An Etiological Investigation of Paraneoplastic Cerebellar Degeneration in Ovarian Cancer Patients: A Systematic Review

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Abstract
Paraneoplastic syndromes (PNS) are uncommon, distinct clinical complications of a primary tumor. Paraneoplastic cerebellar degeneration (PCD) is a PNS that is described as an autoimmune response targeting Purkinje cells in the cerebellum. Ovarian cancer (OC) is one of the most prevalent causes of cancer-related deaths in women. Anti-Yo is the most common onconeural antibody produced in the PCD immune response and is most typically found in ovarian and breast cancer patients. While the current literature highlights the predisposing genetic factors, diagnostic workflows, and treatment options, the pathophysiology of PCD, among other considerations, remains largely unestablished. This review aimed to systematically observe procedural solutions to facilitate an early diagnosis and improve the prognosis of patients with OC-associated PCD. To that end, we examined literature published from 01/01/2015-11/10/2022 indexed in PubMed by using the keywords "paraneoplastic, cerebellar degeneration" combined with "ovarian cancer." Inclusion criteria were met if PCD and OC diagnoses were made and if studies provided adequate patient information. After screening and assessing records for eligibility using the inclusion and exclusion criteria, 18 articles involving 102 patients were included. The typical patient observed in this sample was diagnosed with International Federation of Gynecology and Obstetrics (FIGO) Stage III, high-grade serous carcinoma. The diagnostic workup typically included a clinical evaluation for dysarthria (50%), ataxia (60%), and gait abnormalities (50%), along with multiple imaging modalities and serological findings (90%). Genetic screening for human leukocyte antigen (HLA) haplotype susceptibility for PCD and immune tolerance modulators regulation may also be recommended prior to starting treatment. Findings support the use of corticosteroids (35%) and intravenous immunoglobulin (IVIg) (40%) as viable treatment options for managing PCD in conjunction with systemic therapy for the primary malignancy. A diagnosis of PCD should be considered if a patient has had a malignancy in the past five years with the presence of explicit cerebellar symptoms. This clinical diagnosis can be further supplemented by serologic and radiologic findings. Recognizing PCD symptoms and scheduling genetic and proteomic testing may help with early diagnosis and better prognosis.

Introduction And Background
Paraneoplastic syndromes (PNS) are a diverse set of clinical complications that occur as a consequence of several primary malignancies. These complications are largely caused by the production of cytokines, hormones, or peptides by the tumor cells or due to an immune response elicited by the primary tumor [1]. Various distinct paraneoplastic syndromes have been reported, including dermatological (vasculitis, myositis), rheumatological (polymyalgia rheumatica, hypertrophic osteoarthropathy), endocrinological (syndrome of inappropriate antidiuretic hormone secretion, Cushing’s syndrome, hypercalcemia), neuromuscular (myasthenia gravis, Lambert-Eaton syndrome), and neurological (encephalitis, opsoclonus-myoclonus, and subacute cerebellar degeneration) [1]. Paraneoplastic cerebellar degeneration (PCD) is a rare complication of certain malignancies affecting less than 1% of all cancer patients. It is commonly seen in breast cancer and pelvic malignancies but has also been reported in Hodgkin’s lymphoma, gastric cancer, prostate cancer, and small-cell lung cancer [2,3].

