A follow up study of patients with paraneoplastic neurological disease in the United Kingdom

P M Candler, P E Hart, M Barnett, R Weil, J H Rees

Objectives: To examine the range of clinical phenotypes, tumour associations, relevant investigations, response to therapy and outcome in a large series of non-selected patients with paraneoplastic neurological disease (PND) affecting the central nervous system (CNS) in the United Kingdom.

Methods: Data were obtained on patients either through direct referral or through the British Neurological Surveillance Unit (BNSU) from February 2000 to January 2001. Physicians were asked to supply information about age and sex of patients, presenting neurological syndromes, the basis of the diagnosis of PND, any associated malignancy, and treatment. Case notes were reviewed and follow up data obtained where possible one year after notification.

Results: A total of 63 patients (48 females, 15 males) were identified, 48 through the BNSU and 15 through direct referral. Of these 52 were diagnosed as having definite PND, 10 probable PND, and 1 possible PND. The median age of onset of PND was 66 years (range 30–80 years) and only 7 patients (11%) were less than 50 years at presentation. In 53 patients (84%) the PND preceded the diagnosis of cancer. Paraneoplastic sensory neuronopathy, paraneoplastic encephalomyelitis, and paraneoplastic cerebellar degeneration (PCD) were the most common syndromes reported. The benefit of magnetic resonance imaging in the diagnosis of the disease was limited, while fluorodeoxyglucose positron emission tomography was shown to be useful for the detection of an occult malignancy in 10 out of 14 patients. Antineuronal antibodies were positive in 44/57 (77%) of cases. The following tumours were diagnosed: small cell lung cancer (30%), breast cancer (14%), ovarian cancer (8%), non-small cell lung cancer (8%), Hodgkin's lymphoma (6%), other (16%). With the exception of PCD associated with mesothelioma all other tumours diagnosed in these patients had been previously documented as being associated with PND. Only treatment of the tumour was found to be associated with a stable or improved neurological outcome at last follow up (Fisher's exact test = 4.7, p<0.03). Median survival time was 43 months (95% CI 28 to 57) from onset of neurological disease as calculated using the Kaplan–Meier survival analysis.

Conclusions: PND has a striking female preponderance usually affecting patients in their sixth decade and above. The median survival in our study was 43 months. The majority of patients with PND are not known to have cancer at the time of diagnosis. Our study confirms the importance of diagnosing and treating the underlying tumour.

See end of article for authors' affiliations

Correspondence to:
Dr J H Rees, Room 724,
Institute of Neurology,
Queen Square, London,
WC1N 3BG; j.rees@ion.
ucl.ac.uk

Paraneoplastic neurological diseases (PND) are a rare group of syndromes that occur in patients with cancer and which are not due to the presence of metastases or direct infiltration of the tumour into the nervous system. They comprise a number of different clinicopathological entities such as paraneoplastic encephalomyelitis (PEM), paraneoplastic sensory neuronopathy (PSN), paraneoplastic cerebellar degeneration (PCD), and limbic encephalitis. PND are most commonly associated with small cell lung cancer (SCLC) and occur in about 3% of cases.[1] Other tumours associated with PND include breast and ovarian cancers and Hodgkin's disease.[2] In many cases the onset of neurological dysfunction occurs in a previously healthy patient and the diagnosis of PND directs the physician to the diagnosis of the underlying cancer.

Few studies have focused on patients presenting with PND before a cancer is diagnosed. The majority of reports consist of series of selected patients with specific cancers,[1] specific antineuronal antibodies,[3 4] or specific neurological syndromes[4–6] but information of a more general nature, particularly where there is an element of diagnostic uncertainty is not readily available.

We used a nationwide reporting scheme run by the British Neurological Surveillance Unit (BNSU) to collect data on patients who were referred by neurologists throughout the UK specifically in relation to PND affecting the central nervous system. We investigated the clinical spectrum of PND, the associated tumours and antineuronal antibodies, and the response of the PND to treatment of the underlying malignancy as well as to immunomodulatory treatment.

