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The incidence and course of paraneoplastic neuropathy in women with epithelial ovarian cancer

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Summary. Sensorimotor polyneuropathy is the most common of the paraneoplastic syndromes involving the nervous system. Its incidence is high (more than 50%) in the patients undergoing neurophysiological investigation, and it is considered to be more frequent in subjects with lung and breast cancers. In this study we evaluated a series of 58 women with epithelial ovarian cancer at FIGO stages I and III. The aim of the study was to assess the incidence and characteristics of peripheral nerve involvement during the course of the disease both clinically and neurophysiologically. Our results suggest that in women with epithelial ovarian cancer (1) the incidence of subclinical polyneuropathy is high; (2) sensory involvement is predominant in stage I, but motor involvement is frequent in stage III; and (3) the incidence of peripheral nerve involvement increases with progression of the cancer.

Key words: Paraneoplastic neuropathy – Ovarian cancer

Introduction

The most common clinical syndrome due to the remote effects of malignant neoplasms on the nervous system is sensorimotor polyneuropathy, which can be detected with electrophysiological methods in more than 50% of cancer patients [17]. Peripheral neuropathy associated with cancer was reported as early as the end of the nineteenth century [4, 12] and since then it has been documented in numerous clinical, neurophysiological and pathological studies [8, 9, 13]. Its incidence is generally considered particularly high in patients with lung and breast cancers [9, 16]. On the other hand, the relationship between other solid neoplasms and neurological complications is less well established. Cerebellar degeneration [1, 3, 8, 11, 24], sensory neuropathy [14] and sensorimotor neuropathy [4, 12, 17] have been reported in associated with ovarian cancer, but so far no large series of patients have been evaluated and the real incidence of paraneoplastic polyneuropathy in this malignancy has not been determined. We designed a clinical and neurophysiological case-control study of a series of 58 patients with epithelial ovarian cancer at different stages with the aim of ascertaining the characteristics and incidence of peripheral nerve damage during the natural course of this neoplasm.

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Patients and methods

All the 61 patients referred to our hospital during 1989 for epithelial ovarian carcinoma who agreed to participate in an ongoing trial on cisplatin neurotoxicity [22] were considered for inclusion in this study. They were screened for the presence of toxic, metabolic, iatrogenic, inflammatory or hereditary diseases known to damage peripheral nerves or a daily alcohol intake higher than 30 g before starting chemotherapy; all subjects with positive findings were excluded. After the screening procedure 12 patients with stage I (mean age = 46.0 years, range 18–67) and 46 patients with stage III (mean age = 56.8 years, range 39–70) epithelial ovarian cancer according to the FIGO (Federation Internationale de Gynecologie et de Obstetrique) classification [20] who fulfilled the selection criteria were enrolled in the study. Briefly, FIGO stage I is when the cancer is limited to the ovary(ies), with or without ascites, and stage III is when there is ovarian involvement with extension to the small bowel or omentum or regional lymph nodes, but without spread to non-adjacent organs. No stage I patients were excluded, while 3 stage III patients were not elegible because of diabetes (2 patients) and hypothyroidism (1 patient). Each patient was matched with a woman whose age was similar (± 3 years) and who had been selected from healthy patients admitted to our hospital for minor head trauma. Cases and controls underwent the same screening procedure, clinical and neurophysiological evaluations. All physical examinations were performed by the same physician and the results were scored according to the Neurological Disability Scale (NDS), which was specifically designed to grade peripheral nerve damage [10]. Sensory and motor conduction velocity, potential amplitude and latency in the median, ulnar, peroneal and sural nerves were recorded in patients and controls with surface electrodes according to standard methods [2]. A statistical comparison of the mean values obtained was performed with the two-tailed

Table 1. Electrophysiological evaluation: statistical comparison between control and patient groups (mean values and standard deviation). A, Potential amplitude (sensory = μV, motor = mV); L, latency (ms); CV, conduction velocity (m/s). *$P < 0.01$

