PRESENTATION INHABITUELLE D'UN SYNDROME DE LAMBERT EATON

AN UNUSUAL PRESENTATION OF LAMBERT EATON MYASTHENIC SYNDROME

K.S. MOALLA[1,2,*]; S. BELGHUITH[1,2]; S. SAKKA[1,2]; H. HAJ KACEM[1,2]; N. FARHAT[1,2]; M. DAMAK[1,2] ET C. MHIRI[1,2]

1: Service de Neurologie, Hôpital Habib Bourguiba, Sfax, Tunisie
2 : Faculté de médecine de Sfax, Université de Sfax, Tunisie

*** E-mail de l'auteur correspondant :** moalla.ks@gmail.com

Résumé

Le syndrome myasthénique de Lambert Eaton est une maladie auto-immune de la jonction neuromusculaire causée par des anticorps produits contre les canaux calciques voltage-gated (VGCC) sur les terminaisons nerveuses présynaptiques. Les caractéristiques cliniques de la maladie sont la faiblesse musculaire proximale, l'absence ou la diminution des réflexes tendineux, les symptômes dysautonomiques et l'atteinte oculo-bulbaire. Les manifestations du système nerveux central (SNC) telles que l'épilepsie n'ont pas été décrites. Nous décrivons le premier cas de syndrome de Lambert Eaton révélé par un état épileptique focal chez un patient de 49 ans.

Mots - Clés : Syndrome de Lambert Eaton ; Canaux calciques voltage dépendants ; Epilepsie ; Syndrome paranéoplasique.

Abstract

LEMS (Lambert Eaton myasthenic syndrome) is an autoimmune disorder of the neuromuscular junction caused by antibodies produced against the voltage-gated calcium channels (VGCC) on the presynaptic nerve terminals. Clinical features of the disease are proximal muscle weakness, absence or diminished tendon reflexes, dysautonomic symptomes and oculobulbar involvment. Central nervous system (CNS) manifestations such as epilepsy had not been described. We describe the first patient to develop a focal status epilepticus as a presenting symptom of LEMS in 49 years old patient.

Key - Words: Lambert Eaton myasthenic syndrome; Voltage-gated calcium channels; Epilepsy; Paraneoplastic syndrome

ملخص

متلازمة لامبرت إيتون للوهن العضلي هي مرض مناعي ذاتي للوصلة العصبية العضلية التي تسببها الأجسام المضادة المنتجة ضد قنوات الكالسيوم الكهربائية على النهايات العصبية قبل المشبكية. السمات السريرية للمرض هي ضعف العضلات العلوية، وغياب أو انخفاض ردود الفعل الأوتارية، والأعراض الخضرية وتورط العين البصلية. لم يتم وصف مظاهر الجهاز العصبي المركزي مثل الصرع. وصفنا الحالة الأولى لمتلازمة لامبرت إيتون التي كشفت عنها حالة الصرع البؤري في مريض يبلغ من العمر 49 عاما.

الكلمات المفاتيح: متلازمة لامبرت إيتون ; قنوات الكالسيوم المعتمدة على الجهد ; الصرع ;متلازمة الأباعد الورمية.

INTRODUCTION

LEMS (Lambert Eaton myasthenic syndrome) is an autoimmune disorder of the neuromuscular junction caused by antibodies produced against the voltage-gated calcium channels (VGCC) on the presynaptic nerve terminals [1] [2]. There are two forms of LEMS: the paraneoplastic form is associated with a malignant tumor that is most frequently a small cell lung carcinoma, and the autoimmune form is often related to other dysimmune diseases. [2]. Central nervous system (CNS) manifestations such as epilepsy had not been described. We describe herein a patient in whom LEMS is associated with epilepsy.

CASE REPORT

A 49-year-old man presented with acute onset of difficulty in swallowing. His past medical history was notable for a 20-pack-year smoking history. The evolution was made towards the slowly progressive aggravation. Neurological and otorhinolaryngological examination were normal in particular no sensory-motor deficit or paralysis of the cranial nerves apart from xerostomia. Routine hematological and chemical tests (such us complete blood count, ionogram, blood sugar, kidney function, C reactive protein) revealed no abnormalities. Esophago-gastroduodenoscopy, electroneuromyogram (ENMG) and brain Magnetic Resonance Imaging (MRI) were normal.

