ORIGINAL CONTRIBUTION

# Paraneoplastic Neurologic Syndrome in the PNS Euronetwork Database

## *A European Study From 20 Centers*

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**Background:** Paraneoplastic neurologic syndrome (PNS) represents the remote effects of cancer on the nervous system. Diagnostic criteria for the syndrome were published by the PNS Euronetwork and form the basis of a database to collect standardized clinical data from patients with PNS.

**Objectives:** To analyze various types of PNS, frequent tumor and antibody associations, clinical characteristics of individual syndromes, and possible therapeutic and prognostic strategies.

**Design:** Prospective case series and database study.

**Setting:** Twenty European centers.

**Patients:** Patients were recruited from January 1, 2000, to December 31, 2008.

**Main Outcome Measures:** Based on diagnostic criteria published by the PNS Euronetwork consortium, clinical characteristics of classic PNS and several other less well-characterized syndromes associated with cancer were assessed.

**Results:** Data from 979 patients were analyzed, representing the largest PNS investigation to date. The findings elucidate the clinical evolution of paraneoplastic cerebellar syndrome according to the onconeural antibodies present, the heterogeneity and prognosis of dysautonomic disorders, and the clinical variability of paraneoplastic limbic encephalitis.

**Conclusion:** The study results confirm that PNS influences oncologic patient survival. Tumors are the main cause of death, but some types of PNS (such as dysautonomia) have a poorer prognosis than malignant neoplasms.

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PARANEOPLASTIC NEUROLOGIC syndrome (PNS) can affect any part of the nervous system.[1,2] Such syndromes usually occur as the first sign of a tumor or lead to its detection. Rarely, they are seen in the course of an oncologic disease. Survival is usually influenced by the oncologic disease, but PNS can cause severe disability and may be fatal. The lack of extensive clinical and epidemiologic studies on these rare disorders prompted establishment of the PNS Euronetwork by 20 consortium members from 11 European countries. Between January 1, 2000, and December 31, 2008, the partnership collected information on 979 patients, resulting in the largest database on PNS to date.

The database was constructed based on consensus guidelines by Graus et al[3] for the diagnosis of PNS (hereinafter, the Graus criteria). Data quality assessment was performed continuously, and structured group meetings were held to assess data quality, exchange results, and discuss recent developments. Because this was a prospective study with defined inclusion criteria, new developments such as the association of surface antibodies with PNS[4] were excluded.

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**Group Information:** The PNS Euronetwork Study Group members are listed on page 334.

## METHODS

This PNS Euronetwork study was a longitudinal, nonconcurrent, prospective observational analysis, which does not permit epidemiologic inferences about the overall frequency of PNS.

All participating centers enrolled their patients according to the Graus criteria between January 1, 2000, and December 31, 2008. The patients were followed up throughout the course of their disease and were recorded at the end of the study period as being alive, dead, or lost to follow-up.

The database was organized in the following 6 main areas: (1) basic patient data, including clinical syndrome and time of symptom onset and diagnosis; (2) laboratory data, including serum and cerebrospinal fluid antibodies and their detection methods; (3) treatment of the neurologic disease and cancer therapy; (4) diagnostic tests, including cerebrospinal fluid analysis, nerve conduction velocities, electromyography, and computed to-

mography and magnetic resonance imaging (brain and spinal); (5) list of the main types of PNS-related tumors; and (6) cause of death and the availability of autopsy material.

The types of PNS included in the database were the classic syndromes reported by Graus et al[3] and several other less well-characterized syndromes associated with cancer. Paraproteinemic neuropathies and myasthenia with thymoma were excluded. A subgroup of "other PNS" was created to include potentially new syndromes.

At each center, a trained neurologist was responsible for data collection. Data were centrally reviewed, and all generated queries were processed at an independent statistical and quality assessment center (Mario Negri Institute of Pharmacological Research, Milan, Italy). The structure of the database was maintained throughout the study, and no modifications were permitted. This guaranteed uniform comparable data but prevented the addition of new diagnostic criteria such as recently detected antibodies associated with PNS.

The clinical characteristics of the individual syndromes were recorded, permitting a descriptive analysis of clinical findings. This allowed a cumulative analysis of clinical symptoms and signs among many rarely occurring entities.

In addition, the database investigated onconeural antibodies (Hu, Yo, Ri, CV2/CRMP5, Ma2, amphiphysin, and Tr) and other relevant antibodies (VGCC, GAD, VGKC, atypical, and others) in serum and often in cerebrospinal fluid. Techniques used to detect these antibodies varied according to the different laboratories but were essentially based on immunohistochemistry, Western blotting, and the use of recombinant onconeural proteins. Radioimmunoassay was used for VGCC and VGKC antibodies. The methods used by each center were reported in the database. When a single center identified an onconeural reactivity, the findings were confirmed by another laboratory to maintain the integrity of the results.

