

# Paraneoplastic Cerebellar Degeneration

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**ABSTRACT:** Paraneoplastic cerebellar degeneration is a rare complication of a number of cancers, particularly small cell lung cancer, gynecologic cancers and Hodgkin's disease. The disorder is clinically characterized by rapid development of pancerebellar dysfunction, which usually does not improve, and pathologically characterized by loss of Purkinje cells with or without inflammatory infiltrates. In some but not all patients, an autoantibody that reacts with the tumor and Purkinje cells can be found in the serum and spinal fluid of patients with paraneoplastic cerebellar degeneration. The presence of the autoantibody suggests, but does not prove, that the disorder has an autoimmune mechanism for its pathogenesis.

**RÉSUMÉ:** Dégénérescence cérébelleuse paranéoplasique. La dégénérescence cérébelleuse paranéoplasique est une complication rare d'un certain nombre de cancers, particulièrement du cancer du poumon à petites cellules, de cancers gynécologiques et de la maladie de Hodgkin. Cette affection est caractérisée cliniquement par le développement rapide d'une dysfonction cérébelleuse généralisée, qui ne s'améliore habituellement pas et qui est caractérisée à l'anatomopathologie par une perte des cellules de Purkinje, avec ou sans infiltrat inflammatoire. Chez certains patients avec une dégénérescence cérébelleuse paranéoplasique, on peut retrouver un auto-anticorps qui réagit avec la tumeur et les cellules de Purkinje dans le sérum et le liquide céphalo-rachidien. La présence d'un auto-anticorps suggère, mais ne prouve pas, que la pathogenèse de cette affection est basée sur un mécanisme autoimmun.

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Paraneoplastic cerebellar degeneration (PCD) is the term applied to a disorder in which patients develop cerebellar dysfunction associated with a cancer that is not in the nervous system. The term "paraneoplastic" implies both that there is a direct relationship between the cancer and the neurological disorder, and that the neurological disorder cannot be ascribed to compression or invasion of the cerebellum by the cancer. In many instances, despite severe cerebellar symptoms, the underlying cancer is localized, small and often extremely difficult to detect. Typically, the neurological disorder evolves rapidly over days or weeks, causing severe pancerebellar dysfunction (see "symptoms" below), usually in the absence of significant sensory loss or muscle weakness. At autopsy, the central nervous system may be normal save for extensive cerebellar Purkinje cell loss sometimes accompanied by lymphocytic infiltrates in meninges and deep cerebellar nuclei. Sometimes more widespread pathological changes can be found (see below).

PCD is rare. In 1982, Henson and Urich were able to identify from the literature only 50 clinically and pathologically proven cases<sup>1</sup> and even with the renewed interest in the disorder generated by the discovery of autoantibodies in the serum and spinal fluid of some patients with PCD, the number of patients reported is still under 300.<sup>2</sup> The exact incidence of PCD is not known but, in a series of 1,476 consecutive patients with cancer surveyed for neurological disability, only 3 were found to have

PCD.<sup>3</sup> These included 2 of 319 patients with carcinoma of the lung and 1 of 55 patients with ovarian cancer. Another survey of 641 patients with small cell lung cancer failed to identify a single patient with PCD.<sup>4</sup> Since the disorder is usually so florid, it is not likely that a patient with PCD would have been missed. However, morphometric studies of patients at autopsy indicate that those who die of cancer generally have fewer Purkinje cells in their cerebellum than do patients who die of other diseases. Furthermore, the loss of Purkinje cells is most striking in patients with ovarian cancer,<sup>5</sup> that cancer that is probably associated with the highest percentage of patients with PCD.

Although paraneoplastic cerebellar degeneration is a rare complication of cancer, the converse is not true: cancer is a common cause of subacute cerebellar degeneration in adults. Henson and Urich<sup>1</sup> estimate that half of all patients with non-familial late-onset cortical cerebellar degeneration "have, sooner or later, proven to suffer from malignant disease of one type or another". Those figures are consistent with my own experience. Thus, the oncologist is unlikely in any given year to encounter a patient with PCD; if he does encounter a patient with a cerebellar disorder, it is more likely to be due to metastatic spread to the nervous system than PCD. Conversely, when the neurologist encounters an otherwise healthy adult with subacutely developing cerebellar degeneration, the likelihood that that patient will have cancer is high.

