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Absent cardiac and muscle sympathetic nerve activities involvement in Ross syndrome: A follow-up study

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ABSTRACT

Purpose: Ross syndrome (RS) is characterized by selective involvement of post-ganglionic skin sympathetic nerve fibres. We report a follow-up study in 4 patients to clarify whether in RS autonomic dysfunction spreads affecting also cardiovascular system.
Methods: The patients underwent cardiovascular reflexes (CVR) and microneurography recording of muscle sympathetic nerve activity (MSNA) for a follow-up mean period of 5 years.
Results: CVR and MSNA were normal at baseline and unchanged over the follow-up.
Conclusions: Cardiovascular autonomic system is spared in RS differently from skin autonomic activity dysfunction which progress over time. However, before drawing any definite conclusion, a large cohort of patients needs to be studied.

1. Introduction

Ross syndrome (RS) is a rare condition characterized by the clinical triad of anhidrosis, tonic pupil and areflexia. Absence of cholinergic sudomotor fibres revealed on skin biopsy is considered to be the pathological hallmark of the disease (Nolano et al., 2006). Whether the autonomic dysfunction remain localized to skin fibres or it spreads more widely affecting also the cardiovascular autonomic system is still not defined.

To ascertain this involvement in RS is important because cardiovascular autonomic dysfunction is usually associated with higher morbidity and mortality of the underlying disorder (Elam, 2003).

With this aim we report cardiovascular autonomic activities in patients with pathologically defined RS during a follow-up study.

2. Methods

We studied 4 patients affected by RS complaining of classical clinical symptom of anhidrosis with heat intolerance in association with areflexia and mydriatic pupil not reacting to light (tonic pupil) on neurological examination.

The patient no. 4 of Tables 1a,1b,1c presented with a cardiac pacemaker at baseline because of a primary bradycardia diagnosed 10 years before the start of focal anhidrosis and mydriatic pupil. The baseline diagnosis was confirmed in all patients by the absence of cholinergic sudomotor fibres on skin biopsy and, in addition, by selective involvement of skin sympathetic nerve activity (SSNA) on the microneurography recording in all the examined affected limbs (Donadio et al., 2012a). Furthermore, patients performed at baseline brain MRI and serologic screening for autoimmune, microbiologic and neuroendocrinological disease which turned out normal. Motor (from median, ulnar and tibial nerves bilaterally) and sensory (median, ulnar and sural nerve bilaterally) nerve conduction studies proved also unaffected. Bilateral absence of H-reflex, recorded from the soleus muscle, was revealed in all patients. During our clinical observation recruited patients did not take any drug potentially inducing RS symptoms. In addition patients were not under any pharmacological treatment for their neurological symptoms except the suggestion to avoid heat and crowd environments. All patients were followed up for a mean period of 5 years (range 1–10 years) to perform cardiovascular tests to ascertain the spread of the autonomic dysfunctions to cardiac or muscle sympathetic nerve activities.

The procedures used followed the Helsinki Declaration regarding international clinical research on human beings, and all subjects gave their written informed consent to the study.

2.1. Cardiovascular reflexes (CVR)

Patients underwent Head up tilt test (10 min), Valsalva manoeuvre (40 mm Hg × 15 s) and deep breathing (6 breath/min × 2 min) to

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Table 1a
HR: heart rate. SBP: systolic blood pressure. DBP: diastolic blood pressure. HUTT: head up tilt test (value express the difference, compared to baseline, after 10 min of standing of SBP, DBP, and HR respectively. VR: Valsalva ratio. OS: overshoot (see the Methods section for details).

Patient	Sex	Age at baseline	Age at follow-up	SBP at baseline	SBP at follow-up	DBP at baseline	DBP at follow-up	HR at baseline	HR at follow-up	HUTT at baseline	HUTT at follow-up	VR at baseline	VR at follow-up	OS at baseline	OS at follow-up
1	F	38	47	115 mm Hg	147 mm Hg	65 mm Hg	77 mm Hg	63 bpm	65 bpm	– 10/0 mm Hg; 11 bpm	– 3/1 mm Hg; 6 bpm	1,36	1,30	18 mm Hg	18 mm Hg
2	M	44	45	102 mm Hg	107 mm Hg	69 mm Hg	72 mm Hg	68 bpm	70 bpm	9/7 mm Hg; 15 bpm	10/6 mm Hg; 10 bpm	2,34	1,80	54 mm Hg	41 mm Hg
3	M	43	47	110 mm Hg	113 mm Hg	65 mm Hg	68 mm Hg	87 bpm	103 bpm	5/6 mm Hg; 10 bpm	21/15 mm Hg; 8 bpm	1,98	1,46	53 mm Hg	53 mm Hg
4	F	60	67	145 mm Hg	123 mm Hg	80 mm Hg	66 mm Hg	80 bpm	61 bpm	9/7 mm Hg; *NA	2;8 mm Hg; **NA	*NA	*NA	*NA	*NA