METHODS

Members of the Association of British Neurologists (435 consultant neurologists and neurophysiologists) were sent a monthly blue reporting card by the BNSU which they were asked to return if they had seen a patient with a suspected PND. Data collection was conducted between February 2000 and January 2001. Patients who had been referred directly to JHR were also included. Patients were deemed eligible for

Abbreviations: AUP, adenocarcinoma of unknown primary; BNSU, British Neurological Surveillance Unit; CI, confidence interval; CIDP, demyelinating polyradiculoneuropathy; CNS, central nervous system; FDG-PET, fluorodeoxyglucose positron emission tomography; GBS, Guillain-Barré syndrome; IVIg, Intravenous immunoglobulin; LEMS, Lambert-Eaton myasthenic syndrome; NSCLC, non-small cell lung cancer; PCD, paraneoplastic cerebellar degeneration; PEM, paraneoplastic encephalomyelitis; PSN, paraneoplastic sensory neuronopathy; PND, paraneoplastic neurological diseases; SCLC, small cell lung cancer

inclusion if they had a neurological disease in association with a known malignancy or recognised antineuronal antibodies in the absence of a tumour. One patient was included on the basis of the clinical phenotype alone. Further information obtained by means of a questionnaire included the patient's age and sex, the basis of the diagnosis, the nature of any associated malignancy, the use of treatments for either the PND or the tumour, and the outcome at one year or until latest follow up. Where possible, case notes were reviewed in order to glean further clinical information but this was at the discretion of the referring neurologist. Follow up data concerning the patient's neurological state were collected by writing to the referring neurologist, oncologist, or general practitioner as appropriate, one year after the reporting period. Follow up letters were sent in January 2002 and again in May 2002 to non-responders. Data collection was terminated in autumn 2002. Due to the method of data collection the period of follow up (from onset of neurological disease) varied for each patient. For some patients follow up data beyond the initial reporting were unavailable. The patients themselves were never contacted.

The study was approved by the local research ethics committee of the National Hospital for Neurology and Neurosurgery, London.

Statistical analysis

Neurological outcome was subdivided into fair (stabilised or improved) or poor (deteriorated or dead) for the purpose of statistical analysis. We used the χ^2 test or Fisher's exact test to determine the prognostic significance of a number of different factors on the outcome of the disease. These included age of onset, sex, neurological or oncological presentation, treatment of malignant disease (with or without immunomodulation), clinical phenotype (localised or multifocal neurological dysfunction), antineuronal antibody status, and the presence or absence of oligoclonal bands. Median survival times from the onset of neurological disease were calculated using the Kaplan–Meier survival analysis.

RESULTS

A total of 48 patients were reported by way of the BNSU. Fifteen patients were seen at the National Hospital or referred prior to the start of the BNSU scheme. Thus a total of 63 patients were studied (48 women (76%), 15 men (24%); female:male ratio 3.2:1). Even after excluding cases of breast and gynaecological cancer, the female:male ratio was 2.3:1. The median age at onset of neurological disease was 66 years (range 30–80) and was similar for both men (median 67 years, range 30–77) and women (median 66 years, range 39–80). Only 11 patients were <50 years old at time of diagnosis. In 53 patients (84%) the onset of neurological symptoms prompted investigation for an underlying tumour. The remaining 10 patients already had a history of malignant disease. Two other patients were initially reported as having PND but were subsequently excluded as the autopsies had shown chronic granulomatous meningitis and malignant meningitis. A summary of the clinical syndromes and associated tumours in the study is presented in table 1.

Clinical phenotype

The three largest groups of patients defined according to the predominant neurological syndrome were sensory neuronopathy, encephalomyelitis, and cerebellar degeneration (table 1). Three patients had opsoclonus-myoclonus and another three had a mixed picture consisting of cerebellar dysfunction and sensory neuronopathy. Two patients had limbic encephalitis and there were single reports of jerky stiff person syndrome, Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP),

Table 1 Clinical syndromes and associated tumours in the patients reported to the study

Syndrome/antibodies/tumour	N (%)
Neurological syndrome	
Sensory neuronopathy	22 (34.9)
Sensory neuropathy	20 (31.7)
Sensorimotor neuropathy	1 (1.6)
Sensory and autonomic neuropathy	1 (1.6)
Encephalomyelitis	15 (23.8)
Cerebellar degeneration	13 (20.6)
Cerebellar syndrome + sensory neuropathy	3 (4.8)
Opsoclonus-myoclonus	3 (4.8)
Limbic encephalitis	2 (3.2)
Miscellaneous	5 (7.9)
Antineuronal antibodies	
Tested	57 (90.4)
Positive	44 (77.0)
Tumour type	
Lung	24 (38.1)
Small cell lung cancer	19 (30.0)
Non-small cell lung cancer	5 (8.0)
Breast	9 (14.0)
Ovarian	5 (8.0)
Hodgkin's lymphoma	4 (6.0)
Adenocarcinoma of unknown primary	4 (6.3)
Miscellaneous	6 (9.5)

and Lambert-Eaton myasthenic syndrome (LEMS). One patient presented with parosmia as the only neurological symptom heralding the presence of an underlying ovarian malignancy. GBS, CIDP, and LEMS were included in the study to provide a complete representation of reported cases despite requesting reports of PND affecting only the central nervous system (CNS).

