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PET follow-up in a case of anti-NMDAR encephalitis: arguments for cingulate limbic encephalitis

Jean-Baptiste Chanson [1], Mihaela Diaconu [1], Jérôme Honnorat [2,3], Thierry Martin [4,5], Jérôme De Seze [1], Izzie-Jacques Namer [6], Edouard Hirsch [1]

[1] Département de Neurologie, CHRU de Strasbourg, France
[2] Hospices Civils de Lyon, Hôpital Neurologique, Centre de Référence Maladies Rares "Syndromes Neurologiques Paranéoplasiques", Lyon, France
[3] Lyon Neuroscience Research Center INSERM U 1028 / CNRS UMR 5292, Université de Lyon-Université Claude Bernard Lyon 1, Faculté Laennec, Lyon, France
[4] Service de Médecine Interne et d'Immunologie Clinique, CHRU de Strasbourg
[5] UPR CNRS 9021, Strasbourg, France
[6] Service de Biophysique et Médecine Nucléaire, CHRU de Strasbourg, France

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ABSTRACT – *Background*. The lack of specific MRI abnormalities in anti-NMDA receptor encephalitis makes the identification of the most affected areas difficult. Functional neuroimaging could be useful to identify brain dysfunction associated with psychiatric symptoms, but few precise data are available up to now. *Case study*. A 27-year-old woman was referred for recent behavioural changes and jerks of the right foot. Serial left fronto-temporal seizures were recorded. Identification of anti-NMDA receptor antibodies in CSF indicated a diagnosis of anti-NMDA receptor encephalitis. Two foci of hypermetabolism, in the left prefrontal cortex and the anterior cingulate cortex, were identified using 18-fluorodeoxyglucose PET and both disappeared after treatment. Brain MRI was normal, except for a mild left prefrontal hypersignal. *Conclusions*. The increase in marker uptake in motor and premotor regions in our case probably corresponds to epileptic activity. Our data suggest that the anterior cingulate cortex could play an important role in psychiatric symptoms. Other studies are needed to better understand the pathophysiology of anti-NMDA receptor encephalitis.

Key words: paraneoplastic syndrome, limbic system, PET

Correspondence:
Jean-Baptiste Chanson
Département de Neurologie,
Hôpital de Hautepierre,
1, avenue Molière,
67091 Strasbourg, France
<jean-baptiste.chanson@chru-strasbourg.fr>

Classic autoimmune limbic encephalitis is associated with predominant hippocampal and mesial temporal lobe dysfunction and results in memory loss, personality changes and/or seizures (Gultekin *et al*., 2000). Abnormalities in neuroimaging are frequently found in the same areas and consist of T2 hypersignals on MRI and an increase in marker uptake during 2-deoxy-2-[F-18] fluoro-D-glucose positron

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emission tomography (FDG-PET), suggesting the presence of hypermetabolism (Gultekin *et al*., 2000; Ances *et al*., 2005). The disease is related to antibodies directed against neuronal intra-cytoplasmic antigens (such as: Hu, Ma2, and CV2/CRMP5) and is almost always associated with cancer (lung, testis, and others) (Gultekin *et al*., 2000).

More recently, new antibodies were identified in paraneoplastic encephalitis. These antibodies were directed against cell surface antigens, especially the leucine-rich, glioma inactivated 1 protein (LGI1) and N-methyl-D-aspartate (NMDA) receptor (Lai *et al*., 2010; Dalmau *et al*., 2011). They arise with or without cancer (thymoma or teratoma). Most patients with anti-NMDA receptor encephalitis present psychiatric disorders or seizures, while memory loss is less frequently met (Dalmau *et al*., 2011). Patients may also present with a decreased level of consciousness, dyskinesia, or autonomic and breathing instability. MRI abnormalities are less common and are not restricted to mesial temporal areas. Pathological lesions are mild (microglial activation) and often widespread in the brain (Dalmau *et al*., 2011; Dalmau *et al*., 2007). These elements suggest a different pattern of lesions in anti-NMDA receptor encephalitis compared to classic limbic encephalitis. New approaches are needed to identify the key regions involved in the genesis of symptoms for this encephalitis.

Here, we report the results of longitudinal FDG-PET in a patient with anti-NMDA receptor encephalitis which showed hypermetabolism in the anterior cingulate cortex, disappearing after recovery of the psychiatric symptoms.

Case study

Our patient was a 27-year-old woman. She had a history of relapsing psychotic disorders associated with right fronto-temporal seizures which began at the age of 17. An autoimmune origin was suspected due to the presence of anti-phospholipid antibodies in serum (only in the first relapses), intrathecal synthesis of immunoglobulin in CSF, and a dramatic improvement of symptoms after corticosteroid treatment. However, brain MRI and other blood analyses (including classic onco-neuronal antibodies) remained normal and thus the exact diagnosis was not identified.

