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# A diagnostic challenge – autoimmune encephalitis as paraneoplastic syndrome of ovarian teratoma. Current state of knowledge

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**ABSTRACT**

Autoimmune encephalitis (AE) is one of the paraneoplastic syndromes of ovarian teratoma. Insufficient knowledge about the evolution of the disease, as well as its manifestation in the form of non-specific clinical symptoms (such as significant deterioration of memory and cognitive functions of patients), is a common cause of a prolonged diagnostic process and delay in the introduction of targeted treatment. The aim of the study was to summarize the data available in the literature, as well as recent reports, to facilitate and accelerate the diagnosis of the syndrome and ensure better care for patients.

A literature review was performed in the PubMed, Google Scholar databases and the guidelines of the Polish Society of Gynecologists and Obstetricians, by using keywords. Making a diagnosis of AE requires the cooperation of a team of specialists (including, among others, neurologists, gynecologists and oncologists). Justification for this is the manifestation of pathology comes in the form of non-specific clinical symptoms. Treatment includes surgery to remove the tumor, pharmacotherapy: corticosteroids and immunoglobulin infusions, in addition to allied modern plasmapheresis treatments – in severe cases.

Sorting out the non-specific symptoms of AE would facilitate faster and more accurate diagnosis, and this improve the functioning of patients suffering from ovarian teratoma. Pertinent tests are necessary to facilitate and optimize the differential diagnosis. Education of doctors about its alarming symptoms is important, as is cooperation between doctors of different specialties.

## INTRODUCTION

Paraneoplastic syndrome is a pathology caused by a disorder resulting from the secretion of hormones, peptides or cytokines by the tumor and from immune cross-reactivity between abnormal tissues and tissues of the host body. These syndromes occur in 5-10% of all cancer patients. They may include different organ systems, mainly the endocrine and nervous systems. Symptoms may also be haematological, dermatological or rheumatological. Tumors, the paranoic syndromes of which manifest in oncological patients with the highest frequency are: small cell lung cancer, breast cancer, gynecological cancers and haematological cancers [1,2].

Ovarian germ cell tumors (OGCTs) are a group of true primary ovarian tumors. Histologically, they are a heterogeneous group of tumours originating from embryonic gonadal cells. The OGCT group includes three types of monstrosis such as mature monstrosis, immature and unilocular monstrosis, ploriferative, follicular tumour formerly called endodermal sinus tumour, embryonic cancer, polycystic cancer and chorionic cancer. Germ cell tumours are the second largest category of ovarian cancer. They are preceded by a group of epithelial cancers, usually of a benign nature [3]. It is estimated that OGCTs account for about 20 to 25% of all ovarian cancers, but they account for about 5% of all occurring ovarian malignancies. Among women aged 10 to 30, embryonic cell tumours account for up to 70% of all ovarian cancers [4].

The Gonzales-Crussi classification describes the prevalence of mature embryonic ovarian tumors over immature or mixed tumors [5]. Autoimmune encephalitis (AE) is a term used to describe a large group of pathologies,

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the symptoms of which include dysfunctions of the limbic system and non-limbic parts of the brain of the human nervous system [6]. In pathologies classified as AE, antibodies specific to synaptic antigens and proteins present on the surface of nerve cells are found in the body fluids of patients [7]. There are many types of paranocarcinoma syndromes allied with the presence of different antibodies. These include antibodies against the NR1 subunit of the NMDA receptor (N-methyl-D-aspartic acid) [8], AMPA (α-amino-3-hydroxy-5-methyl-4isoxazole-propionic acid) [9], GABA (6-aminobutyric acid receptor) [10], GlyR (7 α1glycine). The incidence of paraneoplastic syndromes involving autoimmune encephalitis was estimated at 2⁄3 per 100,000 patients per year in a Northern European study.

Autoimmune encephalitis may have not only the causes of immunization in oncological patients. It has been estimated that 40% of all patients with AE develop these pathologies as a result of an infectious disease. In the next 40% of the toal number of patients, the causes have not been established and specified, while the background of immunization occurs in 20% of all patients suffering from AE [11]. Median age of patients with AE has also been calculated. It ranges from 50 to 60 years for AE with the character of a rigid personal syndrome (SPS). The median for patients with cerebral ataxia (CA) is the same, while for LE (limbic encephalitis), it ranges from 25 to 45 years [12].

