められるが、その程度は軽度である。細菌性心内膜炎を疑わせるような多核球を主体とした強い細胞浸潤は認められない。これらの所見からもウイルス感染が一因をなしていることが示唆される 6)。

V. 診断・鑑別診断：

基礎疾患のない 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、可及的に乳児の僧帽弁形成または僧帽弁置換術が行える小児病院もしくは専門施設に紹介する。

急速な左心不全のために心拡大が顕著でないことが多く、心疾患として認識されないことがあり、また上気道炎症状のあとに左心不全による肺うっ血をきたすため、肺炎と初期診断する可能性があるので注意を要する。

川崎病の回復期や退院後間もなく、心雑音を伴った急性呼吸循環不全が発症したら、本疾患を疑う。まれにリウマチ熱 8)、マルファン症候群 9)、鈍的外傷 10) でも同様な腱策断裂が報告されているが、これらでは一般に年長児に発症する。

VI. 治療：

診断がつけばまず呼吸循環動態の改善に努める。呼吸困難が強く血液ガス所見でアシドーシスや乳酸値の上昇が見られる場合は、挿管人工呼吸管理、アシドーシスの補正、強心薬の持続静脈投与、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行う。末梢血管拡張薬は理論的に有効であるが、血

圧が維持できない症例では使用を控え、血圧が維持された軽〜中等症例において動脈圧をモニターして注意深く投与する。これらの管理によっても循環動態が維持できない場合、もしくは入院時より大量の僧帽弁閉鎖不全により重度のショック状態および挿管人工呼吸管理にても対応が困難な呼吸不全で搬送された症例では、時期を逃さず外科手術に踏み切る。

手術は一般に人工腱索を用いた僧帽弁腱策形成術を行う。僧帽弁輪が拡大した症例では弁輪縫縮術も併用する。ただし複数の献策が断裂した場合や、断裂が前尖と後尖の広範囲にわたり人工腱索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 11)。

本疾患がウイルス感染を主体とした弁および腱策の炎症性疾患であると考えられること、また日本人に多く一部では川崎病や SSA 抗体陽性例のように免疫学的機序による弁/腱策の変性が原因と考えられることから、免疫グロブリンや抗炎症薬などによる炎症抑止が病像の進行予防や形成術後の再発予防に役立つ可能性が示唆されるが、現時点でのエビデンスはない。今後症例を蓄積することによりこれらの問題を解決する必要がある。

VII.予後：

平成 22 年に行われた全国調査では、過去 16 年間に死亡例が 6 名（6.8%）、人工弁置換症例が 25 例（28%）報告されており 6)、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。人工腱索による弁下組織の修復が功を奏すると僧帽弁閉鎖不全では、症状が軽快して比較的予後良好であ

るが、人工弁置換例ではワーファリンの内服や再弁置換など長期的な経過観察とともに再治療が必要となる。

おわりに

乳児特発性僧帽弁腱索断裂は、生来健康な生後４～６ヶ月の乳児に発症し、数日の感冒様前駆症状に引き続いて突然の呼吸循環不全で発症する疾患である。本疾患の初期には心拡大は目立たず、肺うっ血を肺炎像と見間違うことがある。断層心エコーで診断が可能であり、診断がつき次第、乳児の心臓外科手術が可能な小児循環器専門施設に紹介する必要がある。適切な診断と外科治療が実施されると救命可能であるが、死亡例や人工弁置換例も多数存在し、生来健全な乳児に発症する急性疾患として看過できない疾患である。本疾患は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、多くの小児科医が本疾患の存在を認識していない。臨床的特徴を広く全国の小児科医が認識することで、死亡例や重篤な合併症を起こさないよう努力する必要がある。

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図の説明

図１：乳児特発性僧帽弁腱策断裂（生後１ヶ月）の入院時胸部Ｘ線像

心拡大は軽度（心胸郭比 55%）であるが、右肺野を中心に肺うっ血像が認められる。（文献 7）より引用）

図２：乳児特発性僧帽弁腱策断裂（生後１ヶ月）の断層心エコー所見ならびに手術所見

僧帽弁後尖の逸脱/翻転の長軸断層像（上段左）、二次元ドップラ断層像（上段左）と断裂した腱策の術中所見（下段）とその模式図（文献 6）より改変引用）

図３：乳児特発性僧帽弁腱索断裂の考えられる原因

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要旨

僧帽弁の逆流により左室左房の容量負荷および肺うっ血をきたす疾患。病因として先天的な僧帽弁および弁下組織の構造異常とともに、感染性心内膜炎、腱索断裂、リウマチ熱、重度心不全など後天的要因により発症する。

