Carcinoma associated paraneoplastic peripheral neuropathies in patients with and without anti-onconeural antibodies

Jean-Christophe Antoine, Jean-François Mosnier, Léna Absi, Philippe Convers, Jérôme Honnorat, Daniel Michel

Abstract

Objective—When to suspect a paraneoplastic disorder is a puzzling problem that has not recently been studied in a large series of patients referred for peripheral neuropathy.

Methods—From 422 consecutive patients with peripheral neuropathy, 26 were analysed who concomitantly had carcinoma but no tumorous infiltration, drug toxicity, or cachexia. Their clinical, pathological, and electrophysiological data were analysed according to the presence of anti-onconeural antibodies, the latency between presentation and cancer diagnosis, and the incidence of carcinoma in the corresponding types of neuropathy of the population of 422 patients.

Results—Seven patients (group I) had anti-onconeural antibodies (six anti-Hu, one anti-CV2) and 19 did not (groups IIA and B). In group I, subacute sensory neuropathy (SSN) was the most frequent but other neuropathies including demyelinating neuropathies were present. Patients in group II A had a short latency (mean 7.88 months), and a rapidly and usually severe neuropathy which corresponded in 11/14 to an established inflammatory disorder including neuropathy with encephalomyelitis, mononeuritis multiplex, and acute or chronic inflammatory demyelinating polyneuropathy (CIDP). Patients in group IIB had a long latency (mean 8.4 years) and a very chronic disorder corresponding in four of five to an axonal non-inflammatory polyneuropathy. In this population, the incidence of carcinoma occurring with a short latency was 47% in sensory neuropathy, 1.7% in Guillain-Barré syndrome, 10% in mononeuritis multiplex and CIDP, and 4.5% in axonal polyneuropathy.

Conclusions—Paraneoplastic neuropathies associated with carcinoma are heterogeneous disorders. Neuropathies occurring with a long latency with tumours probably resulted from a coincidental association. Neuropathies which occurred within a few years of the tumour evolved rapidly and corresponded mostly to inflammatory disorders. As dysimmune neuropathies are probably paraneoplastic in a limited number of cases, patients with these disorders should probably not be investigated systematically for carcinoma in the absence of anti-onconeural antibodies, except when the neuropathy is associated with encephalomyelitis and probably with vasculitis. Questions remain concerning CIDP.

Keywords: paraneoplastic neurological syndromes; peripheral neuropathy; Guillain-Barré syndrome; chronic inflammatory demyelinating neuropathy

Depending on diagnostic criteria, up to 50% of patients with carcinoma develop peripheral neuropathy.1 Treatment toxicity, tumorous infiltration, metabolic disturbances, or terminal cachexia account for most cases.7 Paraneoplastic neuropathies are rare and heterogeneous disorders.9 Some of them are part of complex syndromes involving simultaneously the central (CNS) and peripheral nervous systems (PNS), the most frequent of which is subacute sensory neuropathy/paraneoplastic encephalomyelitis (SSN/PEM).7 This disorder, when occurring with small cell lung cancer, is almost invariably associated with anti-Hu antibodies.7 Paraneoplastic syndromes associated with the other known anti-onconeural antibodies often involve the PNS, but the neuropathies are less characterised.10 11 Although attention has been mainly focused on antibody positive cases, there also exist true paraneoplastic neuropathies and no known antibodies.11 These cases are difficult to define because many of the previous reports did not use modern investigation methods,12 13 and most of the recent studies concern single or few cases so that it is difficult to know which type of neuropathy should be investigated for cancer. We have therefore performed a study on 26 patients selected from 422 consecutive patients with peripheral neuropathy who developed their neurological disorder in association with carcinomas. This led us to discuss the classification of these neuropathies, their links with tumours, and when to investigate a patient with peripheral neuropathy for carcinoma.