The clinical presentation of PCD includes altered gait, diplopia, and difficulty with fine motor skills, with eventual progression to limb and truncal ataxia [4,5]. These symptoms usually occur over several weeks but can progress rapidly in certain cases [6]. The pathophysiology of PCD is hypothesized to be from antibodies produced in response to an onconeural antigen; this antigen is the cerebellar degeneration-related protein 2 (CDR2) and is expressed by tumor cells [3]. This antigen is also found in the Purkinje cells of the cerebellum. The etiology of PCD is thought to be a cross-reactive immune reaction where antibodies targeted at antigens present in the tumor cells attack the same antigens present in the cerebellum [3]. However, the presence of...
PCD is a well-established indicator of occult malignancy. Peterson et al. (1992) reported that in 34 out of 55 patients with PCD studied, the diagnosis of a neoplasm was preceded by symptoms of neurological origin [6]. Furthermore, in all but one of the 19 patients with gynecological cancer, malignancy preceded the evidence of the onset of neuropathy [12]. Identifying PCD requires a multitude of criteria, including the presence of neurological symptoms. The discovery of PCD should be accompanied by an immediate investigation of the primary malignancy, and the discovery of associated onconeural antibodies could indicate an underlying malignancy. Imaging studies alone cannot be used for a conclusive diagnosis of PNS; however, they are essential in ruling out other diagnoses. Surgical removal of the primary tumor is likely the most effective treatment, although it is not effective in all cases [5]. The previous literature highlights key diagnostic features, clinical presentation, and pathology of PNS through onconeural antibody identification and malignancy screening [5]. However, with established diagnostic criteria for neuronal surface antibodies syndrome (NSAS) and improved diagnostic tools, the incidence of PCD has risen in the last few years [5]. This review aims to develop a complete clinical profile of PCD and propose a diagnostic framework while evaluating potential treatment modalities. By including genomics, radiologic findings, and the complete clinical picture, a provider can effectively narrow down a PCD diagnosis.

**Review**

**Methods**

**Literature Search**

This systematic review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [13] and is registered with the National Institute for Health Research (PROSPERO). Reviewers examined published studies from 01/01/2015 to 11/10/2022, using PubMed as the sole search database. The following search queries were used to elicit articles of relevancy: ((paraneoplastic) OR (cerebellar degeneration)) AND (ovarian cancer).

**Study Selection**

Three reviewers (A.A., A.F., J.R.) assessed a list of relevant articles to guarantee that the inclusion criteria were met. The following study designs were included: case reports, case series, and retrospective and prospective cohort studies. For inclusion, the study had to describe the findings of patients with a known PCD and OC diagnosis. The study also had to provide evidence of significant cerebellar dysfunction in cases where the patient was diagnosed with a non-specific PNS. In studies with a sample size >1, data were only gathered for the subsets of patients reporting PCD and OC.

**Data Extraction**

The following data were collected from each study: study design, presence of anti-Yo antibodies, sample size, the mean age of the sample, prognosis, patient history, treatments, imaging modalities, the time between the onset of cerebellar dysfunction and tumor identification, histological subtype, International Federation of Gynecology and Obstetrics (FIGO) staging, neurological assessment, explorative surgery performed, and laboratory results. Statistical analysis was not performed due to the heterogeneity of the included studies. This review was analyzed purely from a thematic perspective with a report on frequencies of items of interest. The following themes were examined: patient characteristics, clinical manifestation, diagnostic workup, treatment regimens, protein expression, and genetic predisposition.

**Results**

The study selection procedure is outlined in Figure 1. The search strategy yielded 176 unique records. After the abstract and full-text screening, 18 publications, including 102 cases, were selected. Table 1 presents a systematic summary of the included studies.
### FIGURE 1: PRISMA 2020 flow diagram depicting the selection of studies

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; PCD: paraneoplastic cerebellar degeneration; PNS: paraneoplastic syndromes

