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"Non-classical" paraneoplastic neurological syndromes associated with well-characterized antineuronal antibodies as compared to "classical" syndromes — More frequent than expected

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ABSTRACT

Objectives: Paraneoplastic neurological syndromes (PNSs) are rare disorders in association with cancer and sub-divided into "classical" and "non-classical" syndromes according to a 2004 consensus paper proposed by a panel of PNS experts. "Classical" PNSs are regarded to account for the vast majority of cases. However, systematic reports on clinical PNS manifestations are rare. Therefore, we analyzed the spectrum of PNS in our clinic.
Methods: We retrospectively investigated medical records from consecutive patients diagnosed with definite PNS and serological evidence of well-characterized onconeural antibodies (anti-Hu, Yo, Ri, CV2/CRMP5, Ma1, Ma2, and amphiphysin) analyzed between 1991 and 2014 in our clinic.
Results: Of the 50 patients identified with onconeural antibody-positive PNS, 28 patients (56.0%) had "classical" PNS, and 22 (44.0%) "non-classical" PNS. Subacute cerebellar degeneration was the most frequent "classical" syndrome, brainstem encephalitis and subacute sensorimotor neuronopathy the most frequent "non-classical" syndromes. Anti-Hu antibodies were most frequent in both groups. 86.1% of patients developed neurological symptoms before the cancer was known. No differences between "classical" and "non-classical" syndromes were detected with respect to age, tumor entities and median time to diagnosis. However, whereas most patients with "classical" syndromes were females, there was no gender predominance in patients with "non-classical" PNS and the latter had significantly more frequent peripheral neurological syndromes.
Conclusions: The so-called "non-classical" PNSs in association with well-characterized onconeural antibodies were more common in our patient population than expected. Therefore, in neurological disorders of unclear etiology with a subacute onset and atypical presentation further diagnostic work-up including investigation of onconeural antibodies is necessary.

1. Introduction

Paraneoplastic neurological syndromes (PNSs) are rare disorders occurring in about 0.01% of all cancer patients [1]. Typically, antineuronal antibodies are directed against ectopic antigens expressed by tumor cells. The so-called "well-characterized" onconeural antibodies (anti-Hu, Yo, Ri, CV2/CRMP5, Ma1, Ma2, and amphiphysin) served to establish the associated neurological disorders as definite PNS [2]. According to consensus criteria based on the recommendations of an international panel of PNS experts "classical" PNSs have to be distinguished from "non-classical" PNSs [2]. "Classical" PNSs are characterized by subacute symptom onset, frequent association with cancer as well as typical clinical presentation and comprise disorders of the central and peripheral nervous systems (Table 1) [2]. Due to their typical clinical presentation, "classical" PNS are generally well recognized by neurologists. By contrast, the term "non-classical" PNS applies to distinct paraneoplastic neurological syndromes listed in Table 1. Since these syndromes have a highly diverse clinical presentation that resembles that of "non-paraneoplastic" disease, correct diagnosis in this subgroup of PNS patients is easily missed and crucial diagnostic work-up including a prompt tumor screening might be delayed [3]. Diagnostic criteria indicative of a paraneoplastic etiology, after exclusion of other differential diagnoses, are a subacute manifestation with symptoms evolving within a few days to weeks, a temporal association with a malignoma (i.e. cancer develops within 5 years of PNS diagnosis) and either the presence of well-characterized onconeural antibodies or, in their absence, improvement after tumor therapy [2].

Studies on the prevalence of PNS are rare [4,5]. A large European multicenter study on 979 patients identified "classical" syndromes in the majority of cases, accounting for 78% of PNS patients, whereas only 22% had "non-classical" PNS [6]. However, our experience from clinical practice suggests that "non-classical" PNS might be more frequent than generally assumed.

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Table 1
"Classical" and "non-classical" paraneoplastic neurological syndromes (modified from [2]). Syndromes of the neuromuscular junction muscle and with antibodies against neuronal surface antigens are excluded.

Syndromes of the central nervous system	Syndromes of the peripheral nervous system
"Classical" syndromes	
Encephalomyelitis	Subacute sensory neuropathy
Limbic encephalitis	Chronic gastrointestinal pseudo-obstruction
Subacute cerebellar degeneration	
Opsoclonus-myoclonus syndrome	
"Non-classical" syndromes	
Brainstem encephalitis	Acute sensorimotor neuropathy
Stiff person syndrome	Acute and chronic polyradiculitis
Optic neuritis	Acute pandysautonomia
Cancer associated retinopathy	Brachial neuritis
Necrotizing myelopathy	
Myelitis	
Motor neuron diseases	
Extrapyramidal disease/chorea	

Therefore, we aimed to identify the demographic, clinical and immunological profile of patients with PNS associated with well-characterized onconeural antibodies against intracellular neuronal antigens in a tertiary care university hospital in southwest Germany with particular focus on the comparison between "classical" and "non-classical" syndromes. Syndromes of the neuromuscular junction and muscle as well as patients with PNS or autoimmune encephalitis in association with antibodies against neuronal surface antigens were not included in this study.

