Paraneoplastic cerebellar degeneration with anti-Yo antibodies – a review

Anand Venkatraman¹ & Puneet Opal²,³

¹Department of Neurology, University of Alabama at Birmingham, Birmingham, Alabama
²Davee department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois
³Department of Cell and Molecular Biology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Correspondence
Puneet Opal, Davee Department of Neurology, and Department of Cell and Molecular Biology, Northwestern University Feinberg School of Medicine, Ward 10-332, 303 East Chicago Avenue, Chicago IL 60611. Tel: 312 5034 699; Fax: 31 2503 0872; E-mail: p-opal@northwestern.edu

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Abstract
The ataxic syndrome associated with Anti-Yo antibody, or Purkinje cell cytoplasmic antibody type 1 (PCA1), is the most common variant of paraneoplastic cerebellar degeneration (PCD). The typical presentation involves the subacute development of pancerebellar deficits with a clinical plateau within 6 months. The vast majority of cases have been reported in women with pelvic or breast tumors. Magnetic resonance imaging of the brain is often normal in the early stages, with cerebellar atrophy seen later. The underlying mechanism is believed to be an immunological reaction to cerebellar degeneration-related protein 2 (CDR2), a protein usually found in the cerebellum that is ectopically produced by tumor cells. Although both B- and T-cell abnormalities are seen, there is debate about the relative importance of the autoantibodies and cytotoxic T lymphocytes in the neuronal loss. Cerebrospinal fluid abnormalities, primarily elevated protein, lymphocytic pleocytosis, and oligoclonal bands, are common in the early stages. The low prevalence of this condition has not allowed for large-scale randomized controlled trials. Immunotherapies, such as steroids, intravenous immune globulins, and plasma exchange, have been extensively used in managing this condition, with limited success. Although some reports indicate benefit from antitumor therapies like surgery and chemotherapy, this has not been consistently observed. The prognosis for anti-Yo PCD is almost uniformly poor, with most patients left bedridden. Further studies are required to clarify the pathophysiology and provide evidence-based treatment options.

Introduction
Paraneoplastic cerebellar degeneration (PCD) is a collection of neurological disorders resulting from tumor-induced autoimmunity against cerebellar antigens. There are nearly 30 different antibodies associated with this condition.¹ In this review, we have focused on the most common subtype of paraneoplastic cerebellar degeneration, the syndrome associated with anti-Yo, or anti-Purkinje cell cytoplasmic antibody 1 (PCA-1)² that accounts for nearly 50% of cases.³

Between 90 and 98% of patients with cerebellar ataxia and anti-Yo antibodies have a cancer detected,⁴,⁵ the vast majority of which are pelvic and breast cancers. A few cases with lung cancers have been reported,⁶ while in male patients, many of the tumors reported were adenocarcinomas of the gastrointestinal system and prostate.⁷,⁸ Given the association with breast and gynecological cancers, females form the vast majority of patients, with less than 20 cases described in males.⁵

It is likely that many of the earliest case reports of PCD, such as those described by Brouwer in 1919⁹ and Parker in 1933,¹⁰ were of the anti-Yo subtype, given their association with pelvic and breast malignancies. The prevalence of anti-Yo PCD, however, is still very low – one study found that only 2.3% of 557 patients with ovarian cancer and 1.6% of 253 patients with breast cancer were positive for the antibody, and only about 12% of those positive for the antibody had PCD.¹¹ Another case series of 181 patients with ovarian cancers showed that four had elevated anti-Yo titers, but none of them developed symptoms within 2 years of follow-up.¹²
Given that anti-Yo PCD accounts for approximately half of all PCD, it is among the best studied of the paraneoplastic cerebellar syndromes. Still, because of its rarity, the majority of the clinical literature on this topic remains in the form of case series and reports. Our goal, with this paper, is to summarize the pathophysiology, clinical presentation, management options, and prognosis of anti-Yo PCD.

**Presentation**

In general, PCD predates the cancer diagnosis. In approximately 30% of patients, the ataxic symptoms occur when the cancer is in remission. Occasionally, in the workup of cancers, anti-Yo antibodies are identified with PCD symptoms occurring up to 5 years later. PCD associated with anti-Yo antibodies usually presents with the subacute development of cerebellar deficits over a period of weeks to months. A differential diagnosis is provided in Table 1. One case series found a median patient age of 61 years (range 26–85 years). The median delay between symptom onset and definitive diagnosis of this condition has ranged between 2 and 3.5 months.

