Case Report

Ictal and interictal FDG-PET in anti–NMDAR encephalitis with mutism

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ABSTRACT

We report a case of a 27-year-old right-handed gentleman with mutism and seizures diagnosed with Anti–N-methyl-D-aspartate receptor (NMDAR) encephalitis without evidence of underlying malignancy. Brain MRI was unremarkable. Clinical seizures were controlled but long-term video-EEG monitoring was needed for better characterization of his clinical manifestations especially that language partially improved. It was crucial to identify whether this mutism was ictal in origin or not. Ictal brain Positron Emission Tomography with 18 F-fluorodeoxyglucose (FDGPET) scan combined with EEG was done. It revealed left fronto-temporal, parietal, and crossed cerebellar hypermetabolism (or diaschisis) concomitant to the underlying rhythmic focal delta activity on EEG. Beside anti-epileptic drugs he was treated with escalating immunotherapy (intravenous solumedrol then immunoglobulins then full rituximab course). Six months later, EEG combined to FDG-PET scan were repeated, and were normal. At 3 years follow up the patient remains neurologically stable and seizure-free, off anti-epileptics drugs. Performing the FDGPET scan combined to EEG was useful to identify non-convulsive status epilepticus and should be performed early in anti–NMDAR encephalitis to guide treatment.

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Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis was first described by Dalmau and colleagues in 2007 and became an increasingly recognized etiology of encephalitis [1]. The associated syndrome is usually severe and includes seizures with wide range of presenting neuropsychiatric symptoms and signs [1,2]. We report a case of anti–NMDAR encephalitis in a young gentleman presenting with mutism and seizures who underwent full investigations including brain ictal and interictal fluorodeoxyglucose-positron emission tomography (PET) combined to video-electroencephalography (Video-EEG).
Case description

A 27 years old right-handed man presented initially to an outside hospital following a seizure described as brief stiffness of his right arm, loss of consciousness, and fall. Subsequently, he was reported to have intermittent episodes of agitation thought to be psychiatric in origin and was prescribed risperidone and alprazolam. Seizures were treated by intravenous valproate followed by oral carbamazepine. Brain magnetic resonance imaging (MRI) was normal. Routine electroencephalogram (EEG) showed intermittent left temporal delta slowing. He was discharged home on oral carbamazepine, but he wasn’t fully compliant with his treatment. He had trouble expressing himself following the initial seizure which urged his family to seek another opinion around 2 weeks later, so he was brought to us for evaluation. At that point, he was completely mute, he could only follow simple commands, and had minimal facial weakness with decreased fine fingers movements on the right. The rest of his neurologic examination was unremarkable. He was admitted to the hospital for long term video-EEG and management. It was crucial to confirm whether mutism was a pure manifestation of an encephalitis or was secondary to non-convulsive seizures or a post ictal state. The patient had focal onset seizures consisting of right eyelid flutter and hemifacial jerks, right gaze deviation spreading at times to the right upper extremity. He also had few secondary generalized tonic-clonic seizures. In the hospital he developed a focal status epilepticus with brief focal seizures that were documented by video-EEG: clinically there was a head turn to the right followed by right arm elevation then tonic posturing of that arm. At times there were more subtle seizures with head and eyes deviation to the right and right more than left eyelid twitches (with or without right face involvement), lasting around 20 seconds. EEG showed left fronto-temporal ictal onset (seen at electrodes Fp1/F3/T7/T3) and a less frequent left fronto-central onset for few brief seizures. The focal status epilepticus was controlled within few hours, by oral carbamazepine, levetiracetam, and clonazepam. Once clinical seizures stopped, he was able to say few words, but language didn’t normalize despite improvement of the EEG background. Brain MRI was repeated with epilepsy protocol and was again strictly unremarkable (Fig. 1). CSF analysis revealed normal glucose, 6 white cells/μL, 0.04g/dL of proteins, IgG index of 0.48 and negative cultures. His thyroid and hepatitis panels were normal. Chest radiography, scrotal ultrasound and total body CT/ PET were within normal limits and ruled out underlying malignancy.

The EEG was repeated following the last clinical seizure to rule out non-convulsive seizures or status epilepticus since his speech didn’t improve. It showed again left fronto-temporal delta slowing, maximal at Fp1/F3/F7, at times evolving more rhythmically with superimposed sharply contoured delta waves suggesting ictal evolution or non-convulsive status epilepticus. An Ictal Positron Emission Tomography brain scan with 18F-fluorodeoxyglucose (FDG-PET) combined with that video-EEG segment was performed (Fig. 2).

