REVIEW ARTICLE

Adv Psychiatry Neurol 2024; 33 (2): 80–92
DOI: https://doi.org/10.5114/ppn.2024.141157

Paraneoplastic neurological syndromes of small cell lung cancer

Maedeh Barahman [1], Gholamreza Shamsaei [2], Davood Kashipazha [2], Mohammad Bahadoram [2], Esma'il Akade [3]

[1] Department of Radiation Oncology, Firoozgar Hospital, Firoozgar Clinical Research Development Center (FCRDC), Iran University of Medical Sciences (IUMS), Tehran, Iran
[2] Department of Neurology, School of Medicine, Musculoskeletal Rehabilitation Research Center, Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[3] Department of Medical Virology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Correspondence to:
Esma'il Akade
Department of Medical Virology
School of Medicine
Ahvaz Jundishapur University of Medical Sciences
Ahvaz, Iran
e-mail: esmailakade@gmail.com

Submitted: 30.03.2023
Accepted: 29.03.2024

Abstract

Purpose: This article reviews the relevant literature on paraneoplastic neurological syndromes of small cell lung cancer and discusses the clinical presentation, pathophysiology, and diagnosis of these syndromes. It also includes a summary of the current treatment options for the management of them.

Views: Paraneoplastic syndromes are a group of signs and symptoms that develop due to cancer in a remote site, mainly triggered by an autoantibody produced by the tissues involved or lymphocytes during anti-cancer defense. Among the cancers associated with paraneoplastic syndromes, lung cancers are the most common type, with small cell lung cancer being the most common subtype. The most common antibody associated with paraneoplastic syndromes is anti-Hu. Neurological and neuroendocrine syndromes comprise the majority of small cell lung cancer-related paraneoplastic syndromes. Classical paraneoplastic neurological syndromes include inappropriate antidiuretic hormone secretion, Cushing's syndrome, myasthenia gravis, Lambert-Eaton myasthenic syndrome, limbic encephalitis, paraneoplastic cerebellar degeneration, opsoclonus myoclonus ataxia, sensory neuropathy, and chorea.

Conclusions: Antibodies mediate paraneoplastic syndromes, and antibody detection is a crucial part of diagnosing these entities. Managing the underlying tumor is the best treatment approach for most paraneoplastic syndromes. Therefore, early diagnosis of small cell lung cancer may significantly improve the prognosis of paraneoplastic syndromes associated with it.

Key words: lung carcinoma, pathogenesis, symptom, diagnosis, treatment.

INTRODUCTION

Lung cancer, a pernicious affliction that deprives millions of their breath, stands as the foremost cause of cancer-related mortalities and ranks as the second most frequently diagnosed malignancy in the United States [1]. Non-small and small cell lung cancer (SCLC) are the two principal types of this disease, each characterized by distinct features. SCLC, a highly aggressive cancer predominantly linked to smoking, accounts for up to 15% of lung cancer cases in the world [2]. Regrettably, SCLC is commonly detected at an advanced stage, with approximately 90% of patients already experiencing metastasis. Survival rates for SCLC are dishearteningly low. The five-year relative survival rate for SCLC ranges from 2.2% to 24.5% in men and 3.6% to 32.2% in women, contingent upon factors such as age, race, and disease stage [3].

SCLC patients manifest symptoms for 2 to 3 months before seeking medical intervention. These symptoms arise from local tumor growth, involvement of neighboring tissues, distant metastasis, or a combination of these factors. Local tumor growth can precipitate coughing, hemoptysis, dyspnea, and pleuritic chest pain intensified by deep inspiration. Infiltration of adjacent regions may result in hoarseness, dyspnea, stridor, dysphagia, and facial and hand edema. Symptoms associated with distant metastasis exhibit variations contingent upon the site affected, encompassing manifestations such as headaches, visual disturbances, nausea, vomiting, limb weakness, cognitive alterations, seizures, back pain, paralysis, loss of bowel or bladder function, bone pain, and right upper abdominal pain [4, 5]. Besides the aforementioned complications, SCLC can, albeit rarely, induce various paraneoplastic syndromes (PNS).

PNS pertains to a constellation of symptoms that manifest as a remote consequence of a tumor, unrelated to direct tissue damage or metastasis. PNS ensues from the immune system's response to antigens released by the tumor. In 1985, the anti-Hu antibody, also known as anti-neuronal nuclear antibody 1 (ANNA1), was discovered in a patient presenting with sensory neuropathy and SCLC. Subsequent investigations revealed that SCLC was responsible for the production of this antibody, leading to the manifestation of it in patient [6]. Following the discovery of the anti-Hu antibody, various other antibodies have been linked to PNS. These investigations have facilitated the establishment of an association between PNS and the type of malignancy, thereby presenting us with a novel perspective to explore. Contemporary studies increasingly propose that PNS can serve as an avenue for early cancer diagnosis. Based on the site of involvement, PNS can be categorized into five subgroups: endocrine, musculocutaneous, neurological, hematological, and non-specific [7].

Paraneoplastic neurological syndromes (PNNS) manifest in approximately 3-5% of SCLC cases, affecting the central and peripheral nervous systems [6]. Early detection of PNS assumes paramount importance, as it can serve as an indicator of an underlying cancer. This article aims to concisely review the fundamental aspects of PNNS associated with SCLC, underscoring the significance of early recognition and diagnosis.

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) represents the most prevalent neuroendocrine PNS associated with SCLC. Approximately 7-16% of SCLC patients develop SIADH, which contributes to a poorer prognosis for SCLC [8]. SCLC-related SIADH is believed to occur due to the ectopic production and release of arginine vasopressin (AVP) by tumor cells [9]. AVP, a 9-amino-acid peptide, is synthesized in the magnocellular neurosecretory cells (MNCs) of the hypothalamus. It is stored in neurosecretory granules within the supraoptic nucleus and paraventricular nucleus until specific triggers, such as increased serum tonicity or a reduced effective circulation of arterial blood volume, induce its secretion into the bloodstream [10]. AVP plays a critical role in maintaining tissue perfusion and responding to physiological and psychological stress. The significance of AVP becomes evident as clinical deficiency (diabetes insipidus) only occurs when more than 90% of hypothalamic AVP neurons are destroyed [11]. Studies conducted on rodents have demonstrated finely regulated defense mechanisms against deviations in blood volume or osmolarity from their set points. For instance, hyperosmolar states trigger a rapid decrease in AVP-secreting neuron activity upon exposure to cues predicting water availability, even before water ingestion [12]. Excessive AVP activity can lead to the manifestation of SIADH, a condition characterized by inappropriate AVP secretion, resulting in water retention, dilutional hyponatremia, and hypo-osmolality [13]. The AVP released by tumors remains functionally active and can bind to its receptors in the renal collecting ducts, causing water retention and the development of hyponatremia. This form of SIADH typically exhibits elevated levels of AVP in both serum and urine, indicating excessive production and secretion by tumor cells. The underlying pathophysiological mechanism involves increased AVP production, disrupting the delicate balance between water intake and excretion, ultimately leading to water overload and dilutional hyponatremia. However, a remaining question pertains to the origin of AVP or AVP-like peptides in the lungs and whether their production is regulated by the pituitary gland or occurs locally [9]. SCLC, arising from neuroendocrine cells in the lung epithelium, has been observed to produce paraneoplastic AVP in approximately 67% of cases [14]. The potential of non-neoplastic pulmonary neuroendocrine cells to release AVP remains uncertain. An alternative hypothesis suggests that the release of pituitary AVP may be stimulated by hypoxia and inflammatory cytokines, such as interleukin-6, produced during pulmonary infections [15]. Initial management of hyponatremia involves assessing neurological symptoms and signs to determine if urgent treatment with hypertonic saline is required in severe cases. Severe hyponatremia can lead to cerebral edema, resulting in seizures, coma, or even fatality [16]. In such situations, immediate intervention is recommended, typically involving the administration of hypertonic sodium chloride [17]. Measuring serum osmolality (below 275 mOsm/kg) can help exclude non-hypotonic causes of hyponatremia, such as pseudo hyponatremia or translocational hyponatremia [9]. Further diagnostic criteria have been established to confirm the diagnosis of SIADH, including urine sodium levels exceeding 40 mEq/l with normal salt intake, absence of diuretic usage, no alteration in extracellular fluid volume, absence of hypovolemia, cirrhosis, nephrosis, or congestive heart failure, no presence of hypoadrenalism or hyperadrenalism, no hyperglycemia, hyperglyceridemia, or hyperproteinemia, BUN levels below 8 mg/dl, uric acid levels below 2.6 mg/dl, urea excretion over 55%, uncorrected hyponatremia with intravenous administration of normal saline, and corrected hyponatremia through fluid restriction [18]. Measurement of AVP is not useful for the differential diagnosis of SIADH, as elevated AVP levels can be observed in various other cases of hyponatremia [19].