Clinically, it is difficult to differentiate anti-Yo PCD from other subacute cerebellar ataxias. As a pancerebellar syndrome, the ataxia affects both the trunk and limbs, but onset can be asymmetric in a subset of patients. Symptoms suggestive of brainstem involvement, such as dysarthria, nystagmus, diplopia, and dysphagia are often noted, and symptoms appear to reach a plateau within 6 months of onset, even without any intervention. Cognitive and psychiatric morbidity, especially memory loss and emotional lability, is also common in these patients, but concomitant dystarthis has made this difficult to ascertain. Extracerebellar involvement such as limbic encephalitis and peripheral neuropathy is less severe and less common in anti-Yo PCD than in anti-Hu syndrome.

The ataxia is usually severe – of the 48 patients reported by Peterson et al., only two could walk unassisted. It was asymmetric in onset in about 40% of patients, but soon became symmetric. Rojas et al. in their study of 34 patients with anti-Yo PCD found that nearly 60% were chairbound at the time of initial diagnosis. Thirty-two of 34 patients eventually became nonambulatory, with 65% of patients taking less than 4 months to reach their clinical nadir.

Early on, magnetic resonance imaging of the brain in the anti-Yo syndrome can be normal, and cerebellar atrophy is usually seen only after the disease is well established. 18-FDG PET can show reductions in mean metabolic rate in the cerebellum. However, a case with extensive MRI signal abnormality in the cerebellar hemispheres early in the course of anti-Yo PCD has been reported. Furthermore, diffuse Purkinje cell degeneration with CD8 lymphocytic infiltration and microglial activation has been found at autopsy in a patient with a normal MRI scan, indicating that the correlation between imaging findings and pathology is not clear.

**Diagnostic Criteria**

The current scientific consensus includes subacute cerebellar degeneration among the “classical” paraneoplastic syndromes. The commonly used diagnostic criteria, based on the guidelines set forth by an international panel supported by the Paraneoplastic Neurological syndrome Euronetwork in 2004, require the development of a severe pancerebellar syndrome in <12 weeks, with no MRI evidence of cerebellar atrophy, other than what would be expected given the patient’s age. However, there have been isolated reports of diffuse T2 signal changes in the cerebellum of patients with anti-Yo PCD. A Rankin score of at least 3 (indicating moderate disability, requiring some help but able to walk unassisted) is required, where symptoms significantly interfere with the lifestyle or prevent independent existence. Clinical evidence of truncal and hemispheric cerebellar involvement is required, and noncerebellar findings do not rule out the diagnosis. A classical syndrome and cancer that develops within 5 years of neurological symptoms meets the criteria for definite PNS, but a neurological syndrome with a well-characterized onconeural antibody is also considered definite PNS. Possible PNS is defined as a classical syndrome with no onconeural antibodies or cancer, but where the patient is at high risk of having one.

The primary complicating factors in making the diagnosis are that the cancer, cerebellar signs and antibody are not always detected simultaneously. Past or family history of cancer and the presence of systemic symptoms such as anorexia and weight loss can raise the index of suspicion for paraneoplastic etiologies for a patient’s ataxia. Abnormal cerebrospinal fluid (CSF) findings can

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**Table 1.** Differential diagnosis for subacute ataxia in adults.

| Demyelinating diseases such as multiple sclerosis |
| Systemic autoimmune disorders such as sarcoidosis, behcet’s, lupus |
| Alcohol abuse, Wernicke’s syndrome, Vitamin E, B12 deficiencies |
| Medication toxicities e.g., Phenytion |
| Miller-Fisher variant of Guillain–Barre syndrome |
| Steroid-responsive encephalopathy associated with thyroid disease |
| Anti-GAD antibody-associated ataxia |
| Gluten ataxia, celiac disease |
| Atypical infections: progressive multifocal leukoencephalopathy, prion disease, Whipple’s disease |
| Paraneoplastic cerebellar degeneration |

