Les syndromes paranéoplasiques auto-immuns aux soins intensifs

DR GORHAM JULIE

17/11/2018

Plan

- Définition

Syndrome paranéoplasique auto-immun

- Tableaux syndromiques repérables
- Tumeur maligne associée
- Anticorps caractérisés

Tableau 2 Anticorps, syndromes paranéoplasiques et tumeurs associées

	Syndromes paranéoplasiques	Cancers associés
Anticorps paranéoplasiques bien caractérisés		
Anti-Hu (ANNA-1)	Encéphalomyélite, Dégénérescence cérébelleuse Neuropathie sensitive, Myélite, dysautonomie	Cancer bronchique à petites cellules et autres tumeurs
Anti-Yo (PCA-1)	Dégénérescence cérébelleuse	Gynécologique et sein
Anti-Ri (ANNA-2)	Dégénérescence cérébelleuse, Encéphalite du tronc cérébral, Opsoclonus-myoclonus	Sein, gynécologique et cancer pulmonaire à petites cellules
Anti-CV2/CRMP5	Encéphalomyélite, Dégénérescence cérébelleuse, chorée, uvéite, névrite optique, neuropathie périphérique	Cancer bronchique à petites cellules, thymome et autres tumeurs
Anti-Ma protéines[a]	Encéphalite limbique, hypothalamique, tronc cérébral et dégénérescence cérébelleuse (moins fréquemment)	Tumeur germinale testiculaire, cancer bronchique non à petites cellules et autres tumeurs solides
Anti-amphiphysine	Syndrome de l'homme raide, Encéphalomyélite et myélopathie	Cancer bronchique à petites cellules et sein
Anticorps paranéoplasiques partiellement caractérisés		
Anti-Tr	Dégénérescence cérébelleuse	Lymphome de Hodgkin
Anti-Zic4	Dégénérescence cérébelleuse	Cancer bronchique à petites cellules
mGluR1[b]	Dégénérescence cérébelleuse	Lymphome de Hodgkin
ANNA-3	Syndromes variés	Cancer bronchique à petites cellules
PCA2	Syndromes variés	Cancer bronchique à petites cellules
Anticorps présent associé ou non à un cancer		
Anti-NR1/NR2 du récepteur NMDA du glutamate[b]	Encéphalite limbique	Tératome (habituellement de l'ovaire)
Anti-VGKC[b] (LGI-1, CASPR2)	Encéphalite limbique, hyperexcitabilité des nerfs périphériques	Thymome, cancer bronchique à petites cellules et autres tumeurs
Anti-VGCC[b]	Syndrome myasthéniforme de Lambert-Eaton. Dégénérescence cérébelleuse	Cancer bronchique à petites cellules
Anti-AChR[b]	Myasthénie	Thymome
Anti-nAChR[b]	Dysautonomie subaiguë	Cancer bronchique à petites cellules et autres tumeurs
Anti-AMPAR[b]	Encéphalite limbique	Cancer bronchique à petites cellules, autres tumeurs
Anti-GABA-B[b]	Encéphalite limbique	Cancer bronchique à petites cellules, autres tumeurs
Anti-GlyR[b]	Encéphalomyélite avec rigidité	Thymome
Anti-GAD	Syndrome de l'homme raide, ataxie cérébelleuse, encéphalite limbique, épilepsies partielles	Thymome et autres tumeurs

Syndrome paranéoplasique auto-immun

- Rare
- Découverte :
  - Avant le diagnostic
  - Au moment du diagnostic
  - Au décours de l'affection néoplasique
- Cancers associés :
  - CBPC le plus fréquent *Darnell et al, Semin Oncol 2006;33:270-98*
  - Thymome, ovaire, sein, testicule, Hodgkin

Lung Cancer. 2017 Apr;106:102-109. doi: 10.1016/j.lungcan.2017.01.015. Epub 2017 Jan 30.

Autoimmune paraneoplastic syndromes associated to lung cancer: A systematic review of the literature.

Durieux V[1], Coureau M[2], Meert AP[2], Berghmans T[2], Sculier JP[3].

Author information

Abstract

The development of new immune treatment in oncology and particularly for lung cancer may induce new complications, particularly activation or reactivation of auto-immune diseases. In this context, a systematic review on the auto-immune paraneoplastic syndromes associated with lung cancer appears useful. This article is the first of a series of five and deals with the methodology applied for the review and with renal and rheumatic syndromes.

Lung Cancer. 2017 Apr;106:93-101. doi: 10.1016/j.lungcan.2017.01.016. Epub 2017 Jan 30.

Autoimmune paraneoplastic syndromes associated to lung cancer: A systematic review of the literature: Part 2: Hematologic, cutaneous and vascular syndromes.

Holbrechts S[1], Gorham J[2], Sideris S[2], Meert AP[3], Durieux V[4], Berghmans T[3], Sculier JP[5].

Author information

Abstract

The development of new immune treatment in oncology and particularly for lung cancer may induce new complications, particularly activation or reactivation of auto-immune diseases. In this context, a systematic review on the auto-immune paraneoplastic syndromes associated with lung cancer appears useful. This article is the second of a series of five and deals with hematologic, cutaneous and vascular syndromes.

PMID: 28285701 DOI: 10.1016/j.lungcan.2017.01.016

Lung Cancer. 2017 Apr;106:83-92. doi: 10.1016/j.lungcan.2017.01.017. Epub 2017 Jan 30.

Autoimmune paraneoplastic syndromes associated to lung cancer: A systematic review of the literature: Part 3: Neurological paraneoplastic syndromes, involving the central nervous system.

Bentea G[1], Sculier C[1], Grigoriu B[1], Meert AP[2], Durieux V[3], Berghmans T[2], Sculier JP[4].

Author information

Abstract

The development of new immune treatment in oncology and particularly for lung cancer may induce new complications, particularly activation or reactivation of auto-immune diseases. In this context, a systematic review on the auto-immune paraneoplastic syndromes that can complicate lung cancer appears useful. This article is the third of a series of five and deals mainly with neurological paraneoplastic syndromes involving the central nervous system.

PMID: 28285700 DOI: 10.1016/j.lungcan.2017.01.017

Lung Cancer. 2017 Sep;111:150-163. doi: 10.1016/j.lungcan.2017.07.025. Epub 2017 Jul 25.