| Author       | Design     | Anti-Yo antibody presence | Sample | Mean age (years) | Prognosis                        | Patient history                                                                                       | Treatments                                                                                     | Imaging modalities used in ovarian cancer or PCD diagnosis |
|--------------|------------|---------------------------|--------|-----------------|----------------------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|----------------------------------------------------------|
| Birch et al. | Case study | Negative                  | 1      | 73              | Worsened impairment              | No history of alcohol, smoking, or familial predisposition. The patient had a history of tuberculosis and hypertension | The patient declined treatment beyond tumor resection                                             | CT, ultrasound, echocardiogram, MRI                                                                   |
| Shibata et al. | Case study | Negative                  | 1      | 65              | Recovery                         | No notable medical history                                                      | Chemotherapy, IVIg                                                                             | CT, MRI                                                   |
| Boujoual et al. | Case study | Not tested                | 2      | 46              | Long-term outcomes not reported  | N/A                                                                             | Treatment not specified beyond tumor resection                                                 | MRI, CT                                                   |
| Butt et al.  | Case study | Negative                  | 1      | 69              | PCD progression prevented        | History of hypertension, asthma, gastroesophageal reflux disease, depression, and familial predisposition to cancer | Chemotherapy                                                                                  | CT, MRI                                                   |
| Chien et al. | Case study | Positive                  | 1      | 44              | PCD progression prevented        | No history of alcohol, smoking, illicit drugs, or familial predisposition         | Plasmapheresis, chemotherapy                                                                    | MRI, CT                                                   |
| Cui et al.   | Case study | Positive                  | 1      | 65              | Recovery                         | N/A                                                                             | Chemotherapy, IVIg, corticosteroids                                                              | Ultrasound, CT, MRI                                       |
| Authors            | Study Type          | Outcome     | N | Age | Length of follow-up | Characteristics | Treatment                              | Imaging                  |
|--------------------|---------------------|-------------|---|-----|---------------------|----------------|-----------------------------------------|--------------------------|
| Dandapat et al.    | Case study          | Positive    | 1 | 60  |                     | Recovery       | No history of psychiatric conditions   | MRI, CT                 |
| Deac et al.        | Case study          | Positive    | 1 | 59  |                     | Death          | The patient's social, familial, and     | MRI, CT, ultrasound      |
|                    |                     |             |   |     |                     |                | medical history was insignificant       |                          |
| Jurkiewicz et al.  | Case study          | Positive (n=2) | 3 | 16  |                     | Recovery (n=3) | N/A                                     | MRI, CT, ultrasound      |
|                    |                     |             |   |     |                     |                | N/A                                     |                          |
| Lehner et al.      | Case study          | Positive (n=5) | 6 | 57  |                     | Death (n=2), worsened impairment (n=3), recovery (n=1) | Chemotherapy (n=4), ERK inhibitor (n=1), corticosteroids (n=5), IVIg (n=3), tacrolimus (n=3), plasmapheresis (n=2) | MRI, CT                 |
| Li et al.          | Case study          | Positive    | 1 | 37  |                     | Recovery       | N/A                                     | Chemotherapy             |
|                    |                     |             |   |     |                     |                | N/A                                     | MRI, CT, ultrasound      |
| Liapi and Sarivalasis | Case study        | Positive    | 1 | 61  |                     | PCD progression prevented | History reported was associated with a favorable oncological prognosis | Chemotherapy             |
|                    |                     |             |   |     |                     |                |                                         | MRI, CT                 |
| Renjan et al.      | Case study          | Positive    | 1 | 65  |                     | Long-term outcomes not reported | No history of alcohol and smoking | Chemotherapy, IVIg       |
|                    |                     |             |   |     |                     |                |                                         | Radiograph, MRI          |
| Smith and Samkoff  | Case study          | Negative    | 1 | N/A |                     | Recovery       | N/A                                     | Broad-spectrum antibiotics, dexamethasone, acyclovir, corticosteroids, IVIg | MRI, CT, ultrasound      |
|                    |                     |             |   |     |                     |                |                                         |                          |
| Raspotnig et al.   | Retrospective study | Positive (n=6) | 16 | 67  |                     | N/A            | N/A                                     | N/A                     |
|                    |                     |             |   |     |                     |                |                                         |                          |
| Small et al.       | Retrospective study | Positive (n=26) | 26 | 64  |                     | N/A            | N/A                                     | N/A                     |
|                    |                     |             |   |     |                     |                |                                         |                          |
| Vialatte de Pernille et al. | Retrospective study | Positive (n=12) | 12 | 62  |                     | N/A            | N/A                                     | N/A                     |
|                    |                     |             |   |     |                     |                |                                         |                          |
| Hillary et al.     | Retrospective study | Positive (n=43) | 43 | N/A |                     | N/A            | N/A                                     | N/A                     |

**TABLE 1: Summary of studies evaluating patients with paraneoplastic cerebellar degeneration and ovarian cancer**

PCD: paraneoplastic cerebellar degeneration; CT: computed tomography; MRI: magnetic resonance imaging; IVIg: intravenous immunoglobulin; N/A: not available

