



**A brief discussion on the diagnosis and management of
Paraneoplastic Neurological Syndromes associated with ovarian cancer.
The importance of not thinking only about what we see**

DOI: <https://doi.org/10.36811/rjnnd.2020.110003>

RJNND: October-2020: Page No: 01-06

Research Journal of Neurology and Neuro Disorders

Short Communication

Open Access

**A brief discussion on the diagnosis and management of Paraneoplastic
Neurological Syndromes associated with ovarian cancer. The importance of
not thinking only about what we see**

Díaz Ortega, Patricia^{1*} and García Manero, Manuel²

¹Department of Obstetrics and Gynecology, Hospital García Orcoyen, Spain

²Chief of Department of Obstetrics and Gynecology, Associate Professor at the University of Navarra, Hospital García Orcoyen, Spain

***Corresponding Author:** Díaz Ortega, Patricia, Department of Obstetrics and Gynecology; Hospital García Orcoyen, Spain, Email: patry.do80@gmail.com

Received Date: Sep 28, 2020 / **Accepted Date:** Oct 06, 2020 / **Published Date:** Oct 08, 2020

Abstract

In relation to a recently published case [13] of a patient diagnosed with serous ovarian cancer which began as a paraneoplastic neurological syndrome, myasthenia gravis, here the importance of an early diagnosis of this type and its multidisciplinary handling is discussed. We want to highlight the early identification of the primary tumor and its treatment, in order to avoid the progression of these disorders which can develop into severe, incapacitating, or even fatal, neurological impairments.

Keywords: Paraneoplastic Neurological Syndromes; Myasthenia gravis; Ovarian Cancer; Gynecological cancer

Cite this article as: Díaz Ortega, Patricia, García Manero, Manuel. 2020. A brief discussion on the diagnosis and management of Paraneoplastic Neurological Syndromes associated with ovarian cancer. The importance of not thinking only about what we see. Res J Neuro N Disord. 1: 01-06.

Copyright: This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. Copyright © 2020; Díaz Ortega, Patricia

Introduction

PNS are a group of rare and heterogeneous disorders from a clinical and developmental viewpoint, which can affect any area of the central or peripheral nervous system and are associated with a malignant underlying process. They can occur in 1% of gynecological tumors, with ovarian cancer being the least common. Its diagnosis is a challenge for the clinic because it

is often confused with a neurological disease and the possibility of a basic malignant pathology is not considered. We recently published the case of a patient who suffered from advanced ovarian neoplasia, and debuted with a paraneoplastic myasthenic syndrome. The speed of diagnosis of these entities is crucial for the early identification and treatment of the underlying malignant pathology. In addition to this case, we conducted a literature

A brief discussion on the diagnosis and management of Paraneoplastic Neurological Syndromes associated with ovarian cancer. The importance of not thinking only about what we see

DOI: <https://doi.org/10.36811/rjnnd.2020.110003>

RJNND: October-2020: Page No: 01-06

review on paraneoplastic syndromes and discussed their management and treatment.

Material and Methods

In relation to a recent publication on a case of advanced ovarian cancer that debuts as a paraneoplastic myasthenic neurological syndrome, a literature review is conducted on these syndromes and discusses their diagnosis and clinical management.

Discussion

In Medicine not everything is what it seems- on numerous occasions we find that illnesses pretend to be others, or serious disorders are hidden behind trivial symptoms. In this sense, it is necessary to talk about paraneoplastic syndromes, and more specifically, about the paraneoplastic neurological syndromes

associated with gynecological malignancies. PNS are a group of rare and heterogeneous disorders from a clinical and developmental viewpoint, which can affect any area of the central or peripheral nervous system and are associated with a malignant underlying process. However, they are not caused directly by the primary tumor, nor the metastasis or its treatment, but instead it has been accepted that they are of autoimmune etiology, indirectly from the cancer, and the activation of the humoral and cellular immune response that affects the cells in the nervous system. Since the 1980's, autoimmune theory is considered as an etiopathogenesis of these processes due to the detection of antibodies that recognize antigens on the surface of tumor cells. These were named onconeural antibodies, which are defined and encompassed in the diagnostic criteria for PSN defined by [1], (Table 1).