診断のポイント

先天性、後天性にかかわらず、断層心エコーおよびドプラ断層で確定診断を行う。左室長軸断面で、弁尖の形態、弁尖逸脱の有無、弁尖の癒合（coaptation）の状態、乳頭筋や腱索など弁下組織の形態、弁尖特に後尖の繋留（tethering）の有無、左室および左房径、ドプラ断層で逆流の程度を観察する。また僧帽弁レベルの短軸像では、弁尖の形態、弁尖裂隙（cleft）の有無、ドプラ断層により逆流部位の同定を行う。また乳頭筋レベルの短軸像では、乳頭筋の構造、乳頭筋間の距離などを確認する。弁下組織の複雑な異常を伴う症例では、リアルタイム３次元心エコーが有力な情報を提供してくれる。

重症度評価

ドプラ断層による逆流シグナルの到達度により、trivial, slight, moderate, severe の４段階に分けられる 1)。また左室造影所見では Sellers の分類により、I, II, III, IV 度に分類されている 2)。

基本病態（基本事項）

僧帽弁閉鎖不全の病因として、先天的な弁/弁下組織の構造異常、および感染等による弁/腱索組織の破壊や粘液変成などによる後天的なもの、さらには重症心不全に伴う左室左房の拡大による機能的な閉鎖不全がある（表）3),4)。病態としては、僧帽弁を経由する逆流血により、左室と左房の容量負荷、心拍出量の低下、肺うっ血および肺高血圧をきたす。発症様式により急性と慢性の経過をたどる。感染性心内膜炎による弁組織の破壊や乳児特発性腱索断裂などで病像が急速に進行する場合は、通常急性の経過をたどる。明らかな心拡大を伴うことなく、低心拍出症候群（全身蒼白、四肢冷感、血圧低下、尿量減少）および重度の肺うっ血（呼吸困難、泡沫状血痰）をきたす。先天性の弁組織異常やなどで病像が徐々に進行する場合、心拡大による代償機転が働く間は症状が顕著ではないが、代償が効かなくなると低心拍出および肺うっ血の症状をきたす。重症左心不全に合併する機能的僧帽弁閉鎖不全では、僧帽弁形成および弁輪縫縮術で心不全自体が軽快することがある。

治療の実際

急性経過の際の治療：大量の僧帽弁逆流により急激に左心不全が進行する場合、動脈圧や中心静脈圧をモニターしながら、利尿薬、強心薬（catecholamine 類）とともに、末梢血管拡張薬（phosphodiesterase III 阻害薬など）の経静脈投与を行う。呼吸困難が強い場合は、気管内挿管により人工呼吸を行う。これらの内科的治療に十分に反応しない場合は、外科手術により弁および弁下組織の形成と弁輪縫縮を行う。弁形成が不可能と判断された場合は機械弁置換術を行う。

慢性経過の際の治療：利尿薬、強心薬（digoxin など）および末梢血管拡張薬（アンギオテンシン変換酵素阻害薬など）の内服により心拍出量を維持するとともに肺うっ血を予防する。これらの治療により心不全症状が改善しない場合には、急性経過の場合と同様の適応と術式により外科的治療を行う 4)。

私の治療方針（管理方針）

僧帽弁閉鎖不全、特に重度な症例を診断した際には、まず原因の同定が重要である。先に診断のポイントで示したように断層心エコーで弁および弁下組織の状態を精査する。先天性疾患に伴う僧帽弁閉鎖不全では、時間経過により左心不全に代償機転が働くために緊急手術になることは希であるが、腱索断裂に伴う急激な発症による僧帽弁閉鎖不全では急速に左心不全から肺うっ血に至るため、早期診断を行うとともに外科手術のタイミングを逸しないように心がける。

最新のエビデンス

我々の施設では、乳児の重症僧帽弁閉鎖不全 24 例（1978 年～2009 年）に対して外科治療を行った。初期手術として弁形成が 15 例に、機械弁置換術が 9 例に実施された。11 例で人工腱索による弁形成がなされた。弁形成術の予後を検討したところ、遠隔期においても良好な成績を示した 5)。

近年のトピックス

著者らは、乳児に特徴的な僧帽弁閉鎖不全の新たな原因疾患として、乳児特発

性僧帽弁腱索断裂の全国実態調査を行った。その結果、本症は生後 4〜6 ヶ月の乳児に好発し、季節的には春から夏に多発し、基礎疾患としては、ウイルス感染、川崎病、母親から移行した抗 SSA 抗体などが考えられる。多くの症例で僧帽弁形成術や僧帽機械弁置換が必要であり、重症例では死亡例も存在する 6)。