Material and methods

PATIENT SELECTION

The patients were selected from the data bank of 422 consecutive patients investigated for peripheral neuropathy in the Department of Neurology of the University Hospital of Saint-Etienne between 1987 and June 1998. Our Department is the referential centre for neurological diseases in an estimated population of
The electrophysiological data were considered as indicative of a primary demyelinating neuropathy when they fulfilled the criteria established by the ad hoc subcommittee for the diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). A significant reduction with normal duration of the sensory and motor action potentials (SAPs and MAPs), and slowing of conduction velocities not exceeding 80% of the lower limit of normal were considered as indicative of an axonal neuropathy. A neuronopathy (involvement of motor neurons in anterior horn or sensory ganglionopathy) was suspected when a significant reduction with normal duration of the SAP or MAP, and normal conduction velocities occurred. In addition, needle EMG evidence of fibrillation potentials, positive sharp waves, or fasciculations were required for the diagnosis of motor neuron involvement.

**NEUROPATHOLOGICAL STUDY**

Samples of superficial peroneal nerve biopsies (18 cases) were fixed in 10% formalin, embedded in paraffin, and stained with haematoxylin and eosin. Others were fixed in 2.5% glutaraldehyde, then in osmium tetroxide for semithin and ultrathin sections and for teased fibre examination. Muscle biopsies (six cases) were processed for paraffin, semithin, and ultrathin sections as nerve biopsies. For postmortem examination (four cases), the brain, spinal cord, certain lumbar sensory ganglia, and samples of peripheral nerves and muscles were fixed in 10% formalin; in addition, the L5 sensory ganglion and samples of the left L5 ventral and dorsal roots, sciatic nerve, and common peroneal nerve at the level of the knee were removed and processed as for nerve biopsy.

**SCREENING FOR ANTI-ONCONEURAL ANTIBODIES**

A serum sample was obtained from each patient and stored at −80°C until required.
Screening for anti-onconeural antiantibodies (anti-Hu, anti-Ri, anti-Yo, anti-ampiphysin, and anti-CV2) was performed by immunohistochemistry and western blotting experiments on rat brain in accordance with the guidelines recommended for their detection, using paraformaldehyde fixed sections of rat cerebellum, as described elsewhere. Positivity for anti-onconeural antibodies was confirmed by western blotting using the recombinant HuD, CDR 62 proteins kindly provided by Dr J Dalmau (Sloan-Kettering Cancer Center, New York, USA), and the recombinant amphiphysin protein kindly provided by Professor P DeCamilli (Yale University, New Haven, USA) and for anti-CV2 antibodies with an S3 subcellular fraction of new born rat brain proteins.

**Results**

Twenty six patients were selected for the study. None of them, except patient 17, had received chemotherapy before the onset of the neuropathy but the disorder (demyelinating Guillain-Barré syndrome) was not consistent with drug toxicity. Results from four of these patients have been published in full detail elsewhere. Seven patients had anti-onconeural antibodies (group I) and 19 did not (group II). Except in group I, the patients were not systematically investigated for cancer and the tumours were diagnosed when clinically apparent.

**GROUP I: PATIENTS WITH ANTI-ONCONEURAL ANTIBODIES (SEVEN PATIENTS)**

The neuropathy preceded the discovery of the cancer by 2 to 23 months (mean 10.00 months, table 1) and was usually severely disabling (Rankin score at 3 or 4 in six of seven patients) within a few months. Patients 1 to 6 had anti-Hu antibodies and small cell carcinoma of lung or prostate. Patient 7 had mediastinal undifferentiated carcinoma and anti-CV2 antibodies which reacted with a unc-33 related and developmentally regulated protein.