Autoimmune paraneoplastic syndromes associated to lung cancer: A systematic review of the literature Part 4: Neurological paraneoplastic syndromes, involving the peripheral nervous system and the neuromuscular junction and muscles.

Ruelle L[1], Bentea G[1], Sideris S[1], El Koulali M[1], Holbrechts S[2], Lafitte JJ[3], Grigoriu B[1], Sculier C[1], Meert AP[4], Durieux V[5], Berghmans T[4], Sculier JP[6].

Author information

Abstract

The development of new immune treatment in oncology and particularly for lung cancer may induce new complications, particularly activation or reactivation of auto-immune diseases. In this context, a systematic review on the auto-immune paraneoplastic syndromes that can complicate lung cancer appears useful. This article is the fourth of a series of five and deals mainly with neurological paraneoplastic syndromes involving the peripheral nervous system and the neuromuscular junction and muscles.

KEYWORDS: Auto-immunity; Lung cancer; Paraneoplastic syndrome

PMID: 28838388 DOI: 10.1016/j.lungcan.2017.07.025

Lung Cancer. 2017 Sep;111:164-175. doi: 10.1016/j.lungcan.2017.07.026. Epub 2017 Jul 24.

Autoimmune paraneoplastic syndromes associated to lung cancer: A systematic review of the literature: Part 5: Neurological auto-antibodies, discussion, flow chart, conclusions.

Sculier C[1], Bentea G[1], Ruelle L[1], Grigoriu B[1], Coureau M[1], Gorham J[1], Sideris S[1], Holbrechts S[2], Lafitte JJ[3], Meert AP[1], Durieux V[4], Berghmans T[5], Sculier JP[6].

Author information

Abstract

The development of new immune treatment in oncology and particularly for lung cancer may induce new complications, particularly activation or reactivation of auto-immune diseases. In this context, a systematic review on the auto-immune paraneoplastic syndromes that can complicate lung cancer appears useful. This article is the last of a series of five and deals mainly with onconeural antibodies involved in neurological paraneoplastic syndromes and provides the final discussion.

Plan

- Définition
- Cas clinique

Cas clinique

Patient de 74 ans,

- Admission à l'ASTI pour insuffisance respiratoire aiguë > pneumonie d'inhalation > Fausses déglutitions

- HAA :
  - Dyspnée, toux et expectorations en majoration depuis 3 jours
  - Dysphagie aux liquides
  - Modification voix
  - Œdème des tissus mous cervico-facial
  - Altération état général avec altération de la marche
  - Eruptions érythro-squameuses

Cas clinique

- ATCD :
  - Syndrome d'apnée du sommeil
  - Obésité
  - HTA non traitée
  - BPCO
- HAN :
  - Carcinome épidermoïde de la corde vocale gauche traité par radiothérapie en avril 2013

Cas clinique

- Examen physique :

- Examens complémentaires :
  - Syndrome inflammatoire
  - CK élevé
  - Foyers pulmonaires
  - Myosite proximale des 4 membres

Cas clinique : Evolution

- J2 :
  - Forte suspicion de dermatomyosite => Biopsie cutanée faite
- J3 :
  - Choc septique
  - Intubation
  - R/ Corticoides 1mg/kg
  - FAN+ à 1/1280
- J13 :
  - Résultat biopsie cutanée : compatible avec une dermatomyosite
  - Amélioration des lésions cutanées
- J15 :
  - Anti-TIF1g +
  - Jéjunostomie mise en place

Cas clinique

- J17 :
  - Ponction adp cervicale
  - Extubation
  - Récidive pneumonie d'inhalation
- J27 :
  - Résultat pct adp cervicale : carcinome épidermoïde peu différencié
  - Transfert en salle
  - Pet scan
  - Kinésithérapie et logo ++

Dermatopolymyosite

- Association avec un cancer 18 à 32% des cas

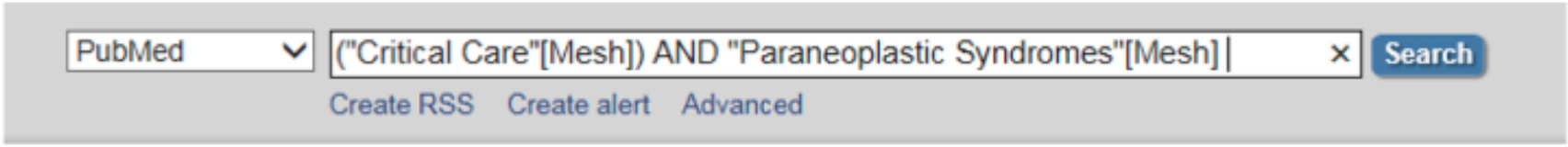
- Diagnostic 5 critères :
  - Faiblesse musculaire progressive et symétrique des ceintures et des muscles fléchisseurs du cou
  - Signes dermatologiques (rash héliotrope périorbitaire avec oedèmes, signe de Gottron)
  - Biopsie musculaire en faveur
  - Elévation des CPK
  - EMG

- Traitement :
  - Cancer sous jacent
  - Corticothérapie

Bohan et al; N Engl J Med, 1975;292:344-7

Plan

- Définition
- Cas clinique
- En réanimation



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Ann Fr Anesth Reanim. 2012 May;31(5):462-5. doi: 10.1016/j.annfar.2012.01.025. Epub 2012 Apr 3.

[Two cases of autoimmune encephalitis with antibodies to N-methyl-D-aspartate receptor in intensive care].

[Article in French]

Mataam K[1], Ilboudo JC, Gazaigne L, Wafo E, Angenard F.

Author information

Abstract

We report here two cases of autoimmune encephalitis associated with antibodies against the N-methyl-D-aspartate receptor. The primary cause was an ovarian teratoma in one case. The outcomes were good. The first case was a late diagnosis, despite a typical clinical presentation. The clinical presentation of this disease remains unknown, especially in the intensive care unit. The treatment was recently codified and transformed the prognosis of this encephalitis. The second case was early treated in the course of the disease, due to the experience related to the previous case. In case of unexplained acute or subacute encephalitis or psychiatric-like disorders without prior medical history, the determination of the level of expression of antibodies against the N-methyl-D-aspartate receptors and other antineuroreceptors antibodies can help to identify this diagnosis. The initial picture of the disease, its variability and the unawareness of the recent reports on this encephalitis may lead to a wrong diagnosis and inappropriate management.