The definitive treatment for chronic SIADH caused by SCLC involves addressing the underlying tumor, typically

through surgical intervention and combination chemotherapy [8]. However, in cases with moderate symptoms, initial treatment involves ensuring adequate solute intake and implementing long-term fluid restriction based on serum sodium levels [20]. Tolvaptan has received approval from the US Food and Drug Administration for the treatment of clinically significant hypervolemic or euvolemic hyponatremia, defined as serum sodium levels below 125 mmol/l, or symptomatic hyponatremia that has not responded to fluid restriction [9]. Trials are currently underway to compare protocolized low-dose tolvaptan versus fluid restriction in SIAD [21]. In cases where patients present with severe SIADH symptoms such as confusion, convulsions, or coma, it is highly recommended to administer 3% normal saline in a volume of 100 to 150 ml over a span of 10 to 15 minutes, which can be repeated 2 to 3 times until a 5 mEq/l increase in serum sodium is achieved, taking care not to overcorrect. It is important to avoid exceeding a maximum increase of 10 mEq/l within the first 24 hours or 0.5 mEq/l within the first hour to reduce the risk of central nervous system damage, leading to complications such as central pontine myelinolysis, coma, and ultimately death [22]. In cases where patients experience symptoms but have chronic hyponatremia, such as paraneoplastic SIADH, a more gradual correction rate of 1.5 to 2 mmol/l/h should be administered [23]. In addition to these measures, several drugs, including demeclocycline, conivaptan, and urea, are emerging as second-line treatment options for SIADH. However, further research is required to determine the efficacy of these therapeutics and their combination in paraneoplastic SIADH [8, 23].

ECTOPIC CUSHING'S SYNDROME

Ectopic Cushing's syndrome (ECS) is a neuroendocrine disorder characterized by excessive corticotropin secretion from extra pituitary cancer cells. ECS represents the second most common PNS associated with SCLC, with an estimated occurrence rate of 1-5% among SCLC patients [24]. Conversely, SCLC accounts for up to 20% of ECS cases [25]. ECS is significantly correlated with a poorer prognosis for SCLC, making it the most severe PNS of this cancer [26, 27]. A study on survival rates in SCLC patients demonstrated that those with ECS (n = 23) had a median survival of 6.6 months, significantly shorter than the 13 months median survival of patients without any PNS or the 8.5 months median survival of those with syndrome of inappropriate antidiuretic hormone secretion [26]. Similarly, a retrospective study by Osswald reported a median survival rate of 5 months in SCLC patients with ECS, significantly shorter than in patients with other forms of ECS (53-119 months) [28]. ECS is characterized by the expression of the pro-opiomelanocortin (POMC) gene and the secretion of bioactive mature adrenocorticotropic hormone (ACTH) [29]. However, the processing quality of pro-POMC varies and correlates with tissue differentiation. Well-differentiated tumors may secrete mature and bioactive ACTH, along with other peptides, resembling the processing that occurs in pituitary corticotrophs. In contrast, less-differentiated tumors and SCLC may secrete varying amounts of mature ACTH with other POMC-derived peptides or unprocessed POMC, indicating altered post-translational processing compared to pituitary corticotrophs [30, 31]. 3.2-4.57% of SCLCs hypersecrete ACTH. Although the hormone produced may be biologically inactive and unable to induce a clinical syndrome, this phenomenon may lead to poorer short-term prognosis due to the rapid tumor spread associated with intense hypercortisolism [32, 33].

While obesity is a common feature of Cushing's syndrome, approximately 10% of ECS patients experience weight loss [34]. Additionally, ECS generally carries a poorer prognosis than classical Cushing's syndrome [26]. Nevertheless, ECS and the classic syndrome share similar clinical features, including head and neck lipodystrophy, hyperhidrosis, facial male-pattern hair growth, insulin resistance, hypertension, hypokalemia, and hypernatremia, with a higher prevalence observed in ECS [35]. In a study of twenty-four ECS patients with neuroendocrine tumors of different origins, fat tissue redistribution characteristic of a Cushingoid appearance and peripheral edema were significantly more common in patients with neuroendocrine tumors. Corticotropin hormone levels were significantly positively correlated with sodium ions (Na) and negatively correlated with phosphate in ECS patients without neuroendocrine tumors, while no substantial correlation was observed in patients with tumors. Moreover, ACTH showed a significant negative correlation with potassium ions (K) in both ECS patients with and without neuroendocrine tumors. Serum chromogranin A levels exhibited a significant positive correlation with K in ECS patients with neuroendocrine tumors. Lastly, ECS patients who did not survive had significantly higher levels of early morning cortisol compared to those who survived, and among patients with and without tumors, significantly higher midnight cortisol levels were observed in those with neuroendocrine tumors [35]. Prompt diagnosis of ECS in SCLC patients is crucial due to the extremely poor prognosis. Inferior petrosal sinus sampling (IPSS) is the most reliable test for ECS [36]. However, since this test is not feasible for many patients, ECS is diagnosed when clinical signs and symptoms are accompanied by a plasma adrenocorticotropic hormone level exceeding 15 pg/ml, evidence of carcinoid in CT scans of the chest, abdomen, and pelvis, positive ACTH immunohistochemical test, Ki-67 antigen labeling index above 10%, and failure of high-dose dexamethasone therapy to lower cortisol levels [37, 38].

The primary approach to managing ECS is the excision of the underlying tumor. In addition to surgery, patients may undergo radiation therapy and systemic chemotherapy, which can prolong survival rates. In cases where other options are not feasible, cortisol synthesis inhibitors can be used, although their efficacy is limited [35]. Ketoconazole, approved by the FDA in 1981, was the first cortisol synthesis inhibitor for ECS. However, it may increase the risk of chemotherapy toxicity due to its strong inhibition of cytochrome P450 3A4. Therefore, metyrapone, a reversible inhibitor of 11β-hydroxylase, has been reported as a better choice [39]. In 2020, the FDA approved osilodrostat, a cytochrome P450 11B1 inhibitor, for patients unable to undergo surgery or experiencing persistent Cushing's syndrome post-surgery [40]. In severe cases, a combination of cortisol synthesis inhibitors and chemotherapy may be prescribed. When Cushing's syndrome symptoms are severe to the extent that the patient cannot tolerate chemotherapy, metyrapone should be administered [35]. Reducing cortisol levels before tumor excision is recommended, as it increases survival rates. ECS patients receiving chemotherapy should be monitored for coagulation indicators such as D-dimer and inflammatory markers such as C-reactive protein, as chemotherapy increases the risk of venous thromboembolism and opportunistic infections [6].

LAMBERT-EATON MYASTHENIC SYNDROME

Lambert-Eaton myasthenic syndrome (LEMS) is the most commonly diagnosed associated with SCLC, with an estimated occurrence rate of 0.44-3% [6, 41, 42]. SCLC accounts for approximately 60% of LEMS cases, and other tumors do not appear to be associated with an increased frequency of LEMS [43]. LEMS can be further classified into two main subgroups: SCLC-combined LEMS and LEMS without SCLC. LEMS combined with SCLC predominantly affects males, reflecting smoking habits. Autoantibodies related to LEMS occur in a higher percentage of SCLC cases but do not result in neuromuscular disease manifestations. LEMS and SCLC patients are generally younger compared to those without SCLC. LEMS patients without SCLC are more susceptible to other autoimmune diseases, possibly attributed to genetic vulnerabilities [44]. LEMS is caused by autoantibodies targeting P/Q type voltage-gated calcium channels (VGCC) within the cell membrane of the presynaptic neuron. These antibodies are significantly sensitive and detectable in approximately 85% of all LEMS cases, offering almost 100% specificity for diagnosing LEMS in individuals experiencing specific muscle weakness [45]. VGCC antibodies are detectable in approximately 3-5% of SCLC cases who do not exhibit any symptoms of autonomic dysfunction or muscle weakness. The presence of VGCC antibodies in other control groups is rare; however, it is noted in clinically pure cerebellar ataxia cases [46]. The same VGCC antibodies responsible for muscle weakness, probably contribute to The autonomic dysfunction observed in LEMS by reducing the expression of the acetylcholine receptors in parasympathetic and sympathetic neurons [47]. The precise involvement of T lymphocytes in LEMS remains unclear. T cells do not accumulate on the presynaptic terminal, and the thymus or other lymphoid organs do not undergo functional or morphological changes. Nevertheless, among SCLC patients with LEMS compared to those without it, the detection of T cells potentially suggests a decrease in immune suppression. Since the immunoregulation of T cells could potentially influence the onset or progression of LEMS, the SCLC-related T cell activity may be relevant to the development of LEMS [48]. Unlike LEMS without SCLC, there is no reported association between SCLC-associated LEMS and HLA. Tumor tissue from SCLC-associated LEMS patients expresses a reduced amount of HLA class I antigens compared to tissue from SCLC patients without LEMS, indicating a pathogenetic difference between the two LEMS subtypes. In approximately half of SCLC-related LEMS cases, the tumor is the initial event for LEMS. SCLC cells can express VGCC on their surface, leading to the production of autoantibodies cross-reacting with the neural antigens. This induction of autoimmunity occurs in the early stages of tumorigenesis, often before the diagnosis of SCLC or even before the presence of malignancy or lung disease is suspected [49]. Additionally, anti-SOX (sry-like high-mobility group box) antibodies are specific seromarkers for SCLC. Although the pathogenesis of SOX antibodies is not well-studied, it is shown that their seroprevalence is higher in SCLC-associated LEMS (67%) compared to SCLC without LEMS (36%) [46].

