominant polymorphonuclear leukocyte infiltration was identified and she was diagnosed with bacterial endocarditis. None of the specimens showed any histopathologic characteristics of rheumatic endocarditis.²⁵ Histopathologic examinations of the 2 autopsied cases revealed no obvious infiltration of inflammatory cells in the ventricular myocardium. No inflammatory reactions were detected in any other organs, such as the liver, kidneys, and gastrointestinal tract. Biopsy specimens were not obtained in the 2 patients with positive anti-SSA antibodies.

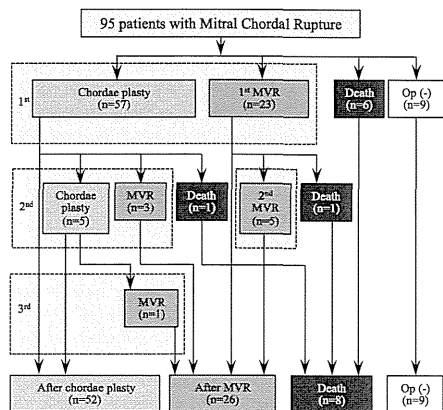


Figure 3. Surgical procedures and prognoses of the 95 patients. MVR indicates mitral valve replacement; and Op, operation.

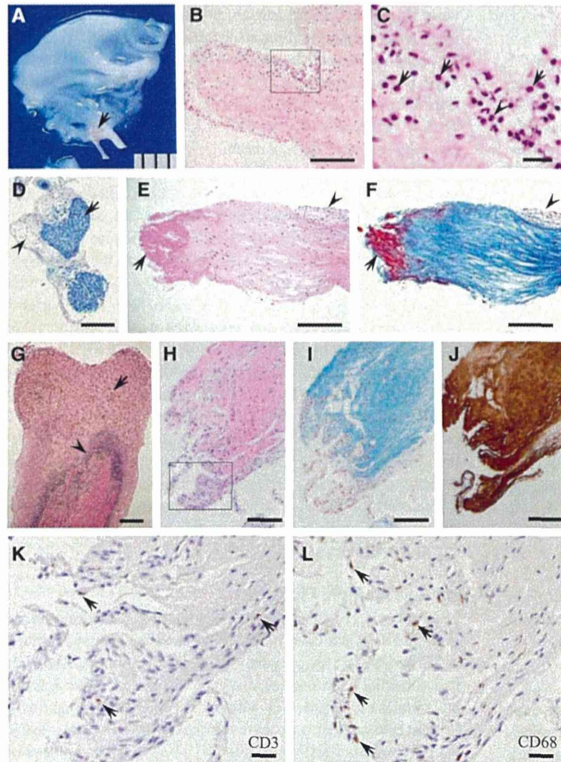


Figure 4. Gross and histopathologic findings of the mitral valves and ruptured chordae tendineae. **A**, Resected mitral leaflet of a patient (4-month-old male). **B** and **C**, Microphotographs of the valve and chordae tendineae of a 4-month-old female. The arrows indicate infiltrated mononuclear cells, and the arrowhead indicates a polymorphonuclear cell. **D–F**, Ruptured chordae tendineae of a 5-month-old female stained with Masson trichrome (**D** and **F**) and hematoxylin and eosin (**E**). **D**, The arrow indicates a central core of dense collagen bundles, and the arrowhead indicates fibrous thickening of the endocardial tissue. **E** and **F**, The arrows indicate fibrin deposition at the ruptured chordae tendineae, and the arrowheads indicate fibrous thickening with mononuclear cell infiltration at the endocardium. **G**, Marked increase of fibrous thickening (arrow) between the endocardium and fibrous core (arrowhead). **H–J**, Microphotographs of chordae tendineae stained with hematoxylin and eosin (**H**) and toluidine blue (**I**), as well as immunohistochemistry with tenascin C antibodies (**J**) of a 6-month-old female. **K** and **L**, Immunohistochemistry with CD3 (**K**) and CD68 (**L**) antibodies at the rectangular area in **H**. The arrows in **K** indicate CD3-positive T cells, and the arrows in **L** indicate CD68-positive macrophages. Scale in **A**, 1 mm. Scale bars in **B** and **D–G**, 200 μ m; **H–J**, 100 μ m; **C**, **K**, and **L**, 20 μ m.

Prognosis

Eight patients (8.4%) died of circulatory failure or multiple organ dysfunctions (2 male and 6 female; 6 before surgery and 2 after surgery). The median ages of the 8 patients was 4 months. All 6 patients who died before surgery exhibited serious cardiorespiratory failure at the initial stage of shock and were immediately transferred to a tertiary care hospital. After the surgical repair or medical treatment, the patients were discharged from the hospital with normal left ventricular FS values in echocardiography (0.36). During the 3 months to 18 years of follow-up (median, 5.4 years), mitral regurgitation persisted in 9 patients; 5 cases were slight and 4 cases were moderate. The left ventricular FS at present were almost within normal limits (median, 0.37; range, 0.24–0.57). Only 3 patients showed impaired echocardiographic FS <0.28 (0.24, 0.25, and 0.26).²⁹ The brain natriuretic protein levels at presentation were within normal range (median, 34.8 pg/mL).

