

Cardiac and Pulmonary Investigations in Bethlem Myopathy

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Background: Bethlem myopathy is considered a relatively mild neuromuscular disorder without significant cardiac and respiratory involvement.

Objective: To investigate cardiac and respiratory involvement in Bethlem myopathy.

Design: Cross-sectional study.

Setting: University hospitals.

Patients: Fifty patients with Bethlem myopathy from 26 families.

Interventions: Cardiac examinations, including electrocardiography and echocardiography (n=37) and pulmonary investigations (n=43). Holter monitoring was performed in 16 patients.

Main Outcome Measures: Cardiac and respiratory abnormalities.

Results: Several cardiac abnormalities were found that were considered unrelated to the muscular disorder. Seven (16%) of 43 patients had a forced vital capacity less than 70% of the predicted value. One of 2 patients with a forced vital capacity less than 50% was also receiving respiratory support. All patients with compromised respiratory function were still ambulatory, and we found no significant correlation between the severity of arm weakness and the severity of respiratory muscle involvement.

Conclusions: There is no evidence of cardiac involvement in Bethlem myopathy. Respiratory failure is part of the clinical spectrum and can occur in ambulatory patients.

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BETHLEM MYOPATHY (ONLINE Mendelian Inheritance in Man [OMIM] 158810) is an autosomal dominantly inherited myopathy that manifests with skeletal muscle weakness and contractures and is caused by mutations in the collagen VI $\alpha 1$ (*COL6A1*) gene (OMIM 120220), *COL6A2* gene (OMIM 120240), or *COL6A3* gene (OMIM 120250). The clinical onset is variable. Prenatal onset with decreased fetal movements and neonatal presentation with hypotonia and/or contractures have been described, but onset is more frequent in early childhood with proximal weakness of the legs.¹ Adult presentation as late as the sixth decade of life has also been reported.² Progression is slow and, after the fifth decade of life, about half of the patients need supportive means (eg, a cane, crutches, or a wheelchair) for outdoor mobility.³

Collagen type VI (COL6) is a major protein of the interstitial matrix and is composed of 3 genetically distinct chains. Se-

creted COL6 molecules form an extended microfilament network that is particularly abundant close to the cells; this network has been suggested to play a role in anchoring the basement membrane of nonepithelial cells to the underlying connective tissue.⁴ Because COL6 is also expressed in cardiac muscle,⁵ we postulated that cardiac involvement might be part of the clinical spectrum of Bethlem myopathy.

Evidence indicates that Bethlem myopathy is genetically heterogeneous.⁶ Clinical criteria were formulated at a recent European Neuromuscular Centre consensus meeting.^{1,6} Respiratory muscle dysfunction, which may lead to a need for mechanical ventilation, is encountered predominantly in advanced stages of neuromuscular disease. In Bethlem myopathy, respiratory muscle involvement is thought to be infrequent.⁷ In this report, we present results of cardiac and respiratory investigations in patients with Bethlem myopathy.

Table 1. Results in Patients With Cardiac Abnormalities

Patient No./ Sex/Age, y	History	ECG Results	Holter Monitoring Results	ECHO Results	Mutation
1/M/71	HT	Incomplete RBBB	Atrial escape	Left atrial dilatation, LVH	G250S
2/M/37	...	Incomplete RBBB plus ST-segment elevation (Brugada syndrome–like mutation)	Normal	Left atrial dilatation	G250S
3/M/64	AF	AF	AF and AV block	Left and right atrial dilatation	G250S
4/F/48	...	Normal	Run of 11 SVESs	Normal	...
5/F/50	HT	T-wave inversions in leads V ₁ through V ₆	ND	Diastolic dysfunction	...
6/M/40	...	Abnormal Q waves in leads I, aVL, and V ₆ ; high R/S ratio in lead V ₁ ; QRS duration = 0.10 s	Normal	Diastolic dysfunction	...