Patients with LEMS typically experience weakness in proximal muscles, areflexia, and autonomic dysfunction. Cranial nerve involvement can cause symptoms such as diplopia and ptosis, resembling those seen in myasthenia gravis. The high specificity of VGCC autoantibodies for LEMS makes them proper diagnostic markers. However, the absence of detectable VGCC antibodies does not rule out LEMS. SOX antibodies also have high specificity for LEMS in SCLC, although with low sensitivity [50]. Blood tests are primarily useful for excluding other potential causes, such as myositis or thyrotoxic myopathy. Neurophysiological tests involving appropriate repetitive nerve stimulation are firmly in favor of the diagnosis of LEMS [46]. Upon confirming or suspecting a diagnosis of LEMS, the investigation for SCLC should promptly begin. Even though smoking substantially elevates the risk, nonsmokers should be equivalently evaluated. Comprehensive imaging, including a positron emission

tomography (PET) scan, if necessary, is required. Should the initial screening yield negative results, it is advisable to repeat the screening after three months, followed by subsequent screenings every six months for up to two years after the onset of LEMS [51]. Intravenous immunoglobulins, pyridostigmine, and amifampridine are commonly used to alleviate the symptoms of LEMS [52]. In the case of SCLC-associated LEMS, treating the underlying SCLC effectively can also lead to an improvement in paraneoplastic LEMS. In cases where LEMS coexists with SCLC, anticancer treatment becomes pivotal. Survival rates for patients with both SCLC and LEMS are marginally higher compared to those with SCLC alone. However, the mere presence of VGCC antibodies without evident LEMS symptoms does not seem to enhance survival rates. Likewise, the presence of SOX antibodies in paraneoplastic LEMS does not correlate with any survival advantage [46].

MYASTHENIA GRAVIS

Myasthenia gravis (MG) is an autoimmune disorder primarily affecting the neuromuscular junction. The incidence of MG in association with thymoma is approximately 15% [53]. However, MG can also rarely occur in the presence of gynecologic cancers and SCLC [54, 55]. In MG, complement formation is mediated by immunoglobulins G1 and G3 against acetylcholine receptors on the postsynaptic membrane, leading to impaired acetylcholine transmission and somatic and autonomic dysfunction. The correlation between anti-acetylcholine receptor (anti-AChR) antibody laboratory values and the development of MG has been extensively documented, given the expression of the receptor subunit α3-nicotinic in neuronal cells and the ability of the human thymus to express it, which contributes to the occurrence of MG in SCLC [56]. Another hypothesis suggests that SCLC cancer cells express the α3-nicotinic subunit gene, which, when cross-reacting with the muscle α1-nicotinic muscle receptor subunit, can phenotypically manifest as MG symptoms [57]. Additionally, the presence of an aberrant expression of nicotinic acetylcholine receptors in squamous cell carcinoma (SCC)-37 and SCC-A9 cell lines in SCLC has been described, leading to increased desensitization rates and heightened transient depolarizations observed in MG [58].

MG initially manifests with symmetrical fluctuating ocular and bulbar weakness as well as weakness of the proximal muscles [59]. Evaluation of neuromuscular weakness in SCLC patients necessitates consideration of various differentials, including weakness related to the disease itself or chemotherapy [55]. Ptosis and diplopia are the most frequent manifestations of MG. Dysphagia, velopharyngeal insufficiency, dysarthria, hypophonia, facial muscle weakness, and, in severe cases, respiratory muscle paralysis may also be present. Continuous physical activity can cause synaptic fatigue and worsen any of these symptoms. The diagnosis of MG involves assessing clinical manifestations, conducting physical examinations, performing blood and pulmonary function tests, and utilizing imaging techniques and electrodiagnostic methods. Two commonly employed electrodiagnostic methods are repetitive nerve stimulation at 2 to 3 Hertz and single-fiber electromyography. The latter test is the most sensitive measure for MG, but it is not specific and demonstrates positive results in other movement disorders as well. During the examination, repetitive tasks may be requested from the patient, and the "curtain sign" can be assessed by holding one eyelid open to determine if the patient can keep their other eyelid open [59, 60].

Serologic tests targeting anti-AChR antibodies exhibit high sensitivity in classical MG cases, although sensitivity may be lower in ocular MG cases. Additionally, it is worth noting that MG can be triggered by antibodies other than anti-ACh, including anti-MuSK, anti-LRP4, anti-agrin, and anti-titin antibodies [61]. Neurophysiological tests play a crucial role in the detection of MG, especially in cases where SCLC patients exhibit MG symptoms despite negative anti-AChR antibody results [62]. Chest computed tomography (CT) and magnetic resonance imaging (MRI) are valuable for identifying potential neoplastic origins of complications, while cranial and orbital MRI can exclude inflammation of cranial nerves and ocular muscles. Forced vital capacity monitoring helps assess ventilation adequacy [59].

Although there is no consensus on treatment strategies and no rigorously tested treatment trials, MG is considered one of the most manageable neurological disorders. Treatment approaches for paraneoplastic MG include tumor excision when feasible, anticholinesterase medication, and immunosuppressive agents such as corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, tacrolimus, sirolimus, rituximab and cyclophosphamide, and other immunomodulatory therapies such as plasmapheresis and intravenous immunoglobulin (IVIg). Plasmapheresis and thymectomy are also utilized in MG treatment, although they are not conventional medical immunomodulating therapies and act by modifying the immune system. Several factors, including disease severity, distribution, and rate of progression should be considered before initiating or altering therapy. Treatment regimens are personalized based on the severity of MG, patient age, serology status, thymic pathology, concurrent medical conditions, patient and physician preferences, and physician experience [63].

LIMBIC ENCEPHALITIS

Paraneoplastic limbic encephalitis (PLE) is a rare autoimmune neurological syndrome that predominantly

affects the limbic areas, including the hippocampus, amygdala, hypothalamus, cingulate gyrus, and limbic cortex, in cancer patients [64]. SCLC, testicular malignancies, and ovarian malignancies are commonly associated with limbic encephalitis, although it has also been reported in other cancer types. Approximately 50% of limbic encephalitis cases have an underlying SCLC [65]. While many patients with PLE exhibit circulating neuronal antibodies, not all patients have detectable antibodies. The specific underlying cause of PLE can be inferred based on the type of autoantibodies present. For instance, anti-NMDA receptor antibodies are primarily linked to ovarian cancers, especially teratomas, while anti-Ma2 antibodies are associated with testicular malignancies and anti-Hu antibodies are associated with SCLC [66]. Among patients with limbic encephalitis and SCLC, around half exhibit anti-Hu antibodies, while a subset of patients may have other antibodies such as anti-CRMP5, anti-GABAb receptor, anti-amphiphysin, and anti-glutamic acid decarboxylase (GAD) [67-71]. Some of these neuronal surface antibodies are thought to directly contribute to neuronal damage, while in cases involving intracellular antigens cellular immune responses rather than antibodies may play a role in neuronal cell damage and death. Nevertheless, the precise immunogenesis mechanisms in PLE remain insufficiently elucidated, and even in the presence of antibodies that are potentially pathogenic, T cell-mediated immune responses may contribute to neuronal injury.

Anti-Hu antibodies serve as an important diagnostic marker for PLE. However, our current understanding suggests that direct cellular immunity plays a greater role than anti-Hu antibodies in neuronal injury. The CD8+ T cells accumulating surrounding neurons in the brain and posterior root ganglion, as well as the oligoclonal T cells in the posterior root ganglion and blood, support the cell-mediated nature of the neuronal injury [72, 73]. Peripheral blood T cells of patients can detect peptides originating from the HuD onconeural antigen and react to them [74]. In cases of limbic encephalitis associated with CRMP5 antibodies, the engagement of the basal ganglia or extralimbic cerebral cortex may be observed [67]. Anti-amphiphysin and GAD antibodies target intracellular synaptic proteins. Anti-GAD antibodies are typically expressed in non-paraneoplastic cerebellar ataxia and stiff-person syndrome, while anti-amphiphysin antibodies were originally identified in breast cancer-associated paraneoplastic cases of stiff-person syndrome. However, these antibodies are rarely observed in cases of SCLC-associated PLE. Anti-GAD antibodies are also linked to pharmacoresistant epilepsy syndrome and MRI findings indicative of limbic encephalitis, although this syndrome is not cancer-related and lacks additional features of limbic encephalitis [75, 76]. Additionally, anti-GABAb receptor antibodies are shown to be present in several non-paraneoplastic or SCLC-associated limbic encephalitis patients. These patients typically present with subacute onset of seizures preceding the full manifestation of limbic encephalitis symptoms by days or weeks [77].