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bring inflammatory conditions higher in the differential diagnosis. After ruling out other etiologies of subacute ataxias (Table 1), a paraneoplastic antibody panel must be done, usually on a blood sample. If an antibody is detected, a search for a primary neoplasm using whole-body computed tomography (CT) must be done, with positron emission tomography (PET) scans if the CT is negative.\(^{23}\) Mammograms, transvaginal ultrasounds and rarely, exploratory laparotomies may be performed in select cases.\(^{24}\) In cases where the initial tumor screen is negative, patients should be followed at regular intervals with scans, for instance every 6 months for the next 4 years.\(^{23}\)

A tumor search should be considered even in cases where antibody testing is negative, if clinical suspicion is high, and repeat antibody testing can be ordered,\(^{22}\) since the tests are not 100% sensitive. Monstad et al. compared various techniques for the detection of anti-Yo antibodies, and found immunoprecipitation to be more sensitive than immunofixation and immune blots.\(^{11}\) Furthermore, there may be a delay in development of the antibodies, and some studies suggest that anti-Yo antibodies are a better marker for a tumor than for a PNS.\(^{11}\) A review\(^{4}\) in 2004 found about 107 cancer patients in the literature till that time with anti-Yo antibodies but no paraneoplastic neurological syndromes, about 1% of the total. Lower titers of the antibody can be found even in healthy individuals, although this is rare.\(^{25}\)

**Pathogenesis**

**Anti-Yo antibody**

The anti-Yo antibody was first identified as a high-titer antibody targeted against Purkinje cells in patients with PCD, by Greenlee and Brashear in 1983.\(^{26}\) Techniques to detect antibodies in patient sera steadily improved over the next decades, moving from amplification using biotin labeling, to western blots.\(^{27}\) Sakai et al., in 1990 and Fathallah-Shaykh et al., in 1991\(^{29}\) cloned the antigenic target of these antibodies, allowing for further research into their mechanisms of action.

The antibody is usually of the IgG1 subtype, although in rare cases, IgG2, IgG3, IgM, or IgA may be seen.\(^{30}\) It is present both in serum and CSF (with titers usually higher in the CSF),\(^{31}\) fixes complement,\(^{32}\) and binds in a coarse, granular pattern to Purkinje cell cytoplasm sparing the nucleus and axons. Some targets outside the cerebellum have been reported, in the brain, retina, dorsal root and autonomic ganglia, adrenal medulla, and myenteric plexus.\(^{33}\) In the PCs, the binding is to free and bound ribosomes, the endoplasmic reticulum, and vesicles of the Golgi complex.\(^{34,35}\)

Two bands are seen on western blot performed with Purkinje cell lysates, a major one at 62kDA and a minor one at 34 kDA.\(^{36}\) The main cellular target, at 62kDA, is the cerebellar degeneration-related protein 2 (CDR2). It is a subtype of the cerebellar degeneration proteins, a group of proteins that are strongly expressed in the cerebellum. Of the other targets, the 34 kDA protein, which is recognized inconsistently, and at lower magnitudes than the 62kDA antigen, has been shown to contain a unique six amino acid consensus sequence (L/FLEDVE).\(^{37,38}\) Anti-Yo sera have also been shown to bind to CDR3, which is similar to CDR2, and to CDR2L (CDR2-like).\(^{27,39}\)

The CDR2 protein is believed to play multiple roles in the regulation of transcription. Although the CDR2 mRNA can be found in almost all neurons, expression is limited to the PCs, some brainstem areas, and spermatogonia – all of which are immune-privileged locations.\(^{32,40}\) It is also known to be overexpressed in ovarian and breast malignancies,\(^{41}\) and loss of immune tolerance to this protein is believed to trigger the synthesis of the autoantibody.