Table 1: Definite and possible PNS according to diagnostic criteria as published by Graus et al. (2004).

Definite PNS	Possible PNS
A classical syndrome and cancer that develop within 5 years of the diagnosis of the neurological disorder	1. A classical syndrome, no onconeural antibodies, no cancer is diagnosed, but at high risk for having an underlying tumor
A non-classical syndrome that resolves or significantly improves after cancer treatment without concomitant immunotherapy provided that the syndrome is not susceptible to spontaneous remission	2. A neurological syndrome (classical or not) with partially characterized onconeural antibodies and no cancer
A non-classical syndrome with onconeural antibodies (well characterized or not) and cancer that develops within 5 years of the diagnosis of the neurological disorder	3. A non-classical syndrome, no onconeural antibodies and cancer present within 2 years of diagnosis
A neurological syndrome (classical or not) with well-characterized onconeural antibodies (antiHu, Yo, CV2, Ri, Ma2 or amphiphysin) and no cancer	

There has also been importance given to the role of cell immunity measured by the T lymphocytes, supported by the presence of cytotoxic T lymphocyte inflammatory infiltrates in the tumors and in the areas affected

by the nervous system. Specific cytotoxic T lymphocytes (CTLs) against the CDR2 antigen that manifest in ovarian cancer and in Purkinje cells in patients with Paraneoplastic Cerebellar Degeneration (PCD) have been proven [2,3]

A brief discussion on the diagnosis and management of Paraneoplastic Neurological Syndromes associated with ovarian cancer. The importance of not thinking only about what we see

DOI: <https://doi.org/10.36811/rjnnd.2020.110003>

RJNND: October-2020: Page No: 01-06

Nevertheless, the role of the onconeural antibodies in the pathogen of these disorders is undeniable [4], and its proven positivity in a suitable clinical context is diagnosed as PNS. Therefore, PNS can be classified into two groups, depending on their clinical and immunological characteristics [5]:

- The processes in which humoral immunity mechanisms are involved, which include the PNS that affect the peripheral nervous system and the motor end plates or limbic encephalitis.
- The processes in which cellular immunity mechanisms are involved, which are the classic PNS that affect the central nervous system and have a worse prognosis.

There are characteristic, or specific, onconeural antibodies that determine a PNS, such as the presence of calcium channel antibodies in the Eaton-Lambert Syndrome, the acetylcholine receptor antibodies found in Myasthenia Gravis, the anti-Yo antibodies in Paraneoplastic Cerebellar Degeneration (PCD), and others that can be identified in various disorders such as anti-Hu, Antiampiphysin antibodies etc [5]. There have even been documented cases of advanced ovarian neoplasia with onconeural antibodies detected in serum, but without the associated PNS [6] That occurs in less than 1% of patients with cancer [3], with it being even rarer to be associated with gynecological tumors. There have been cases associated with breast, cervical or ovarian tumors; the latter with a 10% incidence rate. The majority of the publications about PNS related to ovarian neoplasia reference Cerebellar Degeneration [7,8] with this being the most frequent manifestation. Other well defined cases that can be documented are in Limbic Encephalitis and NMDAR Encephalitis, Opsoclonus Myoclonus Syndrome, Paraneoplastic Subacute Sensory Neuropathy, and Sensorimotor Neuropathy [9]. Their clinical manifestations are so heterogeneous that there have even been cases reported with combined cerebellar and spinal

cord deficits [10]. It needs to be pointed out that two extremely infrequent cases exist that belong to this group of disorders, one of which is the Lambert-Eaton myasthenic syndrome related to small cell carcinoma of the cervix and uterine sarcoma [11], and the other, Myasthenia Gravis. Myasthenia Gravis (MG) is an illness of the motor end plate, which is due to the existence of acetylcholine receptor antibodies which act on a postsynaptic level blocking the action of the motor end plate and causing muscle weakness. The late diagnosis of this can result in generalized weakness affecting the respiratory muscles. Only 10% of Myasthenia Gravis cases correspond with paraneoplastic syndromes, mainly those linked to thymomas and hardly ever to ovarian tumors [12]. Its appearance in elderly patients or its atypical first appearance leads us to believe it is a PNS.