For statistical analysis, proportion was used as a descriptive statistic for categorical and ordinal variables, the median and interquartile range for ordinal and continuous variables, and the mean (SD) for continuous variables.

Survival curves were computed using the Kaplan-Meier method and were compared using the log-rank test. Patients lost to follow-up or alive at the time of study analysis were right censored at the date of their last visit. Analyses were performed using commercially available statistical software (SAS, version 9.1; SAS Institute, Cary, North Carolina).

## RESULTS

A total of 979 patients were included in the database. Diagnoses were according to the Graus criteria. Almost all patients (n=968) had definite PNS, and 11 patients had possible PNS. In 65% of patients, the neurologic syndrome preceded tumor detection.

Although PNS is believed to affect several systems and to cause multifocal disorders, a single PNS was identified in 885 patients (90.4%). The most frequent entities were paraneoplastic cerebellar degeneration (PCD) and sensory neuronopathy (SN). Limbic encephalitis constituted another major entity, followed by paraneoplastic encephalomyelitis and brainstem encephalitis. The frequencies of other types of PNS are listed in **Table 1**.

A multifocal PNS was found in 94 patients (9.6%). After excluding patients with paraneoplastic encephalomyelitis and Hu antibodies, several patients with limbic encephalitis still showed involvement of other areas. The most frequent combinations were limbic encephalitis associated with dysautonomia (8 patients), with PCD (6 patients), and with Lambert-Eaton myasthenic syndrome (5 patients). None of these patients had Hu antibodies.

**Table 1. Paraneoplastic Neurologic Syndrome (PNS) in the PNS Euronetwork Database**

| Type of PNS | Patients, No. (%)[a] (N=979) |
|---|---|
| Central nervous system | |
| Cerebellar degeneration | 238 (24.3) |
| Limbic encephalitis | 98 (10.0) |
| Paraneoplastic encephalomyelitis | 55 (5.6) |
| Brainstem encephalitis | 55 (5.6) |
| Opsoclonus or myoclonus | 23 (2.3) |
| Motor neuron disease | 20 (2.0) |
| Necrotic myelopathy | 3 (0.3) |
| Stiff person syndrome | 6 (0.6) |
| Peripheral nervous system | |
| Sensory neuronopathy | 238 (24.3) |
| Acute inflammatory polyradiculopathy | 16 (1.6) |
| Chronic inflammatory polyradiculopathy | 13 (1.3) |
| Dysautonomia | 51 (5.2) |
| Mononeuritis neuropathy | 6 (0.6) |
| Lambert-Eaton myasthenic syndrome | 43 (4.4) |
| Neuromyotonia | 10 (1.0) |
| Muscle | |
| Dermatomyositis or polymyositis | 14 (1.4) |
| Necrotic myopathy | 2 (0.2) |
| Other | |
| Central nervous system | 60 (6.1) |
| Peripheral nervous system included | 117 (12.0) |
| End-plate disorder | 23 (2.3) |
| Cancer-associated retinopathy | 4 (0.4) |

[a] The data do not sum to 979 because many cases had more than 1 syndrome.

### CLINICAL PROFILE OF SYNDROMES

In 238 patients with PCD, the most frequent findings were subacute onset of moderate (76.1%) or severe (80.0%) ataxia with truncal (74.8%) or limb (82.4%) involvement. Dysarthria (67.6%) and nystagmus (62.2%) were less commonly observed. Rankin scale analysis showed that patients with PCD and Yo antibodies had greater disability than patients with PCD and Hu or Tr antibodies (**Table 2**).

Ninety-eight patients had limbic encephalitis, and symptoms involving other areas of the central nervous system were reported in 49 patients. Psychiatric symptoms (55.5%) and seizures (48.0%) were present in half of these patients, and limbic involvement was detected on routine magnetic resonance imaging in 57.1%.

Paraneoplastic encephalomyelitis was observed in 55 patients, among whom the cerebellum was the most frequent site of involvement (55.6%), followed by the limbic system (42.6%), brainstem (46.3%), and dorsal root ganglia (37.0%). Chronic pseudoobstruction was observed in 11.1%.

Motor neuron diseases occurred in 20 patients. Paraneoplastic stiff person syndrome was characterized by rigidity of limbic muscles in 6 patients and of axial muscles in 3 patients.