The identification of a leucine zipper motif on the amino terminus of the protein initially led to the suggestion that it might be involved in gene expression.\(^{29}\) However, further studies localized it to the cytoplasm, not the nucleus, where it was found both in the free form and associated with ribosomes.\(^{35}\) There is evidence to suggest that the normal function of CDR2 is to interact with transcription factor c-Myc, sequestering it in the cytoplasm and thus inhibiting c-Myc-dependent transcription. It is intriguing that in cell-based assays, this process is blocked by sera from anti-Yo PCD patients.\(^{42}\) A similar transcriptional regulatory role has been suggested for CDR2 vis-a-vis NFkB,\(^{43}\) a transcription factor believed to be involved in neuronal development and synaptic plasticity, and MRGX, a transcriptional regulator involved in cell growth, DNA repair, and apoptosis.\(^{44}\)

**Pathology**

Microscopically, mild perivascular cuffing by lymphocytes, microglial activation and the infiltration of the cerebellar Purkinje layer by CD8 lymphocytes are the early changes in PCD.\(^{20}\) Both B and T cells are seen, as are plasma cells, cells of microglia/macrophage lineages,\(^{45}\) and reactive Bergmann cell gliosis. Inflammatory infiltrates can also be seen in the brainstem and cerebral cortex, albeit of lower magnitude than in the cerebellum.\(^{32}\) As the disease progresses, massive loss of PCs without inflammation is noted.\(^{36,47}\) The loss of PCs is often very rapid, and the absence of inflammatory cells, immunoglobulin, and complement deposits in some earlier histopathological studies may owe to the fact that these patients were already at the final “burn-out” stage.\(^{16,45,48}\)

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The precise mechanism of cell death in anti-Yo PCD is not clear. The presence of high titers of anti-Yo antibodies in the CSF of patients early in the course of the disease, synthesized by B cells in the intrathecal compartment, combined with the findings of selective death of PCs on autopsy studies, suggested a relationship between these processes. Anti-Yo antibodies can be taken up and lead to Purkinje cell death in cultures and cerebellar slices through a mechanism other than apoptosis. However, neither passive nor active immunization of animals, with patient sera, recombinant fusion proteins or cDNA, has been able to reproduce PCD. Given that the target of the anti-Yo antibody in PCs was intracellular, not on the cell membrane, there were efforts to look for other mechanisms for the death of Purkinje cells. It was suggested that the antibodies represented humoral immune system coactivation alongside a cytotoxic T-cell response, as several pathological and pathophysiological studies suggested a major role for sensitized CD8+ T cells in the death of PCs. The binding of the antibodies to their targets was thought to cause the appearance of sensitized T cells in patients’ CSF as well as the peripheral blood. However, CDR2-specific cytotoxic T cells were not reported in all studies, and transfer of lymphocytes from patients with anti-Yo PCD did not produce PC damage.

A significant recent advance was the finding that the anti-Yo antibody caused PC death in rat cerebellar slices by binding to its intracellular antigen, without involvement of other factors, antibodies, or brain mononuclear cells. Adsorption of the antibody by the 62kDA antigenic target was able to stop PC death. Macrophages and microglia did not infiltrate the PC layer until significant amounts of PC loss had already happened, indicating that the cell death process was not initiated by the monocytes in the brain. It was not the mere accumulation of IgG that caused the pathologic process, since antibodies to other intracellular antigens were taken up by the PCs without causing cell death. These findings led the authors to hypothesize that the 62kDA antigen was essential for PC survival.

Another recent study has suggested that dysregulation of calcium homeostasis by anti-Yo antibodies may be the initial mechanism of attack on PCs. When anti-Yo from human and rabbit sera bound to PCs in rat cerebellar slices, calbindin D28K and a protein modulating the P/Q-type calcium channel were downregulated, and reduced PC dendritic arborizations were seen. Given that CDR2 co-immunoprecipitates with calbindin in PCs, it is possible that the binding of the anti-Yo antibody to its target leads to the interruption of calbindin signaling. The authors suggest a pathway where PCs are first silenced by interruption of calcium signaling by internalized anti-Yo antibodies, and then cleared by cytotoxic T cells and microglia. PKCγ, a calcium-dependent kinase, Cav2.1, a voltage-gated calcium channel, and the calcium-dependent protease calpain-2 were upregulated, which would increase intracellular calcium levels, potentially triggering cell death pathways.

**CSF changes in paraneoplastic syndromes of the CNS**

CSF abnormalities were noted in 93% of patients with paraneoplastic neurological syndromes reported by Psimaras et al., without no difference between the various autoantibody types. Of 53 patients with anti-Yo syndrome, 51 had abnormal CSF with mild pleocytosis, protein elevation, and/or oligoclonal bands. Median WBC count in this group was 4/mm³ (interquartile range 1–22). Pleocytosis was more common when the study was done soon after symptom onset, with median of 5 WBC/mm³ before the third month and 2 WBC/mm³ after the third month. Other studies have also confirmed that lymphocytes often predominate when pleocytosis is detected.

