Rigid Spine Syndrome: A Noninvasive Cardiac Evaluation

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Abstract

Rigid spine syndrome (RSS) is a group of childhood-onset muscle disorders characterized by marked limitation of flexion of the spine. Various cardiac changes have been documented in case reports. This study reports on a cardiac evaluation of nine patients with the "vacuolar variant" of RSS. Noninvasive cardiac evaluation entailed creatine kinase levels, full-inspiration chest roentgenograms, standard 12-lead ECG, and 24-h ambulatory ECG recording, as well as M-mode and two-dimensional echocardiography with Doppler study. Heart auscultation was abnormal in five patients. Creatine kinase MB fraction was normal in all patients. Chest roentgenogram showed scoliosis (five of nine), kyphosis (one of nine), severe anterior-posterior flattening of the chest cavity (two of nine), elevated hemidiaphragm (one of nine), caved-in appearance of upper lobes (two of nine), and symmetry of lung volumes (one of nine). Twelve-lead ECG abnormalities indicated right-sided heart disease (three of nine). Echocardiogram showed mitral valve prolapse (five of nine) with regurgitation (three of five) and evidence of pulmonary hypertension (three of nine). Ambulatory ECG recorded paroxysmal tachyarrhythmias in hypoxic or hypercapnic patients (three of nine). There was no correlation between any cardiac abnormalities and patient weakness. Mitral prolapse/regurgitation may have a developmental association with this congenital myopathy. Findings of cor pulmonale were due to the restrictive chest wall defect and respiratory muscle weakness. Paroxysmal tachyarrhythmias were due to hypoxia or hypercapnia. There was no evidence of a primary cardiomyopathy.

Rigid spine syndrome (RSS) is a rare childhood-onset muscle disorder characterized by marked limitation of flexion of the spine; progressive scoliosis; contracture of limb joints, especially the elbows; mild and nonprogressive, proximal weakness; moderately elevated muscle enzymes; a "myopathic" electromyogram pattern in spinal muscles; and histologic features of a nonspecific myopathy with marked fibrosis [*5*, *6*]. Doubts have been expressed whether RSS is a single nosologic entity, as the hereditary patterns,

degree and distribution of weakness, cardiac involvement, and muscle histology vary considerably in reported cases [*2*, *13*, *19*].

Various cardiac changes have been reported, including complete heart block, interventricular septum hypertrophy, and enlargement of the left atrium and ventricle [*2*, *17*, *18*]. It appears that cardiomyopathy occurs concomitantly with the skeletal manifestations in some patients with this syndrome.

We described the phenotype and muscle histopathology findings of nine patients with RSS. The salient pathology features were autophagic vacuoles, vacuoles containing capillaries, muscle spindle swelling, and type 1 muscle fiber predominance. The term "vacuolar variant" of RSS was proposed [*10*]. The respiratory manifestations of these patients included severe restrictive chest wall defect and limited mobility of the spine associated with clinically significant respiratory muscle weakness [*15*]. In some patients the slowly progressive respiratory muscle disease led to hypercapnic ventilatory failure. During this study clinical features of cor pulmonale without right-sided cardiac failure were detected in three patients. Therefore, a detailed noninvasive cardiac evaluation was performed as part of a complete systems review. There was no clinical indication to perform any invasive testing.

Methods

Patients

Nine patients were identified who fit the phenotype description of RSS [*10*]. Patients attended the Neuromuscular Clinic (a tertiary referral center) of the University of Pretoria, South Africa. Identified patients were enrolled in this study, performed over a period of 18 months. There were seven males and two females; all patients were of South African Afrikaner descent. Age at clinical disease onset was before 6 years in all patients and likely since birth in five patients (recognized as infantile hypotonia); patient age at examination ranged from 11 to 36 years. There was no parental consanguinity, but in two families two siblings were affected.

The characteristic skeletal muscle histology features were autophagic vacuoles, vacuoles containing capillaries, muscle spindle swelling, and type 1 muscle fiber predominance. Other nonspecific myopathic findings included variation in muscle fiber diameter; central nuclei; fiber splitting; degenerating, regenerating, and necrotic muscle fibers; and increased fatty and fibrous connective tissue in the endomesium and perimesium. Biopsy specimens were obtained from lumbar paraspinal muscles, mm. tibialis anterior, triceps, or infraspinatus.