The diagnosis of PNS poses a challenge for doctors, generally Neurologists, who are usually the first to assess these patients, seeing as PNS usually rears its head months or years before the symptoms of the primary tumor. There have been documented cases of tumors diagnosed up to 10 years after the appearance of neurological symptoms [8]. Although the majority of the cases are of subacute development, their clinical heterogeneity allows us to see cases with a sudden onset which can progress quickly or be recurrent. Regarding challenges, knowledge of these disorders will allow us to make early diagnoses, and along with that, be more aware of the possible existence of a malignant underlying process. The importance of that knowledge and early diagnosis not only consists in it [1] being possibly the first symptom of a neoplasia, but also that the treatment and monitoring of the primary tumor can be the best step in monitoring neurological symptoms. A late diagnosis can result in progressive, incapacitating, and irreversible neurological deficits, and the development of the primary tumor. We recently published the case of an 83-year-old patient who presented with a rapid

A brief discussion on the diagnosis and management of Paraneoplastic Neurological Syndromes associated with ovarian cancer. The importance of not thinking only about what we see

DOI: <https://doi.org/10.36811/rjnnd.2020.110003>

RJNND: October-2020: Page No: 01-06

onset and quick progression of myasthenic syndrome, as a paraneoplastic syndrome of serous ovarian cancer at an advanced stage [13]. In many cases it is a diagnosis of exclusion; previously ruling out infections or other pathologies of the nervous system. If a PNS is suspected, onconeural antibodies should be looked for. In our case, the onconeural ACH receptor antibodies were positive, therefore the time of onset together with the rapid development of the case, plus the presence of those antibodies, created suspicions about the possible existence of an underlying neoplasia. As we explained at the beginning, the importance of the diagnosis of these conditions lies in the possibility of carrying out an early diagnosis and treatment of the primary neoplasia. The majority of the onconeural antibodies are of the IgG type, and can be detected in high numbers in the serum and CLR of patients with PNS. Nevertheless, its figures are not directly related to the behavior of the illness. The usefulness of the CLR in these cases has been debated. In recent studies where the CLR was analyzed of several patients who had been diagnosed with PNS, diverse changes were observed such as high CSF protein concentrations, pleiocytosis, oligoclonal bands, [14] and some onconeural antibodies like the anti-Tr and the antiNMDA which are not detectable in serum, could be analyzed in CLR.

This could be useful in cases of encephalitis with anti-NMDAR, but not in other processes like PCD or MG. An electroencephalogram will be altered in cases of encephalitis or partial epilepsy, but it will not provide information about the paraneoplastic origin of the illness. With respect to the imaging techniques, the echography is well known for its role in diagnosing adnexal tumors, however, on occasions the ovarian tumor is not visible on the ultrasound and it is necessary to rely on other imaging tests. There are numerous studies that have proven the sensitivity of the FDG-PET scan in the diagnosis of a malignant pathology that is not evident with other techniques

[15,16]. In the case of our patient, the PET/CT scan revealed a suspicious increased uptake in the uterine area. The transvaginal ultrasound did not show evidence of adnexal masses, but it did show an endometrial enlargement whose biopsy was reported as being ovarian serous carcinoma. According to the conclusions of a meta-analysis carried out in 2011 [17], the transvaginal ultrasound is the diagnostic tool of choice if an ovarian neoplasia is suspected. If this result is negative, we would then rely on other techniques such as the CT scan or MRI. The European Federation of Neurological Societies recommends carrying out the imaging tests before the presence of a PNS with positive onconeural antibodies, and if initially there is no neoplasia shown, then to repeat the test every 6 months for 4 years. Up to 80% of patients will be diagnosed due to the presence of these onconeural antibodies [18]. Currently, given the rarity of these syndromes, not enough studies exist to create a guide about therapeutic recommendations when it comes to dealing with these pathologies. It cannot be denied that the early treatment of these syndromes is fundamental to prevent irreversible, or fatal, neurological impairments, therefore starting early on an empirical treatment is recommended [19]. Based on possible autoimmune etiology, empirical treatment trials have been carried out with corticoids, intravenous immunoglobulins, plasmapheresis, immunosuppressants, even an autologous bone marrow transplant and the monoclonal antibody Rituximab; all of which had varying results [20]. When choosing a treatment, two types of syndromes can be distinguished: Syndromes associated with antibodies against antigens of the cell membrane - these usually respond well to treatment with high doses of methylprednisolone for 3-5 days; and those combined or followed by plasmapheresis and/or intravenous immunoglobulins. The patients that do not respond to this line of treatment could benefit from the treatment of Rituximab or cyclophosphamide. What is more