Rev Neurol. 2014 Nov 1;59(9):428-9.

[Recurrence of encephalitis after 25 years due to anti-NMDA receptor antibodies].

[Article in Spanish]

Rodriguez-Osorio X, Fernandez-Pajarin G, Arias-Rivas S, Requena-Caballero I, Lopez-Gonzalez FJ, Arias M[1].

Author information

PMID: 25342057

[Indexed for MEDLINE] Free full text

Anaesth Intensive Care. 2010 Jul;38(4):748-50.

Acute psychiatric syndrome leading young patients to ICU: consider anti-NMDA-receptor antibodies.

Varvat J[1], Lafond P, Page Y, Coudrot M, Reynaud-Salard M, Tardy B.

Author information

Abstract

We report on a case of anti-N-Methyl-D-Aspartate receptor antibody encephalitis, and review cases and series previously published in the literature. Anti-N-Methyl-D-Aspartate receptor antibody encephalitis usually occurs in young female patients with no past medical history, in whom an ovarian teratoma is often detected. They subacutely develop predominantly psychiatric symptoms, followed by severe neurological disorders requiring transfer to the intensive care unit and prolonged ventilatory support. Complete or substantial recovery depends on early diagnosis, removal of the teratoma and immunotherapy. Our purpose is to focus intensivists' attention on this potentially lethal disorder, which should always be considered in young women admitted to the intensive care unit with characteristic neuropsychiatric disorders.

Challenges in Providing Critical Care for Patients With Anti-*N*-Methyl-d-Aspartate Receptor Encephalitis

Christopher M. Howard MD [a], Joseph S. Kass MD, JD [b, c], Venkata D.P Bandi MD, FCCP [a, d], Kalpalatha K. Guntupalli MD, FCCP [a, d]

Rinsho Shinkeigaku. 2015;55(12):921-5. doi: 10.5692/clinicalneurol.cn-000772. Epub 2015 Oct 28.

[Anti-Hu antibody-positive paraneoplastic limbic encephalitis with acute motor sensory neuropathy resembling Guillain-Barré syndrome: a case study].

[Article in Japanese]

Sakurai T[1], Wakida K, Kimura A, Inuzuka T, Nishida H.

⊕ Author information

Abstract

A 69-year-old man experienced general malaise, weight loss, amnesia, gait disturbance, and restlessness a month prior to admission. Brain MRI showed high intensity areas in the bilateral medial temporal lobes and insular cortices on FLAIR images, and therefore, he was diagnosed with limbic encephalitis. After admission, quadriplegia and respiratory failure progressed rapidly, and he needed ventilatory management. A nerve conduction study revealed low compound muscle action potential amplitude with loss of sensory nerve action potential, which indicated axonal sensorimotor neuropathy. We administered intravenous immunoglobulin and methylprednisolone pulse therapy, but he did not recover. Although no tumor was found on CT, his serum was positive for anti-Hu antibody; therefore, we diagnosed him with paraneoplastic neurological syndrome. An FDG-PET study showed accumulation at lesions on two hilar lymph nodes. Small cell lung carcinoma was detected by endobronchial ultrasound-guided transbronchial needle aspiration. Although paraneoplastic acute sensorimotor neuropathy with respiratory failure resembling Guillain-Barré syndrome is rare, identification of antibodies and servey of tumors aids accurate diagnosis.

J Neurol Neurosurg Psychiatry. 2007 Oct; 78(10): 1143–1145.
doi: [10.1136/jnnp.2007.117994]
PMCID: PMC2117560
PMID: 17878194

Central hypoventilation as the presenting symptom in Hu associated paraneoplastic encephalomyelitis

Manuel J Gómez-Choco, Juan J Zarranz, Albert Saiz, María I Forcadas, and Francesc Graus

Table 1 Clinical features of Hu positive patients who presented with central hypoventilation

ıtient ›	Age (y) /sex	Cancer	Associated symptoms	Dysautonomia	Time to intubation	MRI	Treatment	Outcome
	77/F	SCLC	Dizziness, gait ataxia	Yes	12 days	Normal	Immunoglobulins	Dead
	70/M	Prostate	Dysphonia	No	3 weeks	Normal	Immunoglobulins, methylprednisolone	Alive with ventilatory support during sleep
	61/M	Enlarged mediastinal lymph node*	Dysphonia, neuropathy	Yes	3 months	Normal	Chemotherapy	Dead

SCLC, small cell lung carcinoma.

*Highly suspicious of lung cancer.

J Clin Neurosci. 2017 Jun;40:72-73. doi: 10.1016/j.jocn.2017.02.015. Epub 2017 Feb 27.

Anti-Hu paraneoplastic brainstem encephalitis caused by a pancreatic neuroendocrine tumor presenting with central hypoventilation.

Najjar M[1], Taylor A[2], Agrawal S[3], Fojo T[4], Merkler AE[2], Rosenblum MK[5], Lennihan L[2], Kluger MD[3].

⊕ Author information

Abstract

Paraneoplastic neurological syndromes are rare autoimmune manifestations of malignancies associated with specific antibodies. Anti-Hu associated brainstem encephalitis, a well-described syndrome, usually presents subacutely with preferential involvement of the medulla. Anti-Hu antibodies target intraneuronal antigens and are therefore highly correlated with neurological syndromes when present concomitantly with a neoplasm. Reported is a case of anti-Hu brainstem encephalitis associated with a pancreatic neuroendocrine tumor (PNET) presenting with central hypoventilation. This is the first described case of brainstem encephalitis associated with a well-differentiated PNET as well as the first case of Anti-Hu antibodies associated with a PNET. There are no standardized protocols for the treatment of paraneoplastic brainstem encephalitis however, as in the present case, surgical resection and oncological treatment of the tumor is the first line treatment.

J Clin Anesth. 2014 Dec;26(8):648-53. doi: 10.1016/j.jclinane.2014.09.009. Epub 2014 Nov 18.

Lambert-Eaton myasthenic syndrome during anesthesia: a report of 37 patients.

Weingarten TN[1], Araka CN[2], Mogensen ME[2], Sorenson JP[2], Marienau ME[2], Watson JC[3], Sprung J[2].