Manual Muscle Testing

To assess strength manually a modification of the British Medical Research Council (MRC) scale was chosen [*12*]. To quantify global strength 17 muscle groups on both sides were examined. For analysis the MRC scale was converted to a 1- to 10-point

system. The average muscle score (AMS) is the numerical average of muscles tested. Of a possible maximum score of 10, the lower the score, the weaker the patient.

Investigations
Investigations were as follows.

- On a day of routine physical activity venous blood was drawn, and creatine kinase (CK) and isoenzyme levels were determined by immunoassay and ELISA techniques, respectively. A MB fraction >5% implied myocardial damage.
- Full-inspiration chest roentgenograms in the standing position were obtained for all patients.
- A standard 12-lead ECG was obtained at rest in the supine position, using a Hewlett-Packard 4745A (amplification, 1 mV; paper speed, 25 mm/s). The evaluation included a classification according to the Minnesota code [*14*]. Bazett's formula was used to correct the QT interval for heart rate.
- Ambulatory ECG monitoring was performed on a two-channel ECG recorder (MR 140; Oxford) for a 24-h period of routine daily activities. A Medilog 2 Oxford analyzer was used to analyze the magnetic tapes. Abnormalities were printed on an ECG chart for detailed analysis. The terms and definitions related to cardiac rhythm and conduction followed the recommendations of Robles de Medina et al. [*20*].
- M-mode and two-dimensional echocardiography and Doppler study on all patients were performed by the same sonographer with a scanning-type ultrasound diagnostic system (Toshiba Sonolayer SSH-40B) with a 2.4-MHz transducer (Toshiba PSA-24B). Recordings and measurements were made following international guidelines [*9*, *16*].

Results

Nine patients (seven males, two females) with the clinical characteristics of RSS were identified. These patients formed a homogeneous group, as muscle biopsies showed characteristic, though nonspecific pathology, including autophagic vacuoles, vacuoles containing capillaries, muscle spindle swelling, and type I muscle fiber predominance. Age at recognized disease onset was early childhood, likely since birth, in five patients (manifested as "floppy infants"). The age range of patients when studied was between 11 and 36 years. The disease duration varied from 8 to 30 years. The AMS varied from 7.9 to 9.1 of a possible score of 10. There was a poor correlation between disease duration or patient age and degree of weakness (AMS; $p = 0.41$ for both). Results are summarized in Table 1.

Table 1. Summary of results of noninvasive tests

Age (yr)	Disease duration (yr)	AMS	Auscultation	ECG	CXR	Echocardiogram	Holter ECG
11	9	9.1	Normal	Normal	Normal	Normal	Normal
12	12	8.9	Normal	Normal	Normal	Normal	Normal
13	9	8.5	Systolic murmur; fixed split S2; RV gallop	R axis	Scoliosis (44%)	MVP; MVR; TVR	Normal
13	8	8.3	Normal	Normal	Scoliosis (10%)	Normal	Normal
15	15	8.7	Normal	Normal	Scoliosis (37%)	Normal	Normal
18	18	8.6	Systolic click	Normal	Elevated L diaphragm	MVP	V-tach
23	23	7.9	Systolic murmur	Normal	Kyphosis; asymmetry	MVP	PAT
31	31	8.3	Systolic click; fixed split S2; RV gallop	p-pulmonale; R-axis RVH	Scoliosis (24%); diameter	MVP; MVR; increased R systolic pressure; decreased RV relaxation	PAT
36	30	8.6	Systolic murmur; RV gallop	R axis; RV fasc. block	Scoliosis (21%); diameter	MVP; MVR: increased R systolic pressure; decreased RV relaxation	Normal

Note. Maximum AMS score is 10. MVP, mitral valve prolapse; MVR, mitral valve regurgitation; TVR, tricuspid valve regurgitation; PAT, paroxysmal atrial tachycardia; V-tach, ventricular tachycardia; RV, right ventricular; L, left; R, right

Auscultation

Fixed split second heart sounds and right ventricular (RV) gallop rhythm (S3 and S4) were audible in patients with cor pulmonale. A midsystolic click was audible in two patients. Systolic mitral valve murmurs were audible in three patients.

Chest Roentgenogram

Notable x-ray abnormalities included variable degrees of scoliosis in five patients, kyphosis in one patient, severe anterior-posterior flattening of the chest in two patients, an elevated left hemidiaphragm in one patient, a caved-in appearance of the upper lobe in

two patients, and marked asymmetry between the right and the left lung volumes in one patient.