Investigations

Results of clinical investigations could only be ascertained when case notes were available for review as they could not be specifically requested in the questionnaire. These data are therefore incomplete.

Imaging

Magnetic resonance imaging (MRI) reports were available for 21 patients. Nine patients had normal brain scans. Three patients, all with limbic encephalitis as a component of their syndrome, had abnormal signal in the medial temporal lobes. One patient with encephalomyelitis had ''diffuse'' changes. Changes compatible with small vessel disease were seen in three patients, while the remaining scans had changes localised to the thalami, medulla, spinal cord, or periventricular spaces. In these patients there was no association between the neurological syndrome and the abnormalities seen on MRI. Only one patient with profound cerebellar degeneration had marked cerebellar atrophy and this was in the context of generalised cerebral atrophy. Whole body fluorodeoxyglucose positron emission tomography (FDG-PET) scans were obtained in 14 patients based on the presence of an antineuronal antibody in 12 patients (seven anti-Hu, three anti-Yo, one anti-Tr, one misc) and a high index of clinical suspicion in two patients. Ten patients (five anti-Hu, three anti-Yo, one anti-Tr, one misc), all with normal routine imaging (chest x ray, computed tomography (CT) scan of the thorax, abdomen, and pelvis, and abdominal ultrasound), had positive scans showing avid FDG uptake consistent with malignancy. Negative scans were obtained in the two antineuronal negative patients and two anti-Hu positive patients.

Table 2 Tumour associations in patients with positive serum antineuronal antibodies

	SCLC	NSCLC	Breast	Prostate	Ovarian	AUP	Endometrial	NE	HD	PLAS	MEL	NTF	Total
Hu	9	3	3	1								9	25
Yo		1	3		3	2	1					1	11
Tr						1			1				2
Amphiphysin			1										1
Misc	1	1	3										5
No antibody	5				2	1			2	1	1	1	13

AUP, adenocarcinoma of unknown primary; HD, Hodgkin's disease; MEL, melanoma; NE, neuroendocrine; NSCLC, non-small cell lung cancer; NTF, no tumour found; PLAS, plasmacytoma; SCLC, small cell lung cancer.

CSF results

The results of cerebrospinal fluid (CSF) analysis were reported for 24 patients and data on CSF oligoclonal bands were available for a further five patients. The protein concentration was elevated (>0.6 g/l) in 15 samples and the white cell count was raised (>5/mm^3) in seven. CSF oligoclonal bands were positive in 24 of the 29 patients for whom results were available. In 16 patients the bands were confined to the CSF and eight had a matched pattern in CSF and serum.

Routine blood tests and antineuronal antibodies

Results of routine blood tests were available for 29 patients of whom six had an elevated erythrocyte sedimentation rate (ESR), four had positive antinuclear antibodies, two had hyponatraemia due to syndrome of inappropriate antidiuretic hormone secretion (SIADH), two had antimitochondrial antibodies and one had a positive rheumatoid factor.

Results of antineuronal antibody screening were positive in 44 out of 57 patients (77%). Of these, 39 had known antibodies (25 anti-Hu, 11 anti-Yo, 2 anti-Tr and 1 anti-amphiphysin). Five further patients had antineuronal antibodies demonstrated by immunohistochemistry or Western blotting that did not recognise known antigens and were therefore classified as ''miscellaneous''. The tumour associations for each antibody are documented in table 2. Of particular note is that anti-Yo antibodies (usually associated with breast and gynaecological cancer) were found in one patient with non-small cell lung carcinoma (NSCLC) and two patients with adenocarcinoma of unknown primary (AUP) and that one patient with anti-Tr antibodies (always associated with Hodgkin's disease) had AUP.

Identification of underlying tumours and diagnosis of PND

Following the investigations 52 patients were classified as having a definite PND—that is, a neurological disorder occurring in association with an identified malignancy for which there was no other explanation. Of these 52 patients, 10 were known to have malignant disease before the onset of PND. The tumours in this group consisted of two small cell lung cancers (SCLC), three breast (one with concurrent colonic cancer), two ovarian, one prostate, one mesothelioma, and one endometrial carcinoma. In the remaining 42 patients the tumour was identified as a result of investigations for a suspected PND. Of these patients 22 were found to have lung cancer (17 SCLC, five NSCLC), six breast cancer, four AUP, four Hodgkin's lymphoma, three ovarian cancer, one melanoma, one malignant neuroendocrine tumour, and one plasmacytoma. A diagnosis of a probable PND was made in 10 patients with positive antineuronal antibodies (nine anti-Hu and one anti-Yo) in whom no tumour was found. FDG-PET scans were conducted in three of these patients. Two had normal scans and the third had an area of increased uptake but definite malignant disease could not be confirmed. One patient who presented with clinical features of limbic encephalitis and motor neuropathy was diagnosed as having a possible PND because the phenotype was compatible with a PND but no tumour (FDG-PET scanning was normal) or antineuronal antibody was identified and no post mortem was conducted after the patient died.