In the study from Psimaras et al., protein levels in the CSF were at a median of 54 mg/dL overall (normal range being between 15 and 45 mg/dL), 73 mg/dL before the third month, and 59 mg/dL after the third month. Oligoclonal bands were checked for in 33 patients, and were positive in 25 patients. The majority of patients with these conditions are known to have oligoclonal bands, often targeted against the same antigen as the anti-Yo antibody.

This temporal pattern of change is thought to be in line with the absence of inflammatory infiltrates when assessed more than 1 year after symptom onset. A total of 12% of patients in the Psimaras et al. case series, who had initially had abnormal CSF with elevated protein and WBC counts, had completely normal CSF after 3 months of neurological symptom onset. They did not find any significant changes in CSF in 12 patients who underwent antitumor and immunological therapies.

**Treatment**

The extremely low prevalence of PCD has not allowed the conduction of randomized controlled trials, with the result that evidence-based guidelines on treatment are lacking. The natural tendency of the disease to plateau around 6 months after onset makes it difficult to determine whether treatments were effective.

Three of the largest case series dealing with anti-Yo PCD have reported that immunotherapies, such as corticosteroids, plasma exchange (PLEX), and intravenous immune globulin (IVIG) to be largely ineffective.
Peterson et al.\textsuperscript{16} reported that PLEX was tried in 22 patients, of whom only one showed moderate sustained clinical benefit. Four patients showed mild, transient improvement in dysarthria and ataxia. High-dose steroids produced mild, transient improvements in 1 of 17 patients. Four patients showed no clinical benefit from cyclophosphamide. Rojas et al.\textsuperscript{15} reported no benefits in 23 patients who received some form of immunosuppression, while Shams’ili et al.\textsuperscript{17} reported that two patients out of four improved or stabilized with immunosuppression. There are, of course, smaller reports which describe benefit from immunosuppressive approaches. Vernino et al.\textsuperscript{59} reported slight clinical improvement after PLEX and cyclophosphamide in two of four patients with anti-Yo PCD, who had no evidence of malignancy. The other two got worse, with one patient later developing a malignancy. Sustained improvement from IVIG has been reported by Schssel et al. and Phuphanich et al. in three patients where the malignancy had been adequately treated.\textsuperscript{60,61} Meloni et al.\textsuperscript{62} described a case of nonparaneoplastic anti-Yo cerebellar ataxia, with extensive investigation not revealing a tumor, that showed significant improvement in response to plasmapheresis. Other cases with PCD associated with metastatic cancer showed brief benefits from plasmapheresis that may have been due to an inability to completely remove the antigenic stimulus causing autoantibody production.\textsuperscript{63,64} A response to a single dose of cyclophosphamide was reported by Thone et al. in an elderly patient who did not receive any antitumor therapy due to her age.\textsuperscript{65} Four cycles of rituximab produced neurological improvement and a decline in CSF antibody titers in one patient reported by Shams’ili et al., who achieved partial tumor remission with surgery.\textsuperscript{66}

Hitherto-undetected pathological antibodies being cleared by immunotherapies might be one explanation for the improvement seen in a minority of patients with anti-Yo syndrome. However, publication bias is likely to be significant in these reports, and overall rates of response are better reflected by the large case series. As opposed to the findings in anti-Yo PCD, immunotherapies are frequently effective against the type of PCD where antigens near the cell membrane are targeted.\textsuperscript{59}

One novel approach involved using tacrolimus to decrease activated cytotoxic T lymphocytes in three patients with PCD, of whom two had ovarian and one had breast malignancies.\textsuperscript{84} The Cytotoxic T lymphocyte count fell from about 30% to <1% of cells in the CSF, but the effect was lost as soon as tacrolimus was stopped. No change was noted in the neurological symptoms, but the patients had already been significantly affected by the time tacrolimus was tried.