A brief discussion on the diagnosis and management of Paraneoplastic Neurological Syndromes associated with ovarian cancer. The importance of not thinking only about what we see

DOI: <https://doi.org/10.36811/rjnnd.2020.110003>

RJNND: October-2020: Page No: 01-06

difficult is the immunosuppressant treatment of the syndromes associated with antibodies against intracellular antigens (e.g. anti-Hu, anti-Yo). Treatments have been done based on a high dose of methylprednisolone in combination with plasmapheresis and intravenous immunoglobulins, but with poor results- the monoclonal antibodies manage to reduce the number of antibodies. Even though none of these previously described treatments induce a complete clinical remission, its early start would lead to a more significant functional improvement [20]. There is evidence that the treatment of the primary tumor improves the neurological symptomatology, which makes it vital in these cases to obtain an early diagnosis of the tumor. In the case published by Simonsen et al, the patient that presented with a MG as PNS of IIIC stage ovarian cancer received chemotherapy tumor treatment using Cisplatin and Paclitaxel which significantly improved the myasthenic symptomatology. In our case, the patient refused any aggressive treatment; not only did the therapy with Pyridostigmine not reduce the symptomatology, but she continued deteriorating rapidly and progressively. Therefore, we reiterate the necessity of the early treatment of the primary tumor, with the aim of preventing the progression of its associated neurological disorders. No correlation has been found between these figures and the development of the illness [21]. However, there have been cases where the neurological symptomatology has reappeared after successful treatment of the primary tumor, associated with a reappearance of said tumor, so the onconeural antibodies could be used as a biomarker in the illness during the monitoring of the patient.

Conclusion

Paraneoplastic neurological syndromes are heterogeneous organisms in every aspect, and are very rare which appear in the form of malignancies in various locations, with gynecological ones being the least frequent. It

is believed that its etiopathogenesis is due to an autoimmune mechanism in which the cellular immunity and humoral immunity seem to intervene. Various characteristic antibodies of the illness have been found, which have been named onconeural antibodies and their positivity in analyses indicate a PNS diagnosis. The diagnosis of these processes is complex and requires clinical skills and knowledge, such as that of the existence of the combination of information about the symptomatology, the latency between the neurological and tumor symptomatology, the presence of specific antibodies, the imaging tests and the response of the neurological syndrome upon treatment of the primary tumor. We insist on the importance of knowing and recognizing these syndromes- think about them, be quick to make its diagnosis and identify the primary tumor. Its treatment requires a coordinated multidisciplinary team. Likewise, more studies need to be undertaken on its etiopathogenic mechanisms, with the objective of identifying an effective framework for treatment.

References

1. Graus F, Delattre JY, Antoine JC, et al. 2004. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry. 75: 1135-1140.
2. Albert ML, Darnell JC, Bender A, et al. 1998. Tumor-specific killer cells in paraneoplastic cerebellar degeneration. Nat Med. 4: 1321-1324. Ref.: <https://pubmed.ncbi.nlm.nih.gov/9809559/>
3. Zaborowski MP, Spaczynski M, Nowak-Markwitz E, et al. 2015. Paraneoplastic neurological syndromes associated with ovarian tumors. J Cancer Res Clin Oncol. 141: 99-108. Ref.: <https://pubmed.ncbi.nlm.nih.gov/24965744/>
4. Darnell JC, Albert ML, Darnell RB. 2000. Cdr2, a target antigen of naturally occurring human tumor immunity, is widely expressed in