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The first report of PCD was that of Brouwer in 1919 of a woman with subacutely developing cerebellar signs who died after several months, probably as an indirect result of her bedridden and disabled condition. (Such a short course to autopsy is now the exception rather than the rule. The casual tumor usually grows indolently and better nursing care maintains good nutrition and general physical state, so that most patients with PCD live many years even though they may be substantially disabled.) At autopsy, in addition to the pathological findings of Purkinje cell degeneration, Brouwer comments on a "polymorphic-cell" pelvic "sarcoma".<sup>6</sup>

From 1919 until 1938 a few case reports appeared describing a peculiar subacutely evolving cerebellar syndrome associated with cerebellar Purkinje cell loss. The disorder was classified as one of the cortical cerebellar degenerations although most authors recognized that its subacute evolution and stabilization after several weeks or months differed from most other late onset cerebellar degenerations. The presence of a cancer, usually small and unexpected, encountered at autopsy was mentioned in most case reports but only in passing. In 1938, Brouwer and Biemond proposed an association between cancer and the cerebellum.<sup>7</sup>

After 1938, the number of case reports began to increase and those associated with cancer were separated from other causes of cerebellar degeneration. In 1951, Brain et al.,<sup>8</sup> were able to collect from the literature and their own experience 16 patients with clinical and pathological evidence of "subacute cortical cerebellar degeneration where the disorder had run its course from onset to death under, or slightly over, 2 years". Eleven of the 16 had carcinoma. In three, the tumors were bronchial (probably small cell lung cancer), 5 had ovarian, 2 uterine and 2 breast cancer. They distinguished this rapid onset and short course from 11 more chronic cases (average duration of symptoms 17½ years) of patients with cortical cerebellar degeneration, only two of whom had cancer. By 1965, the clinical entity was well enough known among neurologists to allow a reasonably certain clinical diagnosis. Brain and Wilkinson<sup>9</sup> were able to find 20 pathologically verified cases of "subacute cerebellar degeneration associated with neoplasms" in the literature and add to that their own series of 19 clinically observed cases, 6 of whom also had pathological verification. In contradistinction to their previous series, in which the patients were mostly women with gynecologic or breast cancer, in this series there were 10 men and 9 women. Ten had carcinoma of the lung, 5 ovary, 2 breast, 1 fallopian tube and 1 Hodgkin's disease.

By 1982, Henson and Urich<sup>1</sup> were able to find 50 pathologically proven cases of cortical cerebellar degeneration associated with neoplasm. For the first time, they subclassified the patients into three groups. In the first group of 27 patients, the pathological picture was purely degenerative and "largely confined to the cerebellar cortex". In this group there were 12 women and 15 men, whose cancers were 9 gynecologic, 8 lung, 2 breast, 4 Hodgkin's disease, 2 non-Hodgkin's sarcomas and 1 colon cancer. Of the lung cancers 6 were classified as either oat cell or small cell. The second category had 12 patients in whom the cerebellar lesion was associated with a prominent inflammatory reaction affecting large portions of the neuraxis. Eight of the 12 were women. The cancers were 5 gynecologic, 1 breast, 11 lung (8 oat cell), 1 Hodgkin's disease and 1 rectal cancer (one patient had both lung and rectal cancer). There were five other patients

in whom the inflammation was restricted to the cerebellum, 3 were women and 2 men. One cancer was pelvic, 1 breast, 1 oat cell, 1 stomach and 1 larynx. Henson's figures confirmed the beliefs of Brain et al. that the disease was associated with a preponderance of small cell lung and ovarian cancers and, considering its low overall incidence, Hodgkin's disease.