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; ECG, electrocardiography; ECHO, echocardiography; HT, hypertension; LVH, left ventricular hypertrophy; ND, not done; RBBB, right bundle branch block; SVESs, supraventricular extrasystoles; ellipses, none.

METHODS

STUDY POPULATION

Partners of the European Union–sponsored project MYO-CLUSTER contributed to our study, which was performed between January 1, 2000, and January 1, 2002. Definition of the clinical spectrum of Bethlem myopathy and associated disorders was the aim of part of the MYO-CLUSTER project. Patients with Bethlem myopathy who had undergone cardiologic examinations, including electrocardiography (ECG) and echocardiography (ECHO) and/or pulmonary investigations, were included in the study. In all, 50 patients with Bethlem myopathy (33 males and 17 females; age range, 4–75 years [median age, 37 years]) were included from 26 families. In 32 patients (from 12 families) the diagnosis of Bethlem myopathy was genetically proved, defined as an autosomal dominantly inherited myopathy with linkage to chromosome 21q or 2p or with mutations identified in the *COL6A1*, *COL6A2*, or *COL6A3* genes. In the other 18 patients (from 14 families), Bethlem myopathy was diagnosed clinically according to consensus diagnostic criteria,¹ which included limb girdle weakness (either with congenital onset with hypotonia and contractures or with elbow and finger flexor contractures in combination with mildly elevated serum creatine kinase activity), myopathic electromyographic results, and a myopathic muscle biopsy specimen. Evidence of autosomal dominant inheritance, which was present in 10 families, supported the diagnosis; 4 cases were sporadic. Mutations in the lamin A/C gene (responsible for autosomal dominant Emery-Dreifuss muscular dystrophy, which shares some clinical features with Bethlem myopathy) were excluded in all cases. Muscle strength was assessed using the British Medical Research Council grading score.⁸

CARDIAC EVALUATION

Cardiac involvement was assessed noninvasively in 37 patients by ECG and ECHO. Medical and family histories were obtained, and a physical examination was performed. A standard 12-lead ECG was performed with the patient at rest in a supine position. The results were classified according to the Minnesota code.⁹ Two-dimensional and color flow Doppler ECHO studies were performed on a commercially available ECHO machine (Sonos 5000; HP Labs, Palo Alto, Calif). Systolic function was impaired if fractional shortening was less than 25% and/or if global hypokinesia was seen on 2-dimensional ECHO examination. Regional wall motion

abnormalities were registered. Valvular abnormalities were assessed by 2-dimensional ECHO and color flow Doppler imaging. Diastolic function was considered impaired if the E/A ratio of the mitral valve was less than 1 or if pseudonormalization was seen. Ambulatory ECG monitoring for a 24-hour period of routine daily activities (Holter monitoring) was performed in 16 patients older than 10 years. A computer was used to analyze the magnetic tapes, which were reassessed by a trained technician and a cardiologist (W.G.d.V.).

PULMONARY FUNCTION TESTS

The maximum spirometric vital capacity was measured in 43 patients in the sitting position and was registered as a percentage of the expected normal value related to age, height, and sex. A value between 50% and 70% was considered moderately reduced; a value less than 50% was considered severely reduced.

STATISTICAL ANALYSIS

We used χ^2 tests to analyze the relation between the severity of pulmonary involvement and the severity of arm muscle weakness. A British Medical Research Council grading score of 3 was considered the cut-off value for the severity of arm muscle weakness because loss of the ability to raise the arms against gravity was considered an important indicator for progression of the disease.

RESULTS

CARDIAC EVALUATION

Two patients were known to have hypertension; in one, hypertension was well controlled. Two patients experienced dyspnea; one of these was known to have atrial fibrillation. Electrocardiographic results were abnormal in 5 patients, the Holter recording was abnormal in 3, and ECHO revealed abnormalities in 5 (**Table 1**).

