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Short Communication

Only some patients with bulbar and spinal muscular atrophy may develop cardiac disease

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ABSTRACT

Objectives: According to recent publications, some patients with spinal and bulbar muscular atrophy (BSMA) develop cardiac disease, manifesting as ST-segment abnormalities, Brugada-syndrome, dilative cardiomyopathy, or sudden cardiac death. Here we present neurological and cardiac data of a BSMA patient who was followed up for 10 y.

Case report: In a male patient aged 47 y, BSMA was diagnosed at age 37 y upon the typical clinical presentation (postural tremor since age 12 y, dysarthria since age 15 y, muscle cramps since age 29 y, general myalgias since age 32 y, general fasciculations since age 34 y, myoclonic jerks, easy fatigability, dyspnea upon exercise since age 36 y) and a CAG-repeat expansion of 47 ± 1 repeats in the androgen-receptor gene detected at age 37 y. During the next 10 y he additionally developed mild but slowly progressive diffuse weakness on the upper limbs and mild proximal weakness on the lower limbs. Cardiologic exam, ECG, and echocardiography were normal at ages 37 y, 41 y, 44 y, and 47 y.

Conclusions: Cardiac involvement may only develop in some BSMA patients within 10 y, whereas neurologic abnormalities slowly progress within 10 y of observation. Cardiac disease may develop at a later stage with progression of age and disease.

1. Introduction

Spinal and bulbar muscular atrophy (SBMA), also known as bulbospinal muscular atrophy (BSMA), Kennedy-Alter-Sung disease, or Kennedy's disease is a hereditary motor neuron disease (MND) due to a CAG-repeat expansion > 36 in the androgen-receptor (*AR*) gene on chromosome Xq12 [1]. BSMA is generally regarded not to manifest in the heart [2]. However, in some patients cardiac involvement has been recently reported, manifesting as ST-segment abnormalities [3], Brugada syndrome [3], dilative cardiomyopathy [4], hypertrophic cardiomyopathy [5], or sudden cardiac death (SCD) [3] (Table 1). Here we present the neurological and cardiac follow-up data of a patient with BSMA who was repeatedly investigated over ten years between 2008 and 2017.

2. Case report

The patient is a Caucasian male (175 cm, 70 kg), aged 47 y, with a history of postural tremor since age 12 y, dysarthria since age 15 y. ubiquitous muscle cramps since age 29 y, general myalgias since age 32 y, generalised fasciculations predominantly of the thighs since age 34 y, myoclonic jerks and dyspnea upon exercise since age 36 y, easy fatigability upon exercise, and muscle weakness since age 39 y [6]. He also had a history of recurrent creatine-kinase (CK) elevation with maximal serum values of up to 820 U/l (n, < 190 U/l). Aldolase and myoglobin were additionally increased. Based upon the clinical presentation and instrumental investigations, genetic work-up for BSMA at age 37 y revealed a CAG-repeat expansion of 47 ± 1 repeats in the *AR* gene. He was seen for follow-up several times since his first visit at age 37 y [6]. Neurologic exam at age 39 y revealed dysarthria, fibrillations of the tongue, weakness of the facial muscles, weakness of head anteflexion (M5-), diffuse weakness of the upper-limbs (M4 to M5-), reduced tendon reflexes, fasciculations and myoclonic jerks on the lower-limbs, and mild wasting of the upper- and distal lower-limbs. Neurologic exam at age 46y showed dysthymia, scepticism, dysarthria, borderline ante- and retroflexion of the head, mild atrophy of the tongue, weakness (M5-) for elbow extension bilaterally, and wasting of the lower arm muscles. Tendon reflexes were generally reduced. On the lower limbs there was mild wasting of the thighs and occasionally myocloni. Work-up at age 46 y revealed severe vitamin D-deficiency,

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Table 1
Reports about BSMA patients with cardiac involvement.

Cardiac manifestations	Age at onset of CI (years)	Reference
ST-abnormalities	68	[3]
Brugada syndrome	40,68	[3]
Dilated cardiomyopathy	31	[4]
Hypertrophic cardiomyopathy	56	[5]
Right bundle branch block	40	[3]
SCD	68	[3]

SCD: sudden cardiac death, CI: cardiac involvement.

mild elevation of estradiol, and normal serum progesterone and prolactin. Needle EMG showed chronic neurogenic changes.

