“Isaacs' syndrome associated with antibodies to Voltage – Gated Potassium Channels (VGKC) in relapsing lymphoplasmacytic lymphoma patient”

A. Silvani[1], P. Gaviani[1], E. Lamperti[1], G. Simonetti[1], C. Ciano[2], A. Botturi[1]

[1]Unit of Neurooncology; [2]Unit of Neurophysiopathology
Foundation IRCCS Neurological Institute “C. Besta”, Milan

INTRODUCTION

Isaacs’ syndrome is a rare neurological condition characterized by pseudomiotonia (Pse), muscle twitching, cramps, stiffness. Furthermore are described sweating, paraesthesia and muscle weakness.Pse is a peripheral motor nerve hyperactivity disorder, due to continuously and spontaneously motor units potentials firing (MUPs). The first description was dated in 1961 by Isaacs. Only in the 1993 Newsom-Davis and Mills reported remission of Pse following plasma exchange or high-dose intravenous human immunoglobulins (ivIg), azathioprine. In 1995 Shillito et al. described presence of antibody to Voltage-gated potassium channels (VGKC) in patients with PSe.

CASE REPORT

A 65-year-old man was admitted to Istituto Neurologico “Carlo Besta” for the evaluation of acute, progressive sensory motor disturbances which started one month earlier.

Three years before he has been treated for lymphoplasmacytic lymphoma (LPL). The initial symptoms were numbness and tingling sensations in his feet and legs, followed by muscle weakness and progressive gait difficulties. The neurological examination on admission revealed mild motor weakness, mainly distally at the legs, reduced deep tendon reflexes at lower limbs and fasciculations. Cranial nerves, bulbar function, were normal. The work-up included electromyography finding fasciculations in distal leg muscles with nearly continuous firing of MUPs at rest, either as doublet, triplet, or multiplet discharges. Motor evoked magnetic potentials examination was normal. Routine hematologic tests, revealed an homogeneous spike-like peak in a focal region of the gamma-globulin zone and increased serum immunoglobulin concentrations (IgM) consistent with the diagnosis of LPL. A lumbar puncture showed normal results.

Onconeural antibodies was negative. VGKC antibodies were present; negative anti Contactin-associated protein-like 2 (Caspr2) and anti leucin-riche glioma inactivated 1 (Lg1).

Symptomatic treatment including Oxcarbazepine and Duloxetine were effective with reduction of fasciculation and sensory disturbances, while therapy with Immunoglobulin failed. An oncology assessment confirmed relapse of illness. Chemotherapy reduced circulating IgM levels and stabilized the neurological picture.

CONCLUSIONS

The term paraneoplastic syndrome includes today a several different clinical neurological conditions, with a disabling clinical outcome. Currently pathophysiology of some of them can be recognized. Acquired Pse, due to the presence of VGKC antibodies, could be inserted into classical paraneoplastic syndromes, according to Graus classification. Pse is an important diagnostic challenge and can now be treated with symptomatic pharmacological therapy and / or acting on the pathophysiological process. In some cases is the first alarm bell of a worsening of oncological disease; for such reasons must be prompt and careful diagnosed.

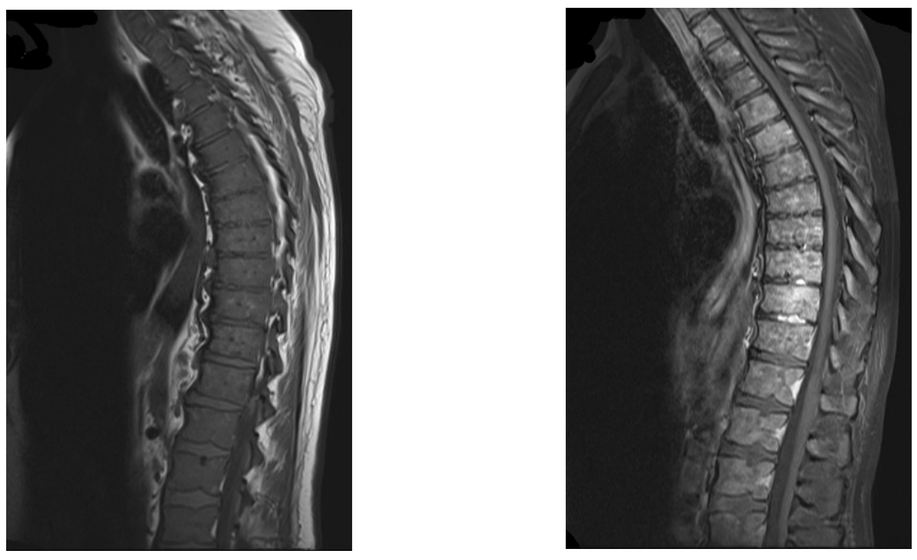

Fig. 1 MRI: Vertebral localization of the disease: loss of signal in T1 and T2 sequences.

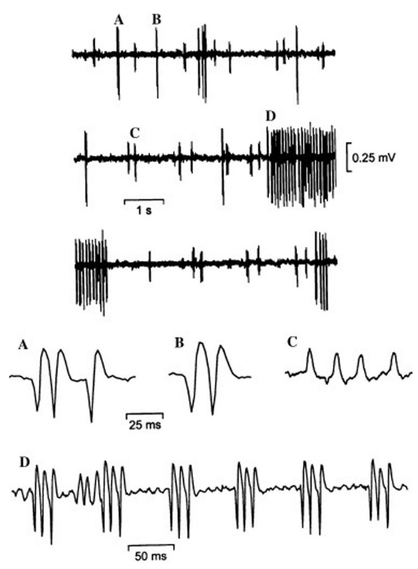

Fig. 2 EMG: presence of doublet (B), triplet (A), or multiplet (C) discharges.

Paraneoplastic Syndromes of the Nervous System:

Central nervous system

Peripheral nervous system
Sensory neuronopathy*
Acute sensorimotor neuropathy
Chronic sensorimotor neuropathy
Neuromyotonia
Chronic gastrointestinal pseudo obstruction/autonomic neuropathy*
Lambert-eaton myasthenic syndrome*
Myasthenia gravis
Inflammatory myopathy
(*Indicates "classical" PNS as defined by Graus et al 2004).

Clinical associations of neuromyotonia

Autoantibody mediated or autoimmune associated
Paraneoplastic:
Thymoma with or without myasthenia gravis
Small-cell lung carcinoma
Lymphoma (Hodgkin's)
Plasmacytoma with IgM paraproteinaemia
Associated with other autoimmune disorders:
Non-immune mediated

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Paraneoplastic syndromes of the CNS