Neurological Autoimmunity Associated With Thymoma: Beyond Myasthenia Gravis

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Introduction

Thymic malignancy is often associated with autoimmune neurological diseases with myasthenia gravis (MG) being the most frequent accompaniment. Recently, novel autoantibodies have been identified that may expand the serological profile of thymoma[1, 2]. Aim of this study was to investigate the neurological manifestations either isolated or associated with MG and the frequency of neural Immunoglobulin G (IgG) autoantibodies in patients with thymoma.

Methods

Study subjects

The study was approved by the Ethic Committee of the Catholic University of Rome, Italy. We retrospectively identified and classified 270 patients with histopathologically confirmed thymoma seen in our Institution. Patients were divided into 3 groups: (1) isolated MG (n = 244); (2) MG plus additional autoimmune neurological manifestations (n = 17); and (3) neurological disorders without MG (n = 9). Groups 2 and 3 are the object of this study.

Neural antibody testing

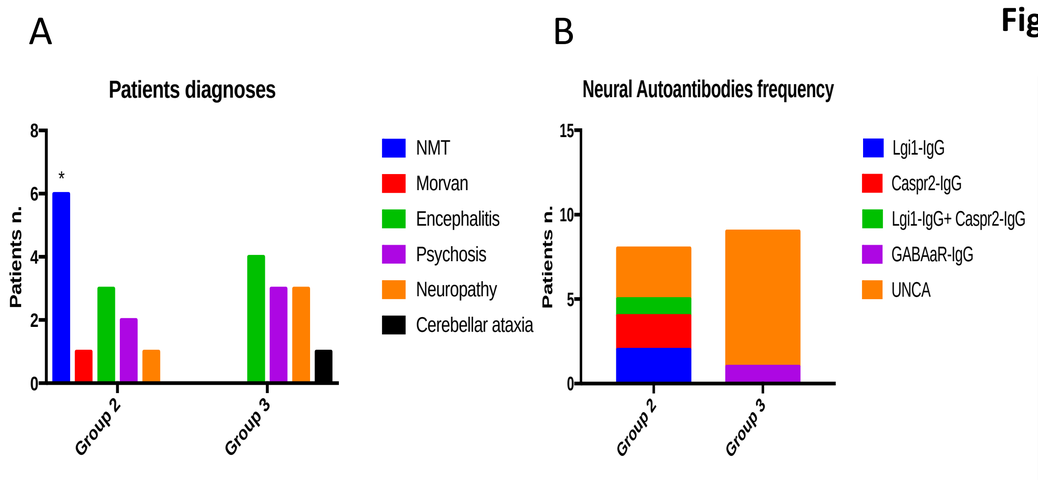
Patients' serum and CSF samples were tested for neural-specific autoantibodies by the following methods:

- immunohistochemistry on a substrate of mouse brain, kidney and stomach
- immunocytochemistry on live rat hippocampal neurons.
- cell-based assays for NMDAR-IgG, LGI1-IgG, CASPR2-IgG, GABA(A)R-IgG, GABABR-IgG AMPAR-IgG, mGluR5-IgG, Glycine receptor-IgG, IGLON5-IgG, DPPX-IgG,
- immunoblot assays for Abs specific to onconeural antigens

Results

We identified 26 patients with autoimmune neurological diseases other MG (group 2=17 patients; group 3=9 patients). Four patients from group 2 were excluded because no stored serum and/or CSF samples were available to test. The remaining 22 patients were included in the final analysis. Ten patients were females, the median patient age at symptoms onset was 56 years. In group 2, neuromyotonia was diagnosed in 6 patients, encephalitis in three, psychiatric disturbances in two, and Morvan's syndrome in a single case. In group 3 the final diagnoses were: encephalitis (4 patients), neuropathy (4), psychosis (1) and cerebellar ataxia (1) (Fig.1A).

Figure 1



Indirect immunofluorescence assays on mouse brain sections revealed IgG in the serum of 17/22 patients binding to the brain neuropil. Neural autoantibodies bound to : LGI1 in 2 patients, Caspr2 in 2, Lgi1 and Caspr2 in 1, GABAAR in 1 patient, and to unclassified antigens in 11 patients (fig.1B). Neuromyotonia and antibodies specific for the voltage-gated potassium channel complex (VGKCC) were more frequent in group 2 (p=0.042 and p=0.039 respectively)

Fig.2. Indirect immunofluorescence assays on patient's serum and thymoma detection. IgG in patient's serum, detected with an Alexa-Fluor 488 conjugated anti-human IgG antibody bind to live rat hippocampal neurons (1:200 dilution) (A) and to HEK293 cells expressing Caspr2 (end-point titer, 1:1920) (B) and Lgi1 (titer, 1:240). (C) CT scan showing an anterior mediastinal mass (arrow). (D) Hematoxylin-eosin staining of a section of the thymoma showing abundant polygonal epithelial cells with limited atypia and few lymphocytes.