**Table 1 continued**

<table>
<thead>
<tr>
<th>CSF</th>
<th>Tumour</th>
<th>Pathology</th>
<th>Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0 g/l 54 lympho</td>
<td>SCLC</td>
<td>Nerve biopsy, fibre loss, axonal degeneration</td>
<td>Anti-Hu</td>
</tr>
<tr>
<td>1.14 g/l 43 lympho</td>
<td>SCLC</td>
<td>Nerve biopsy, fibre loss, axonal degeneration</td>
<td>Anti-Hu</td>
</tr>
<tr>
<td>0.42 g/l 1 lympho</td>
<td>SCLC</td>
<td>Nerve biopsy, fibre loss</td>
<td>Anti-Hu</td>
</tr>
<tr>
<td>0.78 g/l 1 lympho</td>
<td>Small cell carcinoma of prostate</td>
<td>Nerve biopsy, axonal degeneration</td>
<td>Anti-Hu</td>
</tr>
<tr>
<td>1.2 g/l 1 lympho</td>
<td>SCLC</td>
<td>Necropsy: mild ganglionitis, fibre loss in distal nerves. Demyelination, onion bulbs endoneurial lymphocytes</td>
<td>Anti-Hu</td>
</tr>
<tr>
<td>1.62 g/l 52 lympho</td>
<td>SCLC</td>
<td>Necropsy: normal sensory ganglia and spinal cord. Fibre loss demyelinated fibers</td>
<td>Anti-CV2</td>
</tr>
</tbody>
</table>

**GROUP II: PATIENTS WITHOUT ANTI-ONCONEURAL ANTIBODIES (19 PATIENTS)**

The characteristics of the neuropathy and the associated cancers were summarised in tables 2 and 3. Patients in this group had very different types of carcinoma. The neuropathies were heterogeneous and can be divided into four types.

(1) In four patients (8–11), a sensory or sensory-motor neuropathy was associated with signs of corticospinal involvement suggesting that PEM was present. This was confirmed by postmortem examination in cases 8 and 9. Electrophysiology was axonal (9 and 10) or neuronal (8 and 11). Inflammatory changes were present in the CSF of three of four of these patients. In the peripheral nerves, biopsies or necropsies showed fibre loss and Wallerian degeneration. Lesions were marked in patients 8, 10, and 11, and mild in patient 9. Mononuclear cell infiltrates were present in the endoneurium and around epineurial vessels in patients 8 and 11.

(2) In two patients (12 and 13), the neuropathy presented as mononeuropathy multiplex (MNM) with systemic or nerve restricted non-necrotising vasculitis. Patient 13 had orthostatic hypotension.

(3) Seven patients (patients 14 to 16 and 22 to 25) had a sensory motor neuropathy that was electrophysiologically axonal. Nerve biopsy performed in three showed chronic axonal neuropathy without inflammatory changes. In the others, who did not have a pathological study, the possibility of metastatic involvement...
### Table 2: Clinical data for the 14 patients with a short delay between the onset of the neuropathy and the discovery of the tumour who had no anti-onconeural antibodies (group II-A). Delay indicates the interval between the onset of neurological symptoms and cancer diagnosis and is expressed in months (m) or weeks (w). In every case, except case 13, the neuropathy preceded the discovery of the tumour. The revised Rankin score is used to estimate the maximal deficit reached by the patients.