Genetically Proved Cases of Bethlem Myopathy

Three members from 1 Dutch family with a G898 G>A (G250S) *COL6A2* mutation (patients 1–3) showed

Table 2. Results in Patients With Respiratory Abnormalities

Patient No./ Sex/Age, y	VCmax in Sitting Position, %*	Shoulder/Arm Weakness, MRC grade	Able to Walk/ Climb Stairs	Age at First Use of Wheelchair, y
7/M/51†	37	4	Yes/no	31
8/F/34†	62	4	Yes/yes	...
9/M/68‡	36	3-4	Yes/no	...
10/M/23†	64	4	Yes/yes	16
11/M/41	51	4	Yes/no	...
12/M/21	56	3	Yes/no	...
13/M/18	64	3	Yes/no	...

Abbreviations: MRC, British Medical Research Council; VCmax, maximum spirometric vital capacity; ellipses, not applicable.

*Percentage of the expected normal value for the patient's age, height, and sex.

†Indicates genetically proved Bethlem myopathy.

‡Indicates that patient received mechanical ventilation.

abnormalities. A 37-year-old man from this family (patient 2) had a Brugada syndrome–like ECG result that showed incomplete right bundle branch block (QRS duration, 100 milliseconds) and ST-segment elevation in the right precordial leads. In addition, he had left atrial dilatation on ECHO. He was proved to have a mutation in the cardiac voltage-gated sodium channel (SNC5A) gene that was causally involved in Brugada syndrome and originated from his mother. His father (patient 1), also known to have Bethlem myopathy and aged 71 years, had hypertension and showed left atrial dilatation and left ventricle hypertrophy on ECHO, with periods of atrial escape rhythm (30 beats per minute) on Holter monitoring. The 64-year-old brother of the father (patient 3), who also had Bethlem myopathy, had atrial fibrillation (AF) and was receiving sotalol hydrochloride and digoxin. He showed left and right atrial dilatation on ECHO, in combination with AF and atrioventricular block, necessitating pacemaker implantation.

Genetically Unproved Cases of Bethlem Myopathy

A 40-year-old Dutch man (patient 6) showed pathological Q waves in leads I, aVL, and V₆; a high R/S ratio in lead V₁; and a QRS duration of 100 milliseconds on ECG. His Holter recording showed no abnormalities. Echocardiography revealed mild diastolic dysfunction (E/A ratio, <1) but no wall motion abnormalities consistent with ischemic heart disease. A 48-year-old Dutch woman (patient 4) was found to have an accelerated atrial rhythm, consisting of a run of 11 supraventricular extrasystoles. Another Dutch woman, aged 50 years (patient 5), showed T-wave inversions on ECG and diastolic dysfunction on ECHO, consistent with her hypertensive heart disease.

RESPIRATORY INVESTIGATIONS

Forced vital capacity (FVC) was assessed in 43 patients. An FVC of less than 70% was found in 7 individuals, all ambulatory (**Table 2**). In 2 ambulatory patients with genetically proved Bethlem myopathy (patients 7 and 9), the FVC was less than 50%. One of these, a 68-year-old Dutch man with an FVC of 36% (patient 9),

received nocturnal invasive mechanical ventilation. The second patient, a 51-year-old Dutch man with a similar FVC (37%) (patient 7) had no symptoms of nocturnal respiratory insufficiency and was observed closely. We found no significant correlation between the severity of arm weakness and the severity of respiratory muscle involvement (data not shown).

COMMENT

Because COL6 is also expressed in cardiac muscle,⁵ we postulated that cardiac involvement might be part of the clinical spectrum of Bethlem myopathy. Cardiac investigations in 37 patients with Bethlem myopathy revealed several abnormalities. Three members from 1 family with a G898 G>A (G250S) COL6A2 mutation (patients 1-3) showed several abnormalities, in which the common denominator was left atrial dilatation. The youngest patient (patient 2) was found to have an ECG result compatible with Brugada syndrome. The left atrial dilatation encountered in this family could well be associated with conditions that are known to cause atrial dilatation, namely atrial fibrillation in one individual and hypertension and left ventricular hypertrophy in the other. About 3% of the population around 65 years of age has atrial fibrillation.¹⁰ Three patients with possible Bethlem myopathy (patients 4-6) showed a range of abnormalities. In the first patient, an early form of cardiomyopathy could not be ruled out. The ECG result was comparable to ECG results in the early phase of a cardiomyopathy in Becker disease.¹¹ The second patient had atrial tachycardia of short duration; although this arrhythmia is common in the normal population, it can also be classified as an atrial arrhythmia, which is a precursor to atrial fibrillation.¹² The third patient had hypertension, which is one of the causes of left precordial T-wave inversions. The existence of hypertension makes the relation of this abnormal ECG to Bethlem myopathy unlikely.

