Received: 30 November 2023 | Accepted: 27 March 2024

DOI: 10.1002/epd2.20225

Epileptic Disorders

CLINICAL VIGNETTE

Ma2 antibody-associated limbic encephalitis: The early etiology treatment may modify the disease clinical trajectory

Pietro Mattioli[1,2] | **Stefano Grisanti**[1] | **Federico Massa**[1,2] | **Silvia Morbelli**[3,4] | **Silvia Boni**[5] | **Alessandro Beronio**[6] | **Giacomo Rebella**[7] | **Luca Roccatagliata**[1,7] | **Lino Nobili**[1,8] | **Diego Franciotta**[9] | **Elisa Micalizzi**[10,11] | **Flavio Nobili**[1] | **Dario Arnaldi**[1,10] | **Flavio Villani**[10] | **Luana Benedetti**[2]

[1]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genoa, Genoa, Italy

[2]IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[3]Department of Health Science (DISSAL), University of Genoa, Genoa, Italy

[4]Nuclear Medicine Unit, IRCCS Ospedale Policlinico S. Martino, Genoa, Italy

[5]Infectious Diseases Department, Galliera Hospital, Genoa, Italy

[6]Neurology Department, Sant'Andrea Hospital, La Spezia, Italy

[7]Neuroradiology Department, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[8]Child Neuropsychiatry Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy

[9]Neuroimmunology Laboratory, IRCCS Mondino Foundation, Pavia, Italy

[10]Division of Neurophysiology and Epilepsy Centre, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[11]Clinical and Experimental Medicine PhD Program, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy

Correspondence
Pietro Mattioli, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genoa, Via Daneo 3, 16122 Genova, Italy.
Email: mattioli.pietro092@gmail.com

KEYWORDS
limbic encephalitis, Ma2 antibody, paraneoplastic neurological syndrome

Paraneoplastic encephalitis includes neurological conditions with autoantibodies against neuronal proteins, likely triggered by the underlying tumor antigens.[1] We report two patients with paraneoplastic limbic encephalitis[1] with "high-risk-for-cancer" antibodies against Ma2 antigen and non-typical tumors. These cases allow consideration of autoimmune epilepsy's pathogenesis, the importance of early diagnosis, and therapy.

A 21-year-old male admitted to the Infectious Disease Unit due to confusion, visual hallucinations, and upper limbs myoclonus, following a 4-month history of antipyretic-resistant fever, sore throat, and hyperphagia. Cerebrospinal fluid (CSF) analysis was normal, blood examinations showed pancytopenia. Brain MRI, [^{18}F]FDG-PET, and EEG (Figure 1A–D) suggested central nervous system inflammation involving basal ganglia and mesial

Pietro Mattioli and Stefano Grisanti equally contributed to this work.

temporal lobes. Screening for infections was negative. Anti-Ma2 antibodies were found in serum and CSF (indirect immunofluorescence on primate cerebellum, and dot-blot; Euroimmun, Germany). IV methylprednisolone (1 g/day for 5 days) and immunoglobulins (IVIg) (.4 g/kg/day for 5 days) yielded no clinical improvement. Total body CT, [^{18}F]FDG-PET, pelvis, and testicular ultrasound excluded neoplasms, but bone marrow analysis, 6 months after symptoms' onset, showed a clonal population of CD19/CD20dim/CD21 B lymphocytes, indicating a mature B-cell indolent lymphoproliferative disorder not requiring treatment. Hospital-acquired sepsis hindered further immunosuppressive therapies and led to death (7 months after symptoms' onset).