<table>
<thead>
<tr>
<th>No</th>
<th>Sex/age</th>
<th>Delay</th>
<th>Clinical manifestations</th>
<th>Course</th>
<th>Rankin</th>
<th>Electro-physiology</th>
<th>CSF</th>
<th>Tumour</th>
<th>Pathological study</th>
<th>Treatments (neuropathy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>M/65</td>
<td>3 m</td>
<td>Proximal and distal sensory motor deficit, pain in four limbs, diffuse areflexia, amyotrophia. Respiratory deficiency. Left Babinski</td>
<td>Subacute</td>
<td>5</td>
<td>Neuronal</td>
<td>1.12 g/l 11 lympho</td>
<td>Lung (CT)</td>
<td>Inflammatory ganglionicis and myelitis, preservation of motor neurons, inflammatory lesions in the nerves, necrotising myopathy</td>
<td>No improvement steroids PE and IgIV</td>
</tr>
<tr>
<td>9</td>
<td>F/71</td>
<td>26 m</td>
<td>Pain, paresthesia, proximal &gt; distal motor deficit in four limbs. Lower limbs areflexia. Bilateral Babinski. Reticular livedo</td>
<td>Progressive</td>
<td>4</td>
<td>Axonal</td>
<td>0.3 g/l 1 lympho</td>
<td>Pancreas adenocarcinoma</td>
<td>Mild inflammatory ganglionicis and axonal neuropathy, vessel thickening, inflammatory myositis</td>
<td>No improvement steroids</td>
</tr>
<tr>
<td>10</td>
<td>M/73</td>
<td>26 m</td>
<td>Severe sensory &gt; motor deficit in four limbs lower limbs areflexia, transient diplopia bilateral Babinski.</td>
<td>Progressive</td>
<td>4</td>
<td>Axonal</td>
<td>1.20 g/l 35 lympho</td>
<td>SCLC lung</td>
<td>Nerve biopsy: fibre loss, axonal degeneration, slight inflammatory reaction, normal muscle</td>
<td>No improvement steroids PE azat</td>
</tr>
<tr>
<td>11</td>
<td>M/74</td>
<td>4 m</td>
<td>Sensory motor proximal and distal deficit in four limbs, amyotrophia, normal tendon reflexes, bilateral Babinski</td>
<td>Progressive</td>
<td>4</td>
<td>Neuronal</td>
<td>2.02 g/l 28 lympho</td>
<td>Urinary (CT)</td>
<td>Nerve biopsy: multifocal axonal lesions, endoneurial inflammatory reaction vasculitis. Muscle: neurogenic atrophy</td>
<td>No improvement steroids</td>
</tr>
<tr>
<td>12</td>
<td>F/72</td>
<td>6 m</td>
<td>Mononeuropathy multiplex. Peroneal and tibial nerves hypeereosinophilia, raised ESR, sinusitis</td>
<td>Acute</td>
<td>3</td>
<td>Axonal</td>
<td>0.32 g/l 1 lympho</td>
<td>Colon adenocarcinoma (recidine)</td>
<td>Nerve biopsy: axonal degeneration, vasculitis in a nasal polypoid formation. Muscle: neurogenic atrophy</td>
<td>Improvement steroids (Rankin 3 to 1)</td>
</tr>
<tr>
<td>13</td>
<td>M/65</td>
<td>2 w</td>
<td>Multifocal sensory motor deficit in right arm and lower limbs. Leg areflexia. Orthostatic hypotension</td>
<td>Relapsing</td>
<td>2</td>
<td>Axonal</td>
<td>0.50 g/l 1 lympho</td>
<td>Tongue epidermoid</td>
<td>Nerve biopsy: fibre loss, degenerating fibres, epineural vasculitis</td>
<td>Spontaneous improvement</td>