**Patient Characteristics**

A total of 119 patients were observed across the 18 articles included. After removing patients without a conjunct discovery of PCD and OC (n=17), we were left with a total of 102 patients. The patient population’s ages ranged from 16 to 85 years, with the mean age being 51 years. The main patient characteristics are summarized in Table 2. Of note, 71% of patients had the histological subtype of high-grade serous carcinoma (HGSC). Most patients were diagnosed with FIGO stage III.

| Characteristics of total sample (n=62) |
|---------------------------------------|
| Histological subtype                  | N (%)  |
| HGSC                                  | 44 (71) |
| Other | 14 (23) |
|-------|---------|
| Not specified | 4 (6) |

### Staging at tumor diagnosis

| I     | 5 (8) |
|-------|-------|
| II    | 6 (10) |
| III   | 31 (50) |
| IV    | 9 (15) |
| Not specified | 10 (16) |

#### Case study subsample (n=20)

### Neurological assessment

| Dysarthria | 10 (50) |
| Dysmetria | 7 (35) |
| Ataxia | 12 (60) |
| Gait abnormality | 10 (50) |
| Labile mood | 2 (11) |
| Diplopia | 4 (20) |
| Vertigo | 8 (40) |

#### Imaging

| MRI | 19 (95) |
| CT | 16 (80) |
| Ultrasound | 8 (40) |
| Radiograph | 2 (10) |

#### Laboratory results

| CSF antibody panel | 9 (45) |
| Serum antibody panel | 13 (65) |
| Lumbar puncture | 10 (50) |
| Serum tumor markers (CA-125) | 10 (50) |
| CDR2/CDR2L | 1 (5) |

#### Explorative surgery

| Laparotomy/ laparoscopy | 9 (45) |

#### Outcome

| Death | 3 (15) |
| Recovery | 9 (45) |
| Further impairment halted at tumor resolution | 3 (15) |
| Worsened impairment | 3 (15) |
| Not specified | 2 (10) |

#### Treatment

| Chemotherapy<sup>c</sup> | 12 (60) |
| ERK inhibitor | 1 (5) |
TABLE 2: Characteristics of patients diagnosed with paraneoplastic cerebellar degeneration and ovarian cancer

| Treatment                        | n (%) |
|----------------------------------|-------|
| Plasmapheresis                   | 3 (15)|
| Corticosteroids                  | 7 (35)|
| IVlg                             | 8 (40)|
| Tacrolimus                       | 3 (15)|
| Methylprednisolone               | 3 (15)|
| No further treatment beyond surgical resection | 2 (10)|
| Not specified                    | 4 (20)|

TABLE 2: Characteristics of patients diagnosed with paraneoplastic cerebellar degeneration and ovarian cancer

aCharacteristics of the total sample, excluding Hillary et al.
bCase study subsample, excluding Raspotnig et al., Small et al., Pemille et al., and Hillary et al.
cIncluded chemotherapy agents: carboplatin, paclitaxel, bevacizumab, doxorubicin, cisplatin, and methotrexate

HGSC: high-grade serous carcinoma; MRI: magnetic resonance imaging; CT: computed tomography; CDR2: cerebellar degeneration-related protein 2; CDR2L: cerebellar degeneration-related protein 2L; ERK: extracellular signal-regulated kinase; IVlg: intravenous immunoglobulin

Diagnostic Evaluation

Among the 102 cases analyzed, a diagnostic process was identified in 20 [4,7,14-25]. Diagnostic measures observed in these studies were grouped into neurological assessments, imaging modalities, laboratory findings, and explorative surgeries performed. Neurological assessments were typically conducted initially and included evaluation for dysarthria (50%), dysmetria (35%), ataxia (60%), gait abnormalities (50%), diplopia (20%), and vertigo (40%). These cases were followed up with several imaging methods, such as MRI (95%), CT (75%), or ultrasound (40%) to detect cancerous growth or indications of cerebellar dysfunction. All 20 cases where a diagnostic process was identified reported the use of multiple imaging modalities in the diagnostic workup, the most frequent pairing being an MRI with an abdominal CT. A serum or cerebral spinal fluid (CSF) paraneoplastic panel was obtained in 18 out of 20 patients [4,7,15-23,25]. Serum tumor markers, notably cancer antigen (CA) 125, were tested in half of these patients to confirm the presence of a tumor, track tumor growth, or establish remission status [4,7,15-19,22-24].

