Cognitive decline and gait ataxia at the crossroad between autoimmunity and neurodegeneration: a case report and narrative review of literature

Carlo Fazio[1,2], S. Regalbuto[2] , S. Arceri[2] , P. Grillo[1,2], A. Calculli[1,2], D. Comolli[1,2], P. Businaro[1,2], M. Gastaldi[2] and A. Pisani[1,2]

[1]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy.

[2]IRCCS Mondino Foundation, Pavia, Italy

OBJECTIVE

To present a case of progressive cognitive decline and gait ataxia with uncharacterized neuronal surface autoantibodies (NS-Ab) with peculiar imaging findings of severe hippocampal and cerebellar atrophy. To review present literature on NS-Abs and their association with neurodegeneration.

METHODS

Neurological examination, blood tests, brain MRI, total body CT, cognitive evaluation, EEG, and comprehensive cerebrospinal fluid (CSF) analysis were performed. CSF antibodies were evaluated via tissue based assay (TBA) on rat brain slices and cell-based assays (CBAs). A narrative review of NS-Abs associated syndromes mimicking neurodegenerative conditions was performed.

Case presentation

64 y, F; no family history

Past history: hypertension, breast cancer (2022, surgery + Tamoxifen)

End of 2022

- **COVID-19 pneumonia** → hospitalization in Infectious Diseases, discharged in good condition.
- **One month later** → onset of gait disturbance and postural instability. Brain MRI with contrast: negative.

2023

- **Progressive worsening** of gait disorder with **new attentional deficits** and low mood. Sertraline 50 mg started, with mild benefit.
- **Brain MRI (09/2023)**: ventricular dilatation suggestive of possible iNPH. Neurosurgical consult: inconclusive, no indication for shunting at that time.
- **Further cognitive decline**, first neurology hospitalization:

End of 2023 (First Hospitalization)

- **CSF**: normal.
- **Neuropsychological testing**: mild attentional deficits.
- **Conclusions → Subjective cognitive decline**

2024

- **FDG-PET**: bilateral temporal hypometabolism
- **Brain MRI**: severe bilateral mesial temporal atrophy (MTA 4), cerebellar and midbrain atrophy, ex vacuo ventricular dilatation.

New hospitalization

Immunotherapy trial with steroids and plasma exchange produced partial, but stable clinical improvement

Scan QR code to see improvement!

Examination (QR CODE) :

Cerebellar syndrome with speech, oculomotor, gait, and limb involvement, alongside memory deficits and frontal release signs

MRI (figure 1):

T1 and T2 weighted sequences showing bilateral mesial temporal atrophy (MTA4), hippocampal T2 hyperintensity, and cerebellar atrophy

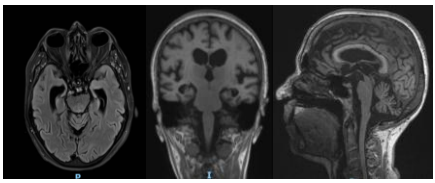

Figure 1.

CSF analysis with TBA analysis (figure 2):

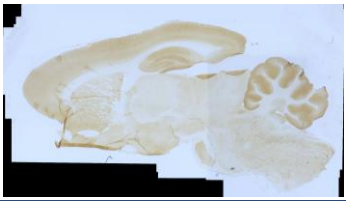

Figure 2.

Chemical-physical analysis within normal limits, neurodegeneration markers within normal range. TBA revealed strong neuropil staining in hippocampus and cerebellum, indicating the presence NS-Abs. A wide panel of live and fixed CBAs for known targets (including NMDAR, LGI1, CASPR2, GLYR, GABAAR, GABABR, IgLON5, DPPX) were negative, leaving the NS-Ab uncharacterized.

Discussion and Review

Our patient exhibited clinical features resembling a neurodegenerative disorder, yet tested positive for NS-Ab.

Similar slowly progressive presentations have been described in IgLON5, CASPR2, and DPPX encephalitis, sometimes mimicking PSP or Parkinson's disease (1). Some progressive cases with LGI1 and DPPX antibodies responded well to immunotherapy (2).

While IgLON5 disease has been linked to both autoimmunity and neurodegeneration, the mechanisms behind the slow progression in other AEs remain unclear. NS-Abs have also been found in primary neurodegenerative disorders, blurring diagnostic boundaries (1).

Our patient's strong TBA neuropil reactivity suggests synaptic surface targeting with possible pathogenic relevance, despite negative results for known antigens.

Conclusions

Our case suggests that **patients harboring potentially relevant NS-Abs can show neurodegenerative features.** Whether in such cases Abs are pathogenetic or merely epiphenomenal, remains a challenging conundrum. Disorders like IgLON5 show similar progression and support a possible autoimmunity-neurodegeneration link. Notably, although slowly progressive courses have been described in some AEs, severe atrophy is uncommon.

REFERENCES:

(1)Giannoccaro MP et Al., Antibodies to neuronal surface antigens in patients with a clinical diagnosis of neurodegenerative disorder. Brain Behav Immun. 2021

(2) Kannoth S et Al., Autoimmune atypical parkinsonism - A group of treatable parkinsonism. J Neurol Sci. 2016

This project was supported by Italian Ministry of Health «Ricerca corrente 2022-2024» granted to IRCCS Mondino Foundation