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Diagnosis and Treatment of Paraneoplastic Neurological Disorders

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Key Words
Paraneoplastic syndromes · Neurological Disorders · Antibodies, anti-neuronal

Abstract
In about two thirds of cases, patients with paraneoplastic neurological disorders present to the neurologist without a known tumor. Due to the ongoing immune response, this tumor tends to stay biologically relatively benign, and therefore difficult to diagnose. In patients with a known tumor, the neurological symptoms often precede a tumor recurrence. In both scenarios, anti-neuronal antibodies are an invaluable diagnostic help to the clinician, and may be supplemented by other diagnostic tests such as MRI, CSF, and electrophysiology. Tumor therapy remains the mainstay of therapeutic options, although early immune therapy must be started in parallel. It is hoped that the recent fundamental advances in understanding the autoimmune pathology of these disorders, especially the role of cytotoxic T cells, will eventually lead to more effective treatment options.

Schlüsselwörter
Paraneoplastische Syndrome · Neurologische Erkrankungen · Antikörper, anti-neuronale

Zusammenfassung
Etwa zwei Drittel der Patienten mit paraneoplastischen neurologischen Erkrankungen kommen zunächst zum Neurologen, da der Tumor nicht bekannt ist. Aufgrund der begleitenden Immunreaktion verhält sich dieser Tumor relativ gutartig, und ist daher auch relativ schwer zu diagnostizieren. Bei Patienten mit bereits bekanntem Tumor ist das Neuauftreten oder die Verschlechterung bestehender neurologischer Symptome immer ein Warnzeichen für ein Tumorrezidiv. In beiden Situationen ist das Vorliegen von anti-neuronalen Antikörpern diagnostisch sehr hilfreich, sie komplementieren andere diagnostische Maßnahmen wie MRT, Liquor- und Elektrophysiologie. Die Tumortherapie ist weiterhin die wichtigste therapeutische Maßnahme; eine begleitende Immuntherapie sollte parallel dazu eingeleitet werden. Die Fortschritte im Verständnis der autoimmunen Pathogenese dieser Syndrome, insbesondere die Rolle zytotoxischer T-Zellen, werden hoffentlich bald zu effektiveren Behandlungsmöglichkeiten führen.

Diagnosis of a Paraneoplastic Neurological Syndrome

Nearly any neurological syndrome (central, peripheral, neuromuscular, muscular) may be of paraneoplastic etiology [1, 2]. Clinically it is of high therapeutic relevance to diagnose a paraneoplastic etiology quickly and correctly, as this will alter the management of the patient dramatically. Either, in a patient without a known tumor, that tumor must be identified and treated, or in a patient with known tumor diagnosis, development of a paraneoplastic neurological syndrome frequently heralds tumor recurrence.

Initially, the term paraneoplastic neurological disorders

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Table 1. Antibody-defined subgroups of paraneoplastic cerebellar degeneration

Group	Most frequent tumors associated	Sex	Clinical symptoms	Start of neurological symtoms	Median survival
Anti-Yo	breast, ovarian	F>>M	subacute, severe	mostly before tumor diagnosis	100 mo if breast, 22 mo if ovarian
Anti-Hu	SCLC	M>F	additional symptoms of PEM / SN	mostly before tumor diagnosis	12 months
PCD and LEMS (Ab neg.)	SCLC	M = F	absent reflexes	mostly before tumor diagnosis	
Anti-CRMP5 /-CV2	SCLC, thymoma	F>M	subacute, severe, additional symptoms of PEM /SN	mostly before tumor diagnosis	
Anti-Tr	Hodgkin's disease	M>F	less severe, partly remitting	mostly after tumor diagnosis	
Anti-Ri	breast	F	opsoclonus/ataxia	before or after tumor diagnosis	
PCA-2	lung	M = F	additional symptoms of PEM / SN	mostly before tumor diagnosis	
ANNA-3	SCLC		additional symptoms of PEM / SN	mostly before tumor diagnosis	
Anti-Ma	various	F>M	subacute, brainstem	mostly before tumor diagnosis	
Atypical or no Ab	various	F = M	various	before or after tumor diagnosis	

Ab = Antibody; F = female; M = male; PCD = paraneoplastic cerebellar degeneration; LEMS = Lambert-Eaton myasthenic syndrome; PEM/SN = paraneoplastic encephalomyelitis / sensory neuropathy.