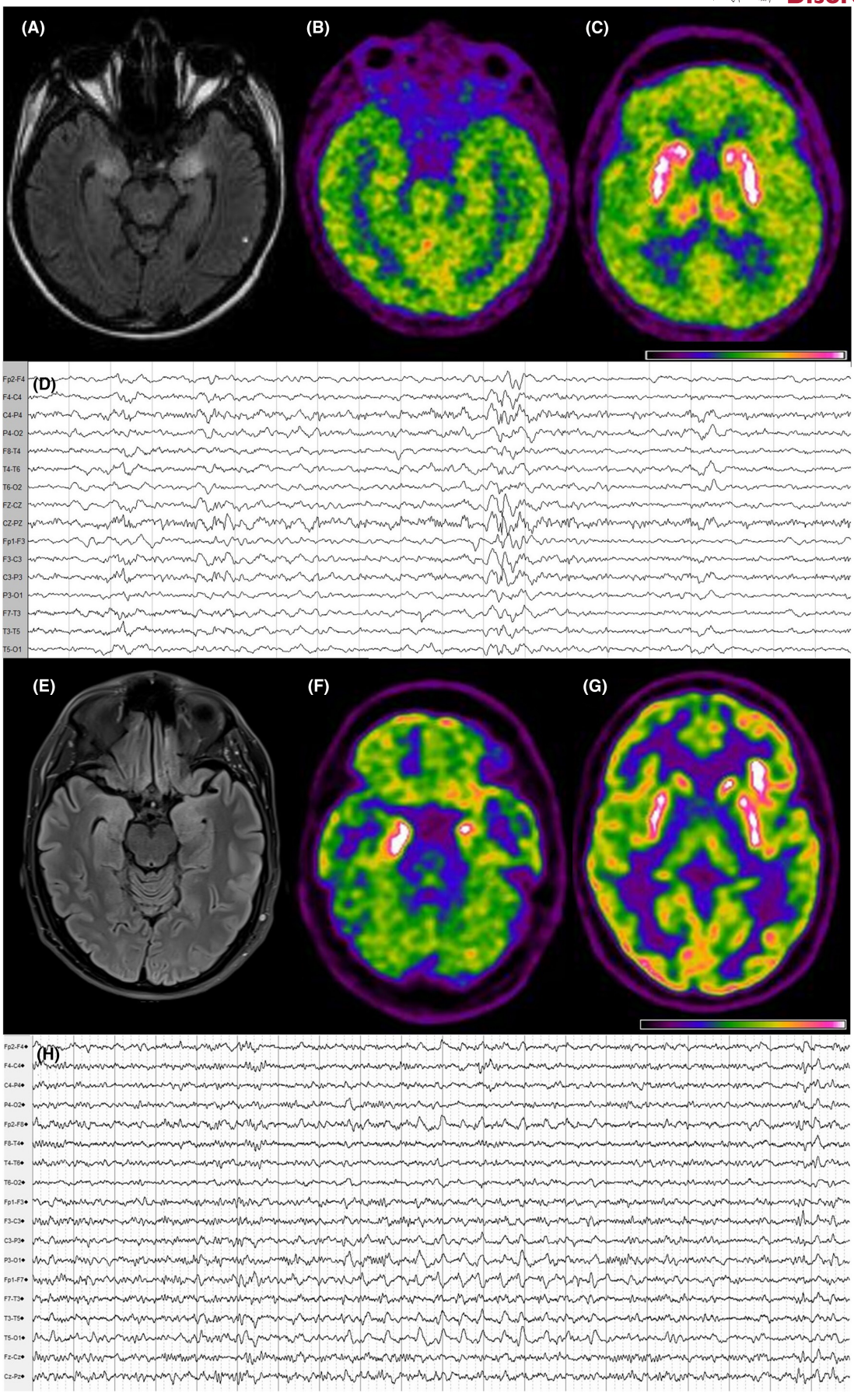
The second patient, a 30-year-old male, presented with asthenia, insomnia, mild fever, and daily, short-lasting episodes of shivering, horripilation, heart palpitations, and unpleasant taste. Subtle sleep-related involuntary movements were reported. No EEG was performed at the time. 1 month after symptom onset, a right testicular mass was noticed and orchiectomy performed. Pathology disclosed a post-puberal teratoma. 2 months later, a scheduled total body CT showed enlargement of retroperitoneal lymphnodes, which were completely removed. Pathology disclosed a post-puberal teratoma with embryonal cancer focus. The patients started clinical and radiological follow-up, with no further localizations detected. 5 months later, he presented a focal-to-bilateral seizure, promptingantiseizure medications. Brain MRI and [^{18}F]FDG-PET indicated limbic encephalitiswith EEG showing interictal epileptiform discharges in left temporal lobe (Figure 1E–H). Anti-Ma2 antibodies were detected in serum and CSF (indirect immunofluorescence on primate cerebellum, and dot-blot; Euroimmun, Germany), but not anti-NMDAR (antigen-specific cell-based assay (Euroimmun, Germany)). IVIg (.4 g/kg/day for 5 days), methylprednisolone (500 mg/day for 3 days) followed by oral prednisone (50 mg/day) led to seizure frequency reduction. IVIg cycles were repeated six times. 9 months after the first IVIg cycle, brain MRI, and [^{18}F]FDG-PET showed reduced T2-hyperintensities of temporal lobes, but mild right temporal-mesial hypermetabolism (Figure S1). Escalation to Rituximab was required for persistent focal aware seizures with vegetative symptoms (horripilation) and mild behavioral abnormalities. At 1-year follow-up, the neurobehavioral status improved along with the persistence of sporadic clusters of focal aware seizures, responsive to oral prednisone boosts (1 mg/kg for 5 days, with subsequent weekly 10% dose tapering). Tumor recurrence in contralateral testis and in other locations were searched, but not found.

Key points

- The treatment of the tumor isnecessary in paraneoplastic encephalitis to obtain a positive outcome.
- Early diagnosis and treatment ofthe aetiological cause leads to a better outcome in paraneoplastic encephalitis.
- Ma2 antibody-associated limbicencephalitis may be associated with other than testicular tumors.