</tr>
<tr>
<td>14</td>
<td>M/84</td>
<td>7 m</td>
<td>Distal sensory painful asymmetric in four limbs, lower limb areflexia</td>
<td>Subacute</td>
<td>3</td>
<td>Axonal</td>
<td>0.49 g/l 1 lympho</td>
<td>Lung undifferentiated adenocarcinoma</td>
<td>ND</td>
<td>No improvement steroids</td>
</tr>
<tr>
<td>15</td>
<td>M/85</td>
<td>9 m</td>
<td>Distal pain, sensory loss and areflexia in lower limbs</td>
<td>Progressive</td>
<td>2</td>
<td>Axonal</td>
<td>0.53 g/l 1 lympho</td>
<td>Lung (CT scan)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>16</td>
<td>M/61</td>
<td>1 m</td>
<td>Motor&gt;sensory asymmetric deficit in four limbs, fasciculations, absent or reduced tendon reflexes</td>
<td>Acute</td>
<td>3</td>
<td>Neuronal</td>
<td>0.30 g/l 1 lympho</td>
<td>Gastric adenocarcinoma</td>
<td>Neurogenic atrophy in muscle</td>
<td>No improvement steroids</td>
</tr>
<tr>
<td>17</td>
<td>M/48</td>
<td>0 m</td>
<td>Sensory motor Guillain-Barre syndrome, areflexia in four limbs, facial nerve palsy</td>
<td>Acute</td>
<td>4</td>
<td>Demyelinating</td>
<td>0.66 g/l 1 lympho</td>
<td>Tongue epidermoid (recidive)</td>
<td>Nerve biopsy: ongoing macrophage induced demyelination</td>
<td>Improvement IgIV (Rankin 4 to 2)</td>
</tr>
<tr>
<td>18</td>
<td>M/73</td>
<td>3 m</td>
<td>CIDP. Sensory motor mainly proximal deficit and areflexia in four limbs</td>
<td>Progressive</td>
<td>3</td>
<td>Demyelinating</td>
<td>1.27 g/l 1 lympho</td>
<td>Pancreas adenocarcinoma</td>
<td>ND</td>
<td>Improvement IgIV (Rankin 3 to 2)</td>
</tr>
<tr>
<td>19</td>
<td>M/73</td>
<td>6 m</td>
<td>CIDP. Sensory motor mainly proximal mainly upper limbs deficit and areflexia in four limbs</td>
<td>Progressive</td>
<td>2</td>
<td>Demyelinating</td>
<td>0.90 g/l 1 lympho</td>
<td>Colon adenocarcinoma</td>
<td>Nerve biopsy: fiber loss, remyelinated fibers, onion bulb formations, slight inflammatory changes</td>
<td>Improvement after surgery (Rankin 2 to 1)</td>
</tr>
<tr>
<td>20</td>
<td>M/61</td>
<td>9 m</td>
<td>CIDP. Mainly motor proximal&gt;distant deficit and areflexia in four limbs</td>
<td>Progressive</td>
<td>4</td>
<td>Demyelinating</td>
<td>1.60 g/l 1 lympho</td>
<td>Liver adenocarcinoma</td>
<td>Nerve biopsy: almost normal fibers endoneurial lymphocytes</td>
<td>Improvement steroid IgIV azat (Rankin 4 to 1)</td>
</tr>
<tr>
<td>21</td>
<td>M/78</td>
<td>+ 2 m</td>
<td>Sensory motor proximal and distal deficit in four limbs. Depressed or abolished tendon reflexes</td>
<td>Subacute</td>
<td>5</td>
<td>Demyelinating</td>
<td>1.60 g/l 1 axonal</td>
<td>Prostate adenocarcinoma</td>
<td>Demyelinated fibers, slight onion bulbs degenerated fibers and regenerating clusters endoneurial macrophages</td>
<td>Improvement steroid (Rankin 5 to 4)</td>
</tr>
</tbody>
</table>