Due to the challenges associated with antibody detection techniques, such as specificity and availability, the differential diagnosis of PLE is time-consuming and can take several weeks. MRI in approximately two-thirds of PLE patients reveals bilateral abnormal T2-weighted or FLAIR signal in the amygdala and medial temporal lobe, and less commonly in the basal frontal cortex and hypothalamus. In many cases, these MRI lesions resolve over time, with or without concurrent improvement in symptoms, and may progress to the atrophy of the temporal lobe [78]. Mild lymphocytic pleocytosis and/or slight elevation of protein is present in the CSF of around two-thirds of patients with limbic encephalitis during the disease course. Nevertheless, normal laboratory CSF findings do not exclude the possibility of PLE, and abnormal CSF findings do not differentiate between the paraneoplastic and non-paraneoplastic nature of limbic encephalitis [79]. Middle-aged patients who have a history of smoking and develop limbic encephalitis should be evaluated for the presence of SCLC. MRI scanning and CT of the chest are more sensitive for detecting small lesions than a plain chest X-ray. If present, serum neuronal antibodies such as anti-Hu, anti-GABAbR, anti-CRMP5, or others are highly specific markers for SCLC or occasionally another tumor. Total body PET scanning may be used to identify lung or other neoplasms in suspected PNS cases with inconclusive or equivocal chest MRI or CT results. If the first search for an underlying tumor is inconclusive, which is not uncommon, the evaluations should be regularly repeated for at least three years [51, 80].

PLE has shown excellent response rates when the underlying tumor is removed. Therefore, prompt tumor treatment is essential for patients with limbic encephalitis as the first presentation. Although no randomized clinical trials have compared the efficacy of different immunotherapies in limbic encephalitis, immunosuppressants, IVIG, and plasmapheresis are generally beneficial in managing this condition [81, 82].

CEREBELLAR DEGENERATION

Paraneoplastic cerebellar degeneration (PCD) is a relatively frequent PNNS characterized by antibody-mediated damage to cerebellar Purkinje cells. PCD is frequently associated with breast and pelvic cancers, although cases have also been reported in Hodgkin lymphoma, gastrointestinal malignancies, prostatic hyperplasia, and SCLC [83, 84]. The prevalence of PCD in SCLC is estimated to be less than 1% among cancer patients, but accurate epidemiological data are limited due to the rarity of the condition [85]. PCD is believed to result from

an autoimmune reaction primarily targeting the Yo antigen or cerebellar degeneration-related protein 2 (CDR2), which is secreted by tumor cells. These antibodies cross-react with a comparative protein on cerebellar Purkinje cells, leading to their degeneration. The degenerative process often begins locally but slowly spreads to completely engage the cerebellum, and show signs of the involvement of the brain stem as well [86]. The rate of damage to the nerve cells varies among patients, with some experiencing an acute and some others a subacute and slowly progressive course [87]. PCD can be mediated by other onconeural antibodies, including anti-mGluR, anti-CV2, anti-CRMP5, anti-VGCC, anti-Ma2, anti-Tr, anti-Ri, anti-Hu, and anti-Yo antibodies. However, anti-Yo (also known as anti-Purkinje cell cytoplasmic antibody type 1) and anti-Hu antibodies are the most frequently detected in SCLC patients [88]. While any paraneoplastic antibody may contribute to PCD development, only anti-Yo, anti-Tr, and anti-mGluR1 antibodies have been specifically associated with isolated cerebellar dysfunction. Neurologic symptoms often precede tumor diagnosis, with antibody detection preceding the diagnosis in over 60% of cases.

The Yo antigen (CDR2) is a cytoplasmic protein that interacts with c-Myc. CDR2 is primarily expressed in the Purkinje cells of the cerebellum, although it can also be found in neurons of the brain stem. Studies suggest that CDR2 sequesters c-Myc in the neuronal cytoplasm, downregulating its activity. Disruption of this interaction by anti-Yo antibodies may lead to increased c-Myc activity, resulting in the apoptosis of Purkinje cells [89, 90]. Postmortem examinations of patients with anti-Yo antibodies have demonstrated gliosis and nearly complete loss of Purkinje cells, supporting this theory [87]. In cases associated with Lambert-Eaton myasthenic syndrome, autoimmunity against VGCC, specifically the P/Q type VGCC found on Purkinje cells, mediated by anti-VGCC antibodies, can cause diffuse loss of Purkinje cells and subsequent cerebellar degeneration [90]. Although antibodies may play an initial pathogenic role in PCD, T-cell immune responses are believed to be the primary effectors of neuronal degeneration. Accordingly, PCD patients often exhibit infiltration of CD8+ T cells in the cerebellum, with cytotoxic T cells observed as being proximal to damaged neurons [87].

The hallmark feature of PCD is cerebellar dysfunction. PCD is typically characterized by muscle weakness, uncoordinated gait, internal tremors, tremors in the arms and legs, dysarthria, dysphagia, vertigo, nystagmus, ophthalmoplegia, or diplopia. The onset of symptoms can be subacute or rapid. After progressing for a few weeks, the symptoms stabilize, leaving the patient severely disabled. Initially, patients may be misdiagnosed with cerebrovascular disease, demyelinating diseases, infectious diseases, vitamin deficiencies, toxic exposures, sarcoidosis, autoimmune diseases (e.g., systemic lupus erythematosus, Sjögren's syndrome), or alcohol-induced cerebellar degeneration. Other conditions that can mimic PCD include late-onset spinocerebellar ataxia, with or without a family history, olivopontocerebellar degeneration, and other degenerative brain diseases commonly seen in elderly patients. The patient's history, physical examination findings, and diagnostic testing are crucial in differentiating PCD from other conditions that are statistically more likely to occur than PCD. Findings inconsistent with a diagnosis of PCD include severe alteration of mental status accompanied by myoclonus and ataxia, predominantly corticospinal tract dysfunction, unilateral cerebellar dysfunction, and familial cerebellar degeneration [87].

MRI or CT scans are necessary to exclude stroke, brain tumors, structural abnormalities, demyelinating diseases, vascular lesions, or infectious causes. Cerebellar atrophy is often visible on MRI after the onset of symptoms, typically occurring months later. Therefore, initial MRI results are often normal in most PCD cases. PET scanning is useful in identifying the underlying tumor. CSF analysis typically reveals mild pleocytosis, mild elevation of protein levels, a high IgG concentration, and the presence of oligoclonal bands [91]. Detection of antibodies in the CSF is considered the definitive indicator of PCD. Although antibody titers can predict the development of encephalomyelitis, they are not associated with the stage and prognosis of the disease [92]. Severe loss of Purkinje cells diffusely throughout the cerebellar cortex is the characteristic histological finding in PCD. Purkinje cells are completely absent in affected specimens, with occasional patchy loss observed. Inflammatory changes, including lymphocytic infiltration, are also observed. Atrophy of the granular and molecular layers, microglial proliferation, and astrocytosis are present, with basket cells relatively spared. The deep cerebellar nuclei and the cerebellar connections to the brain stem remain normal. Patients with anti-Yo antibodies tend to exhibit more inflammatory changes and show characteristic immunofluorescence patterns, including coarse granular staining of Purkinje cell cytoplasm, as well as proximal axons and dendrites, without the staining of nuclei or systemic tissues. In PCD associated with anti-Hu antibodies, staining is observed in cortical and cerebellar neuronal nuclei [93].

Early detection of the underlying tumor and prompt treatment, often involving resection with the potential addition of chemotherapy, are crucial objectives in managing PCD. The response of PNNS, including PCD, to immunosuppressive agents or antitumor treatment is highly influenced by the underlying neuropathology. The combination of IVIG, cyclophosphamide, and methylprednisolone has shown limited effectiveness in patients with PNNS or PCD and antineuronal antibodies. This may be partly attributed to the involvement of

T cells in cerebellar damage. However, considering the severe disability associated with the condition and the positive responses observed in some cases, it is reasonable to consider immunotherapy in an attempt to reduce morbidity [94].

OPSOCLONUS MYOCLONUS ATAXIA SYNDROME

Opsoclonus myoclonus ataxia syndrome (OMAS), also known as dancing eye syndrome, is a rare neurological disorder that affects both pediatric and adult populations. In adults, OMAS is predominantly associated with SCLC, although it can also occur following viral infections, particularly in individuals with a history of OMAS. Among a cohort of 21 patients with OMAS, 1 was found to have underlying SCLC [95]. OMAS can also be associated with other tumors such as neuroblastoma, ganglioneuroblastoma, and Wilms tumor [96]. Additionally, there are cases of idiopathic OMAS where no underlying tumors or viral infections are detected. Anti-Ri antibodies are frequently detected in the CSF of OMAS patients and are believed to contribute to cerebellar damage by causing glutamic acid accumulation in the brain [95]. The target antigens for these antibodies are the Nova proteins, Nova-1 and Nova-2, which are widely expressed in the central nervous system and play a role in synaptic protein regulation. However, in SCLC patients, the presence of anti-Hu antibodies may have greater significance [97]. Although the diagnosis of PNS remains challenging due to its heterogeneous timing and symptomatology, underlying cancer is only found in 20-40% of cases [98]. The pathogenesis of paraneoplastic OMAS is still not fully understood.