ピットフォールと対策

腱索断裂や感染性心内膜炎にみられる急性に発症する僧帽弁閉鎖不全では、左心不全の代償機転が働く時間的猶予がなく、病初期より顔面蒼白や尿量減少などの低心拍出症状とともに、肺うっ血による強い呼吸困難を呈する。胸部 Xp では心拡大は目立たない。一方、慢性的に経過する僧帽弁閉鎖不全では、一般に臨床症状に乏しいが、胸部 Xp では著しい心拡大がみられる。断層心エコーでは左心室の収縮能は比較的保たれるが、僧帽弁閉鎖不全に伴う見かけ上の数値であることが多い。重症度は左心室拡張末期径、心拍出量、さらには臨床症状などを総合的に判断し、適切な手術治療時期を逸しないよう注意が必要である。

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小児期にみられる僧帽弁閉鎖不全の原因疾患

1. 弁尖/弁下組織の先天性構造異常

弁尖の異常

僧帽弁裂隙（房室中隔欠損に伴うものなど）

重複僧帽弁口、僧帽弁副組織など

乳頭筋および腱索の異常（僧帽弁狭窄を伴うことが多い）

乳頭筋の位置異常、過長腱索、異常乳頭筋下架橋、

Hammock 弁、Parachute 弁など

2. 結合織疾患、先天代謝異常/蓄積病

僧帽弁逸脱症候群、Marfan 症候群、I cell 病など

3. 後天性疾患

感染もしくは炎症ましくは免疫学的異常が原因と考えられるもの

感染性心内膜炎、川崎病、リウマチ熱、乳児特発性僧帽弁腱索断裂

僧帽弁逸脱および腱索断裂

高血圧、外傷、妊娠、など

機能的僧帽弁閉鎖不全

拡張型心筋症、慢性重症心不全

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ORIGINAL PAPER

Clinical characteristics of acute mitral regurgitation due to ruptured chordae tendineae in infancy—experience at a single institution

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Abstract In infants, acute mitral regurgitation resulting from ruptured chordae tendineae is very rare, but often fatal. There are a few case reports, but the characteristics and etiology of chordae tendineae rupture have not been elucidated. Our aim was to determine the clinical characteristics of idiopathic acute mitral regurgitation due to chordal rupture in infancy. A retrospective analysis was performed on ten consecutive patients, with a mean onset age of 4.6±1.3 months. Despite nonspecific initial symptoms, all patients developed respiratory distress and four required resuscitation within a few days (mean, 1.8±1.8 days). Chest radiographs showed pulmonary congestion with a normal or mildly increased cardiothoracic ratio in all ten patients. Laboratory data and electrocardiograms showed nonspecific findings. Echocardiography revealed ruptured chordae in all patients; locations were anterior (50%), posterior (20%), and both (30%). Surgical intervention was performed within 24 h of admission in eight patients (mean, 3.6±5.1 h). Pathological findings included inflammatory cells in six specimens and myxomatous degeneration in two. No bacteria were isolated from preoperative blood cultures, pathological tissues, or excised tissue cultures. Autoantibody levels were insignificant. Three preoperatively resuscitated patients developed neurological sequelae and arrhythmias occurred in four after mitral valve replacement. Acute onset and rapid deterioration in patients with ruptured chordae tendineae necessitates early surgical intervention to improve outcomes. Though the etiology remains unknown, onset is in infants approximately 4 months of age, suggesting a definite disease entity.

Keywords Acute mitral regurgitation · Ruptured chordae tendineae · Infant · Mitral valve replacement · Complication

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Introduction

Acute mitral regurgitation (MR) is characterized by acute onset, rapid deterioration, and failure of the left heart, frequently requiring surgical intervention [11]. MR results from various abnormalities, including leaflet, annulus, chordae tendineae, papillary muscle, and left ventricular (LV) wall lesions. In adults, acute MR often occurs in ischemic heart disease due to papillary muscle ischemia. However, in pediatric patients, acute MR is rare.

Rupture of the chordae tendineae of the mitral valve was first described by Corvisart in 1806 [5]. Thereafter, many cases were reported [14]. Reported etiologies include ischemia [1, 13, 14], infectious endocarditis [10], rheumatic heart disease [14] and, less frequently, Kawasaki disease [12], blunt chest trauma [7], acute rheumatic fever [2, 6], connective tissue disease [17, 22], and LV volume overload causing chorda stretching [14]. Although some reports have indicated that myxomatous valve disease is also a cause of primary chordal rupture [10, 16], this etiology remains speculative. It is unclear whether myxomatous degeneration is a primary cause or the result of mitral valve insufficiency.

Recent case reports on acute MR caused by chordal rupture in neonates describe an association with transplacental passage of the anti-SSA antibody [8, 21]. However, our cases were normally developed 4-month-old infants with acute MR caused by ruptured chordae tendineae showing no association with anti-SSA antibody. There are few case reports on ruptured chordae tendineae during childhood, and no infant series has been reported. We reviewed the clinical characteristics of ruptured chordae tendineae cases.