Author information

Abstract

STUDY OBJECTIVE: Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune disorder of the neuromuscular junction that manifests with muscle weakness, autonomic and bulbar dysfunction, and increased sensitivity to neuromuscular blocking drugs. The objective of this study is to review perioperative outcomes on a series of patients with LEMS.

DESIGN: The medical records of surgical patients with LEMS from January 1, 1990, to December 31, 2012, were retrospectively reviewed.

SETTING: Major academic hospital.

PATIENTS: Surgical patients with LEMS.

MEASUREMENTS AND MAIN RESULTS: Thirty-seven patients underwent 60 surgeries, with most performed to diagnose or treat lung malignancy (n = 31; 51.7%). Equal number of patients had LEMS associated with small cell lung cancer (n = 16; 43.2%) or an autoimmune process (n = 16; 43.2%), with the remainder having various malignancies. Neuromuscular blocking drug medications were used in 23 (38.3%) of cases, including 8 patients who were not treated for LEMS symptoms. Four patients (11%) had respiratory complications. Interestingly, 3 patients were either undiagnosed or not treated for LEMS at the time of perioperative complication, and developed weakness after use of neuromuscular blocking drugs.

CONCLUSION: Patients with LEMS have increased sensitivity to neuromuscular blocking drugs. The risk for the development of prolonged muscle weakness or postoperative respiratory failure after being exposed to neuromuscular blocking drugs is increased in patients with undiagnosed or untreated LEMS.

Nihon Kokyuki Gakkai Zasshi. 2010 Dec;48(12):918-22.

[Long-term survival case of small-cell lung cancer with Lambert-Eaton myasthenic syndrome without anticancer therapy].

[Article in Japanese]

Nakamur S[1], Kawagishi Y, Kato S, Tsuji H, Takagawa K, Fukuoka J.

Author information

Abstract

A 78-year-old man with complaints of appetite loss and weight loss visited our hospital in November 2006. Positron-emission tomography and computed tomography (PET/CT) showed swollen lymph nodes in the abdominal para-aorta, mediastinum and neck, with intense FDG accumulation. The pathological findings of the cervical lymph nodes revealed small-cell cancer. We diagnosed extensive small-cell lung cancer (SCLC), which occurred primarily in the left upper lobe. As subsequent CT revealed spontaneous shrinkage of the pulmonary nodule and swollen lymph nodes, the clinical course was monitored without anticancer therapy. In February 2007, progressive muscle weakness of the lower extremities developed. In July he was admitted with respiratory failure and required mechanical ventilation. Although we did not administer anticancer therapy due to his poor performance status, he survived for 30 months receiving mechanical ventilation, and the tumors continued to grow moderately. We diagnosed Lambert-Eaton myasthenic syndrome (LEMS) based on the clinical symptoms, the presence of anti-VGCC antibodies and waxing phenomenon on electromyography obtained in April 2009. Chemotherapy with amrubicin shrank the tumors, but his muscle weakness did not improve. Previous reports showed that a prognosis of SCLC with LEMS was better than that without LEMS. In this case, the tumors showed spontaneous regression without any anticancer therapy, and then increased moderately. The immune response was considered to have affected tumor growth.

Neurologist. 2006 Nov;12(6):322-6.

A diagnostic and management dilemma: combined paraneoplastic myasthenia gravis and Lambert-Eaton myasthenic syndrome presenting as acute respiratory failure.

Roohi F[1], Smith PR, Bergman M, Baig MA, Sclar G.

Author information

Abstract

BACKGROUND: Neuromuscular junction disorders are usually categorized as either presynaptic or postsynaptic. The most frequently encountered disorder of the postsynaptic neuromuscular junction is acquired myasthenia gravis. Lambert-Eaton myasthenic syndrome is a well-known prototype of the presynaptic autoimmune disorders of neuromuscular transmission. These major disorders of neuromuscular transmission are relatively common and distinctly recognized, but co-occurrence of these disorders (overlap myasthenic syndrome) is rare and has so far attracted little attention.

REVIEW SUMMARY: This report describes a patient with acquired myasthenia gravis and immunologic coexistence of Lambert-Eaton myasthenic syndrome (overlap myasthenic syndrome) in association with abdominal/uterine leiomyosarcoma. The patient presented with acute respiratory failure, making identification and management of her illness challenging. A general overview of the complexities associated with overlap between myasthenia gravis and Lambert-Eaton myasthenic syndrome is provided and this patient's complicated clinical course and response to therapy are discussed.

CONCLUSION: To our knowledge, this is the first report of overlap myasthenic syndrome in conjunction with abdominal leiomyosarcoma. The immunologic coexistence of acquired myasthenia gravis and Lambert-Eaton myasthenic syndrome in a patient with a malignant smooth-muscle tumor is intriguing and suggests that a common paraneoplastic process targeting 2 different onconeural antigens was the underlying pathogenic mechanism in this patient.

Muscle Nerve. 1996 Oct;19(10):1328-33.

Lambert-Eaton myasthenic syndrome presenting with severe respiratory failure.

Nicolle MW[1], Stewart DJ, Remtulla H, Chen R, Bolton CF.

Author information

Abstract

Two cases of Lambert-Eaton myasthenic syndrome (LEMS) who presented with primary respiratory failure are reported. In each case, although not initially suspected clinically, the electrophysiological findings, which included reduced compound muscle action potential amplitudes, decrement to 3-Hz stimulation, and potentiation after 40-Hz stimulation, led to the diagnosis in the critical care unit. Electrophysiological studies of the respiratory system, including repetitive nerve stimulation of the phrenic nerve, were extremely valuable in management. As shown by these cases, the severe respiratory failure in LEMS is reversible with treatment. Thus, LEMS should be considered in cases of unexplained respiratory failure, other clinical features of the disorder sought, and the electrophysiological hallmarks looked for including studies of the respiratory system.

J Formos Med Assoc. 2002 Dec;101(12):871-4.

Small-cell lung cancer presenting with Lambert-Eaton myasthenic syndrome and respiratory failure.

Jiang JR[1], Shih JY, Wang HC, Wu RM, Yu CJ, Yang PC.

Author information

Erratum in

J Formos Med Assoc. 2003 Jun;111(6):1202.