**Table 2. Rankin Scale Score According to Detected Onconeural Antibodies Among 238 Patients With Paraneoplastic Cerebellar Degeneration**

| Rankin Scale Score[a] | % | | |
|---|---|---|---|
| | Yo | Hu | Tr |
| At diagnosis | | | |
| 1-3 | 39.5 | 60.0 | 62.5 |
| 4-5 | 50.9 | 20.0 | 37.5 |
| Unknown | 9.5 | 20.0 | . . . |
| Final | | | |
| 1-3 | 12.7 | 46.6 | 62.5 |
| 4-5 | 61.9 | 33.3 | 37.5 |
| Unknown | 25.4 | 20.0 | . . . |

Abbreviation: ellipses, not applicable.
[a]Scores of 1 to 3 represent less disability, and scores of 4 to 5 represent greater disability.

**Table 3. Onconeural Antibody Profile in the PNS Euronetwork Database**

| Antibody | Patients, No. (%)[a] (N=979) |
|---|---|
| Hu | 380 (38.8) |
| Yo | 131 (13.4) |
| Ri | 50 (5.1) |
| CV2 | 59 (6.0) |
| Tr | 17 (1.7) |
| Amphiphysin | 33 (3.4) |
| Ma or Ta | 44 (4.5) |
| VGCC | 39 (4.0) |
| VGKC | 10 (1.0) |
| Atypical | 30 (3.1) |
| Other | 67 (6.8) |
| None | 179 (18.3) |
| Unknown | 14 (1.4) |

Abbreviation: PNS, paraneoplastic syndrome.
[a]The data do not sum to 979 because many cases had more than 1 antibody.

A total of 238 patients with SN were initially seen with subacute onset (79.8%) and with asymmetric involvement of the extremities (60.7%). Other frequent findings were joint position alterations (77.5%) and abolished sensory potentials in nerve conduction velocities (75.7%). Dysautonomia was present in 22.5% of patients.

One hundred seventeen patients with features of an SN also had distal motor involvement. We called this sensorimotor neuronopathy. It is unknown whether additional motor involvement in some patients could be "motor neuronopathy" affecting the anterior horn cells or distal axonal neuropathy.

Among the cohort, end-plate disorders manifested as Lambert-Eaton myasthenic syndrome in 43 patients (4.4%) and as neuromyotonia in 10 patients (1.0%).

Dysautonomia was diagnosed in 51 patients, 14 with isolated intestinal pseudoobstruction and 37 with SN, limbic, or brainstem encephalitis. Autoimmune neuropathies of the chronic inflammatory demyelinating polyneuropathy and Guillain-Barré syndrome were found in 3.0% of patients, which makes a chance association likely. Muscle involvement was found in 16 patients. Fourteen patients had dermatomyositis. There were no reported cases of poliomyositis. Two patients had necrotizing myopathy, which may be a subtype of dermatomyositis or poliomyositis. Cancer cachexia and muscle atrophy were not evaluated in this study.

Several types of PNS that did not fit into our classic syndromes were heterogeneous. However, this group did not lend itself to further analysis except for patients with extrapyramidal disorders. Fifteen patients had extrapyramidal movement disorders associated with cancer, the most frequent being chorea (n=11). Finding 2 patients with Parkinson disease (one with progressive supranuclear palsy and the other with dystonia) might again be a chance association.

## ONCONEURAL ANTIBODY PROFILE

The onconeural antibody profile (**Table 3**) confirmed Hu as the most frequent antibody (38.8%), followed by Yo (13.4%). All other antibodies had frequencies below 10.0%. The antibody types were within the spectrum for onconeural antibodies and in association with PNS have significant diagnostic value for an underlying cancer. The atypical antibodies had a frequency of 3.1%, but no consistent pattern was found.

Surface antibodies such as VGKC were identified in few patients and were searched for only in the latter part of the study after their description in the literature.[5] N-methyl-D-aspartate receptor antibodies were not included in the panel, as they were only recently discovered.[6]

The "other" group includes antibodies such as GAD and GM1, which are related to autoimmune syndromes but not necessarily to PNS.

Despite having definite PNS, 18.3% of patients harbored no onconeural antibodies. This finding of clinical manifestation of PNS in the absence of antibody reactivity is a significant finding.

## TUMOR PROFILE

Among the cohort, 1 tumor was found in 802 patients, 2 tumors in 53 patients, and 0 tumors in 124 patients. Tumors may subsequently develop in patients without neoplasms. For 899 patients with available data, the tumor types are listed in **Table 4**, which confirms small cell lung cancer, ovary, breast, and non–small cell lung cancer as the malignant neoplasms most frequently associated with PNS, accounting for 66.5% of cancers in our series. The tumor diagnosis was histologically definite in 86.0% of patients. Hematologic diseases were much less prevalent than solid tumors, with PNS occurring in association with lymphomas in 58 patients (31 with non-Hodgkin lymphoma and 27 with Hodgkin lymphoma).