2. Patients and methods

We retrospectively investigated medical records from consecutive patients with definite PNS whose sera were analyzed in the laboratory of the Department of Neurology of the University Hospital Freiburg (Germany) between 1991 and 2014. In a stepwise manner onconeural antibody testing identified PNS candidates whose medical records were then investigated for occurrence of "classical" or "non-classical" PNSs according to recommendations of an international panel of PNS experts [2]. According to these guidelines "classical" PNSs are characterized by subacute symptom onset, frequent association with cancer as well as typical clinical presentation. They comprise disorders summarized in Table 1. By contrast, the term "non-classical" PNS applies to distinct paraneoplastic neurological syndromes for which diagnostic criteria were not well defined despite the presence of cancer and onconeural antibodies in some cases (Table 1). In addition, the clinical presentation of "non-classical" PNS often resembles that of other neurological disorders of "non-paraneoplastic" origin.

Only patients with serological evidence of well-characterized onconeural antibodies and PNS diagnosis according accepted criteria [2] were included and underwent further retrospective analysis. For reasons of consistency, we included only cases in which antibody testing was performed with a commercial immunoblot (Ravo Diagnostika, Freiburg, Germany) using highly purified recombinant antigens (HuD, Yo, Ri, CV2/CRMP5, Ma1, Ma2, and amphiphysin). This test was established as standard procedure in our laboratory since 2005. Since some PNS patients were diagnosed prior to 2005 when the commercial immunoblot used in this study was not yet established, we reassessed their serum that had been stored at −80 °C, in order to have the same detection method applied to all patient samples and to avoid inter-assay variations. The immunoblot was performed according to the manufacturer's guidelines. Demographic and clinical data, antibody results, and routine cerebrospinal fluid (CSF) laboratory findings were obtained from clinical records.

Fisher's exact test for nominal data and the two-tailed Mann–Whitney test for continuous variables, respectively, were used for statistical analyses. A p-value of <0.05 was regarded as statistically significant.

The local ethics committee of the Albert-Ludwigs-University Freiburg (Germany) approved the study.

3. Results

From 1991 to 2014, 92 in- and outpatients with definite PNS were identified. Sufficient clinical data and samples from our blood serum bank for retrospective antibody reassessment with immunoblot were available from 50 patients (20 males, 30 females; mean age at PNS ?thyc=5?> onset: 61.3 years [range 17–81 years, standard deviation (SD) = 14.0]). Twenty-eight patients (56.0%) had "classical" PNS, and 22 (44.0%) "non-classical" PNS. All patients initially presented with a monosyndromal manifestation, 9 developed a second PNS during the further course of the disease. Subacute cerebellar degeneration (22.0%), limbic encephalitis and encephalomyelitis (14.0% each) were the most frequent "classical" syndromes, whereas brainstem encephalitis (16.0%), subacute sensorimotor neuronopathy (14.0%) and chronic polyradiculitis (12.0%) were the most frequent "non-classical" syndromes. Table 2 shows the frequency of different PNS and their associated paraneoplastic antibodies. Nine patients (18.0%) harbored more than one onconeural antibody. Overall, anti-Hu antibodies hold the majority (n = 28), followed by anti-CV2/CRMP5 (n = 15), anti-Yo (n = 7), anti-Ri (n = 6), anti-amphiphysin (n = 5), anti-Ma2 (n = 2), and anti-Ma1 (n = 1).

Results from CSF analysis were available in 40 patients (80.0%), whereas the remaining had their lumbar puncture done in other (e.g. referring) hospitals and therefore detailed CSF data was not available. CSF was altered in 85.0% of patients with available data: White blood cell (WBC) count was elevated in 40.0% (median 3/μL, range 1–112, SD = 20.8), protein in 72.5% (median 644 mg/L, range 160–2270, SD = 537.9), and 50.0% had an intrathecal immunoglobulin production defined as positive oligoclonal bands restricted to or predominant in CSF compared to the corresponding serum and/or increased intrathecal immunoglobulin fractions of the IgG, IgA and/or IgM type (Table 4). In most cases positive oligoclonal bands were associated with central PNS (data not shown). However, this result was not significant (p = 0.560).

Frequency of proven cancer was 72.0% with a vast majority of bronchial carcinoma (61.1%). The remaining patients without a tumor in first

Table 2
Frequency of paraneoplastic neurological syndromes (PNS) and their association with well-characterized onconeural antibodies.

Syndrome	n (%)	Hu	Ri	Yo	CV2	Ma1	Ma2	Amphiphysin
Peripheral PNS								
Subacute sensory motor neuronopathy	7 (14.0)	5	–	–	2	–	–	–
Subacute sensory neuronopathy	6 (12.0)	2	–	1	1	–	1	1
Chronic polyradiculitis	6 (12.0)	4	–	–	4	1	–	–
Central PNS								
Subacute cerebellar degeneration	11 (22.0)	3	–	5	3	–	–	2
Brainstem encephalitis	8 (14.0)	4	2	–	1	–	1	1
Limbic encephalitis	7 (14.0)	5	1	1	1	–	–	–
Encephalomyelitis	7 (14.0)	5	2	–	3	–	–	1
Extrapyramidal disease/Chorea	1 (2.0)	–	1	–	–	–	–	–
Total antibody frequency		28	6	7	15	1	2	5

"Classical" syndromes are italicized.