Images were acquired 45 minutes after intravenous injection of F18-FDG revealing hypermetabolism in the left frontal, parietal and temporal regions and contralateral cerebellum. Antiepileptic drugs were adjusted. NMDA receptors antibodies in CSF came back elevated (titer of 1 of 64) with evidence of oligoclonal bands. He was diagnosed with anti-NMDAR encephalitis without underlying malignancy. As first line treatment of his encephalitis, he was given intravenous methylprednisolone followed by a 5-day course of intravenous immunoglobulins. His naming partially improved but not his verbal fluency despite resolution of the rhythmic delta pattern on subsequent follow up EEGs. This prompted an escalation of immunotherapy. He subsequently received 4 courses of weekly intravenous rituximab (375 mg/m²) followed by total clinical recovery. EEG combined to FDG-PET scan (Fig. 3) were repeated at 6 months and were normal. At 3 years follow up the patient remains neurologically intact and seizure-free, off all anti-epileptic drugs.

Fig. 1 – Axial brain MRI images showing no abnormalities on (A) FLAIR (Fluid attenuated inversion recovery) and (B) T2-weighted sequences with (C) corresponding left sided abnormalities on FDG-PET scan slice (white arrows).
Fig. 2 – Ictal findings: (A) FDG-PET scan showing left fronto-temporal, parietal (white arrows) and crossed cerebellar hypermetabolism (or diaschisis, yellow arrow). (B) EEG during FDG uptake showing continuous left fronto-temporal semi-rhythmic delta activity. Clinically patient was mute and only following simple commands (Color version of the figure is available online.)
Fig. 3 – Interictal findings once patient recovered showing resolved abnormalities on (A) FDG-PET and (B) EEG.
Discussion

We report a case of anti-NMDAR encephalitis with aphasic status epilepticus and clinical fluctuations where PET and/or CT combined to video-EEG were highly useful in guiding management. Our patient presented with psychiatric symptoms and seizures similar to approximately 70% of anti-NMDAR encephalitis [1] but the most interesting clinical feature was his speech disturbance. The latter was primarily considered as an ictal or post ictal manifestation because of the clinical presentation and the evolution of the rhythmic delta on EEG. It is known that functional imaging may help identify the epileptogenic region when EEG shows no clear ictal activity or in the setting of focal aware seizures such as in this case.

In particular, positron emission tomography (PET) imaging with $^{18}$F-fluorodeoxyglucose (FDG) has been useful in the presurgical evaluation of patients with epilepsy and is routinely done interictally to identify focal areas of hypometabolism. It is rarely acquired ictally but, if performed in this situation, can demontrate ictal hypermetabolism involving the epileptogenic zone. Ictal PET scans were reported in the settings of coincidental seizures happening at the time of injection of FDG or in case of prolonged seizures or even epilepsy partialis continua [3]. We also know that apha- sic status epilepticus can be particularly challenging to identify on the basis of clinical manifestations alone [4]. Our case had an unremarkable brain MRI, which urged more exhaustive search for a functional disorder underlying his speech difficulties.

The persistence of mutism for days after clinical seizures cessation along with EEG fluctuation patterns, pointed to possible subclinical intermittent ictal activity versus prolonged post ictal state versus encephalitic changes. The presence of semi-rhythmic delta activity as described above pointed more toward an ictal origin rather than structural since repeated brain imaging was strictly normal. That was the reason behind performing brain PET and/or CT coupled to EEG (Fig. 2) in order to better guide medical treatment. The left cortical and crossed contralateral cerebellar hypermetabolism is an aspect reported previously in ictal PET studies [3] and not typically seen in this type of encephalitis [1]. Actually, various PET patterns were described in anti-NMDAR encephalitis including: diffuse cortical or bilateral occipital hypometabolism or mild hypermetabolism of frontal regions or basal ganglia were described in anti-NMDAR encephalitis [1,5], or even a clear increased fronto-temporal to occipital gradient [6]. The pathophysiological basis of those metabolic aspects is still unknown but few studies have shown that it could be secondary to a potentially reversible disruption of synaptic NMDAR function by the specific antibodies [6,7]. One interesting case report by Probasco et al. [8] described an autoimmune encephalitis recurring after years in a 34 years old woman causing aphasia, seizures and rhythmic pattern on EEG such as in our case. The patient required anesthetic induced coma to control seizures and at some point, the authors raised the question whether the rhythmic delta on EEG was epileptic or not and decided to investigate by implanting depth electrodes to differentiate between limbic encephalitis and limbic status epilepticus. The authors concluded that “in the absence of clear ictal pattern, this increased metabolic activity was attributed to limbic encephalitis.” One limitation to that study was the fact that only the hippocampus and amygdala were covered intracranially thus cannot rule out an underlying epileptiform activity over the lateral temporal or fronto-temporal cortex. This is differentiated from our case where PET and/or CT was done simultaneously to ictal EEG.

