Autonomic dysfunction in Hodgkin and non-Hodgkin lymphoma. A paraneoplastic syndrome?

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Abstract

We wanted to determine whether autonomic dysfunction in patients with lymphoma is related to chemotherapy or represent a paraneoplastic syndrome. 40 patients with current or cured Hodgkin or non-Hodgkin lymphoma and 40 healthy controls, matched for age, gender, hypertension and diabetes mellitus underwent autonomic evaluation (Deep Breath, Valsalva Maneuver, Hand Grip, Lying to Standing, Tilt Test). Current patients also suffering from diabetes or hypertension, or still on chemotherapy revealed autonomic changes, while cured or healthy subjects did not. Autonomic dysfunction in lymphoma is a transient manifestation of a paraneoplastic syndrome.

Introduction

There is some controversy regarding the association between autonomic dysfunction and Hodgkin disease. Some papers report acute dysautonomia involving the parasympathetic and sympathetic system, like a paraneoplastic syndrome, in Hodgkin lymphoma[1-4] and others describe improvements after the treatment of the disease.[5] Some studies suggest that such autonomic changes are related to the malignant disease,[6] but others claim that they are the consequence of chemotherapy.[7,8]

Given these conflicting findings, we tried to verify whether lymphoma per se or chemotherapy for this disease genuinely influence the autonomic system. We considered two groups of patients with lymphoma: the first one was formed by subjects who had been cured, while the other one was constituted by cases still receiving treatment. These two groups were matched with a control group of healthy subjects. All individuals underwent to the classic autonomic tests.

Materials and Methods

In a period of over one year, we studied 40 cases (M 20; F 20; mean age 58.7±7.3), 18 of them of non-Hodgkin (NH) lymphoma and 22 of Hodgkin (H) lymphoma, all attending our outpatients clinic for regular follow-up and/or treatment. All the cured subjects had received both chemotherapy (CT) and external beam radiotherapy (RT), the latest dose having been administered almost a year previously. The current patients were still receiving combined CT (including toxic agents such as vinca alkaloids) and/or RT based on international protocols. The control group was of 40 subjects (M 20; F 20; mean age 59.5±6.7) (Table 1).

All subjects underwent to the autonomic evaluation.

Autonomic evaluation

Subjects underwent cardiovascular autonomic nerve function tests,[9] in the following order: Deep Breathing Test, Valsalva Test, Isometric Hand Grip Test, Laying to Standing Test and Tilt test. In the Deep Breathing Test, a test of vagal heart rate control,[9] the duration of the expiratory and inspiratory breaths was 5 seconds each for a total of 40 seconds (4 respiratory cycles). The ratio of the longest to the shortest respiratory rate (RR) intervals was determined from the ECG for each respiratory cycle, and the mean of the four ratios was taken as the expiratory/inspiratory (E/I) ratio.

In the Valsalva Test, which measures both parasympathetic and sympathetic functions, subjects blew into a manometer, maintaining an intrathoracic pressure of 40 mmHg for 15 seconds. The ratio between the shortest RR interval during the expiratory effort and the longest RR interval during the 20 seconds afterwards (Valsalva ratio) was calculated.

In the Isometric Hand Grip Test, subjects squeezed a dynamometer in their dominant hand for 3 minutes using a force corresponding to 30% of their maximal squeezing force. Heart rate and blood pressure were measured at rest, before and after gripping the dynamometer.

In the Laying to Standing Test, subjects suddenly stood up after resting quietly in a supine position for 5 minutes. Heart rate and blood pressure were measured at rest and then 1, 3, 5 and 7 minutes after standing up.

In the Tilt Test, subjects laid supine on an electric tilt table. A restraining strap, applying a negligible pressure to the surface of the body put across the upper abdomen, secured the patients to the tilt table during the upright tilt. Humeral blood pressure and electrocardiograms were recorded continuously throughout the test, which lasted 30 minutes and was judged to be positive only in the case of symptoms fully reproducing the patient's original pre-syncopal or syncopal symptoms accompanied by arterial hypotension, bradycardia or both.[10,11]

Statistical analysis

Autonomic test results were compared using Student's two tailed t-test for matched data. Statistical significance was set at $P<0.05$.