Treatment

Patients had various combinations of treatments for the underlying tumour with or without immunomodulation for the PND in the form of steroids, plasma exchange and/or intravenous immunoglobulin (IVIg). One patient died as a result of complications associated with chemotherapy. Of the 52 patients with a definite PND 37 received treatment for the underlying tumour. Of these, 10 received radiotherapy, 21 received surgery and 29 received chemotherapy as appropriate. Immunomodulatory therapy was also used in 21 of these patients—steroids in 15 patients, IVIg in 12 patients and plasma exchange in one patient. In the 10 patients with a probable PND six received steroids and five also had IVIg. The one patient with a possible PND received a course of IVIg.

Follow up and outcome

Follow up data of 59 patients (94%) were collected. Seventeen patients died and the median survival time from the onset of neurological symptoms was 43 months (95% CI 28 to 57) (fig 1). The median follow up for the surviving patients was 14 months (range 2–91). The neurological syndrome improved in 4 patients, stabilised in 18, and deteriorated in 20. Tumour dissemination occurred in two patients both of whom had SCLC. The mortality data for the three largest groups of patients with PSN, PEM, and PCD were considered separately. The median survival for patients with PSN was 64 months (95% CI 42 to 86). Four patients had died by the last follow up. The median survival for patients with PEM patients was 30 months (95% CI 21 to 40). Five patients had died by last follow up. The median survival for patients with PCD was 42 months (95% CI 32 to 52). Three patients had died by last follow up. The nine anti-Hu positive patients in whom no tumour was found had a median follow up of 16 months (range 5–54). One patient
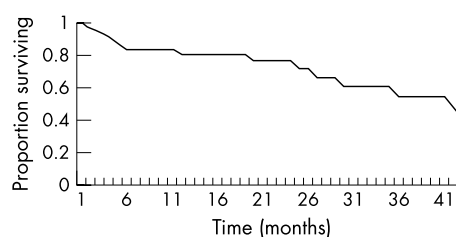

Figure 1 Kaplan–Meier survival curve for all 63 patients with PND. Median survival time was calculated as 43 months (95% CI 28 to 57).

died after 27 months but no autopsy had been conducted. The patients with follow up at 54 months remained neurologically stable and no tumour had been detected. The cause of death (oncological or neurological) was not determined for the individual cases.

Factors influencing the outcome of the neurological disease

We examined the influence of sex, age of onset, neurological or oncological presentation, clinical phenotype (unifocal or multifocal disease), treatment of the tumour (with or without immunomodulation), and the presence of antineuronal antibodies and oligoclonal bands on the outcome of the PND at the last follow up (table 3). Of these factors only treatment of the tumour was significantly associated with stabilisation or improvement of the neurological disease at the final follow up (Fisher's exact test, 4.7; p<0.03). Patients who received tumour therapy were 1.5 (95% CI 1.1 to 2.3) times more likely to have stable or improved neurological disease compared with those who were not treated.

DISCUSSION

To the best of our knowledge this is the largest reported series of unselected patients with PND affecting the CNS. We acknowledge that these data are unlikely to be a complete representation of all cases of PND seen within the UK since inclusion within the study was dependent upon active reporting by consulting neurologists. In addition, since oncologists were not consulted a number of patients may not have been identified especially when neurological signs were minimal. Furthermore, follow up information was incomplete, in particular, if the patient had been seen only once by the neurologist. With these caveats in mind this study has highlighted some findings that will be of interest to neurologists who encounter these rare diseases.

We demonstrated a large female preponderance that could not be accounted for by the association with breast and gynaecological tumours alone since the corrected ratio was still 2.3:1. This sex bias has not been described previously in selected patient groups. For example, Dalmau et al described a female:male ratio of 1.2:1 in their series of 71 anti-Hu positive patients.[4] In contrast Graus et al found a male predominance in 200 patients with PEM[7] and concluded that their findings differed from previous reports as a result of the varying demographics of SCLC in the European populations compared with the USA.