Among patients in whom tumor stage at the time of detection was available, the disease was local in 262 patients, regional in 360 patients, and metastatic in 150 patients. This confirms that PNS most frequently manifests in cancers with limited disease spread.

**Table 4. Tumor Types in the PNS Euronetwork Database**

| Tumor Type | Patients, No. (%) (n=899) |
|---|---|
| Small cell lung cancer | 345 (38.4) |
| Ovary | 94 (10.5) |
| Breast | 87 (9.7) |
| Non–small cell lung cancer | 71 (7.9) |
| Non-Hodgkin lymphoma | 31 (3.4) |
| Hodgkin lymphoma | 27 (3.0) |
| Thymoma | 24 (2.7) |
| Prostate | 23 (2.6) |
| Metastasis from unknown primary | 18 (2.0) |
| Colorectal | 16 (1.8) |
| Esophagus or gastric | 16 (1.8) |
| Testicular | 15 (1.7) |
| Kidney or bladder | 11 (1.2) |
| Neuroblastoma | 7 (0.8) |
| Merkel carcinoma | 6 (0.7) |
| Melanoma | 4 (0.4) |
| Other | 104 (11.6) |

Abbreviation: PNS, paraneoplastic syndrome.

## THERAPEUTIC OPTIONS

Corticosteroids were the most frequently used immunomodulatory drugs (33.4%), followed by high-dose immunoglobulins (22.9%), plasma exchange (7.2%), and immunosuppression (6.4%). Chemotherapy was the most frequent therapeutic option (51.2%), followed by surgery (30.0%) and radiation therapy (23.7%) (**Table 5**).

The database did not record symptomatic treatments, including anticonvulsants in neuromyotonia, 3,4-diaminopyridine in Lambert-Eaton myasthenic syndrome, treatment of neuropathic pain in SN, and nonspecific treatments such as physiotherapy and coordination training that comprise individual patient support.

**Table 5. Treatment of Paraneoplastic Neurologic Syndrome (PNS) and Tumors**

| Treatment | Patients, No. (%) (N=979) |
|---|---|
| PNS | |
| Corticosteroids | 327 (33.4) |
| High-dose immunoglobulins | 224 (22.9) |
| Plasma exchange | 70 (7.2) |
| Immunosuppression | 63 (6.4) |
| Tumor | |
| Chemotherapy | 501 (51.2) |
| Surgery | 294 (30.0) |
| Radiation therapy | 232 (23.7) |

**Table 6. Causes of Death Among 403 Patients With Paraneoplastic Neurologic Syndrome (PNS)**

| Cause of Death | Patients, No. (%) |
|---|---|
| Total | (n=403) |
| PNS | 109 (27.0) |
| Tumor progression | 150 (37.2) |
| Other | 59 (14.6) |
| Unknown | 85 (21.1) |
| Patients with dysautonomia | (n=32) |
| PNS | 18 (56.3) |
| Tumor progression | 6 (18.8) |
| Other | 4 (12.5) |
| Unknown | 4 (12.5) |

## OUTCOMES OF PATIENTS WITH PNS AND CAUSES OF DEATH

Outcome status was available in 403 patients (41.2%), of whom 109 had died of PNS, 150 of tumor progression, 59 of other causes, and 85 of unknown cause. A notable finding was the poor prognosis of patients with dysautonomia: a tumor was found in 37 of 51 patients (mostly small cell lung cancer), and the diagnosis in 28 patients followed manifestation of the neurologic syndrome after a median of 4.6 months. Only 4 of 36 patients improved after tumor treatment. Thirty-two patients died, including 18 of PNS, 6 of tumor progression, 4 of other causes, and 4 of unknown cause (**Table 6**).

## COMMENT

This is the largest systematic series of patients with PNS to date. Although the database was not designed for epidemiologic studies, we believe that our data represent the prevalence of each syndrome. The relative distribution of disorders confirms cerebellar degeneration and SN as the most frequently appearing types of PNS. An additional large number of SNs had significant motor involvement, called sensorimotor neuronopathy. If less well-characterized neuropathies are included, the peripheral nerves are the predominant target of paraneoplastic attack,[7] whereas muscle tissue is rarely involved.[8]

The clinical profile of collected syndromes in our study confirms the results of previous studies[9-14] but is based on a much larger case series.