The discovery of inflammatory infiltrates, along with a known phenomenon of acute but reversible cerebellar disorders associated with childhood exanthems, caused many neurologists of the time to consider the disorder an infectious one. Russell, in 1961,<sup>10</sup> suggested that the inflammatory infiltrates might well have represented an immune response and proposed that the disorder was autoimmune. However, the autoimmune hypothesis was not given additional credence until 1976 when Trotter, Henden and Osterland<sup>11</sup> reported a 21-year-old woman who, over several months, developed disabling cerebellar signs and was subsequently discovered to have an anterior mediastinal mass diagnosed on biopsy as stage I nodular sclerosing Hodgkin's disease. They found an antibody in her serum that reacted by immunofluorescence with cerebellar Purkinje cells. That reaction was not present above a dilution of 1:20. In two other patients with Hodgkin's disease, but without cerebellar degeneration, there was either no reaction or a trace of fluorescence. Two normals were studied; one had a trace of Purkinje cell fluorescence, the other had no reaction. A patient with multiple sclerosis was described as having 1+ Purkinje cell reaction as opposed to the index case of PCD where the reaction was 3+. Subsequent events have proved that some but not all patients with cerebellar degeneration associated with Hodgkin's disease do have low titers of anti-Purkinje cell antibodies.<sup>12</sup> The patient described by Trotter and colleagues is still alive, cured of her Hodgkin's disease but disabled by her cerebellar degeneration. Examination of serum recently drawn from the patient and examined in this laboratory does not reveal an antibody.

In 1983, Greenlee and Brashear<sup>13</sup> reported two patients with ovarian cancer and high titers of an anti-Purkinje cell antibody that gave a granular reaction pattern relatively restricted to cytoplasm of cerebellar Purkinje cells. In 1985, Jaeckle et al.<sup>14</sup> reported that the sera of 6 of 12 patients with PCD (2 ovarian, 3 breast, 1 unknown primary, probably ovarian) contained an antibody with a similar reaction pattern but six other patients with paraneoplastic cerebellar degeneration (1 breast, 2 small cell lung cancer, 2 Hodgkin's disease and 1 "pre-leukemic") did not contain such antibodies.

In 1986, Western blot analyses of the antigens recognized by these antibodies produced bands at approximately 62 and 34 kd.<sup>15</sup> This polyclonal IgG autoantibody was subsequently designated anti-Yo (after the first two letters of the last name of Jaeckle's index patient) by the Memorial group.<sup>16</sup> That designation was applied only to serum that reacted histochemically relatively specifically with the cytoplasm of Purkinje cells in a granular pattern and recognized bands at 62 and 34 kd on Western blot of Purkinje cell extracts. Probably the same antibody, identified only by immunohistochemical characteristics, is called Purkinje cell cytoplasmic antibody (PCAb) by the Mayo Clinic group.<sup>17</sup>

With the discovery of anti-Yo and other antibodies associated with cerebellar degeneration, it became easier to distinguish paraneoplastic cerebellar degeneration from cerebellar disorders, which were coincidentally associated with cancer, and the

number of case reports increased. A recent review by Hammack includes 199 patients (Table 1) with at least another 40 or 50 currently unreported cases.<sup>2</sup>

This recent discovery of anti-Yo and several other anti-Purkinje cell antibodies has given impetus to the autoimmune hypothesis as the cause of neurological paraneoplastic syndromes. The hypothesis is that an immune response against antigens shared between the cancer and Purkinje cells (onconeural antigens) leads to a misdirected immune attack on cerebellar Purkinje cells. Furthermore, the presence of the antibodies appears to predict an indolent course for the underlying neoplasm, suggesting a specific and effective immune response against the tumor.

Particular antibodies are associated with particular cancers. Since many of the cancers are occult, when the patient develops cerebellar symptomatology, the identification of a particular antibody can direct the search for the underlying cancer.

### CLINICAL MANIFESTATIONS

PCD can be associated with any cancer but the most common culprits are lung cancer (particularly small cell lung cancer), ovarian cancer and lymphomas (particularly Hodgkin's disease). In the majority of patients, it is the neurological symptoms that bring the patient to the physician before the cancer is symptomatic. The cancer is usually found within months to a year of the onset of clinical symptoms but occasionally the cancer may elude detection for 2 to 4 or even more years and, in some instances, has been found only at autopsy. In recent years the presence of specific autoantibodies has allowed physicians to make the diagnosis of cancer much earlier, often when the tumor is still microscopic in size.<sup>17,18</sup> Typically, the disorder begins with slight incoordination in walking, but evolves rapidly

over weeks to a few months with progressive ataxia of gait, incoordination in arms, legs and trunk, dysarthria and often nystagmus associated with oscillopsia (the subjective sensation of oscillation of viewed objects). Within a few months the illness reaches its peak and then stabilizes. By this time, most patients are unable to walk without being supported by one or two individuals; many are unable to sit unsupported; handwriting is impossible and feeding oneself is difficult. Speech may be understood only with great effort. Vision, compromised by the oscillopsia, may prevent reading or even watching television. The neurological signs are always bilateral and usually symmetrical although, at times, one side may be more affected than the other. In occasional patients, asymmetry is quite prominent. Diplopia is an early symptom in many patients although abnormalities of visual axis are often not detected by the examiner. Vertigo is also a common early symptom.

