

Diagnosis of paraneoplastic neurological syndromes

Diagnóstico de trastornos paraneoplásicos del que afectan el sistema nervioso

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RESUMEN

Aproximadamente 3 por ciento de todos los pacientes con cáncer pulmonar de pequeñas células (SCLC) y el 0,2 por ciento de todos los pacientes con cáncer de los ovarios desarrollarán un síndrome neurológico paraneoplásico (SPN). En la mayoría de los casos el síndrome neurológico precede el diagnóstico del cáncer primario. Aunque hay múltiples presentaciones, hay varios síndromes considerados clásicos con criterios diagnósticos bien definidos y cánceres bien identificados. Cuando el SPN precede al diagnóstico del cáncer y los pacientes son evaluados inicialmente por el neurólogo éste debe tener la perspicacia clínica para reconocer el desorden. Esta revisión incluye las características clínicas de cuatro síndromes paraneoplásicos clásicos: la encefalitis límbica, la degeneración cerebelosa subaguda, la neuronopatía subaguda sensitiva y el síndrome miasteniforme de Lambert-Eaton (LEMS). Los tipos más frecuentes del cáncer que causan la encefalitis límbica son el cáncer de pulmón de células pequeñas SCLC y el cáncer testicular que ocasionan el 60 por ciento de los casos. Los anticuerpos más frecuentes en el SCLC y en la encefalitis límbica son los ANTI Hu y los CV2/CRMP5, mientras que en los pacientes con cáncer testicular son los anti-Ma2. Con frecuencia estos pacientes desarrollan disartria y disfagia.

En cerca del 84 por ciento de los pacientes con degeneración cerebelosa subaguda se identifica un cáncer de ovario (ANTI Yo), o de pulmón (ANTI Hu), o de seno (ANTI Ri), o enfermedad de Hodgkin (ANTI Tr); y se manifiesta por ataxia y vértigo. A diferencia de otros síndromes paraneoplásicos, el anti-Yo asociado a degeneración cerebelosa ocurre con mayor frecuencia en pacientes que ya tienen diagnosticado el cáncer ovárico.

La neuronopatía sensitiva suele manifestarse por disestesias dolorosas y se acompaña de alteraciones por desmielinización y neuronopáticas en los estudios electrofisiológicos. El síndrome de Eaton-Lambert se caracteriza por debilidad próximal en piernas más que en brazos y por síntomas de disfunción autonómica (seca boca, hipotensión ortostática, disfunción eréctil) y disminución o ausencia de reflejos. Los estudios electrofisiológicos revelan pequeños potenciales de acción compuestos en el músculo, con un marcado incremento en la respuesta a los estímulos repetitivos rápidos sobre el nervio. En cerca del 60 por ciento de los pacientes, este síndrome está asociado a SCLC.

PALABRAS CLAVE: carcinoma, encefalitis límbica, síndrome paraneoplásico, cáncer de testículo, anticuerpos, neuropatía.

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SUMMARY

Approximately 3 percent of all patients with SCLC and the 0,2 percent of all patients with cancer of the ovaries they will develop a paraneoplastic neurological syndrome (PNS). In most cases the neurological syndrome precedes the diagnosis of the primary cancer. Although there are multiple presentations, there are some classical syndromes with well definite diagnostic criteria and frequent well recognized cancers. When the PNS precedes the cancer diagnostic and the patients are initially seen by the neurologist this should have the clinical insight to recognize the disorder. This review includes the clinical characteristics of four classical paraneoplastic syndromes: limbic encephalitis, cerebellar degeneration, subacute sensitive neuropathy and miasteniform syndrome of Lambert-Eaton (LEMS). The most frequent types of cancer that cause limbic encephalitis are: the small cells lung cancer (SCLC) and the testicular cancer. They can cause 60 percent of all syndromes. The most frequent antibodies in the SCLC and limbic encephalitis

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are ANTI Hu and CV2/CRMP5, while in the patients with testicular cancer are the anti-Ma2. Frequently these patients develop dysarthria and dysphagia.

The cancer most identified, in around 84 percent of the patients with cerebellar degeneration comes from: ovary (ANTI I), or lung (ANTI Hu), or breast (ANTI Ri), or Hodgkin disease (ANTI Tr) the illness itself is characterized by ataxia and vertigo. Opposed to other paraneoplastic syndromes, the anti-Yo associated to cerebellar degeneration occurs with greater frequency in patients that already have diagnosed one ovarian cancer. The sensitive neuropathy causes painful dysesthesia and neuronopathic and demyelinating alterations in electrophysiological studies. The Eaton-Lambert syndrome is characterized for proximal weakness in legs more than in arms and by symptoms of autonomous dysfunction (drought mouth, orthostatic hypotension and, erectile dysfunction) and decrease or absence of reflex. Electrophysiological studies reveal small and composed action potentials in muscles, with a marked increment in the answer to repetitive stimuli on the nerve. In about 60 percent of the patients, this syndrome is associated to SCLC.

