# PALILALIA AS A PROMINENT FEATURE OF ANTI-NMDA RECEPTOR ENCEPHALITIS IN A WOMAN WITH COVID-19

Andrew W. McHattie1, Jan Coebergh1,2, Faraan Khan3, Francesca Morgante4,5#

1 Department of Neurology, St George’s University Hospitals NHS Foundation Trust, London, UK

2 Department of Neurology, Ashford St. Peter’s Hospital NHS Foundation Trust, Chertsey, UK

3Department of Neuroradiology, Atkinson Morley Regional Neuroscience Centre, St George’s University Hospitals NHS Foundation Trust, London, UK

4 Neurosciences Research Centre, Molecular and Clinical Sciences Research Institute, St George's, University of London, London, United Kingdom

5 Department of Experimental and Clinical Medicine, University of Messina, Messina, Italy

**Manuscript type:** Letter to the Editor

**Running title:** NMDARE and COVID19

**Character count (title):** 92

**Word count (text):** 749

**Figure:** 1

**Supplementary material**: 1 video

**References:** 7

**Key words:** NMDAR encephalitis; COVID19; SARS-CoV-2; palilalia; autoimmune

**#Correspondence to:**

Dr Francesca Morgante, MD, PhD

Neurosciences Research Centre, Molecular and Clinical Sciences Research Institute, St George's, University of London, Cranmer Terrace, London, SW17 0RE, United Kingdom

e-mail: [fmorgant@sgul.ac.uk](mailto:fmorgant@sgul.ac.uk)

# DECLARATIONS

**Funding sources**

Nothing to declare

**Financial disclosure related to research covered in this article**

None

**Financial disclosures and Conflicts of interest**

* Francesca Morgante: Speaking honoraria from Abbvie, Medtronic, Zambon, Bial, Merz; Travel grants from the International Parkinson’s disease and Movement Disorder Society; Advisory board fees from Merz; Consultancies fees from Boston Scinetific, Merz and Bial; Research support from Boston Scientific, Merz and Global Kynetic; Royalties for the book “Disorders of Movement” from Springer; member of the editorial board of Movement Disorders, Movement Disorders Clinical Practice, European Journal of Neurology.
* Jan Coebergh: Speaking honoraria from Bial, UCB; travel grants from Bial and Medtronic; named on Patent for testing GABAa antibodies.
* Andrew McHattie: no disclosures.
* Faraan Khan: no disclosures.

**Ethics approval**

The patient has given her consent to anonymously report her clinical reports and videos in accordance with current ethical standards. This case report did not need ethic committee approval

**Data access and responsibility statement**

F. Morgante had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data.

**Authorship statement**

* Andrew McHattie: conception of the case report, drafting the article and revising it critically for important intellectual content
* Jan Coebergh: interpretation of data, revising the article it critically for important intellectual content.
* Faraan Khan: interpretation of data, revising the article it critically for important intellectual content.
* Francesca Morgante: conception of the case report, interpretation of data, revising the article it critically for important intellectual content.

All the co-authors listed above gave their final approval of this manuscript version.

All the co-authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dear Sirs,

Anti-N-methyl D-aspartate (NMDA) receptor (anti-NMDAR) encephalitis is a common autoimmune encephalitis characterized by the combination of psychiatric symptoms, epileptic seizures and hyperkinetic movement disorders1.

Here we report on a 53-year-old female whose prominent anti-NMDAR clinical manifestations at onset were palilalia and echolalia and who developed concomitant infection with SARS-CoV-2.

On 13 April 2020, she was admitted to a district general hospital with a 2-week history of confusion, fever and myalgia. Her past medical history included ductal breast carcinoma under remission, depression and plaque psoriasis. She was treated with sertraline and ciclosporin, which was stopped one month before admission. On admission, she was afebrile, alert and scored 7/10 in the abbreviated mental test score. Blood tests were normal, except for elevated C-Reactive protein (34 mg/L) and lymphopenia (0.8). CT head performed with intra-venous contrast was normal. Treatment with intravenous acyclovir was initiated for suspected viral encephalitis. Naso-pharyngeal swab for SARS-CoV-2 RNA was negative.