The signs and symptoms are frequently limited to those of cerebellar or cerebellar pathway dysfunction but, in as many as half the patients, other neurological abnormalities (usually mild), may be found on careful examination. Such findings include sensorineural hearing loss, dysphagia, hyperreflexia (with or without extensor plantar responses), extrapyramidal signs and peripheral neuropathy. Dementia and other abnormalities of mental status have been reported in as many as half the patients. However, a recent study using formal cognitive testing, found that dementia was not common when controlled for impaired motor and language skills, suggesting that perceived clinical changes in intellectual function may be more apparent than real.<sup>19</sup> Despite this, positron emission tomography, performed in a few patients with PCD, has revealed hypometabolism in all areas of the neuraxis including cerebral cortex as well as cerebellum and brainstem.<sup>19</sup>

Once the disease has reached its peak, it usually does not change and the patient remains neurologically stable despite treatment (and even cure) of the underlying cancer. Treatment directed at the cerebellar disorder, including immune suppression with corticosteroids and other drugs and plasmapheresis, usually does not help. Symptomatic improvement in the ataxia has been reported in a few patients with use of the drug Clonazepam in doses varying from .5 to 1.5 mg a day.

There are exceptions to all of the above statements. The onset of the disorder may be abrupt (one of our patients went from normal to totally disabled by cerebellar signs overnight) or more gradual. Occasional patients progress over a year or more. The disorder may be relatively mild so that the patient can walk, write and be understood albeit with some difficulty. On occasion, the disorder may remit spontaneously or coincidentally with treatment of the tumor or with plasmapheresis or corticosteroid treatment.<sup>20,21</sup> Nonetheless, the typical clinical picture is common enough to allow the neurologist and the oncologist to make a presumptive clinical diagnosis of PCD with or without confirmative antibody studies. The value of the antibody studies lies in their confirmation of the disorder as paraneoplastic and in the association of specific antibodies with specific neoplasms.

### LABORATORY EVALUATION

Early in the course of the disease, computerized tomography and magnetic resonance images reveal no abnormality. If patients are followed over a period of months to a few years,

**Table 1. Malignancies Associated with PCD in 199 Cases**

Ovarian	50	Lymphoma	32
papillary	3	Hodgkin's	27
serous	3	NHL	1
unspecified	43	unspecified	1
epithelial	1	T cell	1
		lymphosarcoma	2
Lung	56	Stomach	2
small cell	36	Larynx	1
squamous	4		
large cell	4	Prostate	3
adenocarcinoma	5	Thyroid	1
unspecified	7	Rectum	1
mixed	1	Bronchus and Rectum	1
Uterus	6	Colon	6
Fallopian tube	4	Ca maxillary antrum	1
Breast	17	Tonsil	1
Adenocarcinoma		Renal cell	1
unknown primary	9	Chondrosarcoma	1
Uterine and Colon	1	AML	1
Ovary and Breast	1	Monoclonal gammopathy	1
"Polymorphic sarcoma"	1		

diffuse cerebellar atrophy appears on both CT and MRI.<sup>22</sup> Occasional patients have been reported in whom hyperdensities have been found in cerebral and cerebellar white matter on T2 weighted images.<sup>17</sup>

In most patients who are studied early in the evolution of neurological symptoms, the cerebrospinal fluid (CSF) contains an increased number of lymphocytes, a slightly elevated protein concentration and an elevated IgG. Oligoclonal bands may be present as well. The pleocytosis in the CSF usually resolves with time and if patients are examined many months or years after the onset of the disorder, the CSF may be entirely normal.

### PATHOLOGY

The central nervous system may appear grossly normal at autopsy but usually the cerebellum is atrophic with abnormally widened sulci and small gyri.