She was referred for recent behavioural and mood changes associated with jerks of the right foot. The rest of the clinical examination was normal. The electroencephalogram showed left anterior epileptic discharges concomitant with right foot abnormal movements. Anti-phospholipid antibodies, CSF cell count, and protein levels were normal, but anti-NMDA receptor antibodies were identified in CSF, indicating a diagnosis of anti-NMDA receptor encephalitis. Pelvic CT and MRI, as well as ultrasound intravaginal investigation, did not indicate any ovarian teratoma. Intravenous immunoglobulins for five days and oral corticoids were administered, with good recovery of symptoms and EEG abnormalities.

A first FDG-PET scan (*figure 1A*) was performed two days following acute onset and showed two areas of hypermetabolism in the left prefrontal cortex and anterior cingulate cortex, contrasting with relative diffuse hypometabolism. These abnormalities disappeared on a second PET scan (*figure 1B*) which was performed after treatment (one month after the onset of symptoms) and clinical recovery (two weeks later). MRI was normal except for a very mild hypersignal in the left prefrontal cortex, corresponding to one of the hypermetabolism areas noted during PET.

Discussion

Our patient presented with the well described phenotype of anti-NMDA receptor encephalitis consisting of psychiatric symptoms, movement disorders, and seizures. The diagnosis was confirmed by the presence of anti-NMDA receptor antibodies in CSF (Dalmau *et al*., 2011). Of main interest in this article are the results of functional neuroimaging at the acute phase and after recovery from symptoms. These results suggest an association between psychiatric symptoms and abnormal metabolism of the anterior cingulate cortex.

Due to the poor sensitivity of MRI, PET may be of particular interest in anti-NMDA receptor encephalitis. However, few data are available in the medical literature. PET was often only performed at the acute phase and the distinction between recent lesions related to current symptoms and chronic abnormalities is therefore difficult. Diffuse abnormalities were frequently reported and generally associated with relative anterior hypermetabolism and posterior hypometabolism. Mohr and Minoshima (2010) described diffuse hypermetabolism of the fronto-temporo-parietal areas compared to the occipital lobes and cerebellum in a 23-year-old woman with bizarre behaviour and orofacial dyskinesia. Bilateral posterior hypometabolism was also found in a 29-year-old woman who presented with an acute onset of delirium (Naeije *et al*., 2010). Pillai *et al*. (2010) observed a diffuse reduction in cerebral metabolism in two young girls (aged three and seven). This diffuse reduction contrasted with more limited hypermetabolism in the basal ganglia and left frontal lobe in the first case and the basal ganglia and right parietal lobe in the second case. Iizuka *et al*. (2008) observed hypermetabolism restricted to bilateral motor and premotor