The classical triad of OMAS symptoms consists of opsoclonus, myoclonus, and cerebellar ataxia. However, additional symptoms such as mutism, fatigue, malaise, slobbering, strabismus, nausea, somnipathy, and emotional disorders can also occur. It is important to differentiate these classical symptoms from features of toxic-metabolic encephalopathy, including hyperosmolar coma, liver disease, and intoxication. Additionally, the presence of genetic abnormalities, metastasis, inflammation, demyelination, hemorrhage and sarcoidosis, in the pons and/or cerebellum, has been reported to contribute to certain neurologic deficits seen in OMAS. Currently, there are no specific laboratory methods available for diagnosing OMAS. However, laboratory tests play a crucial role in ruling out other conditions. Single photon emission computed tomography (SPECT) may aid in the diagnosis by demonstrating increased blood flow in the cerebellum. Patients with OMAS should be screened for the presence of an underlying tumor. In cases where the initial screening is negative, repeat evaluations should be conducted after several months. While many OMAS patients exhibit elevated levels of certain antibodies, the sensitivity and specificity of autoantibody screening in this population are low, and it is not considered routine. Cerebrospinal fluid analysis, electroencephalography, and neuroimaging of the brain often yield normal results [99].

Due to the rarity of OMAS, specific treatments are limited, and current management primarily focuses on symptomatic relief and addressing the underlying tumor. The National Organization for Rare Disorders recommends a front-loaded high-dose combination of adrenocorticotropin hormone, intravenous immunoglobulin, and rituximab for the treatment of OMAS, which has shown efficacy in alleviating symptoms in 80-90% of OMAS patients. Further research is needed to elucidate the underlying mechanisms of OMAS and develop effective treatments for this rare disorder [100].

SENSORY NEUROPATHY AND NEURONOPATHY

Sensory neuropathy is a broad term used to describe the loss of sensation throughout the body, which can be attributed to various underlying diseases. SCLC is the most commonly associated cancer with sensory neuronopathy, with up to 16% of cases stemming from it. In patients with SCLC, the production of anti-Hu and anti-CV2 antibodies can lead to cytotoxic T-cell-mediated dorsal root ganglia neuropathy [101]. Compared to anti-Hu antibodies, anti-CV2 neuropathy appears to exhibit more frequent sensorimotor involvement and asymmetric polyradicular involvement [102]. It should be noted that immune checkpoint inhibitors, which enhance antitumor immunity, have been linked to various immune-mediated diseases, including neuropathies and rapidly progressive polyradiculoneuropathies [103]. Other partially characterized antibodies in SCLC include ANNA-3, which has been observed in certain cases of sensory, sensorimotor, and autonomic neuropathy; anti-Zic4, a marker of cerebellar degeneration found in some neuropathy cases, often in conjunction with anti-Hu and/or anti-CV2 antibodies; and anti-PCA2, initially described in both central and peripheral syndromes, including neuropathy [102, 104]. The target antigen of anti-PCA-2, identified in 2017, is MAP1B, a microtubule-associated protein. It is demonstrated that paraneoplastic sensory neuropathy is the most frequent presentation among anti-MAP1B-positive SCLC patients [102].

One of the prominent symptoms of sensory neuropathy is early-onset ataxia, primarily resulting from the impairment of afferent neurons responsible for transmitting impulses from the body's extremities [105]. As the condition progresses, patients may exhibit "writhing" movements in their hands and feet when their eyes are closed [106]. Positive sensory symptoms are also common

when small and medium-sized fibers are affected, manifesting as a stocking-glove pattern of "pins and needles" sensations. In individuals with diabetes, careful assessment for negative neuropathic symptoms, such as non-length dependent and multifocal numbness in the feet, is essential for the diagnosis of small-fiber neuropathies. In paraneoplastic cases, motor output may be compromised, leading to absent stretch reflexes [107]. Electromyography studies typically reveal reduced or absent sensory nerve action potentials in sensory neuropathies. Autonomic sensory testing encompasses quantitative examinations to assess hot and cold sensations, transient changes in skin electrical potential (e.g., sweat gland activity), and non-invasive electrochemical skin conductance studies for detecting sudomotor dysfunction. The current gold standard for diagnosing small fiber neuropathy is a skin biopsy, often performed on the distal leg, approximately 10 cm proximal to the lateral malleolus, or the lateral distal or proximal thigh. Nerve biopsy is generally unnecessary for diagnosing sensory neuropathy, and imaging studies can provide visualization of dorsal column pathology [108].

The treatment of paraneoplastic sensory neuropathy lacks specific guidelines and involves various therapeutic modalities, including medications for neuropathic pain, antidepressants, antiepileptics, infliximab, transcutaneous electrical nerve stimulation therapy, a gluten-free diet, psychological counseling, and most importantly, management of the underlying tumor. However, treatment efficacy may vary depending on the severity of the neuropathy and the specific neoplasm involved. Further research is needed to investigate the underlying mechanisms of paraneoplastic sensory neuropathy and identify more effective treatment options [109].

CHOREA

Chorea is a movement disorder that can occur rarely as a PNS associated with cancers such as SCLC, thymoma, non-Hodgkin lymphoma, and tonsillar carcinoma. Paraneoplastic chorea is caused by damage to the basal ganglia mediated by antibodies such as anti-CRMP5 and anti-Hu. In about 70% of SCLC cases with paraneoplastic chorea, anti-Hu and anti-CRMP5 antibodies can be detected in the cerebrospinal fluid [110]. Anti-CRMP5 antibodies are known to be associated with the development of myasthenic syndrome, often seen in thymoma or paraneoplastic polyneuropathy associated with SCLC. Other less common syndromes associated with these antibodies include cerebellar ataxia and eye disorders [111]. Recent studies have also implicated phosphodiester 10A IgG in the etiology of paraneoplastic chorea [112]. The presence of these antibodies in the cerebrospinal fluid, along with signs of chorea, can serve as a warning sign for the presence of an underlying tumor, often weeks before the onset of its direct manifestations [113].

The term "chorea" is derived from the Latin word "Choreus," meaning "dance." Regardless of its underlying cause, chorea has similar signs and symptoms. It is characterized by random, brief, semi-directed, dance-like contractions primarily affecting the distal limbs and facial muscles. These contractions typically occur at rest and resolve during sleep. Individuals with chorea have difficulty maintaining ongoing motor activities, such as holding onto objects. The differential diagnosis of chorea relies on clinical findings, age, and mode of onset. To rule out secondary causes, a basic workup may include blood tests such as complete blood count, blood sugar, electrolytes, calcium, magnesium, vitamin B_{12}, and parathyroid levels, as well as kidney, liver, and thyroid function tests. In certain cases, a pregnancy test may also be performed [114].

While managing the underlying tumor is crucial, it may not always lead to the resolution of chorea symptoms. Currently, there are no randomized or large clinical trials specifically outlining optimal treatment algorithms for paraneoplastic neurologic diseases. Therefore, treatment approaches are based on expert opinion and extrapolated from general paraneoplastic encephalitides. Options may include glucocorticoids, plasma exchange, and intravenous immunoglobulins as immunomodulatory treatments. Additionally, dopamine receptor blockers and antipsychotic drugs may be used to manage chorea symptoms, regardless of the underlying cause [113].

CONCLUSIONS

In the realm of oncology, lung malignancies exhibit the highest incidence of association with PNS. Among the various subtypes and classifications of lung cancer, SCLC demonstrates the highest probability of a patient developing PNS. Paraneoplastic neurological and neuroendocrine syndromes are the most prevalent and clinically consequential complications in these patients. This article has provided a concise overview of classical PNS that are associated with SCLC, comprising the syndrome of inappropriate antidiuretic hormone secretion, Cushing's syndrome, myasthenia gravis, Lambert-Eaton myasthenic syndrome, limbic encephalitis, PCD, opsoclonus myoclonus ataxia syndrome, sensory neuropathy, and chorea. The majority of these syndromes are mediated by onconeural autoantibodies; nevertheless, the etiology is not limited to the abovementioned antibodies. Several other onconeural antibodies including anti-amphiphysin, ANNA3, PCA2, anti-Zic4, antinicotine AchR, anti-NR1, anti-NR2, and anti-glutamic acid decarboxylase can occasionally present various complications in SCLC patients. Although challenging, the detection of these antibodies in cerebrospinal fluid can be highly valuable for the early diagnosis and confirmation of underlying cancer. Tumor resection or management is the primary therapeutic approach for many PNS. Sup-

portive and symptomatic therapy varies between the condition and features of the patients but mainly relies on immunomodulatory agents. The study of PNS is a rapidly evolving field in oncology, and one of the principal concerns in this area pertains to the absence of specific molecular tests and targeted therapies. As we gain a deeper understanding of onconeural antibodies and pathways, we are presented with an increasing number of opportunities to design precise diagnostic assays and targeted therapeutics.