**Course** corresponds to the onset of neurological symptoms: acute, <1 month; subacute 1–2 months; progressive, >2 months. **CIDP**=chronic inflammatory demyelinating polyneuropathy; **TD**=temporal dispersion; **CB**=conduction block. **PE**=plasma exchanges. **IgIV**=intravenous immunoglobulins. **azat**=azathioprine. When improvement occurred after immunotherapy, the Rankin score before and after treatment is given in parentheses. Other abbreviations are the same as in table 1.
of peripheral nerves was low as CSF examination showed no tumour cells and patients were followed up several months or years after tumour diagnosis with stabilisation of the neuropathy.

(4) Six patients (patients 17 to 21 and 26) had an electrophysiological demyelinating neuropathy. In patient 17, it was a typical Guillain-Barré syndrome that occurred simultaneously with a rapidly lethal (within 3 months) recurrence of tongue carcinoma. The other patients had a CIDP-like neuropathy which conformed to the diagnostic criteria of the ad hoc subcommittee.\(^1\) Patient 21 had mixed axonal and demyelinating features on electrophysiology. Nerve biopsy showed fibre loss, regenerating clusters suggesting distal axonal degeneration, and demyelinated fibres, onion bulb formations, and endoneurial macrophages.

**TYPE OF NEUROPATHY ACCORDING TO DELAY IN GROUP II**

Patients in group II can be subdivided into two groups according to the delay between the onset of the neuropathy and the diagnosis of cancer. Group II A consisted of 14 patients (table 2) in whom the delay was between 0–26, mean 7.88 months. They usually had a severe neuropathy (Rankin score 2–5, mean 3.4) with either acute, subacute, progressive, or relapsing course. When progressive, the maximal disability was reached within 6 to 9 months. The neuropathy was sensory-motor in 12 of 14 patients and purely sensory in two. None of them had sensory ataxia. In 11 of 14 patients, the neuropathy corresponded to an established inflammatory disorder (SSN/EM, mononeuropathy multiplex, Guillain-Barré syndrome, or CIDP). Immunosuppressive treatments were performed in 11 patients. Patients with CIDP or Guillain-Barré syndrome, and one patient with MNM improved. None of the patients with CNS involvement or non-specific axonal neuropathy improved. Group II B (table 3) consisted of five patients in whom the delay varied from 4 to 14 (mean 8.4), years. In all of them, the neuropathy was very slowly progressive and evolved over many years. The disability was minor (Rankin score 1 or 2). Four of these five patients had an axonal sensory motor polyneuropathy without inflammatory changes. The last patient had a very chronic and indolent CIDP. After 10 years, he developed malignant melanoma. He had no vitiligo and the research for anti-GM1, GD2, GD3, GM3, GD1a, and GD1b antibodies was negative.

**INCIDENCE OF CARCINOMA ACCORDING TO THE TYPE OF NEUROPATHY**

The 26 patients reported above represent 6.2% of the patients referred for the diagnosis of neuropathy and 9% of patients over 50 years of age. However, when taking into account only patients in whom the tumour appeared within 2.5 years, the distribution was different according to the type of neuropathy. Among our patients with sensory neuronopathy, 47% had a carcinoma. These patients usually had a subacute or rapidly progressive disorder with symptoms of PEM while patients without cancer had an isolated and slowly progressive neuropathy. Comparatively, one patient among 59 with Guillain-Barré syndrome (1.7%) had carcinoma simultaneously. Patients with CIDP or mononeuropathy multiplex, had almost the same incidence of carcinoma (10%) and it was 4.5% in patients with axonal sensory-motor polyneuropathy of otherwise unknown origin.

**Discussion**

Contrary to studies originating from cancer centres,\(^2\) our population of patients was first referred to a department of neurology. This can explain why in our series, the neurological disorder usually preceded the diagnosis of tumour. None of the patients selected for the present study had cachexia, tumorous infiltration, or chemotherapy as the cause of the neuropathy suggesting that their disorders were paraneoplastic. Currently, the detection of high titres of one of the anti-onconeural antibodies is the best way to identify a neurological syndrome as paraneoplastic. We found one of them (mainly anti-Hu antibodies) in 28% of patients (group I) only. These patients had a subacute or rapidly progressive and usually
severely disabling neurological disorder involving both the CNS and PNS in most of them. Although most patients with anti-Hu antibodies had SSN, 24–27 we also found axonal or demyelinating neuropathies in accordance with recent studies which indicate that neuropathies associated anti-Hu antibodies can be heterogeneous. 24–27

In 19 of 26 patients, anti-onconeural antibodies were not detected. The neuropathies in this group (group II) were also heterogeneous, including neuropathy with encephalomyelitis, mononeuropathy multiplex, Guillain-Barré syndrome, CIDP, and axonal polyneuropathy. Although individual cases or small series of each of these disorders have been reported to depend on a remote effect of cancer, 26–31 their paraneoplastic origin cannot be ascertained except when the neuropathy is associated with encephalomyelitis. 7 In the absence of specific markers, arguments in favour of a remote effect of carcinoma can only be drawn from indirect criteria. In our study, we used (1) the latency between onset of the neuropathy and diagnosis of cancer, (2) the characteristics of the neuropathy, and (3) the incidence of cancer in the corresponding type of neuropathy.