Patients with PND usually present over the age of 50 years. Only two patients were less than 40 years old at onset (one with breast cancer and a cerebellar syndrome, and one with melanoma and a sensory neuropathy). With the exception of parosmia, all the neurological syndromes have previously been described in association with malignant disease. As expected PEM, PSN, and PCD were the most frequent manifestations of PND. However, the rare occurrence of syndromes such as parosmia, GBS and CIDP suggests that a diagnosis of PND should be entertained in the absence of an obvious explanation.

In concordance with other studies SCLC was the commonest tumour, but our study has demonstrated that PND can occur in association with a wide range of malignancies. Of interest is the report of PCD in a patient with mesothelioma. We believe that this is the first time that this tumour has been reported in association with PND.

Standard blood testing and serological studies (with the exception of antineuronal antibodies) were frequently non-contributory. MRI changes were non-specific, except for cases of limbic encephalitis. In contrast, FDG-PET scanning was helpful in detecting malignant disease not seen with conventional imaging as has been previously reported from this institution.[8]

The utility of antineuronal antibodies in both diagnosis and directing the search for an underlying malignancy is well documented.[9–12] However, while most tumour associations were consistent with those described in the literature we found four unusual associations: one anti-Yo antibody associated with NSCLC and two with AUP and one anti-Tr antibody associated with AUP. The association of anti-Yo antibody with AUP has been previously reported[6 13] but is rare. The association of anti-Tr with AUP has not been previously described. In the case of anti-Hu positive patients the commonest tumour found was SCLC. However, in almost 40% of anti-Hu positive patients, no tumour was detected. The apparent absence of malignant disease is not inconsistent with a diagnosis of PND as on occasion the tumour may be too small to be found even by sensitive imaging techniques.[14 15] The unexpectedly high percentage of tumour negative anti-Hu patients in this study may be a consequence of limited autopsy or PET investigations in these patients.

In our study 83% of patients tested were positive for oligoclonal bands with the majority (66%) having evidence for intrathecal synthesis. Stourac et al[16] reported that five out of ten patients with PND had matched oligoclonal bands and that their presence was associated with a more severe neurological disability. We were unable to confirm this observation.

We found that tumour therapy with or without immuno-modulation was the only factor significantly associated with stabilisation of the neurological syndrome. This response of the neurological syndrome to tumour therapy has been documented in single case reports.[17–19] In a study of 50 patients with PCD, seven experienced an improvement in their neurological status following antitumour therapy, however, the observed effect was not statistically significant.[20] Similarly in 73 patients with PEM/PSN, antitumour therapy was associated with a higher, but not statistically significant, probability of experiencing a successful neurological outcome.[3] A recent study from two centres in Europe of patients with anti-Hu associated PEM found that tumour treatment was an independent predictor of stabilisation or improvement of the neurological disease.[7] While statistical

Table 3 Influence of various variables on stabilisation of the neurological disease

Factor	Stable at last follow up N (%)	p value
Sex		
Male	6 (43)	
Female	17 (38)	0.73
Age of onset		
≤60 years	7 (44)	
>60 years	16 (37)	0.65
Presentation		
Tumour	1 (14)	
Neurology	22 (42)	0.23†
Clinical phenotype		
Unifocal	15 (40)	
Multifocal	8 (38)	1.00†
Tumour treatment		
Yes	18 (50)	
No	5 (21)	0.03*
Antineuronal antibody status		
+ve	18 (44)	
−ve	3 (27)	0.49†
Oligoclonal bands		
+ve	9 (38)	
−ve	3 (60)	0.62†

*p<0.05.
†p value calculated using Fisher's exact test.

significance is not always achieved there is a trend to suggest that treatment of the tumour may prevent further deterioration of the PND and on occasion produce dramatic recovery. In the light of the ''aberrant expression hypothesis'' it is tempting to speculate that removal of the antigenic stimulus by treatment of the tumour results in the cessation or reduction of the damaging immune mediated response against the CNS. However, since many treatments do not selectively target tumour cells it is difficult to ascertain if the beneficial effects are due to antigen removal or are a result of a global immunosuppression that occurs with cancer therapy. Our findings add weight to the importance of early identification of an underlying tumour in order to prevent irreversible neuronal loss.

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Authors' affiliations
P M Candler, P E Hart, M Barnett, R Weil, Institute of Neurology and National Hospital for Neurology and Neurosurgery, London
J H Rees, Department of Molecular Sciences, Institute of Neurology and National Hospital for Neurology and Neurosurgery, London

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