Abstract

Lambert-Eaton myasthenic syndrome (LEMS) is a neuromuscular disorder characterized by defective neurotransmitter release at presynaptic terminals. It is caused by an IgG autoantibody reacting against voltage-gated calcium channels. Severe LEMS complicated by ventilatory failure is rare. We report a case of small-cell lung cancer (SCLC) presenting with LEMS and ventilatory failure in a 67-year-old man who initially presented with progressive limb weakness for 6 months and tachypnea with shallow breathing for 1 week. LEMS was diagnosed through electrophysiologic studies. Chest radiography and computerized tomography showed a huge mass lesion over the left anterior and middle mediastinum with an encasement of the left pulmonary artery. Cytologic examination of ultrasound-guided fine needle aspiration disclosed SCLC. Successful treatment in combination with plasma exchange and chemotherapy resulted in dramatic tumor regression and LEMS remission, which were confirmed by chest radiography and electrophysiologic studies. This case suggests that plasma exchange and chemotherapy can be effective in treating SCLC with severe LEMS that produces ventilatory failure.

Br J Dermatol. 1999 Feb;140(2):313-6.

Paraneoplastic pemphigus with fatal pulmonary involvement in a woman with a mesenteric Castleman tumour.

Wolff H[1], Kunte C, Messer G, Rappersberger K, Held E, Löhrs U, Plewig G, Meurer M.

⊕ **Author information**

Abstract

A 42-year-old woman presented with oral and labial erosions, conjunctivitis, facial rash and lichenoid erythematous papules on the trunk. Paraneoplastic pemphigus (PNP) was suspected, and a search for a neoplasm revealed an intra-abdominal Castleman tumour sized 7 x 5 x 6 cm. After removal of the Castleman tumour, the skin and mucosal inflammation gradually subsided over the next 12 months. However, due to irreversible pulmonary involvement the patient died of intractable respiratory distress 2 years after the onset of the disease. Systemic corticosteroids, azathioprine, cyclophosphamide, high-dose intravenous immunoglobulins and thalidomide were ineffective. The diagnosis of PNP was confirmed by keratinocyte antigen immunoprecipitation with the patient's serum.

Comment in

Paraneoplastic pemphigus triggered by Castleman's disease. [Br J Dermatol. 2002]

Syndromes neurologiques paranéoplasiques (SNP)

- Nombreux et variés
- Atteinte de toutes les parties du système nerveux
  - Muscles
  - Nerfs périphériques
  - Moelle épinière
  - Tronc cérébral
  - Cervelet
  - Encéphale

Table 1 Classical and non-classical paraneoplastic neurological syndromes

Syndromes of the central nervous system
Encephalomyelitis
Limbic encephalitis
Brainstem encephalitis
Subacute cerebellar degeneration
Opsoclonus-myoclonus*
Optic neuritis†
Cancer associated retinopathy†
Melanoma associated retinopathy†
Stiff person syndrome
Necrotising myelopathy‡
Motor neuron diseases‡
Syndromes of the peripheral nervous system
Subacute sensory neuronopathy
Acute sensorimotor neuropathy
Guillain-Barré syndrome‡
Brachial neuritis‡
Subacute/chronic sensorimotor neuropathies*
Neuropathy and paraproteinaemia†
Neuropathy with vasculitis‡
Autonomic neuropathies
Chronic gastrointestinal pseudo-obstruction
Acute pandysautonomia‡
Syndromes of the neuromuscular junction and muscle
Myasthenia gravis†
Lambert-Eaton myasthenic syndrome‡
Acquired neuromyotonia‡
Dermatomyositis‡
Acute necrotising myopathy‡

Classical syndromes are underlined.
*Associated with onconeural antibodies only with particular tumour types.
†Syndromes not included in the present recommendations.
‡Neurological syndromes not associated with known onconeural antibodies.

Graus J Neurol Neurosurg Psychiatry 2004; 75:1135-40

Syndrome neurologique paranéoplasique

- Encéphalomyélite paranéoplasique
  - Variable selon l'atteinte
- Encéphalite limbique
  - Tr du comportement, humeur, mémoire, convulsions
- Dégénérescence cérébelleuse paranéoplasique
  - Prodrome de virose, ataxie, diplopie, dysarthrie, dysphagie, tr vision
- Syndrome opsoclonus-myoclonus
  - Dyskinésie oculaire avec secousses des membres et du tronc, ataxie cérébelleuse, tremblements, encéphalopathie
- Neuropathie sensitive paranéoplasique
  - Paresthésies ou hypoesthésies
- Syndrome de Lambert-Eaton

Tableau 2 Anticorps, syndromes paranéoplasiques et tumeurs associées

	Syndromes paranéoplasiques	Cancers associés
Anticorps paranéoplasiques bien caractérisés		
Anti-Hu (ANNA-1)	Encéphalomyélite, Dégénérescence cérébelleuse Neuropathie sensitive, Myélite, dysautonomie	Cancer bronchique à petites cellules et autres tumeurs
Anti-Yo (PCA-1)	Dégénérescence cérébelleuse	Gynécologique et sein
Anti-Ri (ANNA-2)	Dégénérescence cérébelleuse, Encéphalite du tronc cérébral, Opsoclonus-myoclonus	Sein, gynécologique et cancer pulmonaire à petites cellules
Anti-CV2/CRMP5	Encéphalomyélite, Dégénérescence cérébelleuse, chorée, uvéite, névrite optique, neuropathie périphérique	Cancer bronchique à petites cellules, thymome et autres tumeurs
Anti-Ma protéines[a]	Encéphalite limbique, hypothalamique, tronc cérébral et dégénérescence cérébelleuse (moins fréquemment)	Tumeur germinale testiculaire, cancer bronchique non à petites cellules et autres tumeurs solides
Anti-amphiphysine	Syndrome de l'homme raide, Encéphalomyélite et myélopathie	Cancer bronchique à petites cellules et sein
Anticorps paranéoplasiques partiellement caractérisés		
Anti-Tr	Dégénérescence cérébelleuse	Lymphome de Hodgkin
Anti-Zic4	Dégénérescence cérébelleuse	Cancer bronchique à petites cellules
mGluR1[b]	Dégénérescence cérébelleuse	Lymphome de Hodgkin
ANNA-3	Syndromes variés	Cancer bronchique à petites cellules
PCA2	Syndromes variés	Cancer bronchique à petites cellules
Anticorps présent associé ou non à un cancer		
Anti-NR1/NR2 du récepteur NMDA du glutamate[b]	Encéphalite limbique	Tératome (habituellement de l'ovaire)
Anti-VGKC[b] (LGI-1, CASPR2)	Encéphalite limbique, hyperexcitabilité des nerfs périphériques	Thymome, cancer bronchique à petites cellules et autres tumeurs
Anti-VGCC[b]	Syndrome myasthéniforme de Lambert-Eaton. Dégénérescence cérébelleuse	Cancer bronchique à petites cellules
Anti-AChR[b]	Myasthénie	Thymome
Anti-nAChR[b]	Dysautonomie subaiguë	Cancer bronchique à petites cellules et autres tumeurs
Anti-AMPAR[b]	Encéphalite limbique	Cancer bronchique à petites cellules, autres tumeurs
Anti-GABA-B[b]	Encéphalite limbique	Cancer bronchique à petites cellules, autres tumeurs
Anti-GlyR[b]	Encéphalomyélite avec rigidité	Thymome
Anti-GAD	Syndrome de l'homme raide, ataxie cérébelleuse, encéphalite limbique, épilepsies partielles	Thymome et autres tumeurs

