

ORIGINAL ARTICLES

Cardiac involvement in patients with Spinal Muscular Atrophies

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The spinal muscular atrophies (SMAs) include a group of disorders characterized by progressive weakness of the lower motor neurons. Several types of SMAs have been described based on age onset of clinical features: Acute infantile (SMA type I), chronic infantile (SMA type II), chronic juvenile (SMA type III), and adult onset (SMA type IV) forms. The incidence is about 1:6,000 live births with a carrier frequency of 1:40 for the severe form and 1:80 for the juvenile form. The mortality and/or morbidity rates of SMAs are inversely correlated with the age at onset. SMAs are believed to only affect skeletal muscles; however, new data on SMA mice models suggest they may also impact the heart.

Aim of the study was to retrospectively examine the cardiological records of 37 type molecularly confirmed II/III SMA patients, aged 6 to 65 years, in order to evaluate the onset and evolution of the cardiac involvement in these disorders. All patients had a standard ECG and a routine echocardiography. The parameters analysed were the following: Heart rate (HR), PQ interval, PQ segment, Cardiomyopathic Index (ratio QT/PQs), ventricular and supraventricular ectopic beats, pauses $\geq 2,5$ msec, ventricle diameters, wall and septum thickness, ejection fraction, fiber shortening.

The results showed that HR and the other ECG parameters were within the normal limits except for the Cardiomyopathic Index that was higher than the normal values (2,6-4,2) in 2 patients. Left ventricular systolic function was within the normal limits in all patients. A dilation of the left ventricle without systolic dysfunction was observed in only 2 patients, aged respectively 65 and 63 years; however they were hypertensive and/or affected by coronary artery disease. Data here reported contribute to reassure patients and their clinicians that type II/III SMAs do not present heart dysfunction.

Key words: Spinal Muscular Atrophies, heart involvement, cardiomyopathy

Background

Spinal muscular atrophies (SMAs) refer to a group of neuromuscular disorders characterized by degeneration of the anterior horn cells of the spinal cord, leading to weakness of the lower motor neurons and progressive muscular atrophy. Several types of SMAs have been described based on age onset of clinical features: Acute infantile (SMA type I), Chronic infantile (SMA type II), Chronic juvenile (SMA type III), and Adult onset (SMA type IV) forms (1). The incidence is about 1:6,000 live births with a mean carrier frequency of 1:50. The mortality and/or morbidity rates of SMAs are inversely correlated with the age at onset. Deletions in the survival motor neuron (SMN) gene (5q11.2-5q13.3) are the major determinants of SMA phenotype (2-9) while deletions in the neuronal apoptosis inhibitory protein (NAIP) gene may correlate with the severity of SMA (10-12).

Humans express a copy gene, SMN2, from the same region of chromosome 5q as a result of duplication and inversion. SMN2 is nearly identical to SMN1 (2-4); however, mutations in SMN2 have no clinical consequence if intact SMN1 is present. The reason that SMN2 cannot fully complement the SMN1 deficiency is that the majority of SMN2-derived transcripts are alternatively spliced (5-7), leading to a truncated and unstable protein that lacks the 16 amino acids encoded by SMN exon 7 (normally the last coding exon) (3, 5, 8-12).

Symptoms range from congenital hypotonia to different degree of muscle weakness, contractures, fasciculations, scoliosis and absence of tendon reflexes (1, 10, 14).

Based on our current knowledge of SMA, motor neurons are the primary tissue affected in SMA. However there are clinical reports suggesting that other tissues contribute to the overall phenotype, especially in the most severe forms of the disease. Upon autopsy, a growing number of congenital heart defects have been recognized, including atrial septal defects, dilated right ventricle (RV) and ventricular septal defects. The most common defect is an anomalous development of the heart, referred to as *hypoplastic left heart syndrome* (15-18). In juvenile type of SMA, cases presenting malignant ventricular arrhythmia or bundle-branch or atrioventricular blocks have been reported needing prophylactic dual-chamber cardioverter defibrillator or pacemaker implantation (19-23). However the authors suggest that such findings are probably provoked by pulmonary and respiratory anomalies, underlining the importance of correct respiratory assistance to prevent the onset of cardiological alterations.

Furthermore new data on SMA mice models suggest that the heart may be also impacted (24-26). These findings reveal a new area of investigation that will be important to address as we move towards emerging treatment options for spinal muscular atrophy, followed by clinical success.

Aim of the study was to retrospectively examine the cardiological records of 37 type II/III SMA patients, aged 6 to 65 years, to evaluate the onset and evolution of the cardiac involvement in these disorders.

Patients and methods

The records of 37 patients with SMA type II/III (mean age at the enrolment 23.3 ± 15.5 years) diagnosed at the Cardiomyology and Medical Genetics, Second Naples University in the period from 1990 and 2010, were retrospectively re-examined in order to assess the onset and evolution of cardiac involvement. The diagnosis of Spinal

muscular atrophy, firstly based on clinical and electro-neurological findings was subsequently confirmed in all patients by molecular analysis of SMN gene.

Cardiac function has been yearly evaluated by standard ECG and Mono, 2D- and Echocolor-doppler-cardiography. When the basic ECG revealed arrhythmias, the patients underwent dynamic 24h Holter monitoring. The following electrocardiographic parameters were analysed: heart rate (HR), PQ interval (PQi, n.v. 0,12-0,20msec), PQ segment (PQs), QT interval (QTi, n.v. 0,30-0,40 msec), Cardiomyopathic Index (ratio QT/PQs, adjusted for HR, n.v. 2,6 – 4,2), T waves anomalies and presence of ectopic ventricular or supraventricular beats.