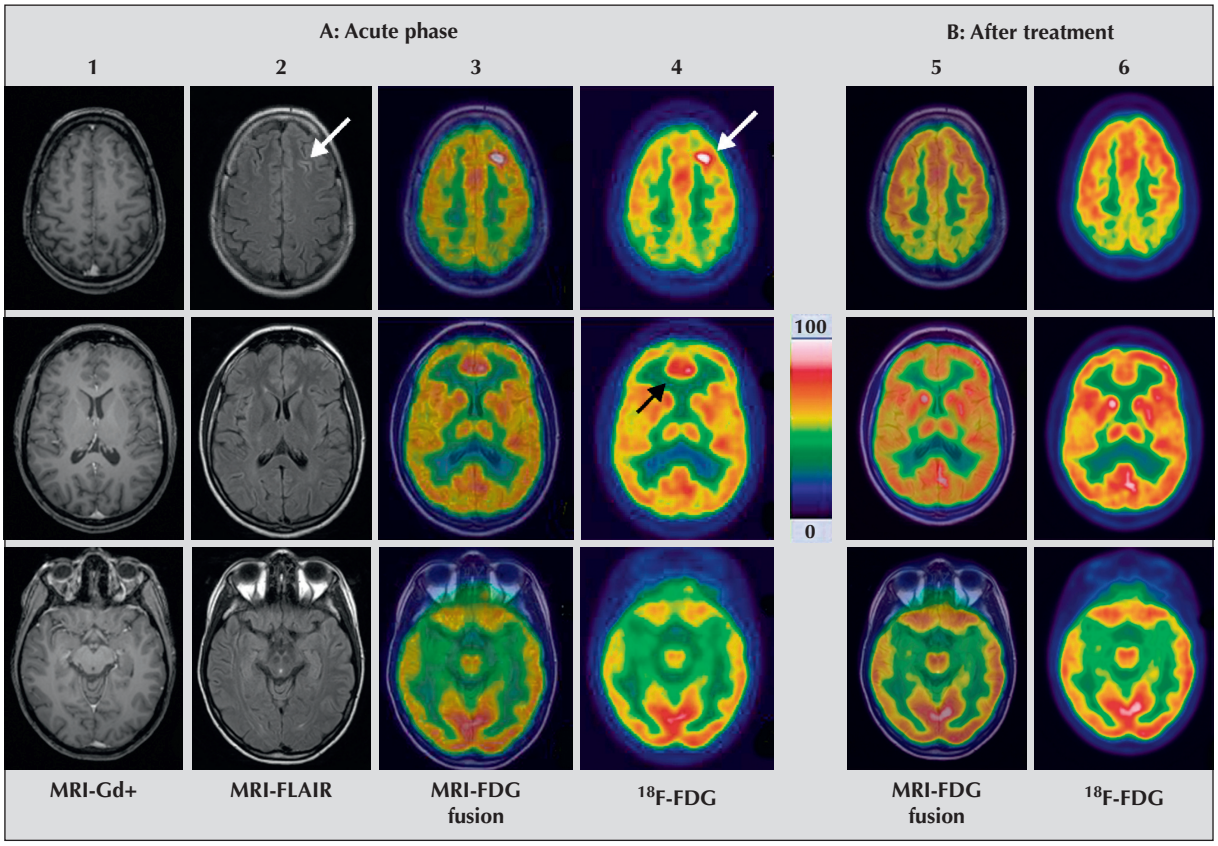

Figure 1. MRI and longitudinal FDG-PET.
(**A**) (1-4) MRI and initial PET performed in the acute phase before treatment. (1) MRI-Gd+: axial MRI slices with gadolinium-enhanced T1-weighted sequences; no gadolinium-enhanced lesion was noted. (2) MRI-FLAIR: MRI fluid-attenuated inversion recovery (FLAIR)-weighted sequences; presence of a mild left prefrontal hypersignal (TR: 10000; TE: 125; TI: 2750). (3) MRI-FDG fusion: fusion images between MRI and FDG-PET. (4) ^{18}F FDG: axial ^{18}F-FDG-PET images showing two areas of hypermetabolism corresponding to left prefrontal cortex (white arrow) and the anterior cingulate cortex (black arrow) contrasting with marked diffuse hypometabolism.
(**B**) (5-6) Subsequent PET performed after treatment. (5) MRI-FDG fusion: fusion images between MRI (the same as in [1]) and the second PET scan. (6) ^{18}F FDG: axial ^{18}F-FDG-PET images show a decrease of previous abnormalities.

areas in a 33-year-old woman presenting with orofacial dyskinesia. Findings from follow-up FDG-PET during convalescence were normal. In these different cases, the hypermetabolism in areas involved in movement control might be explained by movement disorders and epileptic activity. These reports did not identify any neuroimaging abnormalities correlating with psychiatric disorders such as personality changes, apathy and bizarre behaviour.

In our case, we found two foci of increased marker fixation. Left prefrontal hypermetabolism was probably related to abnormal movements of the right foot and the left anterior epileptic discharges, as in the previous reports. No right foot jerks were noted during PET examination, but imaging was performed during days of intense epileptic activity. Interestingly, in our case, the epileptic abnormalities were located on the right side, at the beginning of disease. They were not associated with isolated foot jerks, as in the present relapse. These data suggest that localisation of epileptic activity may change through the course of the disease; however, this has not yet been thoroughly explored and deserves further investigation.

The main hypermetabolism was noted in the anterior cingulate cortex. The disappearance of this hypermetabolism after clinical recovery suggests that it was directly linked to symptoms, especially those associated with psychiatric disorders. The anterior cingulate cortex is a part of the limbic system and is involved in emotion formation and processing. Our data are consistent with a role of this structure in the genesis of psychiatric symptoms in anti-NMDA receptor encephalitis. Obviously, this role cannot be established through a single case. Similar hypermetabolism isolated in the anterior cingulate cortex was not found in the other case reports, but was

possibly present as diffuse anterior hypermetabolism (Mohr and Minoshima, 2010). Larger series of PET for this disease would be interesting.

Another argument for this role of the anterior cingulate cortex is provided by the effect of anti-NMDA receptor antibodies and ketamine. *In vitro* studies demonstrated that these antibodies cause a reversible decrease of synaptic NMDA receptor expression (Hughes *et al*., 2010; Moscato *et al*., 2010). Since they predominantly act on the post-synaptic receptors of the inhibitory GABAergic pathways, this results in a decreased activity of these pathways and subsequently an increased activity of cortical neurons (Moscato *et al*., 2010). Such an increase in cortical activity was observed in rats after exposure to anti-NMDA receptor antibodies (Manto *et al*., 2010). Other experiments also demonstrated a decrease of inhibitory GABAergic pathways (Manto *et al*., 2011). This action is mimicked by the administration of low doses of ketamine, a pharmacological agent blocking the NMDA receptor complex. PET performed in humans under ketamine showed increased metabolic activity in the anterior regions of the brain and particularly in the fronto-medial and anterior cingulate cortex. This hypermetabolism was associated with symptoms of psychosis in the subjects (Vollenweider *et al*., 1997). A different effect of antibodies, such as inhibition of other activating pathways, could account for the diffuse hypometabolism. However, there is no data in the medical literature supporting this hypothesis. The diffuse hypometabolism might be only relative to the increased metabolism of the two anterior areas. It could also result from the disturbances of brain functioning due to the increased anterior metabolism.

In conclusion, the mechanism responsible for psychiatric disorders in anti-NMDA receptor encephalitis remains unknown, however, our data, along with other clinical reports and pharmacological studies, suggest a specific role of the anterior cingulate cortex. Other studies are needed to correlate more precisely the symptoms with brain dysfunction. □

Disclosures.

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