Methods

We reviewed the medical records of all patients diagnosed with acute MR due to ruptured chordae tendineae at the National Cerebral and Cardiovascular Center between December 2001 and June 2009. Diagnoses were MR and ruptured chordae tendineae, detected by transthoracic echocardiography (TTE) and later confirmed by intraoperative findings. Patients with congenital cardiac anomalies and Kawasaki disease were excluded.

We analyzed age at onset, sex distribution, symptoms at the first visit and upon admission to our institute, period of exacerbation, chest radiography, electrocardiograms (ECG), laboratory data, bacterial tests (preoperative blood culture, pharyngeal culture, and excised tissue culture), TTE findings (grade of MR, location of affected chordae, LV size and function, pulmonary hypertension, and vegetations), pathological findings, surgical procedures, and complications.

Hypertrophy of the atria and ventricles was defined using ECG; left atrial hypertrophy exhibited a broad (more than 0.10 s) bimodal P wave in leads I, II, and aVL, and a biphasic P wave with a negative prolonged latter portion in lead V1. LV hypertrophy exhibited a strain pattern of ST–T in leads V5 and V6, a high R wave (more than 2.5 or 3.5 mV in lead V6 or V5, respectively), and high total amplitude (more than 4.0 or 5.0 mV) of the S wave in lead V1 and the R wave in lead V6, or the S wave in lead V1 and the R wave in lead V5.

MR grading by TTE was classified based on extension of regurgitation on color Doppler imaging. Severe MR was defined as extension to pulmonary veins.

Statistical analysis

Continuous data are expressed as means±SD. Statistical analyses were performed using StatView for Windows version 5.0 (SAS Institute Inc, Cary, NC, USA). Comparisons between groups were conducted using the Fisher exact test. Differences were considered to be statistically significant at p values less than 0.05.

Results

Patient characteristics

Our study included ten consecutive patients (five boys and five girls) with acute MR due to ruptured chordae tendineae. Two patients with chordal rupture due to Bland-White-Garland syndrome and Kawasaki disease, respectively, were excluded. Mean age at onset was 4.6± 1.3 months. Most patients had no significant medical history, the exceptions being two patients with low birth weights and breath-holding spells (Table 1). There were no physical signs of connective tissue diseases (e.g., Marfan or Ehlers–Danlos syndrome). All patients showed normal development and had no heart murmurs during routine medical examination in infancy or at an outpatient clinic. All had an uneventful familial history. All patients had been transferred to our institute for further intensive treatment due to congestive heart failure with severe MR, as detected by TTE.

Symptoms at the first visit and on admission to our institute

During the first visit to previous hospitals, most patients showed nonspecific symptoms, including common cold-like symptoms, such as cough, fever, rhinorrhea, and poor feeding (Fig. 1). Only three exhibited pallor during the initial visit. These three patients were immediately administered inotropic agents and mechanical ventilation within 24 h of the first visit.

The mean duration between the first visit and admission to our hospital was 6.2±5.4 days. When transferred to our hospital, all patients had respiratory distress (Fig. 1), six were on mechanical ventilation, and five had received inotropic agents for circulatory insufficiency. Cardiopulmonary resuscitation (CPR) was provided for three patients before transfer. One patient required resuscitation upon arrival at our hospital. Despite these aggressive medical interventions, all patients developed respiratory distress within a few days of onset (mean, 1.8±1.8 days), which then progressed to circulatory insufficiency.

Table 1 Patients diagnosed as having acute mitral regurgitation due to chordal rupture

Age (month)	Mean, 4.6±1.3 (range, 2.0–6.6)
Sex (boy/girl)	5:5
Weight (g)	Mean, 6,439.2±1,349.6 (range, 3,944–8,320)
History	None, 8
	Low birth weight, 2
	Breath-holding spells, 1

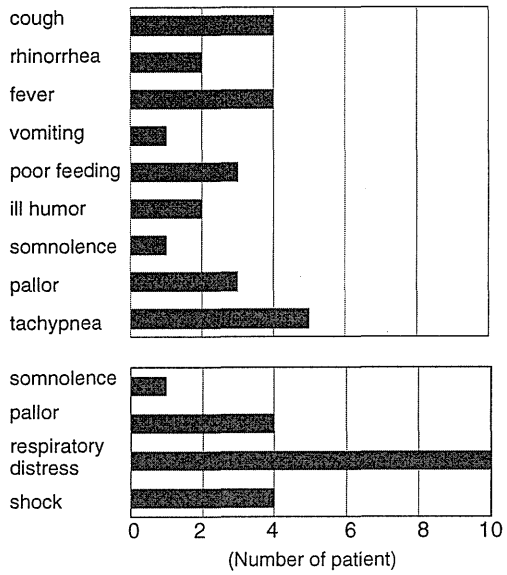

Fig. 1 Symptoms of acute mitral regurgitation due to chordal rupture at the first visit (*upper figure*) and on admission to our institute (*lower figure*). Note that six patients were already mechanically ventilated under sedation at the time of admission

