Autonomic nervous system involvement in spinal muscular atrophy.

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Background

SMA has traditionally been classified as a selective lower motor neuron disease. However, the SMN protein is ubiquitously expressed. There are numerous clinical reports indicating the involvement of additional peripheral organs contributing to the complete picture of the disease in severe cases (Shababi et al.).

Additional complications in SMA patients include autonomic nervous system involvement (Gombash et al.).

A series of autonomic tests on SMA1 patients revealed a sympathetic-vagal imbalance, fluctuation of blood pressure, and irregular skin responses to temperature changes (Hachiya et al.).

Some patients with SMA have autonomic dysfunction, especially sympathetic nerve hyperactivity, that resembles dysfunction observed in SLA (Arai et al.).

Detailed studies evaluating ANS function in SMA2 and 3 patients have never been performed.

Aim

•To assess possible autonomic dysfunction in patients with a diagnosis of SMA type 2 and 3

•To correlate the autonomic dysfunction with the degree of clinical severity

Materials and methods

Patients evaluated between November 2015 and May 2016

Inclusion criteria

Patients with a genetically confirmed diagnosis of SMA type 2 and 3.

Age > 6 years

Exclusion criteria

High blood pressure (> 160/100 mmHg)

Diabetes;

Renal, adrenal, pituitary and coronary disorders

Therapy with drugs influencing the ANS: β-blockers, anticholinergics, α- blockers, neuroleptics.

Salbutamol was stopped 7 days before the tests

Tests performed

• Symptoms of autonomic dysfunction were assessed using the Composite Autonomic Symptom Scale (COMPASS 31):

6 domains explored: orthostatic intolerance (4); vasomotor (3); secretomotor (4); gastrointestinal (12); bladder (3); pupillomotor (5).

• Additional questions to better assess sweating:

1. "Ha notato una eccessiva sudorazione rispetto alla temperatura ambientale? Se SI, questo sintomo è stato presente sin dalla nascita?"
2. "E' localizzata in particolari aree del corpo? Se si, quali?"

• Specific autonomic tests
- Head-up tilting (HUT) parasympathetic and sympathetic (cardiac and vascular)
- Valsalva maneuver parasympathetic (eff. and aff.); sympathetic (eff.)
- Deep breathing test parasympathetic (efferent)
- Cold pressure testsympathetic (eff.)
- Skin sympathetic reflex sympathetic

• Plasma levels of catecholamines
- adrenaline and noradrenaline, supine and tilted.

Conclusions

• In our cohort, a significant number of SMA patients reported symptoms of autonomic dysfunction.

• The gastrointestinal involvement was the most common.

• Overall autonomic cardiovascular tests were normal.

• We showed for the first time abnormal epinephrine basal levels in SMA2 and 3, suggesting an hyperadrenergic status.

• No rising of norepinephrine after tilt in SMA pts.

• No significant differences in clinical signs or cathecolamines concentration between SMA2 and SMA3 patients.

These preliminary data indicate an autonomic dysfunction in SMA2 and 3 patients, characterized by an hyperadrenergic status, despite a larger cohort is required to confirm this evidence.

Future research

To enlarge the cohort of patients
To evaluate possible correlation between ANS involvement and motor function, through HFMSE and 6MWT
To assess catecholamine level in controls in our lab
To perform specific exams assessing the adrenal gland function.

Results

• Overall 18 patients (9 and 9) were prospectively included: 9 SMA2 and 9 SMA3, 8 of whom were ambulant.
• Age range 7-48 years, median age: 30 (mean: 28)
• COMPASS 31:
- 4/18 pts: no symptoms reported (3 SMA3 and 1 SMA2)
- 14/18 pts: at least 1 domain involved, all 14 pts had GI symptoms

COMPASS 31		
DOMAINS (n. items)	pts with symptoms (tot 14)	Description
Orthostatic intolerance (4)	11.12%	Dizzy or "Goofy" Severity: mild
Vasomotor (3)	27,8%	5/14 hands, 1 also feet
Secretomotor (4)	0	--
Gastrointestinal (12)	100%	9/14 persistently full 7/14 Constipation 2/14 diarrhea
Bladder (3)	5,5%	--
Pupillomotor (5)	27,8%	Occasionally "bright light bothered eyes"

• Additional questions to assess sweating revealed:
- 6/18 pts complained of excessive sweating, all since childhood.
- 5/6 referred sweating at hands and feet.