		Stage 1 ($n = 12$)				Stage 3 ($n = 46$)			
		Controls		Patients		Controls		Patients	
Median nerve									
Sensory	A	10.1	(2.85)	6.7	(2.42)*	10.4	(4.54)	5.3	(2.23)*
	L	2.62	(0.27)	2.88	(0.35)	2.66	(0.31)	3.16	(0.47)*
	CV	56.8	(5.36)	56.0	(6.66)	57.1	(5.03)	49.3	(5.83)*
Motor	A	12.5	(4.41)	6.8	(4.24)*	13.6	(5.26)	8.1	(4.31)*
	L	3.37	(0.42)	3.51	(0.27)	3.35	(0.39)	4.03	(0.89)*
	CV	57.8	(4.59)	59.3	(4.45)	58.6	(4.49)	54.9	(6.27)*
Ulnar nerve									
Sensory	A	9.2	(2.76)	6.8	(2.45)*	9.8	(3.61)	6.0	(2.73)*
	L	2.13	(0.23)	2.40	(0.26)*	2.31	(0.29)	2.68	(0.54)*
	CV	59.2	(5.93)	52.4	(4.20)*	57.4	(5.44)	48.6	(5.53)*
Motor	A	10.7	(3.37)	10.9	(1.89)	11.7	(4.22)	10.2	(4.11)
	L	2.40	(0.35)	2.65	(0.37)	2.38	(0.35)	2.84	(0.37)*
	CV	59.5	(4.41)	59.8	(5.29)	59.1	(4.34)	57.9	(4.38)
Peroneal nerve									
	A	7.0	(3.82)	5.5	(2.85)	8.5	(4.96)	4.2	(3.06)*
	L	3.90	(0.46)	4.62	(1.63)	3.95	(0.45)	4.35	(1.14)*
	CV	52.3	(2.25)	49.5	(4.01)	52.2	(3.53)	48.9	(4.47)*
Sural nerve									
	A	13.3	(4.88)	9.8	(5.59)	16.7	(7.11)	11.1	(7.55)*[a]
	L	2.10	(0.23)	2.60	(0.35)*	2.26	(0.32)	2.75	(0.61)*[a]
	CV	52.7	(3.53)	51.3	(4.23)	52.2	(3.95)	48.0	(9.19)*[a]
Age (years)		46.00	(13.28)	46.00	(13.52)	56.82	(9.34)	57.10	(9.43)

[a] Values not detectable in 6 patients and therefore excluded from calculations

Student's *t*-test. Furthermore, the values of each patient were compared both with the normal reference values obtained in the age-matched controls selected for this study and with the normal reference values of our laboratory, previously obtained in 60 healthy volunteers. Conduction velocities and latencies were considered normal when their values were within control mean values (2.5 SD) while potential amplitudes were considered normal if they were higher than the minimum values obtained in controls (see Table 1 for reference values). Abnormal conduction velocity and/or latency and/or potential amplitude in at least two different nerves in each patient were considered indicative of subclinical neuropathy [2].

Results

All the patients had a World Health Organization (WHO) performance status of 0 (normal activity) or 1 (symptoms, but fully ambulatory) [25].

At physical examination, none of the patients in the stage I group met the selected criteria for the diagnosis of neuropathy. Two patients in the stage III group had sensory impairment and decreased or absent deep reflexes in the legs, with an NDS score of 8 and 14 respectively (normal value < 6). The overall neurophysiological comparison between the mean values obtained in cases and controls is shown in Table 2. Statistically significant differences were found for both the stage I and the stage III patients in comparison with the controls. Sensory conduction values of ulnar, median and sural nerves in the stage I patients showed several abnormalities, while the motor conduction values were similar to those of the controls and only the potential amplitude recorded in the median nerve was significantly impaired. In contrast, the values obtained in the patients at stage III showed marked and widespread alterations in both motor and sensory nerves compared with control values, so that only the motor conduction velocity and potential amplitude recorded in the ulnar nerve did not show a statistically significant difference. The most striking differences between controls and stage III patients were seen in the potential amplitudes (peroneal nerve = −50.4%; median nerve, sensory = −48.5%; median nerve, motor = −40.1%; ulnar nerve, sensory = −38.9%; sural nerve = −33.3%). The latencies and conduction velocities were less severely affected. In 6 patients (13%) the sural nerve potential could not be detected. The number of pathological values discovered in the nerves of the patients during the individual screening for subclinical neuropathy did not differ when each of the two different series of reference values (i.e. age-matched subjects and laboratory

Table 2. Reference values used for the individual evaluations. A, Potential amplitude (sensory = μV, motor = mV); L, latency (ms); CV, conduction velocity (m/s). L and CV are indicated as mean (2.5 SD)

		Laboratory controls ($n = 60$)	Stage I controls ($n = 12$)	Stage III controls ($n = 46$)
Median nerve				
Sensory	A	>5	>5	>5
	L	2.0–3.4	2.0–3.2	2.0–3.3
	CV	44–68	46–67	46–67
Motor	A	>4	>4	>4
	L	2.4–4.3	2.5–4.3	2.5–4.2
	CV	47–69	48–66	48–67
Ulnar nerve				
Sensory	A	>4	>4	>4
	L	1.6–3.0	1.6–2.7	1.7–3.1
	CV	44–69	47–70	46–71
Motor	A	>4	>4	>4
	L	1.5–3.3	1.6–2.7	1.6–3.1
	CV	49–70	50–68	48–71
Peroneal nerve				
	A	>2	>2	>2
	L	2.7–5.2	2.6–5.0	2.9–4.9
	CV	44–60	47–57	45–59
Sural nerve				
	A	>5	>5	>5
	L	1.5–3.2	1.6–2.8	1.6–3.0
	CV	43–61	45–60	44–61
Age	Range	25–75	18–67	38–72
	Mean	49.50	46.00	57.10
	DS	(12.61)	(13.52)	(9.43)