Réanimation (2011) 20:397-407
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Encéphalites auto-immunes à anticorps antirécepteurs-NMDA, une cause fréquente d'encéphalite en réanimation

Anti-NMDA-receptor encephalitis, a frequent cause of encephalitis in the intensive care unit

M. Lamarque · D. Psimaras · F. Ducray · I. Pelieu · R. Sonneville · S. Demeret · F. Bolgert · C. Dehais · J.-P. Camdessanche · J.-C. Antoine · J. Honnorat · J.-Y. Delattre · N. Weiss

Reçu le 4 avril 2011 ; accepté le 19 avril 2011

Encéphalites à Ac anti-R-NMDA

- 4% des causes d'encéphalites

Granerod et al, Lancet Infect Dis 2010 ; 10:835-44

- 25% paranéoplasique

- Symptômes neurologiques précèdent la tumeur dans 65% des cas

- Associé à :
  - tératome ovarien le plus souvent

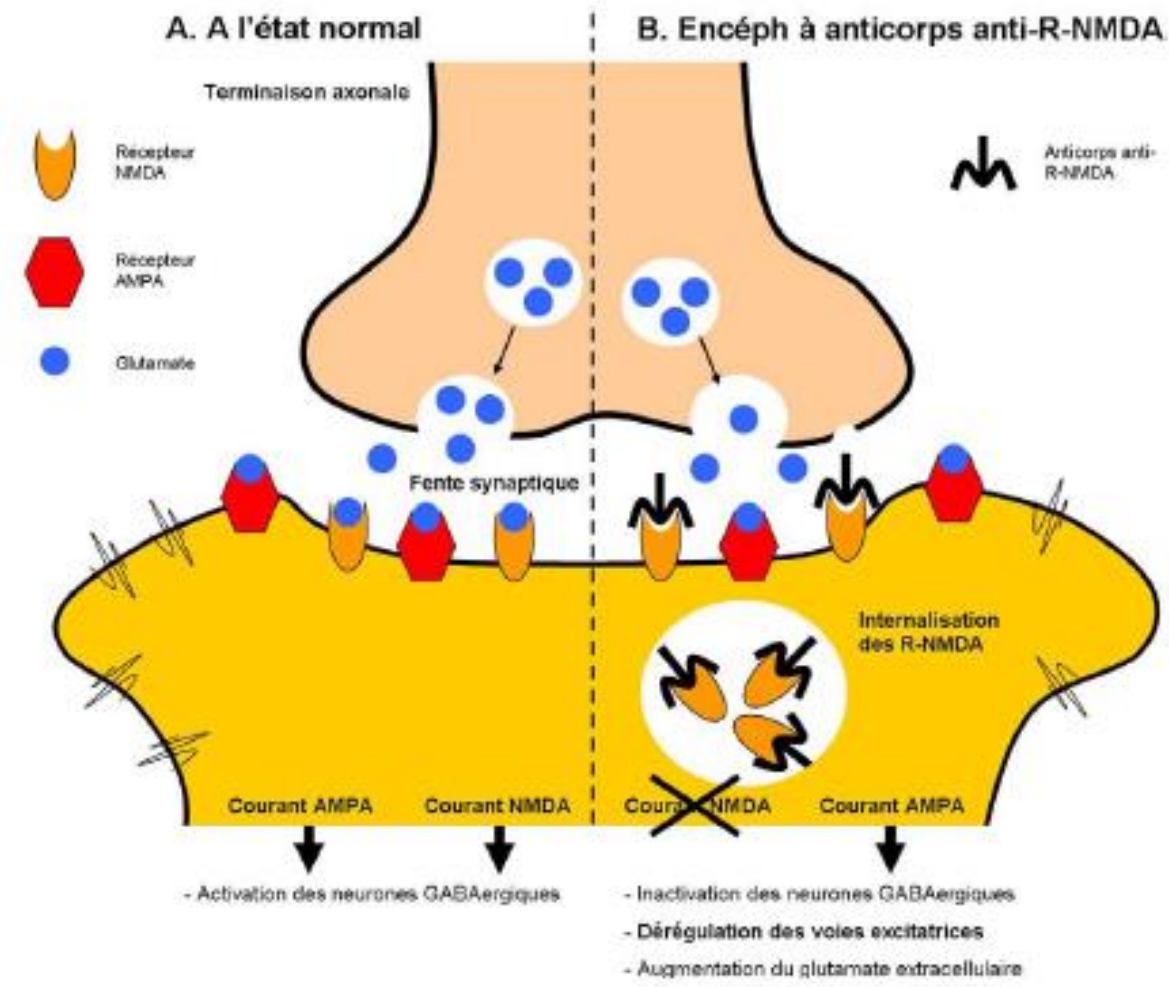

A. A l'état normal
B. Encéph à anticorps anti-R-NMDA
Terminaison axonale
Récepteur NMDA
Récepteur AMPA
Glutamate
Anticorps anti-R-NMDA
Fente synaptique
Internalisation des R-NMDA
Courant AMPA
Courant NMDA
Courant NMDA
Courant AMPA
- Activation des neurones GABAergiques
- Inactivation des neurones GABAergiques
- Dérégulation des voies excitatrices
- Augmentation du glutamate extracellulaire