Chest radiography findings

Chest radiographs showed pulmonary congestion in all ten patients. The cardiothoracic ratio was normal or mildly increased. Seven patients had cardiothoracic ratios under 60% (Table 2).

ECG findings

One patient had tall P waves in leads II, III, and aVF, but not in lead V1. None of the other patients had findings of atrial or ventricular hypertrophy, prolonged PR interval, arrhythmias, or ST–T changes (Table 2).

Laboratory data

Table 3 shows the laboratory data of all ten patients. Five had leukocytosis (>15,000/μL), while the others had white blood cell counts within normal range. C-reactive protein was within normal range (<0.5 mg/dL) in four patients and elevated in six. Creatine phosphokinase was slightly elevated in three patients. However, two of these patients had been administered with CPR before blood tests, and none of the three had evidence of ischemia on ECG or TTE. Human atrial natriuretic peptide (hANP) and brain natriuretic peptide (BNP) were markedly elevated in all patients. Three patients tested negative for anti-streptolysin O. Pharyngeal cultures were negative for group A *Streptococcus* in all patients.

Autoantibodies, including antinuclear, anti-ds DNA, anti-ss DNA, anti-RNP, anti-sm, anti-SS-A, and anti-SS-B antibodies, were measured. Only one patient had slightly

Table 2 Chest radiography, echocardiography, operative procedures, resuscitation, and complications

Patient	Sex	Onset (month)	CTR (%)	Pulmonary congestion	ECG	MR grade	Location of chorda	LVDd (mm, %)	LVEF	Operative procedure	CPR	Complications
1	F	2.0	65	+	–	Severe	Bilateral	22.3 (114.0)	0.79	Repair	+	CNS
2	M	6.6	47	+	Tall P	Severe	Anterior	30.0 (115.6)	0.94	Repair	+	CNS
3	F	5.3	67	+	–	Severe	Bilateral	28.5 (121.0)	0.83	Repair	–	–
4	M	4.9	59	+	–	Severe	Anterior→ bilateral	27.0 (114.0)	0.87	Replace	–	–
5	M	3.7	60	+	–	Severe	Bilateral	28.1 (114.0)	0.86	Replace	–	AT
6	F	3.7	57	+	–	Severe	Anterior	21.4 (96.0)	0.81	Replace	+	AT, CNS
7	M	5.5	68	+	–	Severe	Posterior	27.2 (112.0)	0.76	Repair	–	–
8	F	6.2	60	+	–	Severe	Anterior	29.1 (131.0)	0.82	Repair→replace	–	SSS
9	F	4.2	53	+	–	Severe	Posterior	27.6 (116.0)	0.76	Repair	+	–
10	M	4.7	57	+	–	Severe	Anterior	30.2 (122.0)	0.74	Replace	–	AFL

LVDd left ventricular diastolic dimension; *LVEF* left ventricular ejection fraction; *CPR* cardiopulmonary resuscitation before surgery; *Tall P* tall P wave in leads II, III, aVF; *Repair* mitral valve repair; *Replacement* mitral valve replacement; *CNS* central nervous system damage; *AT* atrial tachycardia; *SSS* sick sinus syndrome; *AFL* atrial flutter

Table 3 Average laboratory values on admission

WBC (per μL)	18,530±8,620 (range, 7,600–33,000)
Hb (g/dL)	8.7±2.2 (range, 6.5–14.4)
Ht (%)	25.8±6.1 (range, 19.5–41.9)
Plt (per μL)	46.1±17.1 (range, 25.7–70.1)
CRP (mg/dL)	2.0±2.5 (range, 0.1–7.8)
AST (IU/L)	274±634 (range, 22–2,067)
ALT (IU/L)	153±224 (range, 7–693)
LDH (IU/L)	1,026±1,373 (range, 181–4,584)
BUN (mg/dL)	11.2±5.7 (range, 5–20)
Cre (mg/dL)	0.35±0.17 (range, 0.1–0.7)
CK (IU/L)	1,045±2,714 (range, 27–8,755)
ANP (pg/mL)	2,377±2,819 (range, 376–7,290)
BNP (pg/mL)	2,322±2,158 (range, 341–6,026)

WBC white blood cell, *Hb* hemoglobin, *Ht* hematocrit, *Plt* platelet, *CRP* C-reactive protein, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *LDH* lactate dehydrogenase, *BUN* blood urea nitrogen, *Cre* creatinine, *CK* creatine phosphokinase, *ANP* atrial natriuretic peptide, *BNP* brain natriuretic peptide

elevated anti-ds DNA and anti-ss DNA antibodies; in all other patients, these autoantibodies were undetectable.