Today, due to the progress of medicine in every specialty and the increase of diagnostic capabilities, there has been a rapid development of knowledge about these paranoic syndromes involving the nervous system and the presence of specific antibodies. This fact has led to a reversal in the clinical paradigms and new insights into the pathogenic mechanisms of pathologies classified as AE. Key to faster recovery and successful outcome is rapid recognition and treatment initiation. The article presents the current state of knowledge on the main clinical features, diagnostic indications and treatment of the above disorders. Our goal was to summarize the available data in the literature, as well as the latest reports and studies. The reason for our work is to enable a better understanding of the disease and effective care for patients with AE, the symptoms of which are a very nonspecific group. This phenomenon tends to delay the diagnosis and inclusion of specific treatments that are key to success in working with the patient for their well-being [13].

## MATERIAL AND METHODS

A literature review of PubMed, Google Scholar, and the guidelines of the Polish Society of Obstetricians and Gynecologists was conducted. Articles were searched using the keywords: encephalitis; limbic encephalitis; stiff-person-syndrome; teratoma; basal ganglia encephalitis; anti-NMDA-receptor encephalitis; synaptic autoimmunity; neuronal surface antigen antibody; GABA. The search yielded 615 results, of which 30 papers were included after rejecting papers that did not meet the authors' criteria.

### Pathophysiology of the disease

Autoimmune encephalitis with the presence of specific anti-NMDAR antibodies occurs most commonly as paranoic tumour syndrome with ovarian monstrosis. According to ur research, 56% of all patients over 18 years of age have unilateral or bilateral ovarian monstrosities with present metabolically reactive nerve tissue [14]. Moreover, all known antibodies present in AE diagnosed as paraneoplastic syndrome fall into two categories. This division is dependent on the antigen target as a carrier for the specific antibody produced by immunization in oncology patients. We therefore distinguish:

- autoantibodies specific to intracellular antigens (e.g., cytoplasmic or nuclear, Table 1);
- autoantibodies specific to cell membrane antigens (Table 2).

The pathomechanism of autoimmune limbic encephalitis (ALE) with the presence of anti-NMDA antibodies as a paraneoplastic syndrome with the presence of oncologic pathology such as ovarian leiomyoma, is very complicated. The cellular composition of ovarian leiomyoma includes leiomyoma tumor cells, neuroglial cells, inflammatory cells in the infiltrate and also tertiary lymphoid structure (TLS) with germinal center (Figure 1A). NMDA receptors are expressed on the surface portion of ovarian leiomyoma cells (Figure 1B). The TLS of ovarian leiomyoma includes a CD4+ T-cell zone, a CD20+ B-cell zone, plasma cells, autoantibodies against NMDA receptors, central memory cells and mature dendritic cells. Mature dendritic cells capture NMDAR nerve antigens and present antigenic fragments to CD4+ T cells via the MHC class II complex, resulting in the induction of T cell activation, differentiation and proliferation. Activated CD4+ T cells then induce the differentiation of B lymphocytes into plasma cells and subsequently produce IgG autoantibodies. Eventually, immunocytes and autoantibodies circulate in the bloodstream and lymphatic system and cross the blood-brain barrier into the cerebrospinal fluid (Figure 1C). Autoantibodies mainly attack the hippocampus and prefrontal cortex of the brain, causing antibody-mediated neuronal damage. Autoantibodies bind to and induce NMDAR cross-linking, altering NMDAR surface dynamics and disrupting interactions with synaptic proteins such as the Ephrin-B2 receptor (EphB2R). These reactions, mediated by the antibody, ultimately lead to the internalization and degradation of NMDARs, reducing the density of NMDARs in both synapses and extrasynaptic compartments (Figure 1D). The basic components of NMDARs