Acknowledgements

Absent.

Conflict of interest

Absent.

Financial support

Absent.

References

1. Schabath MB, Cote ML. Cancer progress and priorities: lung cancer. Cancer Epidemiol Biomarkers Prev 2019; 28: 1563-1579.
2. Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. Nat Rev Dis Primers 2021; 7: 3. DOI: 10.1038/s41572-020-00235-0.
3. Browse the tables and figures. SEER Cancer Statistics Review (CSR) 1975-2015. Available at: https://seer.cancer.gov/archive/csr/1975_2015/index.html.
4. Dingemans AC, Früh M, Ardizzoni A, Besse B, Faivre-Finn C, Hendriks LE, et al. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2021; 32: 839-853.
5. Yu JB, Wilson LD, Detterbeck FC. Superior vena cava syndrome – a proposed classification system and algorithm for management. J Thorac Oncol 2008; 3: 811-814.
6. Soomro Z, Youssef M, Yust-Katz S, Jalali A, Patel AJ, Mandel J. Paraneoplastic syndromes in small cell lung cancer. J Thorac Dis 2020; 12: 6253-6263.
7. Henry K. Paraneoplastic syndromes: definitions, classification, pathophysiology and principles of treatment. Semin Diagn Pathol 2019; 36: 204-210.
8. Iyer P, Ibrahim M, Siddiqui W, Dirweesh A. Syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) as an initial presenting sign of non small cell lung cancer-case report and literature review. Respir Med Case Rep 2017; 22: 164-167.
9. Warren AM, Grossmann M, Christ-Crain M, Russell N. Syndrome of inappropriate antidiuresis: from pathophysiology to management. Endocr Rev 2023; 44: 819-861.
10. Brown CH, Bains JS, Ludwig M, Stern JE. Physiological regulation of magnocellular neurosecretory cell activity: integration of intrinsic, local and afferent mechanisms. J Neuroendocrinol 2013; 25: 678-710.
11. Verbalis JG. Acquired forms of central diabetes insipidus: mechanisms of disease. Best Pract Res Clin Endocrinol Metab 2020; 34: 101449. DOI: 10.1016/j.beem.2020.101449.
12. Mandelblat-Cerf Y, Kim A, Burgess CR, Subramanian S, Tannous BA, Lowell BB, Andermann ML. Bidirectional anticipation of future osmotic challenges by vasopressin neurons. Neuron 2017; 93: 57-65.
13. Esposito P, Piotti G, Bianzina S, Malul Y, Dal Canton A. The syndrome of inappropriate antidiuresis: pathophysiology, clinical management and new therapeutic options. Nephron Clin Pract 2011; 119: c62-c73; discussion c73.
14. Coulson JM, Stanley J, Woll PJ. Tumour-specific arginine vasopressin promoter activation in small-cell lung cancer. Br J Cancer 1999; 80: 1935-1944.
15. Mastorakos G, Weber JS, Magiakou MA, Gunn H, Chrousos GP. Hypothalamic-pituitary-adrenal axis activation and stimulation of systemic vasopressin secretion by recombinant interleukin-6 in humans: potential implications for the syndrome of inappropriate vasopressin secretion. J Clin Endocrinol Metab 1994; 79: 934-939.
16. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, Thompson CJ. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med 2013; 126 (10 Suppl 1): S1-S42. DOI: 10.1016/j.amjmed.2013.07.006.
17. Garrahy A, Dineen R, Hannon AM, Cuesta M, Tormey W, Sherlock M, Thompson CJ. Continuous versus bolus infusion of hypertonic saline in the treatment of symptomatic hyponatremia caused by SIAD. J Clin Endocrinol Metab 2019; 104: 3595-3602.
18. Ali K, Najjar Y, Mehta S, Faddoul G. Syndrome of inappropriate antidiuretic hormone secretion as a presentation of untreated Parkinson's disease. Cureus 2023; 15: e37286. DOI: 10.7759/cureus.37286.
19. Pham PC, Pham PM, Pham PT. Vasopressin excess and hyponatremia. Am J Kidney Dis 2006; 47: 727-737.

20. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Eur J Endocrinol 2014; 170: G1-G47. DOI: 10.1530/EJE-13-1020.
21. Warren AM, Grossmann M, Hoermann R, Zajac JD, Russell N. Tolvaptan versus fluid restriction in acutely hospitalised patients with moderate-profound hyponatraemia (TVFR-HypoNa): design and implementation of an open-label randomised trial. Trials 2022; 23: 335. DOI: 10.1186/s13063-022-06237-5.
22. Rose BD. New approach to disturbances in the plasma sodium concentration. Am J Med 1986; 81: 1033-1040.
23. Mentrasti G, Scortichini L, Torniai M, Giampieri R, Morgese F, Rinaldi S, Berardi R. Syndrome of inappropriate antidiuretic hormone secretion (SIADH): optimal management. Ther Clin Risk Manag 2020; 16: 663-672.
24. Mayer S, Cypess AM, Kocher ON, Berman SM, Huberman MS, Hartzband PI, Halmos B. Uncommon presentations of some common malignancies. J Clin Oncol 2005; 23: 1312-1314.
25. Ghazi AA, Abbasi Dezfooli A, Amirbaigloo A, Daneshvar Kakhki A, Mohammadi F, Tirgari F, Pourafkari M. Ectopic Cushing's syndrome secondary to lung and mediastinal tumours – report from a tertiary care centre in Iran. Endokrynol Pol 2015; 66: 2-9.
26. Nagy-Mignotte H, Shestaeva O, Vignoud L, Guillem P, Ruckly S, Chabre O, et al. Prognostic impact of paraneoplastic cushing's syndrome in small-cell lung cancer. J Thorac Oncol 2014; 9: 497-505.
27. Piasecka M, Larsson M, Papakokkinou E, Olsson L, Ragnarsson O. Is ectopic Cushing's syndrome underdiagnosed in patients with small cell lung cancer? Front Med (Lausanne) 2022; 9: 954033. doi: 10.3389/fmed.2022.954033.
28. Osswald A, Deutschbein T, Berr CM, Plomer E, Mickisch A, Ritzel K, et al. Surviving ectopic Cushing's syndrome: quality of life, cardiovascular and metabolic outcomes in comparison to Cushing's disease during long-term follow-up. Eur J Endocrinol 2018; 179: 109-116.
29. Ye L, Li X, Kong X, Wang W, Bi Y, Hu L, et al. Hypomethylation in the promoter region of POMC gene correlates with ectopic overexpression in thymic carcinoids. J Endocrinol 2005; 185: 337-343.
30. Page-Wilson G, Freda PU, Jacobs TP, Khandji AG, Bruce JN, Foo ST, et al. Clinical utility of plasma POMC and AgRP measurements in the differential diagnosis of ACTH-dependent Cushing's syndrome. J Clin Endocrinol Metab 2014; 99: E1838-E1845. DOI: 10.1210/jc.2014-1448.
31. Dutta D, Mukhopadhyay S, Maisnam I, Ghosh S, Mukhopadhyay P, Chowdhury S. Neuroendocrine carcinoma of the thyroid causing adrenocorticotrophic hormone-dependent Cushing's syndrome. Thyroid 2013; 23: 120-123.
32. Tsoli M, Dimitriadis GK, Androulakis II, Kaltsas G, Grossman A. Paraneoplastic syndromes related to neuroendocrine tumors. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al. (eds.). South Dartmouth (MA): MDText.com, Inc.; 2000.
33. Jeong C, Lee J, Ryu S, Lee HY, Shin AY, Kim JS, et al. A case of ectopic adrenocorticotropic hormone syndrome in small cell lung cancer. Tuberc Respir Dis (Seoul) 2015; 78: 436-439.
34. Ilias I, Torpy DJ, Pacak K, Mullen N, Wesley RA, Nieman LK. Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. J Clin Endocrinol Metab 2005; 90: 4955-4962.
35. Paleń-Tytko JE, Przybylik-Mazurek EM, Rzepka EJ, Pach DM, Sowa-Staszczak AS, Gilis-Januszewska A, Hubalewska-Dydejczyk AB. Ectopic ACTH syndrome of different origin – diagnostic approach and clinical outcome. Experience of one Clinical Centre. PLoS One 2020; 15: e0242679. DOI: 10.1371/journal.pone.0242679.
36. Bekci T, Belet U, Soylu AI, Uzunkaya F, Ozturk M, Atmaca A. Efficiency of inferior petrosal sinus sampling in the diagnosis of Cushing's disease and comparison with magnetic resonance imaging. North Clin Istanb 2019; 6: 53-58.
37. Beuschlein F, Weigel J, Saeger W, Kroiss M, Wild V, Daffara F, et al. Major prognostic role of Ki67 in localized adrenocortical carcinoma after complete resection. J Clin Endocrinol Metab 2015; 100: 841-849.
38. Zhang HY, Zhao J. Ectopic Cushing syndrome in small cell lung cancer: a case report and literature review. Thorac Cancer 2017; 8: 114-117.
39. Shirley M. Ketoconazole in Cushing's syndrome: a profile of its use. Drugs Ther Perspect 2021; 37: 55-64.
40. Dormoy A, Haissaguerre M, Vitellius G, Do Cao C, Geslot A, Drui D, et al. Efficacy and safety of osilodrostat in paraneoplastic Cushing syndrome: a real-world multicenter study in France. J Clin Endocrinol Metab 2023; 108: 1475-1487.
41. Wirtz PW, Nijnuis MG, Sotodeh M, Willems LNA, Brahim JJ, Putter H, et al. The epidemiology of myasthenia gravis, Lambert-Eaton myasthenic syndrome and their associated tumours in the northern part of the province of South Holland. J Neurol 2003; 250: 698-701.
42. Elrington GM, Murray NM, Spiro SG, Newsom-Davis J. Neurological paraneoplastic syndromes in patients with small cell lung cancer. A prospective survey of 150 patients. J Neurol Neurosurg Psychiatry 1991; 54: 764-767.
43. Spillane J, Ermolyuk Y, Volynski K, Kullmann D. Lambert-Eaton myasthenic syndrome antibodies decrease synaptic vesicle exocytosis in neuronal cultures. J Neurol Neurosurg Psychiatry 2013; 84: e2. DOI: https://doi.org/10.1136/jnnp-2013-306573.35.
44. Guntinas-Lichius O, Prengel J, Cohen O, Mäkitie AA, Vander Poorten V, Ronen O, et al. Pathogenesis, diagnosis and therapy of facial synkinesis: a systematic review and clinical practice recommendations by the international head and neck scientific group. Front Neurol 2022; 13: 1019554. DOI: 10.3389/fneur.2022.1019554.
45. Lennon VA, Kryzer TJ, Griesmann GE, O'Suilleabhain PE, Windebank AJ, Woppmann A, et al. Calcium-channel antibodies in the Lambert-Eaton syndrome and other paraneoplastic syndromes. N Engl J Med 1995; 332: 1467-1474.
46. Gilhus NE. Lambert-eaton myasthenic syndrome; pathogenesis, diagnosis, and therapy. Autoimmune Dis 2011; 2011: 973808. DOI: 10.4061/2011/973808.
47. Waterman SA, Lang B, Newsom-Davis J. Effect of Lambert-Eaton myasthenic syndrome antibodies on autonomic neurons in the mouse. Ann Neurol 1997; 42: 147-156.
48. Tani T, Tanaka K, Idezuka J, Nishizawa M. Regulatory T cells in paraneoplastic neurological syndromes. J Neuroimmunol 2008; 196: 166-169.