KEY WORDS: carcinoma, limbic encephalitis, paraneoplastic syndromes, testicular neoplasm, neuropathy.

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INTRODUCTION

The term paraneoplastic neurological disorders (PND) describes a heterogeneous group of syndromes that can affect any structure of the nervous system, most frequently associated with cancer and thought to be caused by an immune mediated process. Nevertheless, the role of the immune system in the pathogenesis of the disease has not been established, except in a few instances, like Lambert-Eaton myastheniform syndrome (LEMS) where antibodies against voltage gated calcium channels (VGCC) are responsible for the clinical manifestations.

Although rare, they are more frequent than previously thought and new syndromes are being recognized (1). In most cases the neurologic syndrome precedes the diagnosis of the primary cancer. Early recognition and treatment might prevent disability, especially since patients can have a better prognosis from the oncologic perspective but be severely disabled by the neurologic condition. Therefore it is necessary for the general neurologist to be aware of the clinical presentations and this review will focus on when to suspect and how to establish the diagnosis of the most frequent entities.

EPIDEMIOLOGY

The actual incidence in a general neurology practice is difficult to establish since the diagnosis is under recognized and there is no systematic central reporting. The incidence in my academic neuro-oncology practice is about 0.5 per cent, diagnosing in average one patient per year. The

incidence will vary according to the primary tumor. Small cell lung cancer (SCLC) has been the most commonly primary cancer associated with these syndromes, probably because this tumor shares antigenic epitopes with the nervous system. Approximately 3 per cent of all patients with SCLC (2) and 0.2 per cent of all patients with cancer of the ovaries (3) will develop a paraneoplastic neurologic syndrome. The incidence of PND for other types of tumors is exceedingly low.

DIAGNOSIS

The diagnosis of PND is difficult and is based on suspicion of the entity upon recognition of the neurologic syndrome, the demonstration of the associated cancer using the appropriate diagnostic studies, the detection of paraneoplastic antibodies and the exclusion of other entities that must be considered in the differential diagnosis.

Clinical syndrome: although there are multiple PND there are several syndromes that are considered classical with well defined diagnostic criteria and more frequently than not associated to cancer (Table 1). The non-classical syndromes are those that are commonly observed as the clinical manifestation of non-paraneoplastic disorders (4).

Diagnosis of cancer: in the 60 per cent of the patients for whom the PND is the first manifestation of the cancer, it might be very difficult to diagnose the cancer since the tumor may be of very small size. New and improved imaging techniques like positron

TABLE 1. MOST FREQUENT “CLASSICAL” PARANEOPLASTIC NEUROLOGICAL DISORDERS.

Syndrome	Pathology
Encephalomyelitis Limbic encephalitis Subacute cerebellar degeneration Opsoclonus-myoclonus	Multiple nervous system location neurons Hippocampus, amygdala Purkinje cells Olivary nucleus, brain stem
Subacute sensory neuronopathy	Dorsal root ganglion
Lambert-Eaton myastheniform syndrome	Neuromuscular junction calcium channel
Dermatomyositis	Muscle

emission tomography (PET) scan, allow a higher likelihood of identifying occult cancers, although there are still false negatives. In some cases observation with periodic cancer screening studies is necessary for several years before the underlying cancer is diagnosed (5).

Identification of paraneoplastic antibodies: the sensitivity of the presence of antibodies in PND is about 60 per cent and they can be present in low titers in patients with cancer but without a paraneoplastic syndrome. The antibodies can be “well characterized” meaning that there is consistency between the laboratories that measure them, associated with well-defined neurologic syndromes, and their presence correlates with cancer in most cases (4). There are “partially characterized” antibodies that do not fulfill the above criteria, or there are antibodies that are associated with both the paraneoplastic and the non-paraneoplastic neurologic syndrome (like VGCC antibodies in LEMS).

CLASSICAL SYNDROMES

When the PND precede the diagnosis of cancer, the patients are seen initially by the neurologist who must have the clinical acumen to recognize the disorder. For this review, the clinical characteristics of four examples of classical paraneoplastic disorders will be described including: limbic encephalitis, cerebellar degeneration, subacute sensory neuronopathy and Lambert-Eaton myastheniform syndrome (LEMS) (Table 2). There are some common characteristics of the classical paraneoplastic

neurologic disorders. Most cases are subacute in presentation and rapidly progress causing important disability.