(PND) was coined for all non-metastatic neurological tumor complications where a specific etiology – such as vascular, infectious, metabolic, or treatment-related causes – could not be defined. Since the detection of the first antibody specific for a paraneoplastic etiology – the anti-Hu antibody – and description of its clinical relevance by Prof. Posner's laboratory the number of clinically relevant antibody reactivities as markers of a paraneoplastic etiology has grown at the speed of about one per year [1–3].

Clinical Suspicion

The first step in diagnosis relies on clinical skills leading to early clinical suspicion. Here, it has become clear in recent years that PND may not only follow the 'typical' subacute time course, but may also be indolent (over years!) or spontaneously relapsing-remitting (cave: misdiagnosis multiple sclerosis!) [4, 5]. Furthermore, PND may present as a 'typical' neurological syndrome, such as LEMS (Lambert-Eaton myasthenic syndrome), cerebellar degeneration, or sensory neuronopathy, but it may also be 'atypical', presenting as depression or memory disturbance (as in limbic encephalitis) or pseudo-ileus (autonomic polyneuropathy) [6, 7].

Limbic Encephalitis

According to a recent large series of 50 patients, diagnostic criteria for a paraneoplastic limbic encephalitis (PLE) may be (1) typical clinical symptoms (see below), (2) less than 4 years to tumor diagnosis, (3) exclusion of other differential diagnoses and (4) pathological results in CSF, MRI or EEG [6]. Most patients have a subacute progressive course. Symptoms are short-term memory disturbance, epileptic seizures, acute confusional syndrome, further psychiatric symptoms (personality change, hallucination, depression), brainstem symptoms, signs of hypothalamic involvement, cognition disturbance, and signs of involvement of other neurological systems. In more than half of all patients, a tumor is diagnosed only after onset of symptoms. In 50% this was a lung tumor, 20% had a testicular tumor, and 8% a breast tumor. Three quarters of all tumors were growing only locally. All except one patient showed pathological results in two of three investigations: MRI, CSF, or measuring anti-neuronal antibodies [2, 8, 9].

Cerebellar Degeneration

A subacutely developing cerebellar syndrome in a woman above age 50 is in almost two thirds of cases a paraneoplastic cerebellar degeneration (PCD) [10]. Clinically, all patients with PCD present in a similar way. Using serological analysis of the associated anti-neuronal antibodies, the patients may be sudivided into several subgroups (table 1). These subgroups differ in the associated tumors, course (neurological stabilisation in anti-Yo, progression in anti-Hu), and regarding survival. Anti-Hu patients show a median survival of 9–12 months, anti-Yo patients with breast cancer 100 months and anti-Yo patients with other gynecological tumors 22 months [8, 11, 12]. In patients who have a SCLC associated with PCD, further diagnostic procedures should be performed to search for an associated Lambert-Eaton myasthenic syndrome (i.e. anti-VGCC and electrophysiology, see below) or the presence of VGCC even in absence of LEMS [13, 14].

Sensory Neuropathy

The 'classical' paraneoplastic polyneuropathy is a sensory neuronopathy (SN) as first described by Denny-Brown in 1948 [15]. Typically, these patients initially have an asymmetrical and painful sensory neuropathy which evolves into typical complete loss of proprioception. The pseudo-athetotic movement of the hands and severe sensory ataxia is clinically impressive and usually very severe. Mostly, anti-Hu antibodies can be identified which have a specificity of 99% and a sensi-

Table 2. Clinically useful antibody reactivities for identifying the paraneoplastic etiology of a given neurological syndrome