Two months later, the patient developed a focal status epilepticus without any prodromal symptoms. He displayed ongoing myoclonic jerks of the right face and right limbs followed by a generalized seizure. The neurological examination objectified incomplete bilateral asymmetrical ptosis. There is no sensory motor deficit. Brain MRI showed a hypersignal of the left insular ribbon on the T2 flair and diffusion sequences which were interpreted as post ictal abnormalities **(figure 1).** The interictal electroencephalogram showed a clear left parietal spikes and slow spikes focus **(figure 2).** A second ENMG does not show abnormal decremental or incremental responses.

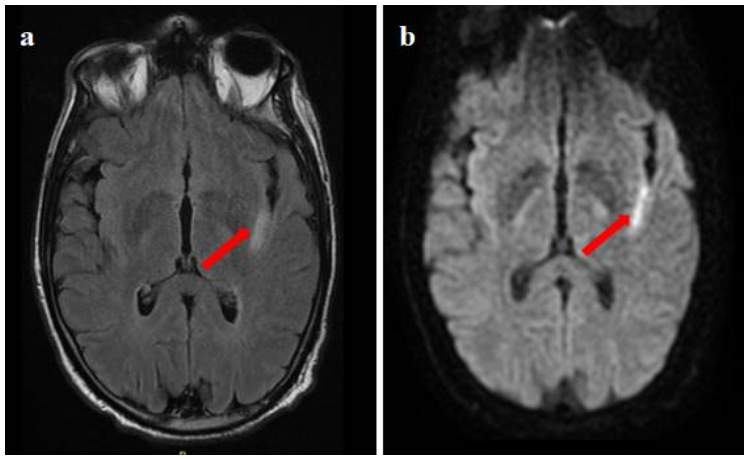

Figure 1: Brain MRI axial T2 flair image (a) and diffusion weighted image (b) showing hypersignal of the left insular ribbon

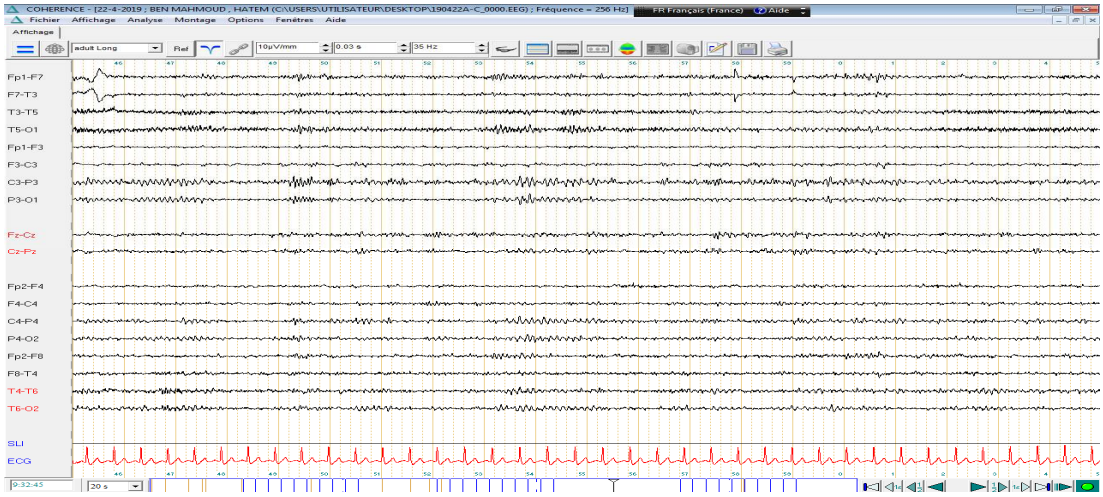

Figure 2: Inter-ictal electroencephalogram showing spikes and low spikes in left parietal area

The diagnosis of Hashimoto's encephalopathy was initially suspected according to Graus and al criteria [3] because of the positivity of anti-microsomal (TPO) antibody titer (108 UI with normal level< 50 UI). Thyroid stimulating hormone (TSH) and thyroid ultrasound were normal.