49. Roberts A, Perera S, Lang B, Vincent A, Newsom-Davis J. Paraneoplastic myasthenic syndrome IgG inhibits 45Ca2+ flux in a human small cell carcinoma line. Nature 1985; 317: 737-739.
50. Titulaer MJ, Lang B, Verschuuren JJ. Lambert-Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies. Lancet Neurol 2011; 10: 1098-1107.
51. Titulaer MJ, Soffietti R, Dalmau J, Gilhus NE, Giometto B, Graus F, et al. Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. Eur J Neurol 2011; 18: 19-e3. DOI: 10.1111/j.1468-1331.2010.03220.x.
52. Lorenzoni PJ, Scola RH, Kay CS, Parolin SF, Werneck LC. Non-paraneoplastic Lambert-Eaton myasthenic syndrome: a brief review of 10 cases. Arq Neuropsiquiatr 2010; 68: 849-854.
53. Roche JC, Capablo JL, Ara JR. Myasthenia gravis in association with extrathymic neoplasia. Neurologia 2014; 29: 507-509.
54. Simonsen M, Miyabe MM, Ouki HT, Galvão ACR, Leite D, Murayama BAR, et al. Myasthenia as a paraneoplastic manifestation of ovarian Cancer. Gynecol Oncol Rep 2018; 25: 35-36.
55. López-Viñas L, Rocío-Martín E, Delis-Gómez S, Wix-Ramos R. Myasthenia gravis related to small cell lung carcinoma. Cureus 2021; 13: e13889. DOI: 10.7759/cureus.13889.
56. Fujita J, Yamadori I, Yamaji Y, Yamagishi Y, Takigawa K, Takahara J. Myasthenia gravis associated with small-cell carcinoma of the lung. Chest 1994; 105: 624-625.
57. Sciamanna MA, Griesmann GE, Williams CL, Lennon VA. Nicotinic acetylcholine receptors of muscle and neuronal (alpha7) types coexpressed in a small cell lung carcinoma. J Neurochem 1997; 69: 2302-2311.
58. Chandrasekaran PN, Pandey A, Idiculla PS. Neuromuscular emergencies in the neuroscience intensive care unit. In: Arora N, Govindarajan R, Kataria S, Nattanmai Chandrasekaran P (eds.). Neuromuscular Urgencies and Emergencies. Cham: Springer International Publishing; 2020, pp. 95-129.
59. Jayam Trouth A, Dabi A, Solieman N, Kurukumbi M, Kalyanam J. Myasthenia gravis: a review. Autoimmune Dis 2012; 2012: 874680. DOI: 10.1155/2012/874680.
60. Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. Mayo Clin Proc 2010; 85: 838-854.
61. Cao M, Koneczny I, Vincent A. Myasthenia gravis with antibodies against muscle specific kinase: an update on clinical features, pathophysiology and treatment. Front Mol Neurosci 2020; 13: 159. DOI: 10.3389/fnmol.2020.00159.
62. Yoganathan K, Stevenson A, Tahir A, Sadler R, Radunovic A, Malek N. Bedside and laboratory diagnostic testing in myasthenia. J Neurol 2022; 269: 3372-3384.
63. Farmakidis C, Pasnoor M, Dimachkie MM, Barohn RJ. Treatment of myasthenia gravis. Neurol Clin 2018; 36: 311-337.
64. Longo R, Wagner M, Savenkoff B, de Castaing MC, Desiro G, Tubail Z, et al. A paraneoplastic limbic encephalitis from an anorectal small cell neuroendocrine carcinoma: a case report. BMC Neurol 2019; 19: 304. DOI: 10.1186/s12883-019-1542-9.
65. Ochenduszko S, Wilk B, Dabrowska J, Herman-Sucharska I, Dubis A, Puskulluoglu M. Paraneoplastic limbic encephalitis in a patient with extensive disease small-cell lung cancer. Mol Clin Oncol 2017; 6: 575-578.
66. Darnell RB, Posner JB. 16 Breast, Gynecologic, and Testicular Cancers. In: Paraneoplastic Syndromes [Internet]. Oxford University Press; 2010. DOI: https://doi.org/10.1093/med/9780199772735.003.016.
67. Yu Z, Kryzer TJ, Griesmann GE, Kim K, Benarroch EE, Lennon VA. CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. Ann Neurol 2001; 49: 146-154.
68. Lancaster E, Lai M, Peng X, Hughes E, Constantinescu R, Raizer J, et al. Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. Lancet Neurol 2010; 9: 67-76.
69. Dorresteijn LD, Kappelle AC, Renier WO, Gijtenbeek JM. Anti-amphiphysin associated limbic encephalitis: a paraneoplastic presentation of small-cell lung carcinoma. J Neurol 2002; 249: 1307-1308.
70. Ariño H, Höftberger R, Gresa-Arribas N, Martínez-Hernández E, Armangue T, Kruer MC, et al. Paraneoplastic neurological syndromes and glutamic acid decarboxylase antibodies. JAMA Neurol 2015; 72: 874-881.
71. Graus F, Dalmau J. Paraneoplastic neurological syndromes: diagnosis and treatment. Curr Opin Neurol 2007; 20: 732-737.
72. Bernal F, Graus F, Pifarré A, Saiz A, Benyahia B, Ribalta T. Immunohistochemical analysis of anti-Hu-associated paraneoplastic encephalomyelitis. Acta Neuropathol 2002; 103: 509-515.
73. Plonquet A, Gherardi RK, Créange A, Antoine JC, Benyahia B, Grisold W, et al. Oligoclonal T-cells in blood and target tissues of patients with anti-Hu syndrome. J Neuroimmunol 2002; 122: 100-105.
74. Roberts WK, Deluca IJ, Thomas A, Fak J, Williams T, Buckley N, et al. Patients with lung cancer and paraneoplastic Hu syndrome harbor HuD-specific type 2 CD8+ T cells. J Clin Invest 2009; 119: 2042-2051.
75. Saiz A, Blanco Y, Sabater L, González F, Bataller L, Casamitjana R, et al. Spectrum of neurological syndromes associated with glutamic acid decarboxylase antibodies: diagnostic clues for this association. Brain 2008; 131 (Pt 10): 2553-2563.
76. Folli F, Solimena M, Cofiell R, Austoni M, Tallini G, Fassetta G, et al. Autoantibodies to a 128-kd synaptic protein in three women with the stiff-man syndrome and breast cancer. N Engl J Med 1993; 328: 546-551.
77. Maureille A, Fenouil T, Joubert B, Picard G, Rogemond V, Pinto AL, et al. Isolated seizures are a common early feature of paraneoplastic anti-GABA(B) receptor encephalitis. J Neurol 2019; 266: 195-206.
78. Moore C. Autoimmune encephalitis. Radiopaedia.org; 2010.
79. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016; 15: 391-404.
80. McKeon A, Apiwattanakul M, Lachance DH, Lennon VA, Mandrekar JN, Boeve BF, et al. Positron emission tomography-computed tomography in paraneoplastic neurologic disorders: systematic analysis and review. Arch Neurol 2010; 67: 322-329.