Treatment

Fourteen articles included treatment regimens for OC patients with PCD. The most common form of treatment (60%) was combination chemotherapy regimens including carboplatin, paclitaxel, bevacizumab, doxorubicin, cisplatin, and methotrexate [7,15-17,19,21-24]. The most common regimen was a combination of carboplatin and paclitaxel. Treatment involved treating the underlying malignancy and then addressing PCD via immunomodulating therapy. Intravenous immunoglobulin (IVlg) (40%) [7,17,19,21,24,25] and corticosteroids (35%) [17,19,21,25] were the most common treatments used for managing PCD symptoms. Other immunosuppressants utilized for managing PCD symptoms were tacrolimus (15%) [16,21] and plasmapheresis (15%) [21]. Inhibition of extracellular signal-regulated kinases (ERK) was also utilized in the treatment of cancer at a rate of 5% [21], and 10% of studies reported no treatment beyond primary tumor resection [4,18]. While managing PCD and cancer symptoms, there was variability in the duration and dosing of treatments. A few studies noted the pairing of common treatment measures. For example, in the study by Renjen et al. (2018), carboplatin, paclitaxel, IVlg, and plasmapheresis were used as combination therapy [24]. IVlg was not used as a standalone treatment in any of the studies. Additionally, IVlg was not recommended in one of the studies due to a lack of adequate evidence [18]. Only 15% of studies used chemotherapy as a standalone treatment [15]. Treatment effects were highly variable and ranged from complete remission to no remission, but no definitive statements could be made because no studies compared therapeutic efficacy between agents, as they used either a single agent or a combination therapy.

Prognosis

Fourteen studies described the long-term effects among OC patients with PCD (n=20) [4,7,14-25]. Among these studies, there were four subgroups: patients who recovered from neuropathy (45%), patients with impairment halted at tumor resolution (15%), patients with progressive neurologic impairment (15%), and patients who succumbed to their condition (15%) [4,7,14-25]. Another key prognostic factor was the presence
observed for long-term prognosis, of which eight displayed gradual recovery of neurological function or antibody panels report that 40% of patients showed no observable antineuronal antibodies in serum or CSF paraneoplastic anti-amphiphysin, anti-CV2, and anti-Ma2/TA. Of these, anti-Yo antibodies have a higher propensity to Six antibodies hold significance in a PCD diagnosis from patients’ serum and CSF: anti-Yo, anti-Hu, anti-Ri, primary tumor and help rule out certain other etiologies for cerebellar degeneration help narrow the differential diagnosis. Diagnostic imaging, including CT and MRI, can identify and stage the sufficient for a conclusive diagnosis of PCD, but additional imaging, serology, and a lumbar puncture can predisposition when presented alongside subacute ataxia deficiencies, alcoholism, immune-mediated non-paraneoplastic causes, metastatic disease, and hereditary demyelinating diseases, atypical infections, systemic autoimmune disorders, medication toxicities, vitamin context of prevalence and pathology. PCD is often a diagnosis of exclusion due to the lack of certainty regarding patient history, imaging results, and diagnostic evaluation [19]. A diagnosis of PCD may be suggested if the following criteria are met: a cancer diagnosis within five years of the onset of neuropathy, the presence of cerebellar symptoms characteristic of PCD, and the exclusion of other diagnoses causing the cerebellar symptoms [7], such as demyelinating diseases, atypical infections, systemic autoimmune disorders, medication toxicities, vitamin deficiencies, alcoholism, immune-mediated non-paraneoplastic causes, metastatic disease, and hereditary predisposition when presented alongside subacute ataxia [24]. The initial neurological assessment is not sufficient for a conclusive diagnosis of PCD, but additional imaging, serology, and a lumbar puncture can help narrow the differential diagnosis. Diagnostic imaging, including CT and MRI, can identify and stage the primary tumor and help rule out certain other etiologies for cerebellar degeneration [4,15].