Creatine Kinase

Serum CK was normal in two patients and elevated in seven patients. The mean CK value was 687 IU/L, with a range of 84–1493 IU/L. The MB fraction was <5% in all patients. There were poor correlations between CK values and patient age ($p = 0.24$) and between CK and AMS ($p = 0.15$).

Electrocardiogram

The standard12-lead ECG showed right-axis deviation in three patients, intraventricular (right) conduction delay in one patient, and p-pulmonale and RV hypertrophy in one patient (Fig. 1).

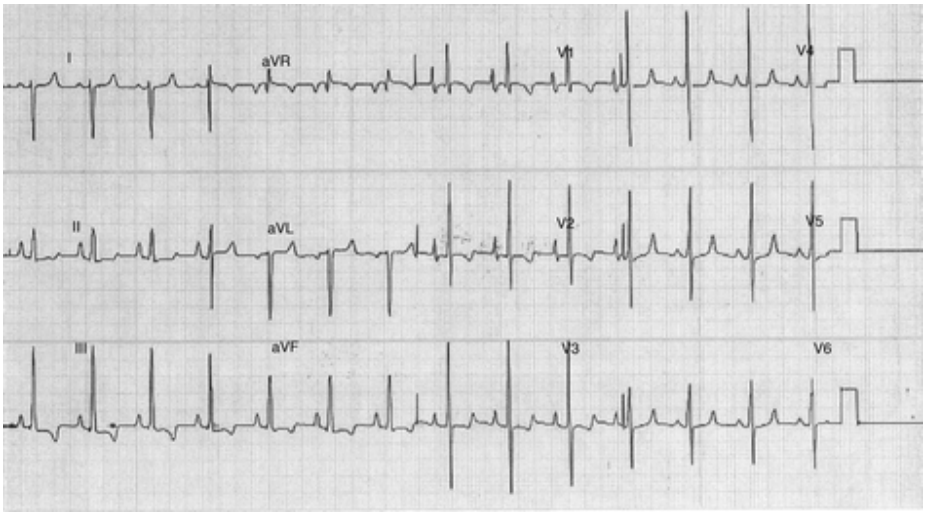

Fig. 1 A 12-lead ECG strip of a 31-year-old male patient with pulmonary hypertension (p-pulmonale, right-axis deviation, and right ventricular hypertophy)

Echocardiogram

Mitral valve prolapse (MVP) was detected in five patients, and mitral valve regurgitation was documented in three of these patients (Fig. 2). Tricuspid valve regurgitation was demonstrated in one patient. Right-sided heart disease secondary to pulmonary dysfunction was detected in two patients, recognized as increased RV systolic pressure and slowed RV relaxation. Left ventricular size and function data were within normal limits in all patients.

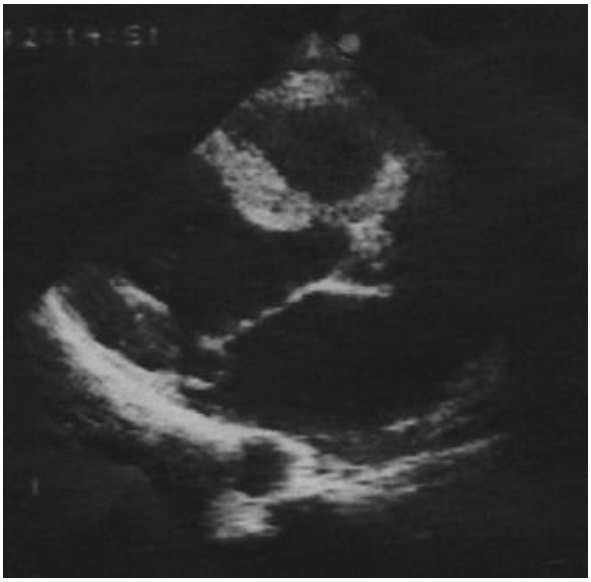

Fig. 2 A still frame of mitral valve prolapse of the posterior leaflet on transthoracic echocardiography (parasternal long-axis view) of a 23-year-old female

Ambulatory (24-h) Electrocardiogram
Atrial ectopic beats were recorded in five patients, while paroxysmal atrial tachycardia was recorded in two patients (maximum rate of 160 and 180 bpm, respectively) during sleep. Premature ventricular beats were recorded in two patients, while a bout of ventricular tachycardia (12 consecutive ventricular beats at a rate of 145 bpm) without symptoms was recorded in one patient.