At age 47 y the patient was still able to climb stairs but had to stop after one floor because of tiredness. He complained about three different types of muscle pain. The first and most severe type was a feeling of spontaneous, painful stretching of the hand extensor muscles and the calves bilaterally. He quantified the pain, which lasted up to three weeks, as maximally VAS 7. During such a period he was unable to walk or to use the upper limbs. During the first week of such an episode he was bedridden. The second type of muscle pain was spontaneous permanent myalgia, which could not be triggered by exercise, food, or drugs. The third type of muscle pain derived from generalised muscle cramps, which only occurred during exercise and could be enhanced by drinking coffee. Muscle cramps were most pronounced at night, quinine-responsive, and accompanied by restless legs [6]. The family history was positive for BSMA in his uncle. Clinical neurologic exam at age 47 y revealed dysarthria, an exaggerated masseter reflex, and a mild "signe des cils" bilaterally. There was mild, diffuse weakness on the upper limbs (left M4-, right M5-), reduced tendon reflexes, and mild diffuse wasting. There was marked positional tremor bilaterally. On the lower limbs patella tendon reflexes were absent and the Achilles tendon reflexes were reduced. No fasciculations or myocloni were noted.

Clinical and instrumental cardiologic investigations were carried out between 2008 and 2017. The patient never complained about cardiac symptoms during this period. The clinical cardiologic exam was normal, Blood pressure was 130/80 mm Hg on several occasions. The electrocardiogram in 2008 and 2017 showed sinusrhythm, small Q-waves in II, III and aVF, QRS width of 88 ms and no repolarisation abnormalities. Echocardiography in 2008, 2011, 2014 and 2017 showed normally sized cardiac cavities, normal cardiac valves, no myocardial thickening, no indications of systolic or diastolic dysfunction, and no pericardial effusion (Fig. 1).

3. Discussion

This case shows that over an observational period of 10 y no cardiac abnormalities developed in a single BSMA patient while muscular and bulbar manifestations of the disease slowly progressed. The most disturbing manifestations at age 47 y were different types of muscle pain, fatigue, exhaustibility, mild progressive muscle weakness, and tremor.

BSMA is well known as a slowly progressive disease concerning muscle weakness and bulbar functions [7]. Slow progression may concern muscle wasting, muscle pain, and the frequently occurring postural tremor. Occasionally, however, rapid progression of the neurological manifestations has been reported [8]. Bulbar dysfunction may more rapidly progress than limb weakness [9]. The speed of progression is generally regarded slower than in spinal muscular atrophy [10]. In a study of 21 patients with BSMA only 3 were wheel-chair-bound by the age of 72 y on the average [11]. The life span is usually not shortened in BSMA patients [12].

Cardiac disease in BSMA is rare (Table 1) and may be coincidental, not disease-related, and due to advancing age. The frequency of cardiac disease in BSMA ranges from 0/25 (0%) [2] to 70/144 (48.6%) [3]. Whether BSMA patients should generally undergo regular follow-up cardiac investigations is unclear but based on the rareness of cardiac involvement in BSMA it appears justified to investigate BSMA patients cardiologically only in case they become symptomatic or in case the family history is positive for cardiac disease including SCD. BSMA patients may develop cardiac disease in the later stages of the disease but this issue needs further investigations. According to Table 1, patients with cardiac involvement were older than the currently presented patient in the majority of the cases.

In conclusion, this case shows that cardiac involvement may not occur in each BSMA patient whereas neurologic abnormalities slowly progress within 10 y of observation. The risk of developing cardiac disease may increase with progression of age and disease since cardiovascular risk may increase with age as well.

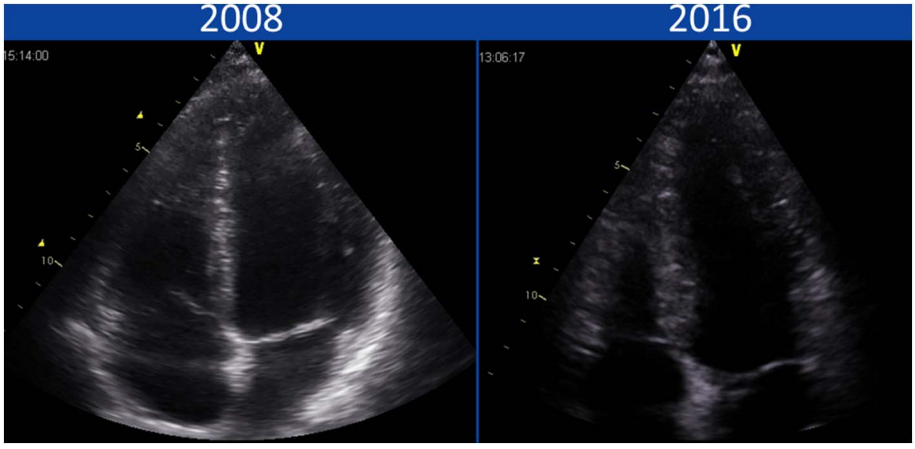

Fig. 1. Echocardiographic apical four-chamber view showing normally sized cardiac cavities, normal cardiac valves and no myocardial thickening.

Conflicts of interest

There are no conflicts of interest.

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Author contribution

JF: design, literature search, discussion, first draft, SZ-M: literature search, discussion, critical comments.

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