Six antibodies hold significance in a PCD diagnosis from patients’ serum and CSF: anti-Yo, anti-Hu, anti-Ri, anti-amphiphysin, anti-CV2, and anti-Ma2/TA. Of these, anti-Yo antibodies have a higher propensity to reverse neurological symptoms, though this association is not necessarily correlated [18]. Cui et al. (2017) report that 40% of patients showed no observable antineuronal antibodies in serum or CSF paraneoplastic antibody panels [17]. These antibodies, notably anti-Yo, appeared in 14 patients (70%) of the subsample observed for long-term prognosis, of which eight displayed gradual recovery of neurological function or
delay in the progression of neurologic impairment [18]. Despite this highly multivariate diagnosis, treatment of the underlying tumor holds precedence before the management of cerebellar symptoms [4]. Treatment of the tumor and timeliness of a diagnosis can be indicative of a stable neurologic outcome and less-severe cerebellar damage. This analysis of PCD studies provides evidence that early diagnosis in combination with therapies targeting both primary malignancy cancer and PCD led to better outcomes in reducing tumor progression as well as controlling neurological symptoms [19]. Lehner et al. (2021) conducted a study involving five patients with OC who received tumor-modulating therapy (n=5), steroids (n=5), IVlg (n=3), tacrolimus (n=3), and plasmapheresis (n=2) [21]. IVlg and corticosteroids were the two most common immunomodulating agents. In patients with PCD, timely diagnosis of the primary tumor and appropriate institution of antitumor therapy and specific PCD-directed therapy can improve neurological outcomes [4].

Although the complete pathophysiology of PCD development has not been established, there have been several hypotheses exploring potential mechanisms of breakdown at different levels. Many autoimmune diseases have been associated with certain HLA haplotypes that increase susceptibility to developing that disease. The findings from a recent study exploring HLA association with PCD suggest it follows a similar pattern. The increased prevalence of the HLA class II haplotypes DRB1*15:01-DQA1*01:05-DQB1*06:03 in OC patients with Yo-PCD could be a predisposing factor for PCD development [29]. HLA class II receptors from antigen-presenting cells (APCs) bind, process, and present extracellular antigens to CD4+ T cells to activate them toward those extracellular antigens [30]. In the case of Yo-PCD, certain HLA class II receptors created from the susceptible haplotypes perhaps have an augmented response to the onconeural antigens resulting in the activation of CD4+ T cells and B lymphocyte production of anti-Yo. Also, CD4+ T cells can prime CD8+ T cells to target specific antigens, such as onconeural antigens [31]. This process significantly amplifies the cytotoxic immune response as CD8+ T cells are believed to be the final effectors of Purkinje cell death [32]. However, HLA haplotype susceptibility alone does not account for all patients with OC and Yo-PCD since the haplotype prevalence within this subpopulation is lower than anticipated (33%). It is very likely that the HLA association only plays a small role in the larger immune tolerance breakdown associated with the pathophysiology behind PCD.

The HLA complex is one of many regulatory mechanisms involved in the maintenance of what is known as immune tolerance. This concept refers to the careful selection of immune cells that are sensitive enough to detect foreign antigens to mark for destruction while also recognizing self-antigens to protect against autoimmunity [33]. The AIRE gene encodes one of the most important proteins for the primary negative selection of T cells in the thymus for maintaining central immune tolerance [33]. Deficiency or mutation in the AIRE gene can lead to an improper presentation of self-antigens and can also lead to problems with autoimmunity [33]. A study exploring the transcriptomic profiles of several OC patients with PCD found that AIRE genes were upregulated along with CDR2L genes [28]. The latter finding is consistent with the other studies [26,27]. Remarkably, the AIRE gene is upregulated contrary to expectations of either neutral or downregulation in the case of PCD’s association with autoimmunity; upregulation could be potentially due to a variety of factors, including epigenetics and crosstalk among molecular pathways. In PCD patients compared to controls, the CDR2L gene was more likely to be upregulated, mutated, and expressed at a protein level while CDR2 was differentially expressed and mutated while no significant changes were noted at a protein expression level [27,28]. Antigen presentation is a key part of positive and negative selection, increased prevalence of onconeural antigens may influence this process, while mutations common in CDR2 and CDR2L may provide an opportunity for genetic screenings. Screenings can be implemented via targeted next-generation sequencing of ovarian tumor samples [27].