Neurological complications, such as significant developmental delays or cerebral palsy, were detected in 10 patients (11%; 95% CI, 4.2%–14.1%). As a whole, significant complications remained in 32 patients (34%; mitral replacement in 26, neurological complications in 10, both in 4), indicating

a mortality and morbidity of the disease of 8.4% (95% CI, 2.73–14.1) and 42% (95% CI, 32.0%–52.2%), respectively.

Forty-eight (51%; 95% CI, 40.3%–60.8%) patients continue to take drugs (ie, angiotensin-converting enzyme inhibitors in 31 patients, diuretics in 22 patients, coumadin in 29 patients, antiplatelet drugs in 17 patients, and antiarrhythmia drugs in 3 patients). At present, arrhythmias persist in 8 patients (8.4%; 95% CI, 2.7%–14.1%), including atrial flutter in 3 patients, atrial tachycardia in 2 patients, and complete atrioventricular block with pacemaker implantation in 3 patients. All arrhythmias are well controlled with medication.

Factors Associated With Artificial Valve Replacement and Death

To detect predictors of artificial valve replacement and death in the patients, the cumulative probability of freedom from artificial valve replacement was analyzed according to the Kaplan–Meier method (Figure 5). The probability of artificial valve replacement–free survival was lower among the patients who developed chordal rupture in summer than among those who developed this complication in other seasons (Figure 5A). The artificial valve replacement–free survival was also lower in the patients who developed 3 to 4 chordae than in those who

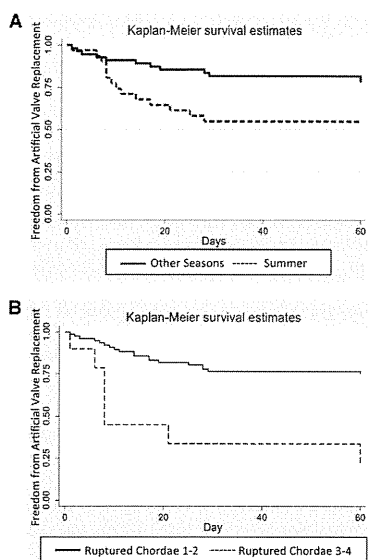


Figure 5. Kaplan–Meier survival estimates of time from diagnosis until artificial valve replacement. **A**, Artificial valve replacement-free survival in patients who developed chordal rupture in summer and those in other seasons. **B**, Artificial valve replacement-free survival in patients who developed 1 to 2 chordal rupture and those who developed 3 to 4.

developed 1 to 2 chordae (Figure 5B). Significant predictors of artificial valve replacement identified in the Cox proportional hazard models are shown in Table 3. Rupture in the summer and the number of ruptured chordae tendineae were significantly associated with the risk of artificial valve replacement. In contrast, no significant clinical or laboratory factors were associated with the risk of death in the univariable analyses.

Discussion

Rupture of the chordae tendineae of the mitral valve in infants is rare. The majority of affected patients present with the sudden onset of severe cardiorespiratory shock.^{19,20} Some patients die, whereas others require urgent surgical treatment, such as mitral chordae plasty or mechanical valve replacement.^{16–22} In infants treated surgically with prosthetic valves, reoperation to “up-size” the valves is likely to be necessary as the patients

Table 3. Univariable Analyses of Risk Factors for Mechanical Valve Replacement

	HR	z	P Value	95% CI
Summer	2.44	2.26	0.024	1.12–5.28
Number of ruptured chordae	1.98	2.88	0.004	1.24–3.14
Number of ruptured chordae >=3	4.86	3.53	<0.001	2.02–11.69

CI indicates confidence interval; and HR, hazard ratio.

grow, depending on the size of initial prosthesis. To improve the prognosis of these patients, providing an early diagnosis, appropriate medical treatment, and successful surgery are crucial. Because the disease is not currently recognized worldwide, some patients may have remained undiagnosed or been misdiagnosed. Some cases may have occurred in other countries as well. Therefore, acute rupture of the mitral chordae tendineae needs to be considered a significant cardiac disease that may cause sudden onset of acute cardiac failure in infants.

Causes of the Disease

In adolescents and adults, the underlying causes of the rupture of the chordae tendineae are diverse^{2–13}; mitral valve prolapse, myxomatous degeneration, and infectious endocarditis are the leading causes, particularly in the last 2 decades.² In infants, causes of the rupture appear to be different from those in adults; most pediatric cases of mitral rupture were diagnosed as idiopathic because a direct cause could not be demonstrated. In a small number of cases, Kawasaki disease, a child-specific cause, was the documented cause for this condition. Rupture of the mitral chordae or papillary muscles may occur in Kawasaki disease after myocardial ischemia or infarction of the ventricular inferior wall.³⁰ Mitral regurgitation without coronary arterial lesions may also occur during the acute or convalescent stage of Kawasaki disease, in which the histopathologic findings indicate the involvement of endocarditis and valvulitis.^{31–33} In our patients, no signs of myocardial ischemia or infarction were detected. Endocarditis or valvulitis in Kawasaki is a potential cause of the chordal rupture.