Bacterial culture

Preoperative blood cultures were obtained in eight patients, half of these before antibiotic administration. All specimens were negative. Pharyngeal cultures showed normal flora.

Echocardiography

TTE showed severe MR with ruptured chorda in all patients (Table 2; Fig. 2). Affected mitral valve leaflets fluttered widely and protruded into the left atrium during systole. These features differed from those of mitral valve prolapse cases. The location of affected chordae tendineae was anterior in five patients, posterior in two, and both in three. Interestingly, one patient with anterior chordal rupture showed sudden deterioration of respiratory distress on the second day of hospitalization. TTE showed progression of MR due to further rupture of the posterior chordae tendineae.

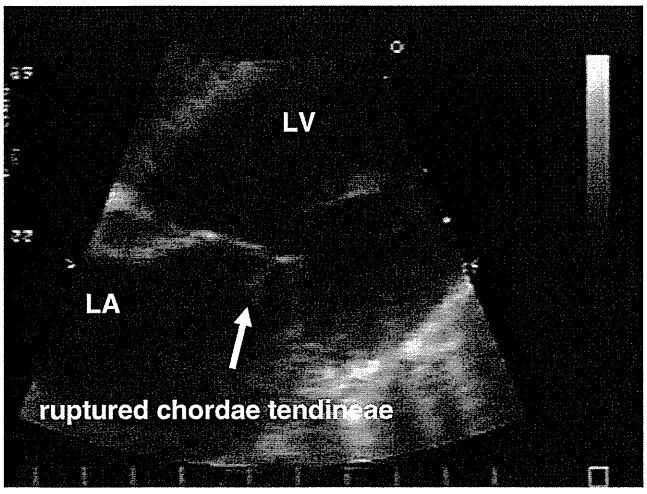

Fig. 2 Preoperative transthoracic echocardiogram from patient 9. This patient had respiratory distress and perfusion failure at the first visit and had been intubated at the previous hospital; the patient was transferred to our institution the same day. Posterior ruptured chorda was detected (*arrow*)

In all patients, the LV diastolic dimension (LVDd) was normal or mildly enlarged. The mean LVDd was 27.1± 2.9 mm, i.e., 115.6±8.8% of normal values as calculated from body surface area. LV ejection fractions were normal (>0.65), and no ventricular asynergy was detected. Five patients had mild pulmonary hypertension, as estimated by tricuspid valve regurgitation flow velocity.

Operation

All patients required surgical intervention for mitral valve repair. Eight of the ten (80%) underwent emergency surgery within 24 h of admission, and the mean period from admission to the operation was 3.6±5.1 h (range, 0.6–16.0 h). Two patients underwent surgery the day after admission. One patient with further posterior chordal rupture on the second day of hospitalization required emergency surgery. Another patient experienced brain hemorrhage, a contraindication for open-heart surgery. He underwent mitral valve repair after stabilization following the acute phase of hemorrhage.

Mitral valve repair, including Kay annuloplasty, edge-to-edge repair, and artificial chorda, was conducted in six patients. One subsequently required mitral valve replacement due to further chordal rupture postoperatively. Five patients underwent mitral valve replacement using 16-mm ATS AP series mechanical valves (ATS Medical Inc., MN, USA) translocated to the supraannular position (Table 2).

Intraoperative findings revealed that all patients had experienced chordal rupture and four had yellow or yellowish-white degeneration at the ruptured chordae; in three of these four, this degeneration extended to the mitral leaflet edge. There were no other abnormalities, such as vegetations, ischemia, infection, and commissural fusion.

In all patients, surgical treatment improved cardiopulmonary insufficiency. Inotropic agents and mechanical ventilation were discontinued. Postoperative echocardiography showed amelioration of MR to mild or moderate in the mitral valve repair group and no cases with mitral valve replacement experienced leakage. The hANP and BNP levels decreased markedly to 164±27.4 and 90±66.7 pg/mL, respectively.

Pathological findings

Pathological examination of excised tissues revealed six specimens to have infiltration of inflammatory cells, including mild lymphocyte or neutrophil and macrophage infiltration, while four showed fibrin adhesion. Myxomatous degeneration was noted in two specimens, fibrosis in one. There was no evidence of bacterial infection in any of the specimens. We stained for acid-fast bacteria to investigate the possible relationship to Bacillus Calmette–Guérin vaccination in two specimens, but the results were negative.