*NA = (not applicable): variation of heart rate and Valsalva ratio were not evaluable in patient 4 due to a PM (see text for details).

explore baroreflex and cardiac vagal activity. In addition, isometric handgrip (1/3 of maximal effort for 3–5 min) and cold face (4°C water on the forehead for 1 min) tests were also performed. Subjects were studied in a temperature-controlled clinical investigation room (23 ± 1 °C). Systolic and diastolic blood pressure (SBP, DBP; Portapres model 2, TNO-TPD Biomedical Instrumentation, Delft, the Netherlands), heart rate (HR; Grass 7P511 [Astro-Med West Warwick, RI, USA] and Light Work Station for digital RR quantification), oronasal and abdominal breathing (Grass DC preamplifier 7P1) were checked continuously. Patients had to fast the night before the test and were instructed to drink only a small amount of water if they were thirsty. They also had to abstain from drinking alcohol or coffee the day before the study.

After 30 min of supine rest, head-up tilt test (HUTT; 10 min at 65°), Valsalva manoeuvre (40 mm Hg for 15 s), deep breathing (6 breaths/min), cold face test (application of 4°C water on the forehead for 1 min) and sustained handgrip (30% of maximal effort for 5 min) were performed as previously described (Mathias and Bannister, 1999).

The manoeuvres were carried out in the described sequence, allowing a period of rest in order to reach basal BP and HR values in-between investigations. The results of each test were automatically obtained by means of home-developed software. Basal values of SBP, DBP and HR were obtained calculating the mean value of the last 5 min of supine rest preceding HUTT.

During Valsalva manoeuvre, the following indices of autonomic activity were considered: the ratio between HR in phases II and IV (Valsalva Ratio, VR) and the overshoot during phase IV (difference between the highest SBP after the expiratory effort and the basal value).

At deep breathing, the sinus arrhythmia (calculated in beats per minute using the 10 longest R–R intervals during expiration and the 10 shortest R–R intervals during inspiration) and the I/E ratio (ratio between the mean of the highest HR values during 10 deep inspiration and the mean of the lowest HR values during expiration) were calculated.

At cold face test, changes compared with the basal value of SBP, DBP and HR were computed after 60 s of application of cold water (4 °C) on the forehead, whereas baseline changes of SBP, DBP and HR were calculated after 5 min of isometric effort.

We were unable to perform blood pressure recovery time (PRT, expressed as interval time between lowest systolic blood pressure in phase III and its subsequent return to baseline in phase IV) and baroreflex sensitivity (Vogel et al., 2005; Schrezenmaier et al., 2007).

2.2. Microneurography

Recordings were performed from the peroneal nerve in the affected limb (anhidrotic skin). The patient sat in an ambient temperature of 25 °C and relative humidity of 30% in a semi-dark sound-proof room lying semi-reclined. Multiunit recordings of efferent postganglionic muscle sympathetic nerve activity (MSNA) and skin sympathetic nerve activity (SSNA) with the corresponding organ effector responses (skin sympathetic response-SSR and skin vasomotor response-SVR) were recorded (Wallin, 1994; Donadio et al., 2012b).

Muscle sympathetic nerve activity (MSNA) was considered acceptable when it revealed spontaneous, pulse-synchronous bursts of neural activity that fulfilled the described criteria previously (Wallin, 1994). A burst of skin sympathetic nerve activity (SSNA) was considered if it: 1) had irregular frequency with variation in amplitude and duration not relating to heart beats; 2) was followed at rest by changes in finger pulse amplitude (skin vasomotor response, SVR) and/or skin electrical potential (sympathetic skin response, SSR); 3) was elicited by various arousal stimuli, including surface electrical stimulation.

To measure SVR and SSR in the corresponding impaled skin fascicles, an infrared photoelectric transducer (model PPS, Grass Instruments) and Ag–AgCl surface electrodes (filter setting 0.2–100 Hz for both) were used, respectively. A search for SSNA and MSNA bursts