The actions of maternally derived anti-SSA/SSB antibodies appear to reflect another child-specific pathogenesis particularly in neonates and early infancy. The transplacental passage of antibodies against SSA or SSB auto-antigens has been proven to be an cause of congenital complete atrioventricular block in neonates.^{26–28} Dilated cardiomyopathy or endocardial fibroelastosis may also develop as a late-onset cardiac complication.³⁴ Molecular studies have clarified that these antibodies initially bind to the L-type calcium channel on fetal cardiomyocytes, where they induce calcium dysregulation, apoptosis, inflammation, and subsequent conduction tissue disturbance.³⁵ Echocardiography has demonstrated high echogenic lesions at the top of the papillary muscles.¹⁷ Obviously, these findings have to be distinguished from echogenic intracardiac focus in the normal fetus.³⁶ Similar cellular mechanisms may be involved, where fibrous scar formation develops during the fetal period and subsequent rupture may occur early after birth.

Myxoid change of the mitral valve leaflets and chordae tendineae was detected in 39% of available specimens. Histological examinations revealed abnormal deposition and disorganization of collagen and elastin and accumulation of proteoglycans in the myxoid mitral valve with ruptured chordae tendineae,³⁷ suggesting that these histological changes are the predisposing cause of the rupture. Because changes in the structure of the mitral leaflets such as those seen in myxomatous degeneration take time to develop, further studies are necessary to elucidate the contribution of myxoid change to mitral chordal rupture in infants.

Indirect evidence supports the theory of an infectious or para-infectious inflammatory cause in many cases: (1) inflammatory cells were detected on the histochemistry analysis in 69% of available specimens; (2) prodromal symptoms similar to viral infections; (3) seasonal epidemics having peaked in summer; (4) high incidence in the middle of infancy when maternal antibodies become undetectable; and (5) lymphocyte predominant infiltration in the specimen. As the presence of inflammatory cells involving the ruptured chordae may have developed as a consequence of rupture rather than be a causal factor, further studies including the detection of viral genomes and isolation of viruses are being considered.

Finally, why acute mitral chordal rupture in infants is predominant in the Japanese population remains uncertain. In countries other than Japan, this condition seems to be rare, as no cases other than 1 case of an anti-SSA antibody-positive infant¹⁸ have been described in literature thus far. Some genetic background factors appear to be responsible for the disease, as Kawasaki disease is dominant in Japanese and Asian children. Further studies are therefore needed to elucidate the genetic susceptibility of the disease.

Medical and Surgical Treatment

The initial treatment should include medical support, such as the intravenous infusion of inotropes, diuretics, and vasodilators, and mechanical ventilation with tracheal intubation. If the circulatory and respiratory failure is uncontrollable, surgical repair of the ruptured chordae tendineae should be immediately considered. Plasty of the lacerated chordae using reinforcement with or without artificial chordae is the first choice of surgery²⁰⁻²² because mechanical valve replacement in infancy always requires upsizing reoperation as the patient ages.³⁸ However, if the rupture includes multiple, particularly ≥ 3 chordae, a risk factor for mechanical valve replacement, and is difficult to repair with the plasty technique, mechanical valve replacement should be considered.²⁰⁻²²

Study Limitations

There are several limitations to this study. First, this study was based on a retrospective nationwide survey of mitral chordal rupture in Japan. Because of the emergent condition of each patient, data concerning clinical manifestations and laboratory findings particularly relevant to the pathogenesis were not satisfactory. Specimens for histochemistry were available in only 28 of 95 patients (presumably weighted toward the most serious cases requiring valve replacement or resulting in death), thus limiting the generalizability of the histological findings to the whole group. Further nationwide prospective studies are therefore essential, including isolation of viruses and investigation of virus genome from blood and tissues samples. Second, appropriate medical and surgical therapy to prevent the progression of rupture has not yet been established. Prospective studies concerning additional medical and surgical treatment are also necessary. Third, this study was conducted in Japanese children only. Although the possible causes are diverse and various ethnic or genetic background factors are likely responsible, it is highly possible that this disease develops in countries other than Japan. Worldwide

surveys are needed to clarify the incidence, pathogenesis, and prognosis of the disease.

Conclusions

Acute rupture of the mitral chordae tendineae in infants is a unique disease that predominantly affects patients aged 4 to 6 months, with high mortality and morbidity. Kawasaki disease, maternally derived anti-SSA antibodies, myxoid change of the mitral valve, and lymphocytic endocarditis are possible candidate causes of the chordal rupture; however, precise pathogenesis is uncertain and the patients are diagnosed as idiopathic. Although the reason why the disease is predominant in Japanese infants remains to be elucidated, acute rupture of the mitral chordae tendineae should be recognized as a significant cardiovascular disorder that may cause sudden onset of cardiogenic shock or death in infants all over the world.

Appendix

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Disclosures

None.

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