In Lambert-Eaton myasthenic syndrome, the risk of cancer decreases sharply after 2 years and becomes extremely low at 4 years, 32 showing that when a disorder is paraneoplastic, cancer becomes apparent within a relatively short delay. In our series, we clearly have two groups of patients. In the first (group IIA), the latency was short and comparable with that of patients with paraneoplastic antibodies, 26–31 suggesting direct physiopathological links between tumour and neuropathy. In the second (group IIB), carcinoma appeared many years after the onset of the neuropathy, suggesting that it was a coincidental association. The number of patients in this group was relatively small but as protracted follow up over more than 5 years was obtained in a small proportion of our population only, several cases may have been missed in group IIB. Conversely, as most of our patients were followed up during the first years of the evolution of their neuropathy only a few patients had probably escaped in group IIA.

The characteristics of the neuropathies were different between group IIA and B. Patients in group IIB had a very chronic, slowly progressive, and mildly disabling disorder as opposed to group IIA in which the neuropathies had a severe and rapid course. Interestingly, 78% of the neuropathies in group IIA correspond to a known inflammatory disorder of the PNS. This contrasts with patients with long latency who for the most part had a non-inflammatory axonal polyneuropathy. Only one of them developed an indolent CIDP which evolved over 10 years before the diagnosis of malignant melanoma. Recently, a particular association of CIDP and melanoma has been reported, possibly involving a shared immunoreactivity against gangliosides. 33 However, our patient had no antiganglioside antibodies and differed from these cases by the delay of tumour diagnosis and the absence of vitiligo.

The pathophysiology of paraneoplastic neurological syndrome is not completely understood, but an increasing amount of data indicates that at least in patients with anti-onconeural antibodies dysimmune mechanisms are involved. 3 The fact that in our series most of the neuropathies which occurred within 2.5 years with a carcinoma correspond to known inflammatory disorders suggests that despite the absence of specific antibodies or other known immunological markers, tumours have in some way induced the immunological perturbations underlying the neuropathies.

Each of the well established paraneoplastic neurological syndromes also occurs without cancer. Thus, 40% of patients with Lambert-Eaton myasthenic syndrome do not have tumours. 32 The proportion is 50% in patients

### Table 4 Incidence of carcinoma according to the type of neuropathy in our series and in several other published series

<table>
<thead>
<tr>
<th>Type of neuropathy (authors)</th>
<th>Number of cases (of carcinoma)</th>
<th>Follow up (mean in our study)</th>
<th>Commentaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population of neuropathies</td>
<td>278 (5.4)</td>
<td>18 months</td>
<td>ND</td>
</tr>
<tr>
<td>Our study</td>
<td>422 (6.2)</td>
<td>&gt;400 days</td>
<td>% of death due to carcinoma within 250 days</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>29 (6.9)</td>
<td>24 months</td>
<td>&lt;2 y</td>
</tr>
<tr>
<td>Italian study group</td>
<td>297 (0.7)</td>
<td>Mean 3 y</td>
<td>5.7 y (0.5-16)</td>
</tr>
<tr>
<td>Our study*</td>
<td>59 (1.7)</td>
<td>NS</td>
<td>These studies include patients with MGUS of unknown reactivity</td>
</tr>
<tr>
<td>CIDP</td>
<td>60 (5.0)</td>
<td>Mean 3.9 y</td>
<td></td>
</tr>
<tr>
<td>Barthol et al*</td>
<td>67 (0)</td>
<td>Mean 7.2 y</td>
<td></td>
</tr>
<tr>
<td>Our study*</td>
<td>38 (10.5)</td>
<td>NS</td>
<td>Patients selected from nerve biopsies</td>
</tr>
<tr>
<td>Vasculitis mononeuritis multiplex</td>
<td>50 (14)</td>
<td>Mean 18.5 months</td>
<td></td>
</tr>
<tr>
<td>Vincent et al*</td>
<td>50 (10)</td>
<td>Mean 3.9 y</td>
<td></td>
</tr>
<tr>
<td>Vincent et al*</td>
<td>33 (9)</td>
<td>Mean 7.2 y</td>
<td></td>
</tr>
<tr>
<td>Our study*</td>
<td>20 (10)</td>
<td>5.7 y (0.5-10)</td>
<td></td>
</tr>
<tr>
<td>Axonal polyneuropathy of otherwise undetermined cause</td>
<td>91 (1.0)</td>
<td>Mean 3.7 y</td>
<td></td>
</tr>
<tr>
<td>Fagius et al*</td>
<td>47 (10.6)</td>
<td>Median 3 y</td>
<td></td>
</tr>
<tr>
<td>McLeod et al*</td>
<td>75 (5.3)</td>
<td>4.7 y</td>
<td>Prospective study</td>
</tr>
<tr>
<td>Notermans et al*</td>
<td>51 (29.4)</td>
<td>Mean 51.4 months</td>
<td></td>
</tr>
<tr>
<td>Camerlingo et al*</td>
<td>67 (10.3)</td>
<td>3.7 y (0.3-11)</td>
<td>4.5% within 2 years after onset</td>
</tr>
</tbody>
</table>