Anti-Yo antibodies have previously been thought to contribute to the direct pathogenicity of Purkinje cells through some form of immune cell migration and infiltration [29]. Interferon-gamma (IFN-γ) is a cytokine that may stimulate a pathway that helps CD4+ and CD8+ T cells to migrate to the cerebellum. This cytokine is often present in high concentrations in the CSF of Yo-PCD patients [40]. Infiltration appears to begin at the tumor site with local differentiation of B cells as an indicator; the presence of naïve B cells, plasmablasts, plasma cells, and memory B cells is evidence of this differentiation [27]. The lymphocytes found in OC samples would support that of an acquired immune response. As stated, CD8+ T cells were in close proximity to apoptotic OC cells, which suggests an antitumor immune response [27]. Disrupting these key immune infiltrates could be helpful in the conversation about immune tolerance and the role of CD4+ cells in initiating this tolerance [26]. Treg cells are thought to also contribute to immune tolerance, as they act to suppress antitumor immune response [34]. When initiating immunotherapy, combination therapy may be more conducive to the permanent discontinuation of PCD symptoms, considering the redundancy in molecular pathways [55].

There has been a recent interest in understanding the mechanisms of PCD because novel cancer immunotherapies often target immune regulation checkpoints to enhance CD8+ T cell activity in killing tumor cells. The inactivation of CTLA4, an important immune checkpoint for the downregulation of CD8+ T cells, has been found to induce PCD and Purkinje cell death in mice [56]. Drugs like monoclonal antibodies that target the PD-1 pathway, another immune checkpoint, are already employed as treatments for certain types of cancer [37]. This therapy has often shown promising results in the regression of cancer, but it also carries an increased risk of autoimmunity if non-cancerous tissue expresses a tumoral antigen, such as in the case of OC with Yo-PCD. When screening for PCD, we can use genetic screens to confirm our clinical diagnosis with the support of patient history, physical exam, serology, and imaging. These genetic changes
could be targeted with immunomodulating therapies.

**Limitations**

This systematic review was limited by the heterogeneity of the included studies, and hence a meta-analysis was not performed. The number of studies reviewed was small due to the rarity of adjacent PCD and OC. The limited sample size of this review may have created a risk of bias. Since the pathophysiology of PCD is not clearly known yet, there was some contradictory information in various reports, making it challenging to synthesize information. When reviewing studies for inclusion, studies at times did not distinguish PNS from PCD or present data exclusively on one type of cancer, which restricted the number of studies included in this review.

**Conclusions**

Paraneoplastic cerebellar degeneration is a unique PNS that is thought to occur due to autoimmune destruction of the cerebellum and is most commonly seen in breast and pelvic malignancies; it tends to begin months or years preceding the cancer diagnosis. Timely recognition and removal of the primary malignancy are critical for overall clinical outcomes concerning patient health and cancer therapy effectiveness. We recommend that PCD diagnosis be considered if the patient has a history of malignancy within the past five years and has new cerebellar symptoms and no significant findings on imaging (ruling out other diagnoses). We can then confirm these suspicions with CDR2 and CDR2L antigen expression and genomic alterations and the presence of the anti-Yo antibody. Recognizing the symptoms of PCD and ordering the appropriate genomic and proteomic testing may facilitate early diagnosis and, consequently, an improvement in prognosis. Antitumor therapy and immunomodulating drugs are the most prominent therapeutic approaches supported by our findings; however, additional research is required before conclusive treatment recommendations can be made. By employing clinical judgment in conjunction with genetic and proteomic markers to diagnose PCD, clinicians may be able to detect malignancies sooner and prevent metastatic disease.

**Additional Information**

**Disclosures**

**Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: Akbar Fidahussain declare(s) employment from Thermo Fisher Scientific. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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