Paraneoplastic Neurologic Syndromes

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KEYWORDS

• Paraneoplastic • Autoimmune encephalitis • Antibody • Neurologic • Cancer

KEY POINTS

- Paraneoplastic neurologic syndromes are immune mediated.
- Paraneoplastic neurologic syndromes can affect any part of the nervous system.
- Paraneoplastic neurologic syndromes often present acutely and before the cancer diagnosis is known.
- Some paraneoplastic neurologic syndromes are highly responsive to treatment.

INTRODUCTION

Paraneoplastic neurologic syndromes (PNS) are mostly immune-mediated disorders that occur in patients with cancer. For some PNS, the immune pathogenesis has been confirmed, whereas in others there is strong evidence supporting underlying immune mechanisms. Once considered medical oddities, it is now known that some PNS are common. Furthermore, contrary to the past concept that PNS predominate in older individuals (neuroblastoma-associated opsoclonus was a rare exception), some recently identified disorders predominately occur in younger age groups. The identification of the paraneoplastic origin of a patient's symptoms is important for several reasons. PNS often develop before the cancer diagnosis is known and recognition of PNS can lead to early cancer identification. Additionally, it has been shown that early initiation of treatment (immunotherapy and tumor treatment, when present) can improve PNS outcomes. In this article, we provide general concepts regarding

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PNS; for detailed descriptions of the clinical features of individual PNS detailed reviews are available.[1–4]

EPIDEMIOLOGY

In general, the classic PNS are rare and occur in approximately 1 in 10,000 patients with cancer.[5] An exception is the Lambert-Eaton myasthenic syndrome (LEMS), which has been reported in about 1% of all patients with small-cell lung cancer (SCLC). In contrast, anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis, which has an age-related tumor association, is considered the second most common cause of autoimmune encephalitis after acute demyelinating encephalomyelitis.[6]

DIAGNOSING PARANEOPLASTIC NEUROLOGIC SYNDROMES

Initial clues that a patient has a PNS are found in the history and symptom presentation and include the patient's age, cancer risk factors, or known cancer history (**Table 1**). Most PNS develop acutely or subacutely and may resemble a viral process. Although the same neurologic syndromes seen in PNS also occur without a cancer association, some syndromes, such as LEMS or limbic encephalitis, are so commonly cancer associated they are referred to as classical PNS and a paraneoplastic cause should be suspected when one of these syndromes is seen.[7] Other disorders have a more variable association with cancer and for some this association is age and sex dependent. It is important to keep in mind that the co-occurrence of a neurologic syndrome and cancer may simply be coincidental. The presence of cerebrospinal fluid (CSF) pleocytosis, elevated protein concentration, intrathecal synthesis of immunoglobulin, and/or oligoclonal bands is supportive of paraneoplasia, although normal CSF studies do not rule out PNS. Neuroimaging is helpful to exclude other nonparaneoplastic causes but may be normal. An exception is limbic encephalitis in which MRI often shows unilateral or bilateral mesial temporal lobe abnormalities best seen on T2-weighted and fluid-attenuated inversion recovery images (**Fig. 1**).[8]

TUMOR SCREENING

If PNS is suspected tumor screening should proceed.[9] The search may initially be focused to those tumor types more commonly associated with the patient's syndrome or type of antineuronal antibody, but should be expanded if no tumor is found because unexpected cancer-antibody associations may occur. Similarly, if the tumor found is not a histologic type that typically associates with the syndrome or antibody, a search for a second neoplasm should be undertaken. Because PNS onset often precedes the cancer diagnosis or occurs when the tumor is small and difficult to detect, a multidisciplinary approach to cancer diagnosis is warranted. The investigating team should be informed that PNS is suspected and that questionable or inconclusive results of tumor screening should be thoroughly investigated. If no cancer is found but PNS remains the likely diagnosis, cancer screening should be repeated periodically up to 4 years. The frequency of cancer screening depends on the type of disorder. For example, for classical paraneoplastic syndromes (anti-Hu usually related to SCLC and similar), cancer screening every 6 months seems reasonable, but for other disorders (eg, anti-NMDAR encephalitis) less frequent and shorter duration of screening is reasonable (evaluation for ovarian teratoma yearly for 2 years). In greater than 90% of patients with solid tumors and PNS, the tumor is found within 1 year of PNS presentation.