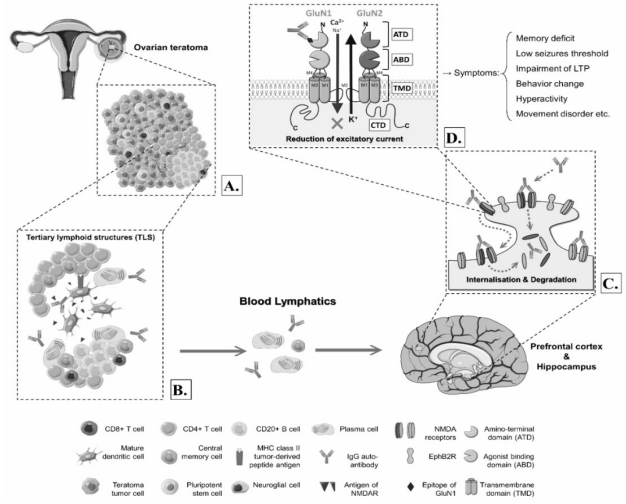



***Figure 1.*** The complicated mechanism of the disease

***Table 1.*** List of autoantibodies specific to intracellular antigens, autoantibodies, in neurological syndromes and types of cancers

| Antigen | Autoantibody | Main Neurological Syndromes | Cancer Types |
|---|---|---|---|
| HuD | ANNA1 | Sensory neuropathy, limbic encephalitis, cerebellar ataxia | SCLC, NSCLC, extra-thoracic cancers |
| Cdr-2 | PCA1 | PCD (majority), brainstem encephalitis, myelopathy | Ovarian, breast, fallopian tube carcnoma |
| SOX1 | SOX1-IgG | LEMS, PCD, limbic encephalitis | SCLC, NSCLC, extra-thoracic cancers |
| Unkonwn | ANNA3 | limbic encephalitis, neuropathies, cerebellar ataxia, myelopathy, brainstem encephalitis | SCLC, NSCLC, tabacco-related airway cancers |
| NOVA1 and NOVA2 | ANNA2 | brainstem encephalitis, opsoclonus, larngospasm, jaw dystonia | Breast, lung, neuroblastoma |
| Ma1 and Ma2 | Ma1 or Ma2-IgG | Limbic encephalitis, brainstem encephalitis | Testicular, lung cancers |
| ZIC4 | ZIC4-IgG | PCD | SCLC, ovarian adenocrcinoma |

ANNA: antineuronal nuclear antibody; Cdr-2: cerebellar degeneration-related protein; HuD: Hu-antigen D; LEMS Lamber-Eaton myasthenic syndrome; Ma: antibodies that react with both Ma1 and Ma2; NOVA: neuro-oncological ventral antigen; NSCLC: non-small-cell lung cancer; PCA: Purkinje cell cytoplasmic antibody; PCD paraneoplastic cerebellar degeneration; SCLC: small cell lung carcinoma; ZIC4: Zinc finger protein 4

***Table 2.*** List of autoantibodies specific to cell membrane antigens, autoantibodies, main neurological syndromes, types of cancers

| Antigen | Autoantibody | Main Neurological Syndromes | Tumor Types | Frequency of Tumor |
|---|---|---|---|---|
| DNER | DNER-IgG (PCA-Tr) | PCD | Hodgkin lymphoma | >95% |
| GluA1, GluA2 | AMPAR-IgG | Limbic encephalitis | SCLC, NSCLC, breast and thymoma | 60-70% |
| P/Q- type VGCC | P/Q-type VGCC-IgG | LEMS and PCD | SCLC | 60% |
| β1 subunits | GABAaR-IgG | Limbic encephalitis, isolated status epilepticus, cerebellar ataxia and opsoclonus myoclonus | SCLC, thymoma and extra-thoracic cancers | 60% |
| GluD2 | GluD2-IgG | Opsoclonus myoclonus ataxia syndrome | Neuroblastoma and ovarian teratoma | 50% |
| α1,β3, γ2 | GABAaR-IgG | Encephalitis with initial psychiatric disturbances, followed by catatonia, dystonia, seizures, aphasia, coma and central hypoventilation | Thymoma and Hodgkin lymphoma | 40% |
| GluN1 | NMADAR-IgG | Encephalitis with seizures, cognitive impairment, and behawior changes | Ovarian teratoma | 20-40% |
| Muscle AChR | Anti-AChR | Encephalitis with initial psychiatric disturbances, followed by catatonia, dystonia, seizures, aphasia, coma, and central hypoventilation | Thymoma | 15% |
| mGluR1 | mGluR1-IgG | Cerebellar ataxia | Hematologic malignancies and prostatę adenocarinoma | 10% |
| DPPX/Kv4.2 | DPPX-IgG | Diarrhea, weight loss, cognitive dysfunction, and CNS hyperexcitability | B-cell neoplasms | 10% |
| Aquaporin-4 | Aquaporin-4-IgG | Neuromyelitis optica spectrum disorders (optic neuritis, longitudinally, extensive transverse myelitis, and area postrema syndrome) | Thymoma, breast and lung | 5% |