A brief discussion on the diagnosis and management of Paraneoplastic Neurological Syndromes associated with ovarian cancer. The importance of not thinking only about what we see

DOI: <https://doi.org/10.36811/rjnnd.2020.110003>

RJNND: October-2020: Page No: 01-06

- gynecological tumors. Cancer Res. 60: 2136-2139. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/10786675/>
5. Alarcón I, Gonzalez C. 2013. Anticuerpos onconeuronales en los síndromes neurológicos paraneoplásicos. Ed Cont Lab. 16: 9-19
 6. Chatterjee M, Hurley LC, Tainsky MA. 2017. Paraneoplastic antigens biomarkers for early diagnosis of ovarian cancer. Gynecol Oncol Rep. 21: 37-44. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/28653032/>
 7. Zoutien O, Benbrahin Z, Amaadour L, et al. 2019. Paraneoplastic neurologic degeneration revealing ovarian cancer recurrence. Pan Afr Med J. 2: 33-281. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/31692829/>
 8. Rojas-Marcos I, Geraldine Picard, David Chinchón, et al. 2012. Human epidermal growth factor 2 overexpression in breast cancer of patients with anti_Yo associated paraneoplastic cerebellar degeneration. Neuro Oncol. 14: 506-510. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/22351748/>
 9. Viau M, Renaud MC, Grégoire J, et al. 2017. Paraneoplastic syndromes associated with gynecological cancers: a systematic review. Gynecol Oncol. 146: 661-671. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/28655412/>
 10. Othman T, Hendizadeh MS, Vankina R, et al. 2020. Combined cerebellar and spinal cord deficits caused by underlying gynecologic malignancy. Case Rep Oncol Med. 8: 9021843. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/31970005/>
 11. Roohi F, Smith PR, Bergman M, et al. 2006. A diagnostic and management dilemma: combined paraneoplastic myasthenia gravis and LambertEaton myasthenic syndrome presenting as acute respiratory failure. Neurologist. 12: 322-326.
 12. Simonsen M, Minamoto Miyabe M, Toshio Ouki H, et al. 2018. Myasthenia as a paraneoplastic manifestation of ovarian cancer. Gynecol Oncol Rep. 25: 35-36. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/29984297/>
 13. Díaz Ortega P, Alcaraz MO, Pérez BB, et al. 2020. No todo es lo que parece: Miastenia Gravis, una rara manifestación paraneoplásica del cáncer de ovario; caso clínico. Clin Invest Gin Obst.
 14. Psimaras D, Carpentier AF, Rossi C. 2010. Cerebrospinal fluid study in paraneoplastic syndromes. J Neurol Neurosurg Psychiatry. 81: 42-45.
 15. Sioka Ch, Fotopoulos A, Kyritsis AP. 2010. Paraneoplastic neurological Syndromes and the role of PET imaging. Oncology. 78: 150-156
 16. Frings M, Antoch G, Knorn P, et al. 2005. Strategies in detection of the primary tumour in anti-Yo associated paraneoplastic cerebellar degeneration. J Neurol. 252: 197-201. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/15729526/>
 17. Titulaer MJ, Soffietti R, Dalmau J, et al. 2011. Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. Eur J Neurol. 18: 19-23. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/20880069/>
 18. Storstein A, Evy Monstad S, Haugen M, et al. 2011. Onconeural antibodies: improved detection and Clinical correlations. J Neuroimmunol. 232: 166-1670. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/21093932/>
 19. Galli J, Greenlee J. 2020. Paraneoplastic diseases of the central nervous system [version1; peer review:2 approved] F1000Research. 9(F1000 Faculty Rev). 167
 20. Lee WJ, Lee ST, Byun JL, et al. 2016. Rituximab treatment for autoimmune limbic encephalitis in an institutional cohort. Neurology. 86: 1683-1691. Ref.:
<https://pubmed.ncbi.nlm.nih.gov/27037228/>
 21. Lladó A, Mannucci P, Carpentier AF, et al. 2004. Value of Hu antibody determinations in the follow-up of paraneoplastic neurologic syndromes. Neurology. 63: 1974-1979.