Figure 2

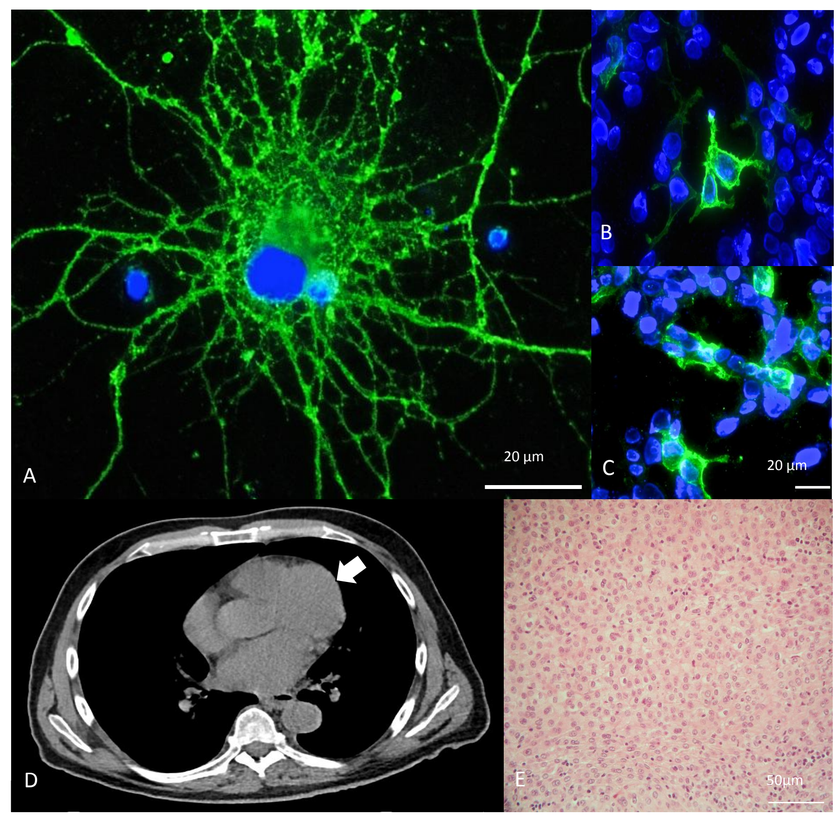


Figure 3

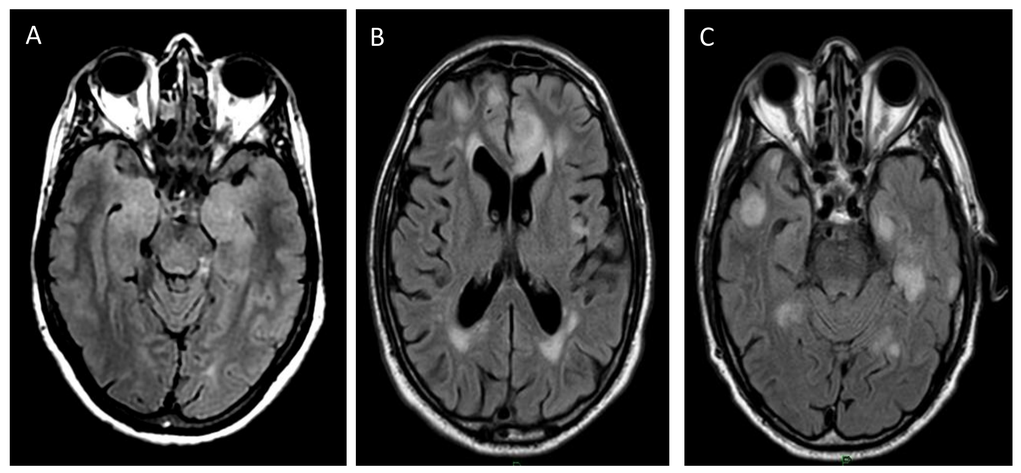


Fig. 3. Brain MRI of patients with thymoma and autoimmune encephalitis. (A) Axial Fluid attenuation inversion recovery (FLAIR) brain MRI of a patient with limbic encephalitis and Lgi1-IgG showing hyperintense lesions in mesial temporal lobes. (B, C)) Axial FLAIR brain MRI of a patient with autoimmune encephalitis and GABAAR-IgG showing multiple cortical-subcortical hyperintense lesions.

Conclusion

Neuromyotonia and encephalitis were the most frequent neurological accompaniments in our cohort

We observed a higher frequency of Neuromyotonia and autoantibodies specific for the VGKCC in patients with thymoma and MG than in patients without MG.

References

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2. Iorio R, Lennon VA. Neural antigen-specific autoimmune disorders. Immunol Rev. 2012 Jul;248(1):104-21. doi: 10.1111/j.1600-065X.2012.01144.x. Review.