	Tot. SMA	SMA 3	SMA 2
COMPASS neg	4	3	1
COMPASS pos	14	6	8

	Salbutamol	
	n. pts Yes	n. pts No
COMPASS neg	2	2
COMPASS pos	7	7

Fisher test: NS

Cardiovascular autonomic tests

•11 patients were able to perform HUT test, the other 7 patients were evaluated on a sitting position due to severe lower limbs contractures

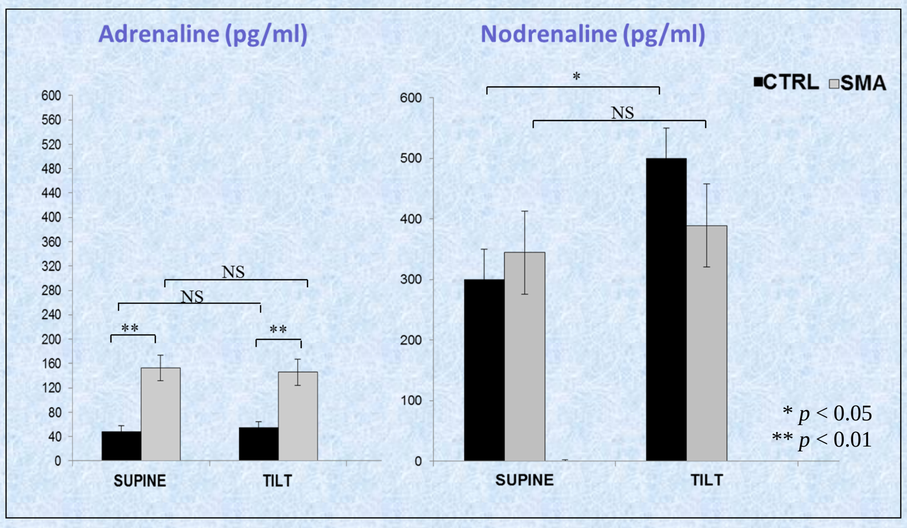
•None experienced orthostatic intolerance symptoms

•All patients showed normal vasoconstrictor sympathetic response at the cold pressure test and normal skin sympathetic reflex

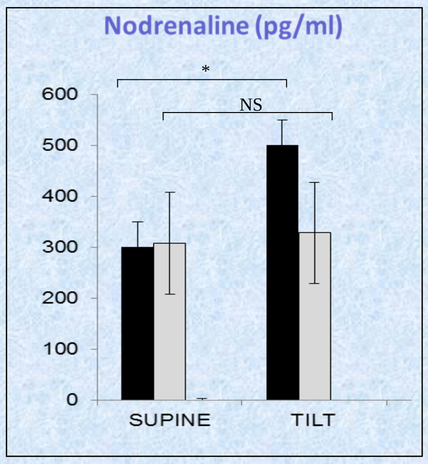
•Due to muscular weakness, Valsalva maneuver and deep breathing test were only performed in two patients (both with normal results)

Catecholamines dosage

High supine level of adrenaline in SMA vs CTRL ($p < 0.001$)
• No rise of adrenaline on tilt (in both CTRL and SMA)
• Supine noradrenaline only mildly elevated (NS)
• Not significant rising of noradrenaline after tilt in SMA (CTRL $p < 0.05$)



•Same noradrenaline results if we include only pts who had a HUT performed.
•Comparing SMA 2 vs SMA 3: similar basal levels
•and changing after tilting



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