Histologically, the hallmark of PCD is severe and often complete loss of Purkinje cells of the cerebellar cortex.<sup>5</sup> The degenerating Purkinje cells may have swellings, called torpedoes, along the course of their axons. Other pathological features which are sometimes present include thinning of the molecular and granular layers of cerebellar cortex, often without marked cell loss, and proliferation of Bergmann astrocytes. The deep cerebellar nuclei are usually well-preserved although there may be some rarefaction of white matter surrounding the nuclei, corresponding to loss of Purkinje cell axons. Basket cells and tangential fibers are usually intact. Lymphocytic infiltrates, if present in the cerebellum, are usually found in the leptomeninges and in the dentate nucleus and surrounding white matter, but not in the Purkinje cell layer.<sup>5</sup>

In many patients, the disorder is a non-inflammatory one with pathological changes restricted to the Purkinje cell layer of the cerebellum. However, pathological changes outside the cerebellum do occur, and differ substantially from patient to patient.<sup>5</sup> Abnormalities include dorsal column and pyramidal tract degeneration of the spinal cord, degeneration of the basal ganglia (specifically the pallidum) loss of peripheral nerve fibers and inflammatory infiltrates in brainstem, spinal cord and cerebral cortex.

The tumors associated with PCD do not differ histologically from similar tumors unassociated with paraneoplastic symptoms. However, in many patients, the tumor, when identified, is still localized rather than widely metastatic. Hetzel et al. have reported that tumors in antibody positive PCD are more likely to be associated with lymphocytic infiltrates than in similar histologic tumors not associated with PCD.<sup>23</sup>

### ANTI-YO POSITIVE PCD

Anti-Yo is the term first applied by Posner and Furneaux<sup>16</sup> to designate a polyclonal IgG autoantibody that reacted primarily with the cytoplasm of Purkinje cells, giving a characteristic granular staining pattern. The sera also reacted by Western blot analysis with extracts of Purkinje cells, identifying two bands at approximately 62 and 34 kd. The genes coding for both 34 and 62 antigens have been cloned, the first by Dropcho et al.<sup>24</sup> and the second by Sakai et al.<sup>25</sup> and independently by Fathallah-Shaykh et al.<sup>26</sup> The 34 kd protein is encoded in a single exon and consists of tandem repeats of six amino acids. The mouse gene is somewhat larger than the human gene but, as in the

human, amino acids 3, 4 and 6 are always glutamate, aspartate, aspartate, respectively.<sup>27</sup> The function of the protein encoded by this gene is unknown.

Analysis of messenger RNA coding for the 34 kd protein confirms its predominance in Purkinje cells but identifies it to a lesser degree in cerebral cortex, and in many tumors and tumor lines from patients who do not have the antibody in their serum and do not have PCD.<sup>28</sup> However, immunohistochemistry and Western blot analysis of ovarian and breast carcinomas reveals both the 34 and the 62 kd antigen to be present only in those tumors of patients with anti-Yo positive PCD.<sup>29</sup> Antibodies raised against a peptide representing part of the sequence of the 34 kd antigen react by Western blot and immunohistochemistry with both cerebellar Purkinje cells and the tumors of anti-Yo positive PCD patients.<sup>30</sup> The 34 kd gene has been mapped to the long arm of the X chromosome near the site of the fragile X gene.<sup>32</sup>

The 62 kd gene encodes for an entirely different protein from the 34 kd gene. The protein has a leucine zipper as well as a zinc finger motif, suggesting that it may play a role in the regulation of gene expression.<sup>26</sup> The gene has been mapped to chromosome 16 (Siniscalco, unpublished data). Northern blot analysis reveals that the transcript of the gene is detected not only in cerebellum and brainstem but also in intestinal mucosa.<sup>25</sup>