Complications

Three of the four patients who required CPR exhibited complex central nervous system damage. The first patient had a convulsion after the operation and was successfully managed using anticonvulsants. As of the latest follow-up, this patient exhibits no developmental delays. The second patient had brain hemorrhage, brain atrophy, and developmental retardation. The third patient had hypoxic encephalopathy, subdural hematoma, and developmental retardation.

Four patients developed atrial arrhythmias after mitral valve replacement. The mitral valve replacement group had a much higher rate of atrial arrhythmias (80%) than the mitral valve repair group (0%; $p<0.05$). Atrial tachyarrhythmias occurring in three patients were all well controlled using anti-arrhythmic agents. One patient required pacemaker implantation due to sinus node dysfunction. In this patient, postoperative ECG showed elevated ST segments in leads V5, V6, II, III, and aVF. TTE showed hypokinesis at the LV inferior wall. We suspected that the prosthetic valve compressed the left circumflex artery (LCX), causing hypoperfusion of the sinus node artery arising from the LCX. Aortography performed after surgery confirmed that the sinus node artery arose from the LCX (Fig. 3).

Discussion

In the present study, we reviewed the clinical characteristics of idiopathic acute MR due to ruptured chordae tendineae in infancy. Symptom onsets were mostly in early infancy, at approximately 4 months of age, with no significant difference in sex distribution. Initial symptoms were nonspecific, resembling those of a common cold. However, all patients developed respiratory distress within a few days and most progressed to circulatory failure despite aggressive medical intervention. Chest radiographs revealed pulmonary congestion, even though the cardiothoracic ratio was normal or only mildly increased. ECGs revealed no atrial hypertrophy, ventricular hypertrophy, or ST–T changes. In some patients, laboratory data indicated inflammation, but this was usually not significant. These nonspecific findings could easily be misinterpreted as representing lung disease. Indeed, some cases in our series were initially misdiagnosed and treated for pneumonia or acute respiratory distress syndrome. Therefore, we advocate performing echocardiography when an infant presents with a vague set of symptoms, i.e., "not doing well," and shows pulmonary congestion on chest radiography.

The major causes of acute MR due to chordal rupture in adult series are reportedly ischemia [13, 14], infectious endocarditis [10], and rheumatic heart disease [11, 14]. However, these etiologies are rare in childhood. Previous reports on acute MR during childhood are limited and include causes such as Kawasaki disease [12], acute rheumatic fever [2, 6], autoimmune disorders [8, 21], connective tissue diseases [22], and chest trauma [3]. However, these cases had known causative factors. We carefully ruled out all known causes of acute MR in our series. Therefore, the cases presented herein appear to be idiopathic.

There are few reports on the pathological findings of ruptured chordae tendineae during childhood. In our series, some patients showed inflammatory cell infiltration, including lymphocyte or neutrophil and macrophage

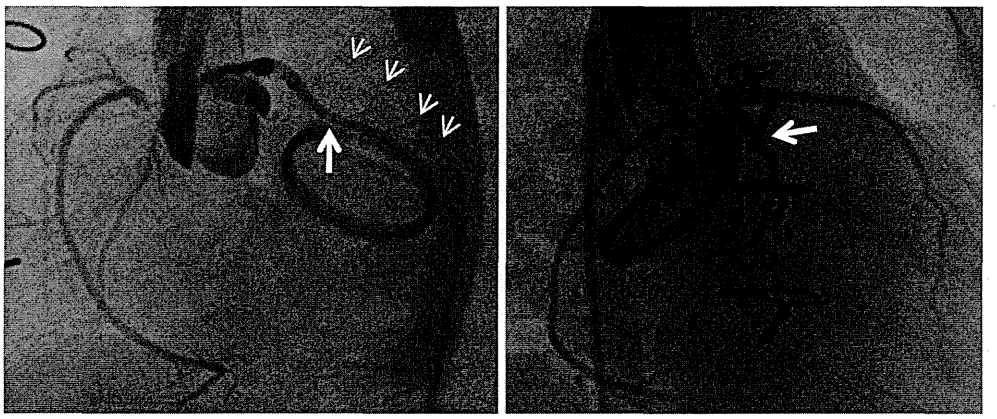

Fig. 3 Aortography after mitral valve replacement in patient 9. Sick sinus syndrome and ischemic change on electrocardiography and echocardiography were recognized after surgery. The prosthetic valve compressed the left circumflex artery from which the sinus node artery (*small arrows*) originated (*arrow*)