Tableau 2 Présentation clinique des encéphalites à anticorps anti-R-NMDA adaptée des travaux de Dalmau et al. [2] Une série de 419 patients, incluant ces 100 patients, a récemment été décrite. Cependant, la description clinique y est moins détaillée [7]

	Patients (*n* = 100)
Sexe féminin	91 %
Âge médian	23 [5–76]
Prodromes (céphalées, fébricule, tableau grippal non spécifique)	72 %
Symptômes psychiatriques ou neuropsychiatriques	100 %
Vus d'abord par un psychiatre	77 %
Vus d'abord par un neurologue	23 %
Crises convulsives	
De tout type	76 %
Généralisées tonicocloniques	45 %
Partielles complexes	10 %
Autres	30 %
Mouvements anormaux et dyskinésies	
De tout type	86 %
Orofaciaux	55 %
Mouvements choréoathétosiques, mouvements complexes des membres, de l'abdomen et du pelvis	47 %
Posture anormale (dystonie, extension), rigidité musculaire, hypertonie	47 %
Autres	25 %
Dysautonomie	69 %
Hypoventilation centrale	66 %

Dalmau et al, Lancet Neurol 2008 ; 7:1091-8

Tableau 3 Résultats des examens complémentaires au cours des encéphalites à anticorps anti-R-NMDA adaptés des travaux de Dalmau et al. [2] Une série de 419 patients, incluant ces 100 patients, a récemment été décrite. Cependant, la description clinique y est moins détaillée [7]

	Patients (n = 100)
Électroencéphalogramme	
Anormal	92 %
Activité ralentie (activité delta ou thêta généralisée ou prédominant dans les régions frontotemporales)	71 %
Activité épileptique	71 %
IRM cérébrale	
Anormale	55 %
Lobes temporaux	22 %
Cortex cérébral	17 %
Cervelet	6 %
Tronc cérébral	6 %
Noyaux gris de la base	5 %
Prises de contraste	14 %
Autres	8 %
Liquide céphalorachidien	
Anormal	95 %
Pléiocytose lymphocytaire	91 %
Protéinorachie augmentée	32 %

Dosage Ac anti-R-NMDA ds LCR = élément clé!!

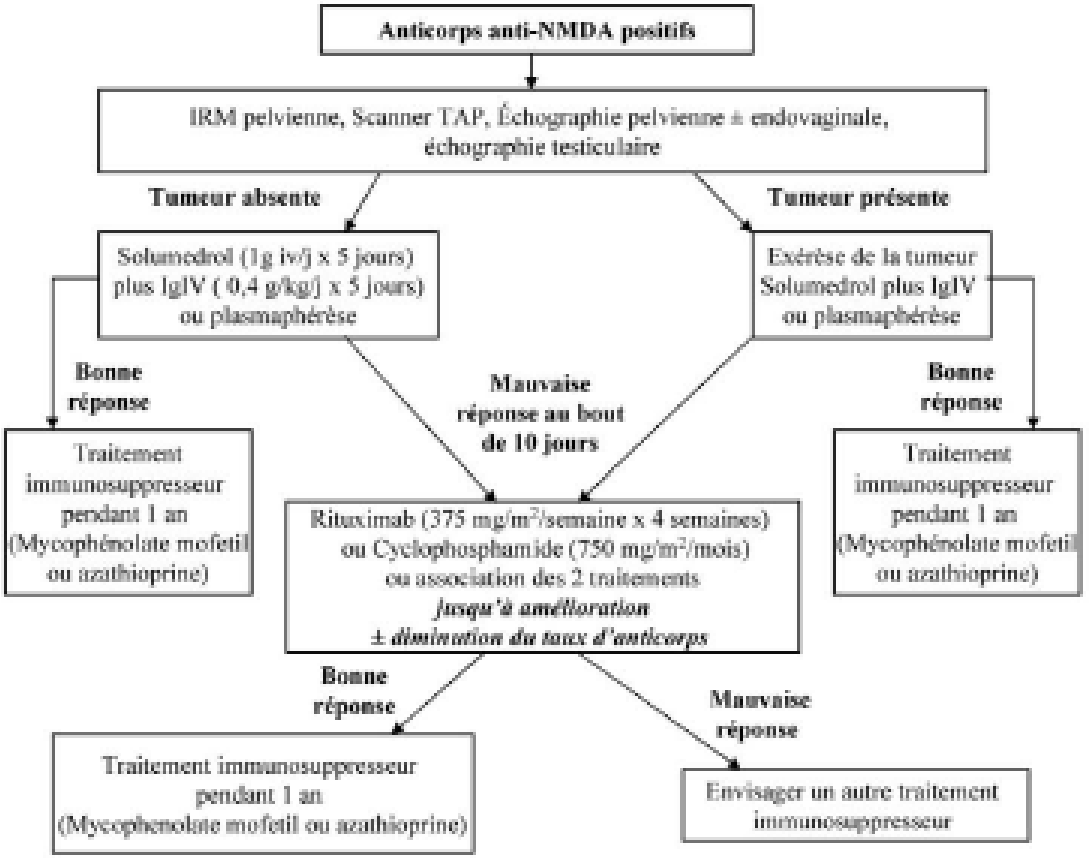
Dalmau et al, Lancet Neurol 2008 ; 7:1091-8

Encéphalites à Ac anti-R-NMDA

- Diagnostic de la tumeur primitive !!!
  - TDM thoraco-abdomino-pelvienne
  - IRM pelvienne chez la femme

TRAITEMENT

! ATTENTION: Ces propositions thérapeutiques ne reposent à ce jour sur aucune étude validée mais uniquement sur une publication de revue (*Dalmau et al. Lancet Neurol 2011;10:63-74*) et sur l'expérience clinique du centre de référence.



! Dans tous les cas, surveillance de la tumeur (*récidive ou apparition*) tous les ans pendant 2 ans.