Using a fusion protein produced by the 62 kd cDNA as an antigen, the anti-Yo antibody has been found by Peterson et al.<sup>32</sup> in 54 patients whose serum (and often CSF) was studied at Memorial Sloan-Kettering Cancer Center. Other investigators, particularly those from the Mayo Clinic, using immunohistochemical criteria but not Western blotting, have also reported series of patients with what is very likely the anti-Yo antibody. Taken together, there are over 100 patients reported with either definite or probable anti-Yo antibodies in their serum. From these data certain conclusions are possible: 1) The antibody does not occur in measurable amount in normal individuals. 2) With two exceptions, the antibody does not occur in patients with cancer who do not suffer PCD. The exceptions, reported by Brashear et al.<sup>33</sup> are two patients with ovarian cancer but no cerebellar signs who maintained higher titers of antibody in their serum. (Because the antibody was examined only by immunohistochemistry and not Western blot, its specificity might be doubted.) Our own study of 170 sera of patients with ovarian cancer, but no PCD, failed to reveal measurable anti-Yo antibody in any patient. 3) All patients harboring the antibody are women with ages ranging from 26 to 85. The cerebellar disease preceded identification of the cancer in two-thirds of patients. The cancer, when identified, is either breast or gynecologic (ovarian, fallopian tube, endometrial). Two exceptions are one woman with adenocarcinoma of the lung who, after four years follow up, still has not developed gynecologic cancer, and one woman with lymphoma.<sup>34</sup> Whether the *antigen* was present in those tumors has not been reported. 4) The cancers do not appear histologically different from cancers in the same organ of patients without PCD. However, there appear to be more lymphocytic infiltrates in PCD tumors than in others.<sup>23</sup> 5) Although some of the tumors are quite aggressive and widely metastatic at the time the PCD develops, most are either localized or have spread only to regional nodes (in some instances the primary tumor is too small to be discovered and only positive nodes are found). The tumor course after discovery usually appears to be

**Table 2: Paraneoplastic Cerebellar Degeneration: Classification**

	Usual Cancer	Sex	Clinical Findings	Onset
Anti-Yo	Gyn	All F	Subacute, severe	Before cancer
Anti-Hu	SCLC	F > M	Part of PEM/SN	Before cancer
Hodgkin's	Hodgkin's	M > F	Less severe, may remit	After cancer
PCD and LEMS (ab neg)	SCLC	M = F	Absent DTR's **	Before cancer
Anti-Ri	Breast	F	Myoclonus/opsoclonus	Before cancer
Misc	Any	F = M	Variable	Either before or after cancer

\* PEM/SN = paraneoplastic encephalomyelitis/sensory neuronopathy

\*\* DTR's = deep tendon reflexes

relatively indolent no matter what the treatment. 6) Plasmapheresis and immune suppression rarely affect the course of the disease (although a few exceptions have been reported). However, the failure of immune suppression to affect the disease does not rule out an autoimmune etiology; plasmapheresis with five plasma exchanges, although successful in lowering the serum titer of the antibody, did not alter CSF titer.<sup>34</sup> Furthermore, Purkinje cell destruction probably develops so rapidly that, considering the usual delays in making the diagnosis, Purkinje cells are probably destroyed by the time treatment is undertaken. To prove an autoimmune hypothesis it will be necessary to have an effective animal model of the disease.

Because the anti-Yo antibody is so tightly coupled to breast and gynecologic cancer in patients with cerebellar degeneration, its presence should focus the search for a primary tumor to pelvis and breasts. If the initial diagnostic work-up of breast and pelvis fails to reveal a mass, then one should consider pelvic examination under anesthesia followed by a D&C and, depending on the findings, a hysterectomy and salpingo-oophorectomy. In six patients who were approached in this way, the diagnosis of a gynecologic tumor was established in five. The exploration of the sixth patient was negative but four months later her mammogram, which had previously been normal, became abnormal and a breast cancer was discovered.

#### OTHER PCD SYNDROMES

Paraneoplastic cerebellar degeneration can occur in the absence of the anti-Yo antibody associated with a variety of tumors. In some patients with other PCD syndromes there are other autoantibodies present (Table 2), but in others no antibody is found at all. Some of the other antibodies are associated with specific tumors, such as the anti-Hu antibody in small cell lung cancer, and others are not.

#### CONCLUSIONS

PCD is a rare but well-recognized syndrome that often causes severe disability in patients with occult or easily-treatable neoplasms. The importance of recognizing PCD rests not in the number of patients, but in the fact that the development of the rather typical paraneoplastic syndrome warrants a search for an occult and potentially curable neoplasm. When a specific autoantibody is identified in the serum, the search can be narrowed to one of a few underlying cancers. When no autoantibody is found a more extensive search must be taken. The

biological importance of the syndrome stems from the fact that a subset of patients with particular kinds of cancer have the ability to mount an immune attack with high titers of antibodies that are relatively specific for individual cells in the nervous system and for the underlying tumor. Why only a subset of patients mount the attack is presently unclear. Understanding the immune mechanisms may give clues to the treatment of the underlying neoplasms.

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