infiltration, or myxomatous degeneration, on pathological specimens. Inflammatory cell infiltration is generally caused by infection, autoimmunity, or other immunological mechanisms, including mechanical inflammation. However, there was no evidence of bacterial infection based on either cultures or pathology results. Moreover, levels of infant serum autoantibodies that could damage chordae tendineae, such as maternal-derived anti-SSA antibody [8], were low or undetectable. A few case reports on chordal rupture associated with anti-SSA antibody described fibrotic scarring and calcification as characteristic intraoperative findings, but histological studies were not conducted. The literature on chordal rupture in adult cases describes myxomatous degeneration as one of the causes of primary chordal rupture [10, 16]. The mechanical strength of the mitral leaflet and chordae tendineae was shown to be decreased because of the matrix remodeling, due in part to both dysregulation of matrix components and abnormal mechanical stress, but the primary stimulus for this degeneration was unclear [9, 15]. Degeneration is primarily idiopathic and may result from age-related changes or excessive hemodynamic loads for prolonged periods. Therefore, it is not reasonable to assume that these effects cause chordal rupture in early infancy. In our series, myxomatous degeneration was a nonspecific finding.

Detailed examinations revealed no evidence of bacterial infection, autoimmune disease, acute rheumatic fever, Kawasaki disease, connective tissue disease, congenital heart disease, or chest trauma in any of the ten cases. Moreover, the onsets were in early infancy, generally at approximately 4 months of age, and the majority of patients initially had symptoms similar to those of the common cold. Hence, we suspect that age-dependent factors, including specific anatomical weaknesses of mitral valve structure and immunological responses associated with viral infections, may have contributed to the onset. Based on our present findings, acute MR due to chordal rupture in infancy is a definite disease entity that differs from chordal rupture in adults. This study was retrospective and did not reveal the origin of chordal rupture. Further prospective studies focusing on immunological mechanisms, such as infant responses to maternal-derived autoantibody and exogenous antigens including those associated with viral infections, are needed to clarify the etiology of this pediatric disease entity.

The anatomical mechanism underlying mitral chordal rupture is also largely unknown. However, a few studies have provided possible insights. Oliveira et al. reported that the major area of the anterior leaflet is tangential to systolic flow, as opposed to the posterior leaflet, which is perpendicular to flow [14]. Sedransk et al. described the marginal and posterior leaflet chordae as being thinner and requiring less strain and load to fail than the basal and anterior leaflet chordae, respectively [18]. Other studies involving adults have also noted that in patients with primary and secondary rupture, posterior rupture is most common [10, 14]. Our results regarding the locations of affected chordae tendineae are not consistent with these studies. This difference might be attributable to specific etiological factors, such as anatomical weaknesses, in infancy that differ from those in adults.

Although successful management with medical interventions only has been reported, most studies found surgery to be required in cases of acute MR during childhood [1, 3, 6, 8, 11, 21]. Early surgical intervention before the development of organ damage is important, particularly for preventing neurological sequelae. In this study, most cases underwent surgery within 16 h after emergency admission. Mitral valve repair is desirable to avoid the complications of prosthetic valve replacement. However, with leaflet edge involvement, the mitral valve is so fragile that repair may not be possible due to leaflet vulnerability. Mitral valve replacement in pediatric patients carries high risks of damaging the conduction system, compressing the LCX, obstructing the LV outflow tract, bleeding, thromboembolism, and general structural or non-structural prosthetic valve complications [4, 19, 20]. Moreover, particularly in infants, prosthetic valves must be placed in the supra-annular position in many cases because of the mismatch between prosthetic valve size and infant annulus size. Supra-annular placement is accompanied by a risk of pulmonary hypertension resulting from reduced left atrial volume and LV failure due to paradoxical motion of the atrium below the prosthetic valve [4, 19]. Fortunately, in our series, these complications had not occurred as of the most recent follow-up.

Study limitations

This was a retrospective study. A prospective study investigating etiologies, including immunological mechanisms and the causes of ruptured chordae tendineae in infants, is required.

Conclusions

Acute MR due to ruptured chordae tendineae in infancy is characterized by acute onset, rapid development of respiratory distress, and left heart failure, despite intensive medical treatment. Pulmonary congestion is a specific finding on chest radiographs even without significant cardiomegaly. Therefore, for early diagnosis, TTE is necessary when an infant appearing unwell shows pulmonary congestion. Early surgical intervention is recommended for good prognosis. Our data indicate no evidence of bacterial

infection or infant autoantibodies. The onsets were in healthy and well-developed infants, approximately 4 months of age. Thus, these factors suggest a definite disease entity, which should be recognized by not just pediatric cardiologists but also pediatric emergency physicians.

Conflicts of interest The authors have no financial interests in any of the treatments or devices described in this article. None of the authors has any conflicts of interest to declare.

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