The association of Ma2 antibodies with other than testicular cancer is rare.[2–8] Indeed, in patient 1 the lymphoproliferative disease showed insidious presentation resulting in a 6-month diagnostic delay and was complicated by hospital-acquired sepsis, hindering second-line immunosuppressive therapies. In patient 2, the tumor was treated 1 month after symptoms onset. In agreement with literature data,[1,4] early immunological treatment, along with earlier eradication of the tumor likely promoted a better prognosis. On the other hand, the persistence of focal aware seizures is consistent with a recent study on autoimmune epilepsy demonstrating frequent drug-refractory epilepsy in Ma2 patients.[9] Mild clinical (neurobehavioral symptoms) and neuroimaging ([^{18}F]FDG-PET hypermetabolism reflecting mesial temporal lobes inflammation) signs of inflammation are important factors which are consistent with the hypothesis that the pathogenesis of autoimmune epilepsy in Ma2 patients may be related to persisting inflammatory process rather than the effect of chronic post-encephalitic lesion,[9] as it has been also suggested by a recently published case report.[10] Our observation advocated in our

FIGURE 1 Brain MRI, FDG-PET, and EEG of patient 1 (A–D) and patient 2 (E–H). Only pictures of the most significant abnormalities of MRI, FDG-PET, and EEG are shown. As for patient 1, brain MRI revealed T2/FLAIR hyperintensity in mesial temporal lobe, amygdala, and basal ganglia (A). Brain FDG-PET showed a global hypometabolism along with a relative hypermetabolism of basal ganglia (C). EEG showed slowing of background activity, diffuse sequences of irregular theta-delta waves, and isolated sharp waves and spike-and-waves over central-parietal regions bilaterally (D). As for patient 2, brain MRI showed bilateral T2/FLAIR mesial temporal hyperintensities, more pronounced on the right side, along with enlargement of the amygdalae bilaterally (E). Brain FDG-PET disclosed hypermetabolism in bilateral mesial temporal regions, more evident in the right (F) and left frontal, insular and fronto-temporal regions (G). Inter-ictal EEG showed diffuse slowing of background activity in the left hemisphere, with the occurrence of theta-delta activity and sharp waves over the left temporal regions (H).



patient the use of immunotherapy to treat persisting seizures despite the long time passed from seizures' onset. Further studies, with the specific aim of identifying biomarkers of inflammation and the consequences of long-term immune treatments in such conditions are needed to confirm such speculations.

In conclusion, in line with the literature,[1] early etiological treatment and continuation of immunotherapy should be considered in paraneoplastic encephalitis.

ACKNOWLEDGMENTS

This work was supported by Italian Ministry of Health (Rete Italiana Neuroscienze e Neuroriabilitazione). Work supported by #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006)—*A Multiscale integrated approach to the study of the nervous system in health and disease* (DN. 1553 11.10.2022).

CONFLICT OF INTEREST STATEMENT

Arnaldi D. received fees from Fidia for lectures and board participation; Morbelli S. has received speaker Honoraria from G.E. Healthcare; Nobili F. has received fees for participating in boards from Roche, and speaker Honoraria from Bial e G.E. Healthcare. Villani F. has received speaker's honoraria and fees for participating in boards from UCB Pharma, Angelini Pharma, EISAI, Lusofarmaco, Bial, Jazz Pharma. Micalizzi E. has received fees for participating in a board from Angelini Pharma. The other authors have nothing to disclose.

ORCID

Pietro Mattioli https://orcid.org/0000-0003-2563-5830

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Mattioli P, Grisanti S, Massa F, Morbelli S, Boni S, Beronio A, et al. Ma2 antibody-associated limbic encephalitis: The early etiology treatment may modify the disease clinical trajectory. Epileptic Disord. 2024;00:1–5. https://doi.org/10.1002/epd2.20225

Test yourself

1. What is the most important therapeutic action that could lead to a positive outcome in paraneoplastic encephalitis?

A. The treatment of the tumor underlying the paraneoplastic encephalitis is necessary to lead a positive outcome

B. Immune therapy alone leads to a positive outcome in paraneoplastic encephalitis

C. Anti-seizure medications and immune therapy are enough to lead a positive outcome in paraneoplastic encephalitis

2. Which neuroimaging techniques may help in the identification of inflammation in paraneoplastic encephalitis?

A. Brain computerized tomography may help in the identification of inflammation in paraneoplastic encephalitis

B. The study of brain glucose metabolism, by using [^{18}F]-FDG-PET, may help in the identification of inflammation in paraneoplastic encephalitis

C. [^{123}I]-FP-CIT SPECT may help in the identification of inflammation in paraneoplastic encephalitis

3. Are there other tumors apart from testicular tumors that can be associated with ma2 antibody-associated limbic encephalitis?

A. No, testicular tumors only can be associated with ma2 antibody-associated limbic encephalitis

B. Yes, but only solid tumors

C. Yes, for example, indolent lymphoproliferative disorders

Answers may be found in the Supporting information