

Clinical Commentary

No evidence of cardiomyopathy in spinal and bulbar muscular atrophy

Querin G, Melacini P, D'Ascenzo C, Morandi L, Mazzini L, Silani V, Romito S, Mandrioli J, Raimondi M, Pegoraro E, Soraru G. No evidence of cardiomyopathy in spinal and bulbar muscular atrophy. *Acta Neurol Scand* 2013; 128: e30–e32.

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Objectives – Spinal and bulbar muscular atrophy (SBMA) is a lower motor neuron disease caused by a CAG repeat expansion within the androgen receptor (AR) gene. Toxic nuclear accumulation of mutant AR has been observed in tissues other than nervous system including cardiac muscle. Moreover, CAG polymorphism length within AR has been associated with an increased risk of heart disease. **Materials and methods** – To test the hypothesis of the presence of cardiomyopathy in SBMA, a full cardiac protocol was applied to 25 SBMA patients.

Results – Patients' age ranged between 32 and 75 years. Cardiologic examination, 12-lead ECG, and echocardiography showed no abnormalities other than those consistent with hypertensive heart disease. One patient showed frequent supraventricular premature beats in absence of other significant arrhythmias at the 24-h ECG Holter. **Conclusions** – Our findings do not support the hypothesis of a primary cardiomyopathy in SBMA.

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Introduction

Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy's disease, is a rare lower motor neuron disorder, characterized by slowly progressive muscle weakness and atrophy of bulbar, facial, and limb muscles (1). SBMA is caused by a CAG repeat expansion greater than 38, which encodes a polyglutamine (polyQ) tract, in the first exon of the X-linked androgen receptor (AR) gene (2). Expanded poly-Q confers a ligand-dependent toxic gain of function to AR, altering its conformation and inducing a diffuse nuclear accumulation of the protein. Mutant AR nuclear pathogenic accumulation (3) is observed in affected neurons as well as in several different tissues, including cardiac muscle, of both SBMA

patients and SBMA mouse models (4, 5). Novel findings suggest that mutant AR may exert cell-autonomous toxicity in these non-neural tissues (6). Furthermore, an association between cardiovascular risk factors, including coronary artery disease, and CAG repeat length has been reported (7). Although the pathogenic significance of expanded polyQ-AR within heart myocytes remains to be established, no clinical data on myocardial function have been reported in SBMA.

Materials and methods

This study was approved by the local ethical committee. Twenty-five caucasian patients affected with molecularly defined SBMA participated in

this study. Age at onset and at the time of this study evaluation and size of the expanded poly-Q repeat (CAGn) within AR exon 1 were recorded in all patients. A cardiac protocol including: (i) collection of clinical history, focusing on possible cardiac symptoms (exertion dyspnea, chest pain, palpitations, syncope, legs edema) and the presence of cardiovascular pathology risk factors such as diabetes mellitus, hypertension, dyslipidemia, smoking, and obesity; (ii) cardiac examination carried out by a Cardiologist with a long-lasting experience in heart disorders in neuromuscular diseases (M.P.); (iii) standard 12-lead ECG; d) 24-h ECG Holter; and e) echocardiography was applied.

Results

The Table 1 summarizes the clinical and cardiac data from 25 SBMA patients. At the time of this

study, the mean age of patients was 54,4 years (range 32–75 years), whereas their symptom onset occurred between 20 and 57 years (mean age 42 years). Their CAGn ranged between 43 and 51 repeats.

Seventeen patients presented heart disease risk factors, including high blood pressure (10/17), mild dyslipidemia (10/17), diabetes mellitus (4/17).

No patients complained symptoms suggestive of a heart disease nor signs of heart dysfunction were detected at the cardiac examination in all cases.

Standard 12-lead ECG was normal in 21 patients. In two patients (P14 and P15), it was consistent with a first-degree atrioventricular block (AVB), whereas in one (P1) with left ventricle (LV) hypertrophy. One patient (P22) showed sinus bradycardia (mean cardiac frequency 35 beats per minute), probably related to the concomitant beta-blockers assumption to control high blood pressure.