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Key words: autonomic dysfunction, lymphoma.

Received for publication: 6 September.
Revision received: 11 November.
Accepted for publication: 20 November 2010.

Hematology Reports 2010; 2:e8
doi:10.4081/hr.2010.e8

Results

Table 1 shows the general characteristics of cases and controls. Table 2 summarizes the results of the autonomic tests in current patients and cured subjects: the latter had no autonomic dysfunction, whereas current patients had altered Deep Breathing Test results and Valsalva ratios. We also evaluated current cases and cured cases versus healthy subjects and we found that the autonomic evaluation was altered only in current cases, while cured patients did not differ from healthy (Tables 3, 4).

Discussion

Autonomic dysfunction is documented in cases of lymphoma,[5] but it is important to clarify whether this is a paraneoplastic manifestation or a consequence of chemotherapy[7,12] because, in the first hypothesis, chemotherapy can cure the alteration, while in the second one it may exacerbate the dysfunction, with all the well-known consequences. In fact, autonomic impairment is responsible for a higher mortality rate due to cardiovascular disease, such as sudden death resulting from cardiac arrhythmia.[1] Our study shows that dysautonomia in lymphoma is a direct consequence of the disease and that cured patients show no more signs of this alteration; so they return to

Table 1. General characteristics of Hodgkin and non-Hodgkin subjects and controls.

	Hodgkin and non Hodgking subjects	Controls
Age (years)	58.7±7.3	59.5±6.7
Gender (%males)	50 %	50%
Diabetes mellitus	1.6%	2.4%
Hypertension	2.4%	3.2%

Table 2. Results of autonomic tests in the study groups (Current vs. Cured patients).

Test	Parameter	Current pts (n°22)	Cured pts (n°40)
Deep breathing	E/I ratio	1.1±0.03	1.4±0.04*
Valsalva maneuver	Valsalva ratio	1.3±0.1	1.9±0.1 *
Hand grip test	Diastolic blood pressure increase in mmHg	19.1±3.1	23.3±3.1
Laying to standing test	Systolic blood pressure decrease in mmHg	-5.2±6.2	-3.4±4.5
Tilt test	RR intervals	1.08±0.01	1.2±0.03

*P<0.05

Table 3. Results of autonomic tests in the study groups (Current patients vs Healthy subjects).

Test	Parameter	Current pts (n°22)	Cured pts (n°18)
Deep breathing	E/I ratio	1.1±0.03	1.42±0.02*
Valsalva maneuver	Valsalva ratio	1.3±0.1	1.86±0.3 *
Hand grip test	Diastolic blood pressure increase in mmHg	19.1±3.1	20.4±4.7
Laying to standing test	Systolic blood pressure decrease in mmHg	-5.2±6.2	-5.5±4.6
Tilt test	RR intervals	1.08±0.01	1.12±0.01

*P<0.05

Table 4. Results of autonomic tests in the study group (Cured vs. Healthy subjects).

Test	Parameter	Cured pts(n°18)	Healthy(n°40)
Deep breathing	E/I ratio	1.4±0.04	1.42±0.02
Valsalva maneuver	Valsalva ratio	1.9±0.1	1.86±0.3
Hand grip test	Diastolic blood pressure increase in mmHg	23.3±3.1	20.4±4.7
Laying to standing test	Systolic blood pressure decrease in mmHg	-3.4±4.5	-5.5±4.6
Tilt test	RR intervals	1.2±0.03	-5.5±4.6

a normal state like control subjects. This result is confirmed also by the fact that our subjects, even if treated with vincristine, did not manifested any neuropathy like Pal reported.[13] However it could be possible that these changes depend on other factors different from chemotherapy. The results confirm that autonomic changes in patients with lymphoma may represent a paraneoplastic disease.

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