LETTER

FDG-PET hyperactivity in basal ganglia correlating with clinical course in anti—NDMA-R antibodies encephalitis

A form of encephalitis associated with anti—*N*-methyl-D-aspartate receptor (anti—NMDA-R) antibodies has recently been described.[1] Reported patients are mainly young women, presenting with severe encephalitis and additional distinctive neurological features. Around 60% have an ovarian teratoma.[1] The severe course of the disease does not rule out favourable prognosis. Immunotherapy is advocated[1–3] and appears to be associated with improved outcome.

We present a patient with anti—NMDA-R encephalitis and serial [18F]-fluorodeoxyglucose—positron emission tomography (FDG-PET) examinations showing markedly increased activity in the basal ganglia as compared with that in the cortex when extrapyramidal features were prominent, which normalised after improvement of this movement disorder.

CASE REPORT

A 25-year old woman developed language difficulties, followed by repeated complex-partial seizures with rare secondary generalisations. On admission 3 weeks later (day 0), the patient had developed fluctuating obtundation, mutism and episodic laughter with dysautonomia (bilateral mydriasis, tachycardia and facial flush), catatonia and progressive limb rigidity with plantar flexor response. The findings of an extended etiological workup (blood cell counts; routine serum chemical analysis and cerebrospinal fluid analysis of infectious, inflammatory, metabolic and paraneoplastic parameters) and a body computed tomographic scan were negative. Five repeated brain magnetic resonance imaging performed over 5 months only showed a mild, diffuse atrophy. From day 10, she received high-dose prednisolone intravenously followed by an oral taper, followed by serial plasma exchanges without improvement. Repeated electroencephalographic (EEG) recordings showed abnormal diffuse slowing over the left temporal region or bifrontally, superimposed on intermittent slow recruiting activity occurring in parallel with paroxysmal mumbling, laughter, tachycardia and facial flush. Non-convulsive status epilepticus was diagnosed but was refractory to 10 antiepileptic medications administered in various combinations. Four sequential EEG burst suppression treatments were attempted over 6 weeks without any improvement. In November 2008 (day 63), the results of positive serum antibodies to NMDA receptors (sampled on admission) were received; these remained positive until day 93 (table 1). No underlying malignancy was found, although examinations were repeated. With the patient still in status epilepticus, 1 g intravenous methylprednisolone combined with plasma exchange was restarted on day 75, but both had to be interrupted within 24 h because of a septic choc. Hereafter, within 2 weeks, she slowly awoke; her EEG improved, allowing her sedation to be weaned off followed by continuous clinical improvement. In March 2009 (day 180), she returned home with a combination of four antiepileptic drugs with only mild mental slowing and memory problems. At the last visit in 5 October 2009 (day 385), she had restarted part-time work.

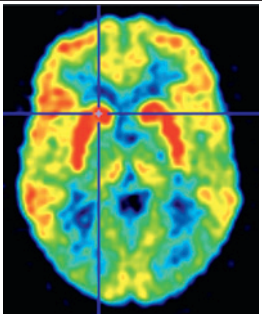
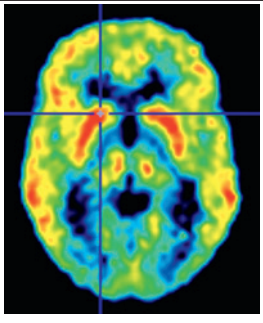
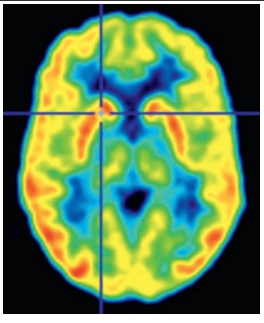
Three brain FDG-PET images were obtained during the course of her illness (days 72, 94 and 154). These showed, initially, during the subacute phase, a striking bilateral increase of the basal ganglia metabolism with a relative diffuse cortical hypoactivity. Over the next 82 days, during the recovery phase, this pattern normalised with a similar metabolic activity in the basal ganglia and cortex (table 1).

Interestingly, the patient had a febrile illness with focal seizures and transitory language problems 10 years earlier. An acute viral encephalitis was suspected, and she improved spontaneously without any treatment other than transitory carbamazepine administration, withdrawn after 12 months.