Over the next three days, she became increasingly confused and she developed urinary retention. Cerebrospinal fluid (CSF) analysis showed a white cell count of 141/microlitre (100% lymphocytes), no growth or organisms, glucose of 2.7 mmol/L and a protein count of 0.54 g/L (normal 0.25-0.45). CSF viral screen was negative, including RNA for the SARS-COV-2. By day 5, she developed severe echolalia, palilalia and high-pitched voice (video supplementary material), echopraxia and behavioural disinhibition. An electro-encephalogram showed slow activity but no evidence of epileptiform discharges. Brain MRI demonstrated an area of hyperintensity on the FLAIR sequence in the left amygdala, in the left anterior putamen and subtle signal changes in the right amygdala (Figure 1A-B). Despite treatment with iv and oral steroids, she deteriorates and was transferred to our tertiary neurosciences centre. On examination, she had severe palilalia, echolalia, motor perseverations, mild left sided weakness and difficulty following commands. Subsequently, she developed progressive hypoxemia requiring oxygen therapy. Chest x-ray showed bilateral airspace opacities, typical for COVID19 pneumonia. On day 14, she tested positive for SARS-COV-2. On day 17 she was transferred to the intensive care unit (ICU) for mechanical ventilation. On day 20, her CSF sample returned a positive result for anti-NMDAR antibodies at a high titre (1:100). Anti-NMDAR antibodies in serum were negative. A CT scan of chest, abdomen and pelvis showed no evidence of malignancy. Transvaginal ultrasound did not show any teratoma or ovarian cancer. From day 17, she developed focal seizures and prominent dysautonomia (increasingly hypotensive with bradycardia). She never developed any hyperkinetic movement disorder. Treatment included hydroxychloroquine, intravenous immunoglobins, tocilizumab, antibiotics, amphotericin, levetiracetam. After one month, she made remarkable progresses with remission of palilalia and seizures, improvement of cognitive functions but persistence of left-side weakness (video supplementary material). IgM for SARS-CoV-2 tested positive. Brain MRI performed on day 70 improvement of the signal changes and atrophy of the left amygdala and hippocampal head (figure 1C-D).

We presented a patient with anti-NMDAR encephalitis (NMDAR-E) and severe COVID19 pneumonia. Her laboratory and instrumental findings as well as the later appearance of epileptic seizures and dysautonomia are consistent with the diagnosis of anti-NMDAR encephalitis1. Remarkably, our case showed prominent palilalia at onset which has been reported previously only in one Japanese case of anti-NMDAR-E2.

Our patient also had comorbid COVID19 pneumonia. Two adults3, 4 and one infant5 with comorbid COVID-19 and anti-NMDAR-E were reported so far. The adult cases presented with psychiatric symptoms3 and new onset refractory status epilepticus4. Only in one case there was evidence of COVID-19 pneumonia3, similarly to our patient. The negative PCR at the onset of behavioural symptoms and the negativity of PCR for SARS-CoV-2 in the CFS supports that our patient got infected with SARS-CoV-2 after the onset of anti-NMDAR-E and that her neurological symptoms were due to anti-NMDAR-E. So far, encephalitis attributable to SARS-COV-2 has been rarely reported and only in 3 cases RT-PCR demonstrated presence of SARS-COV-2 in CFS6. If SARS-CoV-2 would have predated the onset of anti-NMDAR-E, we might have speculated this was a para-infectious consequence of SARS-CoV-2, similarly to herpes simplex encephalitis which is a well-recognized risk factor for NMDAR7.

Our case highlights the diagnostic challenge when dealing with anti-NMDAR-E and reports prominent palilalia as a rare clinical manifestation at onset, which might support the diagnosis together with laboratory and neuroimaging findings.

In the COVID-19 era, the bias of attributing any clinical syndrome as a direct consequence to SARS-CoV-2 might carry the harmful risk to miss concomitant treatable disorders such as anti-NMDA-R encephalitis whose prognosis depends onto recognizing associated triggers (i.e. ovarian teratoma) and starting early immunotherapy1.

# ACKNOWLEDGEMENTS

We are grateful to the patient for having provided consent to share her clinical history.

# LEGEND TO THE FIGURE:

Panels A-B: Brain MRI at day 5. Axial FLAIR Sequences. A well-demarcated area of hyperintensity was visible in the left amygdala. There was also a separate area of hyperintense signal change in the left anterior putamen. None of these lesions demonstrated contrast enhancement or restricted diffusion.

Panels C-D: Brain MRI at day 70. Axial FLAIR (C) and coronal T1 weighted (D) images. The hyperintense signal change improved but persisted in the left amygdala and was associated with atrophy of the left amygdala and hippocampal head.

# LEGEND TO VIDEO SUPPLEMENTARY MATERIAL:

Segment 1, day 5 since onset: the video shows prominent palilalia and high-pitched voice. Segment 2, day 79 since onset: the video shows no evidence of palilalia and normal speech.

# REFERENCES

1. Dalmau J, Armangue T, Planaguma J, et al. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models. Lancet Neurol 2019;18:1045-1057.

2. Tsutsui K, Kanbayashi T, Tanaka K, et al. Anti-NMDA-receptor antibody detected in encephalitis, schizophrenia, and narcolepsy with psychotic features. BMC Psychiatry 2012;12:37.

3. Panariello A, Bassetti R, Radice A, et al. Anti-NMDA receptor encephalitis in a psychiatric Covid-19 patient: A case report. Brain Behav Immun 2020;87:179-181.

4. Monti G, Giovannini G, Marudi A, et al. Anti-NMDA receptor encephalitis presenting as new onset refractory status epilepticus in COVID-19. Seizure 2020;81:18-20.

5. Burr T, Barton C, Doll E, Lakhotia A, Sweeney M. N-Methyl-d-Aspartate Receptor Encephalitis Associated With COVID-19 Infection in a Toddler. Pediatr Neurol 2021;114:75-76.

6. Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. Lancet Neurol 2020;19:767-783.

7. Armangue T, Spatola M, Vlagea A, et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. Lancet Neurol 2018;17:760-772.