AChr: acetylcholine receptor; AMPAR: α-amino-3-hydroxy-5methyl-4-isoxazolepropionic acid receptor; DNER: delta and notch-like epidermal growth factor-related receptor; CNS: central nervous system; DPPX: dipeptidyl-peptidase-like protein 6; GABAaR: GABA type A receptor; GABAbR: GABA type B receptor; GluA1: glutamate receptor 1; GluA2: glutamate receptor δ2; LEMS Lamber-Eaton myasthenic syndrome; mGlur1: metabotropic glutamate receptor 1; NMDAR: N-methyl-D-aspartate receptor; NSCLC: non-small-cell lung cancer; PCD paraneoplastic cerebellar degeneration; SCLC: small-cell lung carcinoma; VGCC: voltage-gated calcium channel

include four domains: the extracellular amino-terminal domain (ATD), the bipartite agonist-binding domain (ABD), the trans-membrane pore-forming domain (TMD) – and the intracellular carboxyterminal domain (CTD) [15].

## Symptoms of pathology and diagnosis

Autoimmune limbic encephalitis (ALE) is characterized at the beginning of the development of the condition by symptoms such as memory deficits, marked changes in behavior (often by an increase in aggressiveness), anxiety, depressive states, psychotic behavior and a reduction in cognitive function [16,17]. Making a correct diagnosis is difficult because the symptoms of autoimmune limbic system inflammation are non-specific and similar to the set of symptoms that occur in other pathologies of the nervous system. However, in order to correctly classify the pathology, the patient must meet certain criteria such as rapid, rapid progression lasting less than 3 months, the presence of working memory deficits, seizures or psychiatric symptoms that may suggest limbic system involvement, bilateral brain abnormalities visible on MRI, and with FLAIR sequence strongly confined to the medial temporal lobes. Moreover, at least one of the following symptoms must be present: CSF pleocytosis (white blood cell count greater than 5/mm3), EEG with epileptiform or slow-wave activity involving the temporal lobes. When one of the first criteria is not met, the diagnosis of limbic encephalitis can be made only after the detection of antibodies against cell surface, synaptic or onconeuronal proteins in the process of deeper diagnostics more invasive and immunologically specific [18].

Autoimmune limbic encephalitis is a pathology that should be suspected in any patient who presents rapidly progressive memory difficulties or behavioral changes. Symptoms such as epileptic seizures of unknown cause or psychiatric symptoms are also not uncommon. It should be noted that a person with sudden neurological symptoms is at higher risk for acute neurological injury, such as stroke or toxic poisoning. The aforementioned are warning signs that should not be underestimated in the diagnostic process. The differential diagnosis of autoimmune limbic system inflammation is a difficult diagnostic process. It is extremely important to exclude other diseases that may cause a similar set of physical and subjective symptoms, such as tumors such as glioblastoma multiforme [19] or hypothalamic tumors, dementia, tuberculosis, epilepsy, herpes-like viral encephalitis and bornavirus [20]. Other conditions that should be excluded that give similar symptoms are psychiatric disorders (such as dissociative disorders) or neurological complications of chemotherapy [21,22]. Prompt correct diagnosis of autoimmune limbic encephalitis allows equally efficient application of immunotherapy, resulting in a marked reduction in seizure frequency, restoration of cognitive function and improved survival [23,24]. The diagnostic process is also followed by tests of a screening nature for malignant tumors, especially in patients with antibodies specific for the presence of a nervous system tumor. Detection of pathology such as latent cancer is invaluable, since the degree of malignancy of the tumor greatly affects the final clinical outcome.