DISCUSSION

Anti—NMDA-R encephalitis was first described in 2007 with an increasing number of cases now being reported. It is most commonly seen in young women with akinetic mutism, refractory seizures, abnormal movements and autonomic signs.[1–3] Clinical workup may disclose an underlying neoplasm, usually an ovarian tumour, in approximately 60% of patients,[1–3] but our patient did not have any neoplasia nor did she develop choreoathetoid movements or hypoventilation. Her previous encephalopathic episode could be consistent with recurrent anti—NMDA-R encephalitis,

Table 1 Evolution of imaging, serum anti-NMDA antibodies, clinical examination, EEG and drug treatment

Date	12 November 2008 (day 72)	4 December 2008 (day 94)	2 February 2009 (day 154)
FDG-PET			
FDG-PET description	Increased activity in the striatum as compared with that in the cortex and hypometabolism of the visual cortex	Increased activity in the striatum but less pronounced and persisting hypometabolism of the visual cortex	Near-normal cerebral metabolism, except a slight increase in striatum metabolism
Serum anti-NMDA antibodies	(+) on 4 September 2008 (day 3) (+) on 7 November 2008 (day 71)	(+) on 3 December 2008 (day 93)	NA
Clinical examination	Coma, mechanical ventilation (tracheostomy) Bilateral mydriasis and bilateral rigidity	Marked mental slowing and disorientation Marked nystagmus, bilateral mydriasis and rigidity	Moderate mental slowing Moderate nystagmus and bilateral mydriasis Brisk tendon reflexes
EEG	Left temporal and bifrontal and intermittent, short (seconds) delta activity (FIRDA) Superimposed beta No status epilepticus	Intermittent, irregular frontal slowing Superimposed beta	Theta—alpha activity during wakefulness; sleep with spindles and K complexes Superimposed beta
Treatment	PHT, PB, MDZ, TPM and verapamil	PHT, PB, MDZ, PGB and verapamil	PHT, PB, PGB, LTG and clobazam

LTG, lamotrigine; MDZ, midazolam; NA, not assessed; PB, phenobarbital; PGB, pregabaline; PHT, phenytoin; TPM, topiramate.

and her favourable response to limited immunotherapy contrasts with some reports underlying the importance for tumour removal.[1–3] Her favourable evolution appears in line with descriptions of non-paraneoplastic anti–NMDA-encephalitis.[1]

We found an interesting correlate of functional brain imaging, which paralleled her clinical course. To the best of our knowledge, this represents the first sequential description of brain FDG-PET in this context and suggests that her marked limb rigidity might have been mediated by basal ganglia hypermetabolism. Her medication, especially the antiepileptic drugs, with gabaergic action, could alter cortical metabolism but should not increase basal ganglia hypermetabolism. A picture similar to our patient was recently reported in Morvan syndrome,[4] a rare condition due to antibodies to voltage-gated potassium channels characterised by peripheral, central and autonomic nervous system involvement. The only two reports describing FDG-PET in anti–NMDA-R encephalitis showed hypermetabolism in cortical areas, brainstem and cerebellum[3] and a reduced cortical metabolism after clinical improvement[2]; none had basal ganglia abnormalities. Recently, reduction of *N*-acetyl-asparatate in the basal ganglia of a patient in the acute phase of an anti–NMDA-R encephalitis was described,[5] suggesting that modification of basal ganglia circuits may be induced by the autoantibody and lead to extrapyramidal symptoms. In this context, it is possible that the hypermetabolism of the basal ganglia in our patient reflects this aspect; unfortunately, we did not perform magnetic resonance imaging spectroscopy. In our patient, the marked symmetrical basal ganglia hyperactivity with a relative diffuse cortical hypoactivity in the FDG-PET and its progressive normalisation were not correlated with clinical and EEG signs of status epilepticus during the fluoride injections, where the cortex should appear hypermetabolic. We thus suggest that our findings represent the correlation of the extrapyramidal dysfunction and the concomitant cortical hypofunctional state during the active illness.

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CORRECTION

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Refractory central supratentorial hiccup partially relieved with vagus nerve stimulation (*J Neurol Neurosurg Psychiatry* 2010;**81**:821–822). In this paper, the author names were published incorrectly with the first name transposed with the surname. They are correctly listed as follows Pierluigi Longatti, Luca Basaldella, Mario Moro, Pietro Ciccarino, Angelo Franzini.