Collagen type VI has been demonstrated to play a role in the morphogenesis of the developing cardiac atrioventricular endocardial cushions into the valve leaflets and membranous septa of the heart.¹³ Collagen type VI is presumed to play a bridging role between

cells and the extracellular matrix. It is linked to the dystrophin-associated glycoprotein complex. To our knowledge, no specific studies about the effects of COL6 deficiency or dysfunction on heart muscle have been published. Seven published reports^{2,14-19} describe families with Bethlem myopathy in which cardiological evaluation, predominantly by ECG, was carried out. The largest detailed study,¹¹ which included ECG, ECHO, and Holter monitoring in 27 patients, showed no cardiac abnormalities except for asymmetrical septal hypertrophy in 1 case. Autopsy studies were performed in 2 patients^{18,20} and showed no abnormalities except for changes consistent with atherosclerotic coronary artery disease. The present study includes 18 patients who have been described previously. The patient with asymmetrical septal hypertrophy (patient 1) developed hypertension, atrial dilatation, and left ventricle hypertrophy.

No abnormality related to cardiac involvement has been reported in several series^{21,22} of patients affected by the more severe Ullrich type of congenital muscular dystrophy, in which recessive mutations in the COL6 genes have been detected. Often, these patients have markedly reduced or no COL6 expression; despite these findings, however, they do not appear to have cardiac abnormalities.^{21,22}

Reports of pulmonary investigations in Bethlem myopathy are scarce. Merlini et al¹⁴ performed pulmonary investigations in 4 patients whose vital capacity appeared to be normal. In another report,¹⁸ 1 patient's death was due to food aspiration, which suggests that the respiratory muscles are compromised. Jöbbsis et al³ and Haq et al⁷ described 1 patient each who had developed respiratory insufficiency, necessitating mechanical ventilation at night. (This patient was a member of one of the families described in this report, but he died before the present follow-up evaluation.) In autopsy studies,^{18,20} the diaphragm was found to be involved in the myopathic process. We found a moderately reduced FVC (<70%) in 7 (16%) of 43 patients. One patient was receiving mechanical ventilation at night. All patients with compromised respiratory function were still ambulatory, and we found no significant correlation between the severity of arm weakness and the severity of respiratory muscle involvement. This corroborates the suggestion by Haq et al⁷ and the results from autopsy studies^{18,20} that the diaphragm is involved in the myopathic process. In the mouse model for Bethlem myopathy,²³ necrotic fibers were particularly frequent in the diaphragm at all ages examined. Early diaphragmatic weakness has also been shown to be the major cause of respiratory failure in adult acid maltase deficiency (Pompe disease).²⁴ The report from a recent workshop²⁵ on congenital muscular dystrophies (which mentioned Ullrich congenital muscular dystrophy only and not Bethlem myopathy) recommends yearly FVC testing with the patient in the sitting position. This should be followed by additional testing in the supine position when the initial FVC result is less than 80%, to detect potential diaphragmatic weakness.

In conclusion, cardiac evaluation in our patients revealed several abnormalities that are probably not

related to Bethlem myopathy. Respiratory failure is part of the clinical spectrum and seems to be due, in part, to relatively early-onset diaphragmatic involvement. Therefore, we recommend yearly pulmonary investigations in patients with Bethlem myopathy; these should include FVC measurement in both the sitting and supine positions because the latter technique can assess the patient's diaphragmatic function.

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Announcement

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