81. Ding JB, Dongas J, Hu K, Ding M. Autoimmune limbic encephalitis: a review of clinicoradiological features and the challenges of diagnosis. Cureus 2021; 13: e17529. DOI: 10.7759/cureus.17529.
82. Grisold W, Giometto B, Vitaliani R, Oberndorfer S. Current approaches to the treatment of paraneoplastic encephalitis. Ther Adv Neurol Disord 2011; 4: 237-248.
83. Frackowiak M, Kowar M, Sippel C, Wilhelm K, Ko YD, Jacobs AH. Paraneoplastic subacute degeneration of the cerebellum in non-small cell lung cancer and positive anti-Tr3 antibodies. Nervenarzt 2020; 91: 156-160 [Article in German].
84. Arratibel N, Sobejano E, Moran JC, Diaz LG, Blázquez A, Baile M, et al. A case of paraneoplastic cerebellar degeneration that preceded the diagnosis of classical Hodgkin's lymphoma by 16 months. Am J Case Rep 2020; 21: e922342. DOI: 10.12659/AJCR.922342.
85. Fanous I, Dillon P. Paraneoplastic neurological complications of breast cancer. Exp Hematol Oncol 2016; 5: 29. DOI: 10.1186/s40164-016-0058-x.
86. Rodriguez M, Truh LI, O'Neill BP, Lennon VA. Autoimmune paraneoplastic cerebellar degeneration: ultrastructural localization of antibody-binding sites in Purkinje cells. Neurology 1988; 38: 1380-1386.
87. Venkatraman A, Opal P. Paraneoplastic cerebellar degeneration with anti-Yo antibodies – a review. Ann Clin Transl Neurol 2016; 3: 655-663.
88. Afzal S, Recio M, Shamim S. Paraneoplastic cerebellar ataxia and the paraneoplastic syndromes. Proc (Bayl Univ Med Cent) 2015; 28: 217-220.
89. Okano HJ, Park WY, Corradi JP, Darnell RB. The cytoplasmic Purkinje onconeural antigen cdr2 down-regulates c-Myc function: implications for neuronal and tumor cell survival. Genes Dev 1999; 13: 2087-2097.
90. Albert ML, Austin LM, Darnell RB. Detection and treatment of activated T cells in the cerebrospinal fluid of patients with paraneoplastic cerebellar degeneration. Ann Neurol 2000; 47: 9-17.
91. Dalmau J, Rosenfeld MR. Paraneoplastic syndromes of the CNS. Lancet Neurol 2008; 7: 327-340.
92. Yshii L, Bost C, Liblau R. Immunological bases of paraneoplastic cerebellar degeneration and therapeutic implications. Front Immunol 2020; 11: 991. DOI: 10.3389/fimmu.2020.00991.
93. Hammack J, Kotanides H, Rosenblum MK, Posner JB. Paraneoplastic cerebellar degeneration. II. Clinical and immunologic findings in 21 patients with Hodgkin's disease. Neurology 1992; 42: 1938-1943.
94. Aly R, Emmady PD. Paraneoplastic cerebellar degeneration. StatPearls. Treasure Island (FL): StatPearls Publishing LLC.; 2023.
95. Klaas JP, Ahlskog JE, Pittock SJ, Matsumoto JY, Aksamit AJ, Bartleson JD, et al. Adult-onset opsoclonus-myoclonus syndrome. Arch Neurol 2012; 69: 1598-1607.
96. McHugh K. Renal and adrenal tumours in children. Cancer Imaging 2007; 7: 41-51.
97. Blaes F, Jauss M, Kraus J, Oschmann P, Krasenbrink I, Kaps M, Teegen B. Adult paraneoplastic opsoclonus-myoclonus syndrome associated with antimitochondrial autoantibodies. J Neurol Neurosurg Psychiatry 2003; 74: 1595-1596.
98. Martins L, Galvão D, Silva A, Vieira B, Reis Ó, Vitorino R, Pires P. Paraneoplastic opsoclonus-myoclonus syndrome as a rare presentation of breast cancer. J Surg Case Rep 2019; 2019: rjy365. DOI: https://doi.org/10.1093/jscr/rjy365.
99. Rossor T, Yeh EA, Khakoo Y, Angelini P, Hemingway C, Irani SR, et al. Diagnosis and management of opsoclonus-myoclonus-ataxia syndrome in children: an international perspective. Neurol Neuroimmunol Neuroinflamm 2022; 9: e1153. DOI: 10.1212/NXI.0000000000001153.
100. Gorman MP. Update on diagnosis, treatment, and prognosis in opsoclonus-myoclonus-ataxia syndrome. Curr Opin Pediatr 2010; 22: 745-750.
101. Spies JM, McLeod JG. Chapter 110 – Paraneoplastic Neuropathy. In: Dyck PJ, Thomas PK (eds.). Peripheral Neuropathy (Fourth Edition). Philadelphia: W.B. Saunders; 2005, pp. 2471-2487.
102. Zoccarato M, Grisold W, Grisold A, Poretto V, Boso F, Giometto B. Paraneoplastic neuropathies: what's new since the 2004 recommended diagnostic criteria. Front Neurol 2021; 12: 706169. DOI: 10.3389/fneur.2021.706169.
103. Dubey D, David WS, Amato AA, Reynolds KL, Clement NF, Chute DF, et al. Varied phenotypes and management of immune checkpoint inhibitor-associated neuropathies. Neurology 2019; 93: e1093-e1103. DOI: 10.1212/WNL.0000000000008091.
104. Graus F, Vincent A, Pozo-Rosich P, Sabater L, Saiz A, Lang B, Dalmau J. Anti-glial nuclear antibody: marker of lung cancer-related paraneoplastic neurological syndromes. J Neuroimmunol 2005; 165: 166-171.
105. Sghirlanzoni A, Pareyson D, Lauria G. Sensory neuron diseases. Lancet Neurol 2005; 4: 349-361.
106. Sheikh SI, Amato AA. The dorsal root ganglion under attack: the acquired sensory ganglionopathies. Pract Neurol 2010; 10: 326-334.
107. Gomatos EL, Rehman A. Sensory Neuropathy. Treasure Island (FL): StatPearls Publishing LLC.; 2023.
108. Lehmann HC, Wunderlich G, Fink GR, Sommer C. Diagnosis of peripheral neuropathy. Neurol Res Pract 2020; 2: 20. DOI: 10.1186/s42466-020-00064-2.
109. Gwathmey KG, Pearson KT. Diagnosis and management of sensory polyneuropathy. BMJ 2019; 365: l1108. DOI: 10.1136/bmj.l1108.
110. Jiménez Caballero PE. Paraneoplastic chorea caused by anti-CRMP5 antibodies associated with small cell lung cancer. Neurologia 2014; 29: 446-447.
111. Cross SA, Salomao DR, Parisi JE, Kryzer TJ, Bradley EA, Mines JA, et al. Paraneoplastic autoimmune optic neuritis with retinitis defined by CRMP-5-IgG. Ann Neurol 2003; 54: 38-50.
112. Zekeridou A, Kryzer T, Guo Y, Hassan A, Lennon V, Lucchinetti CF, et al. Phosphodiesterase 10A IgG: a novel biomarker of paraneoplastic neurologic autoimmunity. Neurology 2019; 93: e815-e822. DOI: 10.1212/WNL.0000000000007971.
113. Kyle K, Bordelon Y, Venna N, Linnoila J. Autoimmune and paraneoplastic chorea: a review of the literature. Front Neurol 2022; 13: 829076. DOI: 10.3389/fneur.2022.829076.
114. Cardoso F, Seppi K, Mair KJ, Wenning GK, Poewe W. Seminar on choreas. Lancet Neurol 2006; 5: 589-602.