Table 1 Main clinical findings in the SBMA patients of our cohort

	Age	Age at onset	CAG Nr	Heart symptoms	Standard ECG	Holter ECG	Ecocardiography	EF(%)	Familiarity	Hyper tension	Smoke	Dyslipidemia	Diabetes mellitus
P1	58	47	49	No	LV hypertrophy	Normal	Diastolic dysfunction	58	No	No	No	No	No
P2	47	37	44	No	Normal	Normal	Diastolic dysfunction	54	No	Yes	No	No	No
P3	41	20	45	No	Normal	Normal	Diastolic dysfunction	52	No	No	No	No	No
P4	64	54	49	No	Normal	Frequent VPB	Thickened IV septum, LVPW hypertrophy	56	No	Yes	No	No	No
P5	75	35	42	No	Normal	Normal	Mild mitral regurgitation	60	No	No	No	No	No
P6	48	37	44	No	Normal	Normal	Normal	62	No	No	No	Yes	No
P7	54	44	49	No	Normal	Normal	Normal	57	No	No	No	Yes	No
P8	45	35	44	No	Normal	Normal	Normal	50	No	No	No	Yes	No
P9	55	35	45	No	Normal	Normal	Thickened IV septum, LVPW hypertrophy	68	No	Yes	Yes	No	No
P10	43	37	44	No	Normal	Normal	Normal	55	No	No	Yes	No	No
P11	56	54	51	No	Normal	Normal	Normal	65	No	No	Yes	Yes	No
P12	58	38	44	No	Left axis deviation	Normal	Mild aortic regurgitation	75	No	Yes	No	No	No
P13	63	50	43	No	Normal	Normal	Normal	65	No	No	No	No	No
P14	43	25	50	No	I degree AVB	Normal	Normal	58	No	No	No	No	No
P15	58	47	43	No	I degree AVB	Normal	Normal	60	No	Yes	No	No	No
P16	60	56	44	No	Normal	Normal	Thickened IV septum, LVPW hypertrophy	52	No	No	No	Yes	No
P17	70	57	44	No	Normal	Rare SVPB	Thickened IV septum, LVPW hypertrophy	54	No	No	No	Yes	No
P18	56	49	44	No	Normal	Rare SVPB	Thickened IV septum, LVPW hypertrophy	64	No	Yes	No	Yes	No
P19	60	45	46	No	Normal	Normal	Thickened IV septum, LVPW hypertrophy	72	No	Yes	Yes	No	No
P20	57	46	43	No	Normal	Normal	Normal	56	No	Yes	No	No	Yes
P21	64	52	47	No	Normal	Normal	Thickened IV septum, LVPW hypertrophy	68	No	Yes	No	Yes	Yes
P22	65	52	46	No	Sinus bradycardia	Sinus bradycardia	Normal	53	No	Yes	No	Yes	Yes
P23	40	28	47	No	Normal	Rare SVPB	Normal	58	No	Yes	Yes	Yes	Yes
P24	32	26	44	No	Normal	Normal	Normal	60	No	No	No	No	No
P25	52	45	44	No	Normal	Normal	Normal	56	Yes	No	Yes	No	No

LV, left ventricle; AVB, atrioventricular block; VPB, ventricular premature beats; SVPB, supraventricular premature beats; LVPW, left ventricle posterior wall; IV, interventricular; EF, left ventricle ejection fraction.

Holter ECG was carried out in 24 patients and was normal in 22. One patient (P4) showed frequent supraventricular premature beats (1593 in 24 h) in absence of other significant arrhythmias. At the time of evaluation, this patient was taking a beta2-agonist (clenbuterol). Sinus bradycardia was confirmed in P22.

Echocardiography was performed in all patients. While normal in 14 patients, it detected signs compatible with hypertensive heart disease of various degrees (from isolated diastolic dysfunction to thickened interventricular septum with or without hypertrophy of LV posterior wall) in 10 cases. One patient (P4) had a subtle aortic insufficiency. Ejection fraction (EF) was normal in all patients and ranged between 52% and 75% (mean EF 60%).

Discussion

We found no evidence of cardiomyopathy in our cohort of SBMA patients. Minor cardiac abnormalities consistent with hypertensive heart disease were detected in patients suffering from high blood pressure or in elderly (8). The mild aortic regurgitation observed in one patient was also likely referred to the hypertensive heart disease (9). Significant heart rhythm alterations, consistent with frequent SVPB, were observed in one patient who was on beta2-agonists, which are known to interfere with heart rhythm (10). AVB, that should be mostly considered a benign, functional finding in the middle-aged men free from overt heart disease (11), was registered in two patients.

AR is strongly expressed in cardiac muscle (12) where it mediates both positive and negative effects induced by androgens on heart function (13). While the pathogenetic significance of AR CAG polymorphism as a heart disease factor remains controversial (14), our findings appear to rule out a role for the expanded AR protein to determine a primary cardiac muscle dysfunction in SBMA. Further studies that consider larger patient populations are, however, needed to confirm our data.

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Conflict of interest

The authors report no conflict of interest.

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