ND = not done; NS = not stated; MGUS = monoclonal gammopathy of unknown significance. * Patients with a short latency are taken into account only.
with subacute sensory neuropathy and around 80% in patients with dermatomyositis and polymyositis. In our series, 9% of patients over 50 years of age with neuropathy developed carcinoma. There are only a few studies considering the problem of the incidence of carcinoma in peripheral neuropathy (see table 4), particularly when they are devoted to one type of neuropathy as patients with tumour are often excluded from these studies. When combining their results with ours, 5% to 15% of patients with neuropathy seem to develop carcinoma. As expected, the highest incidence is found with sensory neuropathy. It is probably very low in Guillain-Barré syndrome and high (up to 15%) in vasculitic neuropathy. Due to a lack of studies, data are less clear with CIDP, but our results indicate an incidence of 10%. In patients with axonal polyneuropathy of otherwise unknown origin, only 4%–5% of patients develop cancer within the first years after the appearance of the neuropathy and an additional similar proportion with protracted follow up.

In conclusion, paraneoplastic neuropathies are heterogeneous disorders even in patients with anti-onconeural antibodies. In patients without antibodies, neuropathies which occurred within 2.5 years of carcinoma were probably paraneoplastic and corresponded mainly to inflammatory disorders whereas in neuropathies in which the cancer appeared after many years the association was probably coincidental. As dysimmune neuropathies are paraneoplastic in a limited number of cases, patients with these disorders should probably not be investigated systematically for carcinoma in the absence of anti-onconeural antibodies, except when the neuropathy is associated with encephalomyelitis and with vasculitis. Questions remain concerning CIDP.

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Armauer Gerhard Heinrik Hansen (1841-1912)

Armauer Hansen of Bergen, the leading authority of his time on leprosy, first identified the leprosy bacillus in Norway where the disease was endemic. Leprosy had been thought to be a hereditary affliction. Hansen concluded from epidemiological studies that it was infectious and that the rod shaped bacilli he observed (in 1873) were the cause of leprosy. His claim was not acknowledged for many years. Hansen never managed to fulfil the postulates of Robert Koch and transmit the disease to animals or men using the bacilli. This difficulty was also met with by later workers. Hansen was forced to resign from the Bergen Leprosy Hospital in 1880 after injudiciously injecting live leprosy bacilli into a patient without first obtaining her permission. Nevertheless, he carried on with his own research. By implementing a policy of limited isolation he succeeded in reducing the Norwegian incidence of leprosy from 2833 cases in 1850 to 140 in 1923. He was honoured philatelicly by France in 1973 on the centenary of the identification of the leprosy bacillus (Stanley Gibbons 2013, Scott 1379).

L F HAAS
Carcinoma associated paraneoplastic peripheral neuropathies in patients with and without anti-onconeural antibodies

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