The clinical course of patients with PCD and Yo antibodies was more severe than that of patients with PCD and other antibodies. At the time of PCD diagnosis, more than 50% of patients with Yo antibodies were unable to walk and had greater disability than patients with other autoantibodies. Although similar results have been described in patients with Tr antibodies,[15] this is a relevant prognostic finding.

Limbic encephalitis was associated with other syndromes in 49 patients. The spectrum of causes of limbic encephalitis has increased since the description of surface antibodies such as VGKC and NMDAR. The impression is that VGCK rarely causes paraneoplastic limbic encephalitis, although it has been associated with dysautonomia.[4,5,7-16] The number of patients with NMDAR is unclear.[4,6] Therefore, the clinical heterogeneity of limbic encephalitis in our series could relate to the antibody heterogeneity of limbic encephalitis and the presence of surface antibodies that were not included in our database.

Several patients had brainstem encephalitis, and a detailed analysis of 14 of these patients has recently been published.[17] The major clinical point of the study was the involvement of respiration, including respiratory arrest, in that manifestation of PNS.

Dysautonomic PNS is underdiagnosed because it develops in the setting of at least 1 other PNS, which may dominate the presentation and mask the autonomic features. The follow-up of patients with paraneoplastic dysautonomia herein showed poor prognosis. These patients did not improve with immunotherapy after tumor treatment and exhibited the highest incidence of PNS-related death.

The group of "other" associated disorders deserves separate analysis, as these could represent newly identified types of PNS. A substantial proportion of patients had chorea associated with their tumor, suggesting that this disorder could be considered a type of PNS.[18]

The analysis of peripheral neuropathies demonstrated that other subtypes (in addition to SN) may be paraneoplastic.[7] The frequent finding of sensorimotor neuronopathy should result in an addition to our current classification system of PNS.

Most patients in the database had onconeural antibodies, confirming that the diagnosis of PNS relies on detection of these serologic markers. The onconeural antibody profile reflects previous data in the literature demonstrating that Hu and Yo are the most prevalent onconeural antibodies.[9-14] The VGCC and VGKC surface antibodies were included in the onconeural antibody profile but were identified in few patients with PNS. Discovery of the NMDAR antibodies[6] occurred in the final stages of the present study, and their role in the onconeural antibody profile cannot be commented on.

An important clinical finding is that failure to detect onconeural antibodies (among 18.3% of patients in our series) does not rule out a paraneoplastic cause or an underlying tumor. It is unknown why no antibodies were found in many of our patients and could be related to unidentified antibodies or to the presence of surface antibodies. This finding highlights the importance of the Graus criterion that PNS may be diagnosed in the absence of a malignant neoplasm or onconeural antibodies when the patient profile fulfills the other criteria for classic PNS.

The distribution of tumors confirms the lung, ovary, and breast as the most frequent sites of neoplasms in PNS. Infrequently, other tumors such as of the prostate, thymus, and testis were observed. Most tumors were detected in patients with limited disease spread, which may support the concept that PNS exerts a protective effect on the host. The hematologic diseases such as lymphoma and Hodgkin disease rarely manifested as PNS.

Based on the assumption that PNS represents immune-mediated disorders, several therapies were used, including corticosteroids, high-dose immunoglobulins, and plasma exchange. The preferred treatment in the cohort was intravenous immunoglobulin,[19,20] probably because of easy availability. Our findings reflects treatment decision trends.[21] Once a tumor was confirmed in association with PNS, the principal treatments were chemotherapy, surgery, and radiation therapy.[22,23] Although specific tumor therapy depends on oncologic requirements, it remains unclear whether tumor treatment and concomitant immunosuppression (often rendered by chemotherapy) are effective against PNS.

The present study confirms that PNS influences oncologic patient survival.[24] Tumors remain the primary cause of death, but some PNS syndromes (such as dysautonomia) have a poorer prognosis than malignant neoplasms.

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## *Announcements*

**New Initiatives: Clinical Trials and Videos.** We have embarked on 2 new initiatives: Clinical Trials and video presentations. We welcome manuscripts that describe double-blind, randomized, placebo-controlled clinical trials as our primary area of interest. We plan on expediting the review process and time to publication and to include them online ahead of print as these studies are time sensitive and of direct benefit to our patients. We hope you will take advantage of this new initiative. Please refer to the Instructions for Authors when submitting a Clinical Trials paper, including the requirement to register the trial with an accepted clinical trials site.

We plan to utilize videos as part of published papers that highlight and provide convincing information about the observational and visual features of a patient's neurologic findings. Please refer to Instructions for Authors for instructions on submitting video presentations.