Syndrome	Antibody for		Associated tumor
	diagnosis	paraneoplastic etiology	
LEMS	anti-VGCC	n.a.	SCLC
Subacute cerebellar degeneration		anti-Hu	SCLC, prostate
		anti-PCA-2	SCLC
		anti-CRMP5/-CV2	SCLC, thymoma
		ANNA-3	SCLC
		anti-Yo	ovary, breast
		anti-Ta/Ma2	testis
		anti-Ma	miscellaneous
		anti-Ri	breast, lung
		anti-Tr	Hodgkin's lymphoma
Opsoclonus/myoclonus (child)		anti-Hu	neuroblastoma
Dermatomyositis		n.a.	ovary, lung, pancreas
Opsoclonus/myoclonus (adult)		anti-Ri	breast, lung
		anti-Hu	SCLC, prostate
		anti-Ma	miscellaneous
		anti-Ta/Ma2	testis
Subacute sensory neuropathy		anti-Hu	SCLC, prostate
		anti-amphiphysin	SCLC
		ANNA-3	SCLC
		anti-CRMP5/-CV2	SCLC, thymoma
Limbic encephalopathy		anti-Hu	SCLC, prostate
		anti-Ta/Ma2	testis
		ANNA-3	SCLC
		anti-CRMP5/-CV2	SCLC, thymoma
Extrapyramidal syndromes		anti-Hu	SCLC, prostate
		anti-Ta/Ma2	testis
		anti-Ma	various
		anti-CRMP5/-CV2	SCLC, thymoma
Myasthenia gravis	anti-AChR, anti-MUSK	anti-titin	thymoma
Sensorimotor peripheral neuropathy		anti-Hu	SCLC, prostate
		anti-amphiphysin	SCLC
		anti-CRMP5/-CV2	SCLC, thymoma
Encephalomyelitis		anti-Hu	SCLC, prostate
Visual loss		anti-Hu	SCLC, prostate
		anti-recoverin	lung
Stiff-person syndrome	anti-GAD	anti-amphiphysin	breast

n.a.: Not available; AChR: acetylcholine-receptor; GAD: glutaminic acid dehydrogenase; LEMS: Lambert-Eaton myasthenic syndrome; SCLC: small cell lung cancer; VGCC: voltage gated calcium channel.

tivity of 82% for a paraneoplastic sensory neuropathy [16]. Other less frequent antibodies are anti-CV2 or anti-amphiphysin.

Lambert-Eaton Myasthenic Syndrome (LEMS)

In about 60% of patients with LEMS an underlying tumor, usually SCLC, rarely a lymphoma may be detected [17]. The associated SCLC have a significantly better prognosis if LEMS is present [18]. Unfortunately, no serological marker for the paraneoplastic etiology exists. Anti-VGCC antibodies are present in almost all patients with LEMS, and they do not differentiate between the paraneoplastic and non-paraneoplastic forms. The prevalence of LEMS in SCLC is about 3%

and must not be overlooked as LEMS responds well to immunomodulatory therapy [19–21].

Anti-Neuronal Antibodies

In case of clinical suspicion of the presence of a PND, anti-neuronal antibodies should be measured in the serum of the patient. Which antibodies should be looked for, depends on neurological syndrome (table 2). Here, only reactivities which are markers for the paraneopalstic etiology are mentioned. Antibodies such as anti-AChR, anti-VGCC or anti-VGKC are clinically most relevant markers, but they are not specifically associated with a paraneoplastic etiology. Depending on the neurological syndromes, anti-neuronal antibodies must be supplemented by other diagnostic tests such as MRI, CSF, or electrophysiology. Combining these diagnostic options may lead to a sensitivity of close to 100% for detecting a paraneoplastic etiology [6].

Anti-Hu Antibody

Since the initial description of anti-Hu, this first clinically fully characterized paraneoplastic antibody has also turned out to be the most frequent [3, 8, 22–24]. The anti-Hu antibody may be associated with a central encephalomyelitis or a peripheral neuropathy. Importantly, the associated tumors tend to be limited and show no metastases (other than to mediastinal lymph nodes) [25]. Anti-Hu (at low titer) is also present in about 16% of patients with SCLC without neurological symptoms [26]. In these patients, the anti-Hu is a positive predictor of complete response to tumor treatment [27].

Anti-Yo Antibody

Anti-Yo defines a subgroup of patients with PCD and breast or ovarian cancer (see above) and is the second most common anti-neuronal reactivity [11, 12]. One of the antigens recognized by anti-Yo sera is cdr2 (cerebellar degeneration-related protein) which is mainly expressed in cerebellar Purkinje cells and some tumors.

Anti-Ma/Ta Antibody

This antibody reactivity has only been recognized recently [5, 9, 28]. The antibody reactivity to Ma proteins is highly specific for a paraneoplastic etiology, and all patients react against the immunodominant Ma2 protein. In an isolated anti-Ma2 reactivity, patients tend to be younger and mainly have PLE associated with a germ cell tumor of testis. A reactivity against other Ma proteins (PNMA1, PNMA3) in addition to Ma2 identifies patients who are older, have a rhombencephalitis and PCD associated with several different tumors [5, 9, 28]. The function of the Ma proteins is still unknown.