This diagnosis was then rejected given the spontaneous normalization of anti-TPO. Cerebrospinal fluid analysis was normal. Screening tests were also negative for paraneoplastic markers. Anti-acetylcholine receptor and anti-Musk antibodies were requested and came back negative. Five sessions of plasmapheresis were instituted followed by oral corticosteroid therapy and the patient was steadily under treatment with valproic acid with good neurological 3-month outcomes: the ptosis disappeared and the patient remained seizure-free. Two months later, the patient developed limb weakness with acute respiratory distress. Neurological examination revealed mild limb proximal weakness, generalized hyporeflexia, diffuse muscular atrophy with induced fasciculations in arms associated to bilateral asymmetrical ptosis.

ENMG study concluded to decreased Compound Muscle Action Potential (CMAP) in motor nerve conduction studies at rest in both upper and lower limbs.

Laboratory findings revealed a high level of voltage-gated calcium channel (VGCC) antibodies. The diagnosis of Lambert-Eaton syndrome was established. The patient was prescribed 3,4-diaminopyridine, after receiving intraveinous immunoglobulin (0,4 g/kg daily for five days), the symptoms were markedly improved. Eight months later, a pulmonary tumor lesion very suspicious for malignancy was detected on a chest CT scan. Subsequent radiological controls showed a regression in the size of the lesion until it disappeared, thus eliminating its malignant nature. The diagnosis of an autoimmune form of LEMS was retained.

DISCUSSION

LEMS is believed to be under-diagnosed and frequent misdiagnoses interfere with accurate epidemiological estimation. It may occur as a paraneoplastic disorder, most commonly in association with small cell lung cancer, or as an autoimmune disease (including autoimmune thyroid disease, diabetes mellitus, rheumatoid arthritis, and systemic lupus erythematosus) in the absence of cancer [4].

Clinical features typically consist of proximal muscle weakness, autonomic features, and areflexia.

Others features may occur such us diplopia, ptosis, dysarthria and dysphagia [5,6].The electrophysiological criteria described by Lambert and Eaton have served as the basis of LEMS diagnosis [4].

Repetitive nerve stimulation is the electrophysiological test of choice, and the classical triad of electrophysiological findings consists of the following[4] :

*An increment in the response greater than 100% demonstrated immediately after a brief 10–30 seconds of maximal voluntary contraction, which is also known as the post-exercise test (PET), or with a high frequency (20–50 Hz) stimulation. This finding is observed in up to 96% of LEMS cases[7].

*A decrement in the CMAP response upon low-frequency (2–5 Hz) RNS that produces a successive decline in CMAP amplitude from its normal baseline[8].

*Reduced CMAP in motor nerve conduction studies at rest that usually reach less than 50% of the inferior limit of normal as it was objectified in our patient[9].

This finding is observed in up to 96% of LEMS cases. In our case, ENMG features showed only this pattern after three repetitive electrophysiological studies.

No central manifestations were described in LEMS. Standing this atypical disease presentation including seizures and chronological correlation of symptoms, it is possible to hypothesize that LEMS could trigger seizures through an autoimmunity and biochemical pathogenic mechanisms [5, 10]. Indeed, VGCC is a large transmembrane protein with multiple subunits [11]. It has an important role as it mediates the influx of calcium into the nerve terminal[11]. Several types of VGCCs are expressed in the central and peripheral nervous systems[12]. Presynaptic P/Q and N-type VGCCs induce neurotransmitter release. Postsynaptic L-type VGCCs, localized on neuronal cell bodies and dendrites, regulate gene expression and neuronal excitability and could explain the occurrence of epilepsy in our patient [12].

The pathophysiological mechanism is not well elucidated yet. But it can be either a lack of calcium release or neuronal hyper-excitability. Furthermore, the hypothesis of autoimmunity, as it is an autoimmune form, seems the most likely. The good response to immunotherapy emphasizes this hypothesis. Overall, we suggest the importance of considering possible central neurological manifestations of LEMS, even as initial presentation.

CONCLUSION

We describe the first patient to develop a focal status epilepticus as a presenting symptom of LEMS. Even in the absence of all electrophysiological features, the recurrence or worsening of paroxysmal neurological events including ptosis and swallowing disorder should raise the diagnostic hypothesis of LEMS. Further data is necessary to understand and assess the real burden of CNS symptoms in LEMS and how those contribute to morbidity and mortality, especially in time-dependent pathologies.

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