The echocardiographic parameters evaluated were the following: left ventricle diameters (DD, SD), inter-ventricular septum thickness (IVS) and left ventricle free wall (LVFW) in mm, end-diastolic volume (EDV), end-systolic volume (ESV) and cardiac output (CO) in ml. At the enrolment, all patients had a standard ECG and 31/37 a routine echocardiography. The cardiological records at the last available control, were re-evaluated in 29 patients followed for periods ranging from 1.5 to 20 years.

Statistical analysis

The observed values, expressed according to the age, height and weight of patients, are indicated as mean and standard deviation. Student T test for paired data was applied to evaluate differences between baseline and last control values. A p value < 0.05 was considered as significant.

Results

The results are summarised in Tables 1 and 2. As regarding the electrocardiographic parameters, only HR shows a decline with age, as expected. At the baseline, the

Table 1. Electrocardiographic parameters in type II/III spinal muscular atrophies patients.

	Basic Values	Values at the F.U.	P value
N. of Patients	37	21	
Mean age (range)	23.3 ± 15.5	29.0 ± 14.9	
HR	83.25 ± 18.35	$72.8 \pm 11.5^*$	0.03
PQi in msec	0.13 ± 0.03	0.14 ± 0.02	n.s.
PQs in msec	0.04 ± 0.01	0.04 ± 0.01	n.s.
QT in msec	0.35 ± 0.03	0.36 ± 0.03	n.s.
Cardiomyopathic Index	3.38 ± 0.74	3.93 ± 0.67	0,05
Mean Follow-up in years		11.4 ± 8.6	

* P value < 0.05

Table 2. Ecocardiographic parameters in type II/III Spinal Muscular Atrophy patients.

	Basic Values	Values at the last control	P value
N° of Patients	29	19	
Mean age (range)	17.2 ± 14.8	28.9 ± 15.1	
DD in mm	43.6 ± 8.7	46.8 ± 7.0	n.s.
SD in mm	28.1 ± 6.3	30.1 ± 4.8	n.s.
IVS in mm	8.4 ± 2.0	9.4 ± 1.2	n.s.
LVFW in mm	8.6 ± 1.9	9.5 ± 1.0	n.s.
EDV in ml	91.5 ± 33.6	104.8 ± 36.4	n.s.
ESV in ml	32.2 ± 14.2	36.7 ± 14.7	n.s.
CO in ml	61.2 ± 20.6	65.4 ± 22.3	n.s.
EF in%	66.4 ± 4.8	65.3 ± 2.5	n.s.
FS in%	36.7 ± 3.4	36.0 ± 1.8	n.s.
Mean Follow-up in years		12.3 ± 9.3	

* P < 0.05

other parameters were within the normal limits except for the Cardiomyopathic Index that presented higher values in 2 patients. Echocardiographic parameters were within the normal limits in all patients. A dilation of the left ventricle without systolic dysfunction, was observed in only 2 patients, aged respectively 65 and 63 year; however they were hypertensive and/or affected by coronary artery disease.

Discussion

The most severe form of SMA presents with clear symptoms at birth, and usually die within 2 years. As these patients have the lowest SMN levels as well as SMN2 copy number, they are the most likely to show defects in cells other than the motor neuron. Cardiac involvement has been described in patients with type 1 Spinal Muscular Atrophy who present since birth a high degree of pulmonary involvement, with acute respiratory failure often leading to the needs of invasive tracheal ventilatory assistance. In these cases heart involvement could be secondary to respiratory insufficiency. A few key studies regarding SMA patients have implicated the involvement of cardiovascular and autonomic nervous systems. A retrospective study of type 1 SMA patients identified that 15/63 SMA patients experienced symptomatic bradycardia (15). Although it is clear that SMA is a neurodegenerative disease, there are clinical reports suggesting that other tissues contribute to the overall phenotype, especially in the most severe forms of the disease.

A retrospective study on 43 patients, age range 3 months to 3 years, 37 of which presented type I (Werdnig-

Hoffmann disease) and 6 type II (intermediate form disease), performed by Distefano et al. (15) showed that no clinical nor instrumental signs of cardiomyopathy were observed. However, ECG revealed signs of right ventricular overload in 37.3% of the patients, probably provoked by pulmonary hypertension due to respiration anomalies.

On the other hand, few cardiological studies mainly concern subjects affected by the juvenile form (Kugelberg-Welander disease) (19-23). The presence of a cardiomyopathy has been reported in these patients but the cardiac involvement is often described as secondary to the chronic respiratory insufficiency typical of the disease.

Three papers recently appeared in the literature (24-26) focus the attention on arrhythmias and cardiac defects as a feature of spinal muscular atrophy model mice. They find that a severe model of SMA mice suffer from severe brady-arrhythmia characterized by progressive heart block and impaired ventricular depolarization. Further investigations showed evidence of both sympathetic innervation defects and dilated cardiomyopathy at late stages of disease. Pathological responses including fibrosis and oxidative stress markers were additionally observed shortly after birth in a less severe model of disease (24-28).

Data here reported confirm our previous observations (31) that at least types II/III SMA do not present primary heart dysfunction. These observations, while confirming SMA patients should be evaluated regularly for cardiac disease, nevertheless they contribute to reassure patients and their clinicians on the use of experimental drugs, potentially contraindicated in cardiopathic patients.

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