Table 3. Individual neurophysiological evaluation. Subclinical neuropathy is defined as when two ore more nerves are involved [2]

No. of nerves involved	Stage I		Stage III	
0	2	(16.6%)	4	(8.7%)
1	6	(50%)	9	(19.6%)
2	4	(33.3%)	17	(36.9%)
3	0		10	(21.7%)
4	0		6	(13.1%)

reference values) were considered. Table 3 reports the number of nerves showing pathological values in each patient. We observed abnormal conduction values in two nerves in 4 of 12 patients with stage I disease (33.3%), but 33 out of 46 patients with stage III (71.7%) were beyond this limit. Interestingly, only 4 patients in the latter group (8.7%) had no peripheral nerve abnormalities, whereas more than one-third had pathological values in three or four nerves. The low number of observations in the stage I group did not allow a useful description of the distribution of the nerve involvement. In the stage III group, the most common association when two nerves were involved was between median and sural nerves (52.9% of the cases), and median, peroneal and sural nerve abnormalities were most frequently associated when three nerves were affected (40% of the cases).

Discussion

Large series of cancer patients with paraneoplastic neuropathy have already been reported, and clinical, neurophysiological and, sometimes, pathological observations have been used in order to assess the incidence of peripheral nerve involvement. Unfortunately, the results obtained by the various groups that considered solid neoplasms are not easily comparable, because of the different criteria of patient selection and the different methods chosen for their evaluation. Moreover, most of the reported series were biased by an unbalanced sample selection, with an overwhelming incidence of some solid malignancies (i.e. lung and breast), where others were only occasionally included [5–9, 13, 18, 23]. The impression gained from these observations was that sensorimotor neuropathy is definitely more frequent in lung cancer than all other types of solid neoplasm [4, 17, 21] and an incidence of 64% has been reported [19]. Epithelial ovarian cancer was only occasionally included in most of the previously reported series, and only one study considered a fairly large number of such patients (11 cases) [19]. The inclusion in our study of FIGO stages I and III patients allowed us to establish the natural course of the effect of ovarian cancer on the peripheral nerves excluding, however, the terminal changes with can be found in women with very advanced cancer. Our findings suggest that, initially, neuropathy is mainly of the sensory type and that, subsequently, peripheral nerve involvement is much more widespread. Stage III patients presented generalized involvement and highly significant alterations were found in almost all the examined sensory and motor variables in comparison with the controls. In this group of patients with more advanced ovarian cancer the most severe effects were seen in potential amplitudes and, to a lesser extent, latencies. In contrast, a less impressive decrease in conduction velocities was found in both sensory and motor nerves, thus suggesting that axonal damage was predominant in the affected nerves [15].

To summarize, the comparison of neurophysiological variables indicates that during epithelial ovarian cancer (1) both sensory and motor nerves are affected, with predominant sensory involvement in the earlier stage of the disease; (2) nerve involvement tends to become more severe in later disease stages, although the WHO performance status of our patients was still consistent with a nearly normal daily activity; and (3) the peripheral nerve damage is mainly axonal.

When the incidence of nerve involvement was studied in single patients, no detectable abnormalities were found

in women with stage I disease, whereas 2 stage III patients had evident polyneuropathy on clinical grounds. On the other hand, the evaluation of the neurophysiological findings in each patient confirmed that peripheral nerve involvement was much more widespread, with a higher incidence in stage III than stage I patients. The number of individuals who could be considered affected by peripheral neuropathy on the basis of the neurophysiological evaluation was definitely higher than that estimated on clinical grounds alone, reaching 33.3% in the stage I group and 71.7% in stage III patients.

In conclusion, these findings in single patients indicate that (1) the incidence of individual neurophysiological abnormalities is not negligible even in the very early stage of the cancer; (2) the incidence of subclinical peripheral neuropathy in individuals with advanced ovarian cancer increases markedly with progression of the neoplasm; and (3) this incidence approximates that of paraneoplastic neuropathy in patients affected by lung cancer.

Thus our study confirms that the incidence of subclinical sensorimotor neuropathy is high during the course of solid malignant neoplasms and, moreover, it challanges the fairly general opinion that paraneoplastic sensorimotor neuropathy in particularly frequent only in subjects with lung cancer.

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