Centre de Référence des Syndromes Neurologiques Paranéoplasiques
Tél: 04 72 35 58 42 – Médecin: francois.ducray@chu-lyon.fr
59, boulevard Pinel – 69677 BRON

Encéphalites à Ac anti-R-NMDA : Evolution et pronostic

- Mortalité faible (+/- 4%)
- Délai médian jusqu'au décès : 3,5 mois
- Pronostic neurologique favorable : plus de > 75% des cas
- Apparition des 1er signes d'amélioration : 8 semaines
- Hospitalisation longue
- Revalidation nécessaire
- Risque de rechute : 25%

Encéphalites à Ac anti-R-NMDA

- Diagnostic aisé
- Découverte récente
- Curable

=> Y penser chez les sujets jeunes de sexe féminin, qui présentent un changement récent de comportement ou un état psychotique aigu, avec des mouvements anormaux, des crises convulsives, une dysautonomie et/ou une hypoventilation d'origine centrale

Tableau 1 Encéphalites auto-immunes/paranéoplasiques selon Graus et al. [1] et Dalmau et al. [3] Les syndromes paranéoplasiques (SPN) sont classés en trois groupes (I à III). Le groupe I correspond aux anticorps reconnaissant un antigène intracellulaire n'étant probablement pas pathogénique. Ce groupe est divisé en groupe Ia qui est donné dans le tableau, en groupe Ib (anticorps contre SOX ou ZIC) qui ne semble pas associé à des SPN et le groupe Ic (anticorps contre le *glutamic acid decarboxylase* [GAD], adénylate-kinase-5 et Homer-3) qui identifie des syndromes non paranéoplasiques (*Stiff-person syndrome*, ataxie cérébelleuse et encéphalite limbique). Le groupe II correspond aux anticorps reconnaissant un antigène neuronal de surface. Le tableau d'encéphalite limbique associe des troubles de l'humeur, du sommeil, des convulsions, des hallucinations et des troubles de la mémoire à court terme pouvant évoluer vers la démence

	Tumeurs (%)	Symptômes neurologiques	Commentaires
Groupe I : anticorps dirigés contre des antigènes intracytoplasmiques (groupe Ia)			
Hu (ANNA1)	CPPC	*Encéphalomyélite, encéphalite limbique, encéphalite du tronc cérébral*, dégénérescence cérébelleuse paranéoplasique (DCP)	Les anticorps peuvent être présents en dehors d'un SPN
CV2 (CRMP5)	CPPC, thymome	*Encéphalomyélite, encéphalite limbique*, chorée, DCP	Les anticorps peuvent être présents en dehors d'un SPN
Amphiphysine	Sein, CPPC	*Encéphalite limbique*, *Stiff person syndrome*, myélopathie et myoclonus, *encéphalomyélite*	
Ri (ANNA2)	Sein, CPPC	*Encéphalite du tronc cérébral*, opsoclonus myoclonus	
Yo (PCA1)	Ovaire, sein	DCP	
Ma2	Testicule, poumon	*Encéphalite limbique, encéphalite du tronc cérébral*	
Groupe I : anticorps dirigés contre des antigènes intracytoplasmiques (groupe Ic)			
GAD	Thymome, autre	*Encéphalite limbique*, *Stiff person syndrome*, ataxie cérébelleuse	
Groupe II : anticorps dirigés contre des antigènes neuronaux de surface			
LGI-1[a]	CPPC, thymome	*Encéphalite limbique*	Prédominance masculine, hyponatrémie fréquente, anomalie du sommeil paradoxal
CASPR-2[a]		Encéphalite avec convulsions, syndrome de Morvan, neuromyotonie	
R-NMDA	Tératome ovarien	*Encéphalite* avec manifestations psychiatriques, mouvements anormaux, crises convulsives, dysautonomie et hypoventilation alvéolaire	Prédominance féminine
R-AMPA	CPPC, sein, thymome	*Encéphalite limbique*, tableau psychotique	Prédominance féminine
R-GABA$_B$	CPPC	*Encéphalite limbique*	Convulsions fréquentes
R-Glycine	Cancer pulmonaire	*Encéphalomyélite* progressive avec rigidité	À confirmer

CPPC : cancer pulmonaire à petites cellules ; SPN : syndrome paranéoplasique ; DCP : dégénérescence cérébelleuse paranéoplasique.
[a] Regroupés au préalable sous l'appellation *voltage gated potassium channel*, VGKC.

Encéphalites auto-immunes paranéoplasiques

- Développement rapide des symptômes
  - Troubles du comportement ou de l'humeur
  - Crises convulsives
  - Troubles de la mémoire
- Signes d'inflammation dans le LCR
  - Pléiocytose lymphocytaire modérée
  - Hyperprotéinorachie
  - Grande concentration d'IgG et bandes oligoclonales spécifiques
- Modifications de l'imagerie cérébrale et EEG

Encéphalites auto-immunes paranéoplasiques

- Diagnostic :
  - Ac dirigé contre un Ag du SNC dans le LCR
- Prise en charge :
  - Corticothérapie
  - IgIV
  - Plasmaphérèses
  - Immunosupresseurs
  - Traitement antinéoplasique

Syndrome myasthénique de Lambert-Eaton

- Blocage immunologique des canaux calciques voltages dépendants situés sur l'élément présynaptique de la jonction neuromusculaire
- Associé à un cancer bronchique dans > 50% des cas
- Clinique :
  - Faiblesse des muscles proximaux
  - Atteinte du SNA
  - Diminution des réflexes ostéotendineux
  - Ataxie cérébelleuse

Syndrome de Lambert-Eaton

- Diagnostic :
  - Clinique
  - EMG : Basse amplitude, réponse décrémentielle à une faible stimulation et incrémentielle à une forte stimulation
  - Ac circulants anti-canaux calciques voltage-dépendants
- Traitement :
  - Cancer sous jacent
  - 3,4-diaminopyridine phosphate

Conclusion

- Rare
- Syndromes Neurologiques paranéoplasiques le + svt
  - Atteinte respiratoire ou neurologique
- Recherche d'un cancer sous-jacent

Titulaer, Eur J Neurol 2011;18:19-e3

- Prise en charge
  - Traitement antinéoplasique
  - Traitement immunosuppresseurs
  - Plasmaphérèse
  - Corticoïdes
  - Ig IV

Merci de votre attention