## Treatment – standard methods

Surgical treatment is the only therapeutic method used for ovarian leiomyoma pathology. Removal of the neoplastic lesion during laparoscopic surgery significantly improves

the condition of patients. This method not only abolishes the negative symptoms resulting from the presence of a pathological mass in the pelvic cavity, but also significantly improves their neurological condition [25]. Downstream of the terpetu process, treatment focuses on curing ALE. Innovative studies report that the condition of a significant number of patients with autoimmune limbic encephalitis can be improved if they are diagnosed early and treatment is initiated rapidly. ALE was once considered an uncommon pathology. Currently, thanks to an increase in the level of knowledge and diagnostic abilities of doctors of various specialties, limbic encephalitis is considered relatively common [26]. There is no doubt that limbic encephalitis has an immunological etiology. Attempts at immunosuppressive treatment seem appropriate. Mono- or polytherapy with immunoglobulins, plasmapheresis or steroid drugs is traditionally used [27]. Among immunosuppressive drugs, glucocorticosteroids such as methylprednisolone are popular, and immunoglobulin infusions are also readily used in therapy [28]. It is also possible to use new-generation drugs, such as rituximab (which is an anticancer drug also applied in immunosuppressive therapy.

### Treatment – innovative methods

A therapeutic method such as plasmapheresis or therapeutic plasma exchange are processes designed to deprive the body of blood plasma without depriving the patient of blood cells. The morphotic elements are then suspended in saline before being reintroduced into the patient's body. This procedure is useful for removing excess antibodies, immunoglobulins or cytokines from the blood in various pathologies, including autoimmune inflammation in gynecological patients with ovarian leiomyoma who have specific antibodies in their plasma [29]. In order to avoid possible complications of activation of coagulation in extracorporeal circulation and thromboembolic complications, patients should undergo anticoagulation therapy before the procedure in the interest of their health. Blood collected from the patient, drawn through a separator, is mixed with an anticoagulant solution (heparin, citrate solutions) and then flows into a centrifuge dish or filter, where the plasma is separated from the cellular elements of the patient's blood. The exact volume of separated plasma from the patient's cells is replaced with replacement fluids, and the recovered morphotic elements of the patient are transfused to the patient. The most common replacement fluids used in these procedures to purify the patient's blood are colloids (5% albumin) and crystalloids [30].

## CONCLUSION

Autoimmune encephalitis with the presence of specific antibodies to antigens present on the cell membrane and inside the cell (in the nucleus or in the cytoplasm) most often in AE anti-NMDA is a relatively rare clinical manifestation of embryonal tumor of the ovary of young women with ovarian monstroma as its paraneoplastic syndrome. It represents a pathology wherein the symptoms of which are identical to the set of symptoms of many other neurological disorders, most notably ailments that involve the sphere of the limbic which causes changes in cognitive thinking and memory. This phenomenon is unfavorable because it usually prolongs the path to a proper diagnosis, since differential diagnosis involves a significant number of pathologies that produce confusingly similar symptoms. This process requires specialists to have extensive knowledge in many areas of medicine (such as oncology, gynecology and neurology). It would be advisable for specialists in the abovementioned aspects of medicine to deal with paraneoplastic syndromes more frequently and with greater knowledge when diagnosing young women suffering from nervous system defects. Popularizing the problem of the diagnostic difficulty of ovarian monstrosity with manifestation of neurological symptoms is a milestone in multiplying the success of ovarian cancer diagnosis.

New treatment methods, among others, plasmapheresis specifically aimed at removing diseased antibodies from the body, are also filling doctors with hope that patients can be cured completely, even from very severe forms of the described paraneoplastic syndrome. Current research into diagnostic and therapeutic methods is aimed at optimizing the treatment of ovarian paraneoplastic patients with neurological manifestations of the pathology.

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