For paraneoplastic neurological syndromes in general, guidelines from the Agency for Healthcare Research and Quality recommend early antitumor therapy as the approach that offers the greatest chance for PNS stabilization.\textsuperscript{23} However, studies limited to anti-Yo PCD have not been uniformly optimistic.\textsuperscript{67-69} Candler et al.\textsuperscript{70} reported that only tumor therapy was effective in stabilizing or improving neurological outcomes, in a study of 63 patients with paraneoplastic neurological syndromes, of which 11 were positive for the anti-Yo antibody. In cases where a tumor is found at the same time as the PCD is diagnosed, using immunosuppressive drugs and monoclonal antibodies is controversial, but is often attempted in conjunction with antitumor approaches.\textsuperscript{61} Two of six patients reported by Shams’ili et al.\textsuperscript{17} improved or stabilized with a combination approach, but most other reports have been negative.\textsuperscript{7,15,71} Surgery after 8 months of symptom onset helped in one patient who did not benefit from IVIG and steroids,\textsuperscript{72} while another experienced stabilization of neurological symptoms after breast surgery.\textsuperscript{73} It is possible that anti-Yo positivity might be correlated with Her2/Neu overexpression in breast cancers, since trastuzumab therapy in addition to paclitaxel produced improvement in the cerebellar symptoms.\textsuperscript{74}

**Monitoring progress with antibody titers**

Monitoring response to therapy is complicated, since antibody titers may not correlate with symptoms. Peterson et al.\textsuperscript{16} noted no correlation between serum and CSF IgG titers and the disease course, with the antibody persisting in all patients even after treatment. PLEX was tried in 22 patients in their series, and produced sustained decline in serum antibody titers in at least six patients, of which one had a moderate sustained clinical benefit, regaining her ability to walk with assistance. CSF antibody titers showed no change in the other four, who did not show any clinical improvement either. One report described decline in serum autoantibody titers with PLEX but no clinical improvement, while subsequent IVIG treatment produced clinical improvement,\textsuperscript{75} although another case showed progression of neurological symptoms even after reduction of anti-Yo titers,\textsuperscript{76} indicating that damage can happen even with titers of antibodies reduced.

**Prognosis**

Progression of disability leads to <10% of patients able to ambulate without assistance over the long term, with the majority left bedridden.\textsuperscript{15,17,77} Long-term survival rates were reported less than 25%.\textsuperscript{78} Peterson et al.\textsuperscript{16} had 19 deaths out of 55 patients within 4 years, while Rojas et al.\textsuperscript{15} had at least 18 deaths out of 34 within 8 years. However, these studies differ on the relative prominence of tumor progression versus neurological disability in
causing mortality. Anti-Yo patients had a median survival of 13 months, which was higher than that for anti-Hu syndrome, but lower than that for anti-Tr syndrome (113 months) which is associated with Hodgkin’s disease. Anti-Yo PCD has better prognosis with breast cancer and worse with ovarian cancer, reporting 100 month survival with breast versus 22 month survival with ovarian malignancies.

Early treatment is thought to be important in impacting the clinical course of paraneoplastic neurological syndromes. Widdess-Walsh et al., reviewing 15 prior case reports of IVIG use in anti-Yo PCD, found that treatment initiation within a month of symptoms was associated with better outcomes. There have been some other cases which showed good response to initiation of immunosuppression within the first month, perhaps before extensive Purkinje cell loss had occurred. However, other large series have not found convincing evidence for earlier treatment initiation. One explanation might be that severe, rapidly progressive disease is likely to be detected earlier, which can result in early-diagnosis groups being disproportionately composed of patients with severe symptoms. Younger patients, and those with less initial disability, appear more likely to show good treatment response.

Conclusions

PCD remains a difficult condition to treat, and anti-Yo PCD in particular is associated with some of the poorest response rates to standard therapies. Involvement of both cellular and humoral responses along with nonimmunological mechanisms, and rapid Purkinje cell death before therapies can take effect, are likely to contribute to this resistance to therapy. Intense rehabilitation is therefore of vital importance. However, a subset of patients with anti-Yo PCD do show improvement, and therefore a trial of therapies is warranted. The precise mechanism of cell death in the cerebellum will be crucial in advancing our understanding of this condition, and will be essential in opening the door to better therapeutics. Novel immunotherapies are under investigation, and it is likely that early detection combined with targeted therapies will be more efficacious in halting or reversing the neurological decline seen in these patients.

Conflict of Interest

None declared.

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