Discussion

RSS is a rare, childhood-onset, muscular disorder characterized by marked limitation of flexion of the spine and mild and slowly or nonprogressive weakness [*5*, *6*]. RSS is unlikely a single nosologic entity, as hereditary patterns, degree and distribution of weakness, cardiac involvement, and muscle histology vary considerably in reported cases [*2*, *13*, *19*]. The literature consists mainly of case reports and small case series. Rare reports of cardiac involvement describe fatal (interventricular septal) hypertrophic cardiomyopathy, complete heart block and other cardiac arrhythmias, and hypertrophy of heart chambers [*2*, *17*, *18*]. Cardiac abnormality typically occurs in Emery-Dreyfuss syndrome, a phenotypically similar, but genetically distinct (X-linked recessive), myopathy [*8*]. We described a pathologically distinct group of nine patients with RSS, named the “vacuolar variant” [*10*]. This is the only detailed, noninvasive cardiac evaluation of a group of homogeneous RSS patients. This study was performed as part of a complete systems review.

Disease duration correlated with patient age, as expected of any early childhood-onset disease. However, as the myopathy was clinically either slow or nonprogressive, there was a poor correlation between disease duration or patient age and well-maintained strength, as quantified by AMS. This clinical impression was supported by muscle biopsy results that were homogeneous in severity and character, independent of patient age and specific muscle biopsied.

We reported on the severe restrictive chest wall defect and limited mobility of the spine associated with clinically significant respiratory muscle weakness [*15*]. This slowly progressive respiratory muscle disease led to hypercapnic ventilatory failure in some patients. Most patients suffered mild to moderate dyspnea, deemed the result of the respiratory manifestations of RSS. There was no clinical evidence of symptomatic cardiac disease. Therefore, only noninvasive cardiac evaluation was indicated.

This study detected a relatively high prevalence of MVP, with or without valve regurgitation. In the general population the incidence of MVP is 6% to 10%, and it is more common in young females. MVP has been found in association with thoracic skeletal disorders such as pectus excavatum, scoliosis, and "straight back syndrome" [*3*]. Our patients suffered a high prevalence of skeletal abnormalities. It has been proposed that MVP and thoracic skeletal abnormalities are frequently associated because they may have a common etiology. In utero, the mitral valve undergoes final differentiation at the same time (between day 35 and day 42) as chondrification and ossification of the vertebral column and the thoracic cage. Any factor influencing growth at this stage might be expected to affect both systems [*13*]. RSS is classified as a congenital myopathy [*7*], but a developmental theory has not been proposed to explain the common association of this group of muscle disorders with MVP. Furthermore, two patients showed clinical and radiographic features of severe anterior-posterior flattening of the chest, a finding that overlaps with features of straight back syndrome [*1*, *4*, *11*]. This straight back phenomenon has a recognized association with MVP. This syndrome has been noted for cardiovascular manifestations and being a cause of "pseudo heart disease," i.e., clinical features simulating organic heart disease. Such manifestations include palpitations and chest pain, a systolic murmur, heart displacement to the left, and MVP. The mechanics of this pseudo heart disease are not well understood.

The second cardiac finding in our RSS patients was right-sided heart disease secondary to pulmonary dysfunction. The findings of pulmonary hypertension were more common in the older patient subgroup, compatible with the progressive nature of the restrictive chest wall defect and respiratory muscle weakness. However, no patient showed evidence of right-sided heart failure. We did not have the opportunity to study these patients by the relatively invasive cardiac catheterization techniques, so that quantification is not available of true pulmonary blood flow dynamics.

A third cardiac abnormality was asymptomatic cardiac tachyarrhythmias. Episodes of paroxysmal atrial tachycardia and ventricular tachycardia were recorded only during sleep in patients with documented daytime hypoxia, with or without hypercapnia, or nocturnal hypoventilation. As there was no clinical indication to perform relatively

invasive electrophysiologic testing (EPS) in any patient, we assumed that the dysrhythmias were triggered by these metabolic disturbances and were not due to primary pathology of the specialized electrical system cell or conduction tissue. Ectopic beats are nonspecific and nondiagnostic and occur frequently in the general population so that no deductions were made.

In summary, this noninvasive cardiac evaluation of patients with RSS did not detect myocardial involvement by the myopathic process. The association between the relatively frequent MVP and RSS is speculatively developmental in nature. Cor pulmonale is secondary to the severe restrictive chest wall defect and clinically significant respiratory muscle weakness. Arrhythmias were likely due to hypoxia and hypercapnia, and not due to primary pathology of the specialized electrical system cells or conduction tissue.

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