LIMBIC ENCEPHALITIS (LE)

As most PND the clinical manifestations of limbic encephalitis have an insidious onset characterized by short term memory difficulties, personality changes, confusion, focal seizures, irritability and psychiatric manifestations(6). Hypothalamic dysfunction symptoms like hyperthermia, weight gain and hypersomnia have been described. Excluding the mental status changes the neurologic examination might be unremarkable, although the limbic encephalitis may be part of a more diffuse process of encephalomyeloneuritis.

The CSF will reveal inflammation with lymphocytic pleocytosis and increased protein and increased immunoglobulin production with oligoclonal bands and high IgG index(6). Brain MRI typically reveals T2 prolongation affecting the medial temporal lobe although the abnormalities may extend beyond the temporal lobe. EEG will frequently show temporal lobe discharges or only a slow background.

The most frequent types of cancer causing limbic encephalitis are SCLC and testicular cancer accounting for 60 per cent of the cases(6). Antibodies frequently seen in SCLC and limbic encephalitis are anti-Hu and CV2/CRMP5, while in patients with testicular cancer and limbic encephalitis is the anti-Ma2. More recently, a paraneoplastic limbic encephalitis associated to

TABLE 2. TYPES OF CANCER, PARANEOPLASTIC ANTIBODIES AND DIFFERENTIAL DIAGNOSIS ASSOCIATE TO FOUR “CLASSICAL SYNDROMES”.

Syndrome	Cancer	Antibodies	Differential diagnosis
Limbic encephalitis	Lung Testicular, Teratoma of ovaries Thymoma	Hu, CV2/CRMP5, VGKC Ma2, NMDAR VGKC	Viral encephalitis
Cerebellar degeneration	Ovary Hodgkin's disease, Lung Breast	Yo, Tr, Hu, Zic4 Ri	Toxic Infectious
Sensory neuropathy	Lung	Hu, CV2/CRMP5	Sjogren's disease
LEMS	Lung	P/Q VGCC	Myasthenia gravis

the N-Methyl-D-aspartate receptors (NMDAR) has been described and it is worth mentioning since they are usually responsive to treatment(1). The NMDAR antibody associated encephalitis is often associated with an ovarian teratoma. The patients develop subacute psychiatric symptoms, rapidly followed by seizures and alteration of consciousness requiring of ventilatory support.

SUBACUTE CEREBELLAR DEGENERATION (SCD)

Dizziness, vertigo, blurred vision and gait unsteadiness are usually the initial symptoms of PND cerebellar degeneration, followed by frank truncal and appendicular ataxia that leaves them wheelchair bound (7). Patients will frequently develop dysarthria and dysphagia. Brain MRI will initially be normal, but over time cerebellar atrophy will be apparent.

A cancer is detected in about 84 per cent of the patients with a subacute cerebellar degeneration and a positive antibody. The most frequent tumors associated with this syndrome are ovary (anti-Yo), lung (anti-Hu), Hodgkin's disease (anti-Tr) and breast (Anti-Ri). Different from other paraneoplastic syndromes, the anti-Yo associated PCD occurs more frequently in patients who already have the diagnosis of ovarian cancer.

SUBACUTE SENSORY NEURONOPATHY (SSN)

Patients with paraneoplastic sensory neuropathy usually present with numbness and painful dysesthesias affecting the distal limbs that is asymmetric and rapidly progressive. Although the sensory symptoms, especially deep sensation, predominate in some cases there is a motor component. The severe proprioception deficit results in sensory ataxia that significantly impairs gait restricting the patient to a wheelchair. In some cases the sensory neuropathy, may be a component of a more diffuse paraneoplastic process of encephalomyeloneuritis and in others it may be associated to only an autonomic neuropathy(8).

Electrophysiology studies reveal an axonal or an axonal/demyelinating pattern of abnormality. The most frequent type of cancer is SCLC and associated with presence of the anti-Hu antibody. Other cases of neuropathy and SCLC have a positive anti-CV2/CRMP5 antibody, but usually it is a combined sensory and motor neuropathy.

LAMBERT-EATON MYASTHENIFORM SYNDROME (LEMS)

Patients usually develop proximal weakness, in legs more than arms, symptoms of autonomic dysfunction (dry mouth, orthostatic hypotension,

erectile dysfunction) and decreased to absent reflexes. On examination there is appearance or facilitation of the reflexes after activity, and frequently patients will feel stronger with physical activity.

Electrophysiologic studies reveal small compound muscle action potentials, with a marked incremental response at fast rates of nerve stimulation. In about 60 per cent of the patients the syndrome is associated to cancer, specifically SCLC. Characteristics of the patients with LEMS that most frequently are found to have an underlying cancer include older age, male gender and a rapid progression of weakness (9).

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