Anti-Tr Antibody

Named after the first descriptor Trotter rather than an index patient [29], anti-Tr is found in PCD associated with Hodgkin's disease and reacts with cytoplasm of Purkinje cells additionally showing a characteristic punctate pattern in the molecular layer of the cerebellum [30, 31]. Most patients recognize a myc-associated zink finger protein that it is not the Tr antigen [32]. Typically and in contrast to other paraneoplastic antibodies, the titer may turn negative during course of treatment and may only be found in CSF and not in serum [31, 33].

Anti-CV2 Antibody / Anti-CRMP5 Antibody

Initially Honnorat et al. described anti-CV2 as a paraneoplastic marker in 1996 [34]. Recently, the group of Lennon described an anti-CRMP5 reactivity in 116 patients which probably constitutes the same antibody [35]. In the series of Yu et al. [35], 26% had cerebellar ataxia, 25% dementia, 17% cranial neuropathy, 11% chorea, 10% loss of taste or olfaction, and 7% optic neuropathy. In 77% a lung tumor and in 6% a thymoma had been identified.

Treatment

Treatment options include tumor therapy, symptomatic treatment, and modulation of the immune system.

Tumor Therapy

In patients without known tumor but a highly likely paraneoplastic etiology finding the tumor is essential but may be difficult. As there is a biologically effective immune response against the underlying tumors, the tumors may initially stay locally or even histologically small [27]. If specific antibody reactivities are present, they direct the tumor search to specific organs. If a tumor is identified which does not fit the known tumor pattern, this tumor should be checked for 'atypical' expression of the relevant antigen [8], and the possibility of a second malignancy must be considered [23]. Recently, the use of whole-body FDG-PET has been advocated for early tumor diagnosis in patients with anti-Hu or clinically suspected PND [36–38]. With all therapeutic approaches in PND it must be kept in mind that the natural course may be fluctuating [5] or indolent [39] and that there may be spontaneous improvement of neurological symptoms [40], or even spontaneous tumor regression [41, 42]. Some PND presentations such as SN or PLE tend to react better to therapy than others, such as PCD [6, 8, 43]. For the majority of PND of the CNS, however, therapy is difficult, and must be started early. Tumor therapy is the mainstay of therapy, and a complete response to tumor therapy shows a favorable influence on the course of PND [44].

Immunomodulatory Therapy

Because of current evidence of an autoimmune pathogenesis, immunomodulatory treatment seems indicated in patients with paraneoplastic neurological syndromes, although studies with a high degree of evidence are lacking due to the low number of patients [1, 2]. However, not all paraneoplastic syndromes respond well to the immunomodulatory options available so far. For some syndromes, immunomodulatory therapy rests on sound clinical evidence for its efficacy, such as GBS, CIDP, LEMS, or stiff-man syndrome.

For the remainder of syndromes – especially of the central nervous system –, all immunomodultory approaches used so far do not seem to be very effective on the whole, but may bring dramatic improvement in single patients. Improvement

is more likely in PLE or paraneoplastic neuropathy [6, 8, 38]. In general, the earlier immunotherapy is started the better are the chances of improvement [45, 46]. As immunomodulatory treatment options protein A absorption, ivIg, cyclophosphamide, or plasma exchange have been tried [1, 2, 47, 48]. Due to the uncertain effect, we would start with one course of i.v. methylprednisolone, such as in MS (5 × 500 mg i.v.), and wait for a possible effect for one or two weeks. If no effect is seen we would proceed to one course of ivIg (e.g. 2 g/kg body weight distributed over 5 days), wait again for a possible effect, and if no effect is seen maybe proceed to plasma exchange or cyclophosphamide according to the individual patient's situation.

Concluding Remark

Paraneoplastic neurological syndromes may present with a varied clinical picture and must be included in nearly any neurological differential diagnosis. As a very helpful tool an ever growing battery of specific antibodies as paraneoplastic markers are available for the clinician. With increasing understanding of the autoimmune pathogenesis of these disorders, effective treatment options besides the oncological therapy may become available to the patients soon.

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