We postulated that the PET findings in our patient reflect an ictal activity rather than an inflammatory alteration of the neuronal network but can possibly be a combination of both. The clinical fluctuation was suspicious of an ictal phenomenon and was confirmed by PET and/or CT when the continuous EEG was insufficient. Despite resolution of the ictal EEG pattern, the clinical symptoms, mostly the speech disturbances, didn’t completely improve until after full rituximab course. The radiological improvement concomitant to the electroclinical evolution confirmed the resolution of all abnormalities and highlighted the utility of FDG-PET imaging combined to video-EEG to identify non-convulsive status epilepticus. It should be performed early in anti-NMDAR encephalitis to guide treatment.

Future studies using functional imaging are needed to better understand the underlying pathophysiological and immunologic mechanisms of this entity.

Author contributions

Concept and design: Dr Karine Abou Khaled; Drafting of the manuscript: Drs Abou Khaled and Azar; Critical revision of the manuscript for important intellectual content: Dr Karine Abou Khaled; Data analysis and technical support: Drs Abou Khaled and Haidar.

Patient consent

Written informed consent was obtained from the patient to publish his case.

REFERENCES

[1] Dalmau J, Arangüé T, Planagumá J, Radosvec M, Mannara F, Leypoldt F, et al. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models. Lancet Neurol 2019;18(11):1045–57. doi:10.1016/S1474-4422(19)30244-3.
[2] Graus F, Titulaer MJ, Balu R, Benseler S, Bijen CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016;15(4):391–404. doi:10.1016/S1474-4422(15)00401-9.
[3] Chugani HT, Rintahaka PJ, Shewmon DA. Ictal patterns of cerebral glucose utilization in children with epilepsy. Epilepsia 1994;35(4):813–22. doi:10.1111/j.1528-1157.1994.tb01517.x.
[4] Dong C, Siriram S, Delbeke D, Al-Kaylani M, Arain A, Singh P, et al. Aphasic or amnestic status epilepticus detected on PET but not EEG: PET for aphasis status epilepticus. Epilepsia 2009;50(2):251–5. doi:10.1111/j.1528-1157.2008.01782.x.
[5] Probasco JC, Solnes L, Nalluri A, Cohen J, Jones KM, Zan E, et al. Decreased occipital lobe metabolism by FDG-PET/CT: an anti–NMDA receptor encephalitis biomarker. Neurol Neuroimmunol Neuroinflammation 2018;5(1):e413. doi:10.1212/NXI.0000000000000413.

[6] Leypoldt F, Buchert R, Kleiter I, Marienhagen J, Gelderblom M, Magnus T, et al. Fluorodeoxyglucose positron emission tomography in anti-N-methyl-D-aspartate receptor encephalitis: distinct pattern of disease. J Neurol Neurosurg Psychiatry 2012;83(7):681–6. doi:10.1136/jnnp-2011-301969.

[7] Hughes EG, Peng X, Gleichman AJ, Lai M, Zhou L, Tsou R, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. J Neurosci Off J Soc Neurosci 2010;30(17):5866–75. doi:10.1523/JNEUROSCI.0167-10.2010.

[8] Probasco JC, Benavides DR, Ciarallo A, Wills Sanin B, Wabulya A, Bergey GK, et al. Electroencephalographic and fluorodeoxyglucose-positron emission tomography correlates in anti-N-methyl-d-aspartate receptor autoimmune encephalitis. Epilepsy Behav Case Rep 2014;2:174–8. doi:10.1016/j.ebcr.2014.09.005.