Brain & Development 38 (2016) 461–470

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Cerebral ^{18}FluoroDeoxy-Glucose Positron Emission Tomography in paediatric anti N-methyl-D-aspartate receptor encephalitis: A case series

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Received 15 July 2015; received in revised form 15 September 2015; accepted 20 October 2015

Abstract

Background: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a frequent and severe cause of encephalitis in children with potential efficient treatment (immunotherapy). Suggestive clinical features are behavioural troubles, seizures and movement disorders. Prompt diagnosis and treatment initiation are needed to guarantee favourable outcome. Nevertheless, diagnosis may be challenging because of the classical ancillary test (magnetic resonance imaging (MRI), electroencephalogram, standard cerebro-spinal fluid analysis) have limited sensitivity. Currently, immunological analyses are needed for the diagnostic confirmation. In adult patients, some studies suggested a potential role of cerebral ^{18}FluoroDeoxy-Glucose Positron Emission Tomography (FDG-PET) in the evaluation of anti-NMDAR encephalitis. Nevertheless, almost no data exist in paediatric population.

Method: We report retrospectively clinical, ancillary tests and cerebral FDG-PET data in 6 young patients (median age = 10.5 - years, 4 girls) with immunologically confirmed anti-NMDAR encephalitis.

Results: Our patients presented classical clinical features of anti-NMDAR encephalitis with severe course (notably four patients had normal MRI). Our series shows the feasibility and the good sensitivity of cerebral FDG-PET (6/6 patients with brain metabolism alteration) in paediatric population. We report some particular features in this population: extensive, symmetric cortical hypometabolism especially in posterior areas; asymmetric anterior focus of hypermetabolism; and basal ganglia hypermetabolism. We found also a good correlation between the clinical severity and the cerebral metabolism changes. Moreover, serial cerebral FDG-PET showed parallel brain metabolism and clinical improvement.

Conclusion: Our study reveals the existence of specific patterns of brain metabolism alteration in anti-NMDAR encephalitis in paediatric population.

Keywords: Encephalitis; N-methyl-D-aspartate; Anti-NMDAR; Cerebral FDG-PET; Brain FDG-PET; FluoroDeoxy-Glucose Positron Emission Tomography; Children; Autoimmune; Rituximab

1. Introduction

N-methyl-D-aspartate receptors (NMDAR) are cation channels of crucial importance in cortical

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http://dx.doi.org/10.1016/j.braindev.2015.10.013
0387-7604/

development, because of their role in synaptic plasticity supporting learning and memory functions [1]. Recently, anti-NMDAR antibodies targeting NR1 subunits have been described as responsible for encephalitis [2]. There are evidences for direct pathogenic role of anti-NMDAR antibodies through NMDAR internalization and synaptic plasticity alteration [1,3,4].

Anti-NMDAR encephalitis was initially described in young women with ovarian teratoma [5], yet non-paraneoplastic forms are not rare. Anti-NMDAR encephalitis concerns all ages, especially young adults, adolescents, and children [6]. Anti-NMDAR encephalitis is relatively frequent, and some studies consider them as the second cause of encephalitis in young individuals besides acute disseminated encephalomyelitis [7,8]. Recent literature provided a better description of anti-NMDAR encephalitis in children and adolescents [9,10] with suggestive clinical features including acute behavioural changes, seizure, movement disorders, and more or less other neurological deficits [2]. Anti-NMDAR encephalitis is a severe disease and the clinical course may be life threatening or leading to severe functional deficit. Efficient immunotherapies exist, but prompt diagnosis and treatment start is crucial to guarantee favourable outcome. Nevertheless, the diagnosis may be challenging because of the limited sensitivity of magnetic resonance imaging (MRI) [11], standard cerebro-spinal fluid (CSF) analysis [12], and the possible lack of specificity of electroencephalogram (EEG) [13]. Some studies suggest potential role of cerebral ^{18}Fluoro-Deoxy-Glucose Positron Emission Tomography (FDG-PET) for evaluation of autoimmune encephalitis [14], but little is known about cerebral metabolism in paediatric anti-NMDAR encephalitis.

Hereafter, we reported cerebral FDG-PET data in a case series of six children with immunologically confirmed anti-NMDAR encephalitis.

2. Methods

We reported retrospectively 6 cases of anti-NMDAR encephalitis identified from May 2009 to June 2014, in all patients referred to the department of Paediatric Neurology Department, Timone Hospital, AP-HM, Marseille, France. According to the French law, this study did not require ethics committee approval because of its design: non-interventional and retrospective. We collected parental informed consents for all patients. Each patient was clinically evaluated and followed-up by specialized practitioners. We performed extensive blood tests and CSF analyses to rule out infectious, systemic, and neurologic inflammatory diseases (including thyroiditis, lupus, sarcoïdosis; for details see Supplemental material). We researched specific oligoclonal banding in CSF. The search for anti-NMDAR antibodies was done in serum (1/80) and CSF (according to the concentration of IgG) with labelled human anti-IgG (H + L) by indirect immunostaining respectively on cerebellum and hippocampal rat acetone-fixed slices and transfected HEK cells expressing NR1 NMDAR subunit. Each patient underwent at least one EEG and one cerebral MRI (sequences: T1, T2, FLAIR, T2 EG, diffusion, T1 after gadolinium). We researched associated neoplasm with: chest radiography; abdomen, pelvis and testicular echography; and whole-body FDG-PET. Patient's treatment included: corticosteroids, intravenous immunoglobulin, plasma exchange, rituximab, and intra-thecal methotrexate injections.

We performed cerebral FDG-PET without sedation. One expert practitioner reviewed retrospectively cerebral FDG-PET data, without clinical context. Brain metabolism was visually evaluated, and expressed in term of relative hypermetabolism or hypometabolism. Even if normal metabolic values have been recently reported [15], no quantification was provided, in absence of inclusions of healthy children for dosimetric reasons, and also considering the lack of reproducibility of SUV indexes between distinct cameras [16]. We performed a quantification of the metabolic changes in patients who had serial FDG-PET exams. We used metabolic uptake ratio, taking as reference the global cortical uptake as recently described in paediatric population [17]. In this line, spatial normalization was performed using SPM8 on MNI space, and segmentation in 116 anatomical regions was obtained [18]. Percentage of metabolic changes between two exams calculated as follow for each region: (uptake ratio of 2nd [or 3rd] PET scan – uptake ratio of 1st [or 2nd] PET scan)/(uptake ratio of 1st [or 2nd] PET scan).

3. Results

3.1. Clinical features

The median age at diagnosis was 10.5 years (range between 3 and 17 years); and gender ratio was 4 girls for 2 boys. One patient had past medical history of heterozygous sickle cell disease; another had cured lymphoblastic B leukaemia.

The initial symptom was behavioural troubles in 3 patients (case 2, 3, 6), seizures in 2 patients (case 1, 4) and movement disorder in one (case 5). During evolution, all patients presented association of seizures, movement disorders, language difficulties, and behavioural changes. We noticed severe movement disorders especially oro-facial dyskinesia (including one case with laryngeal spasm and cyanosis: patient 1) and dystonia leading to a *status dystonicus* (patient 5, 6). The other symptoms were: parkinsonism, loss of consciousness, swallowing difficulties, hemiparesis and central hypoventilation with apnea. The clinical status were severe with median modified Rankin Score (mRS) of 4 at initial

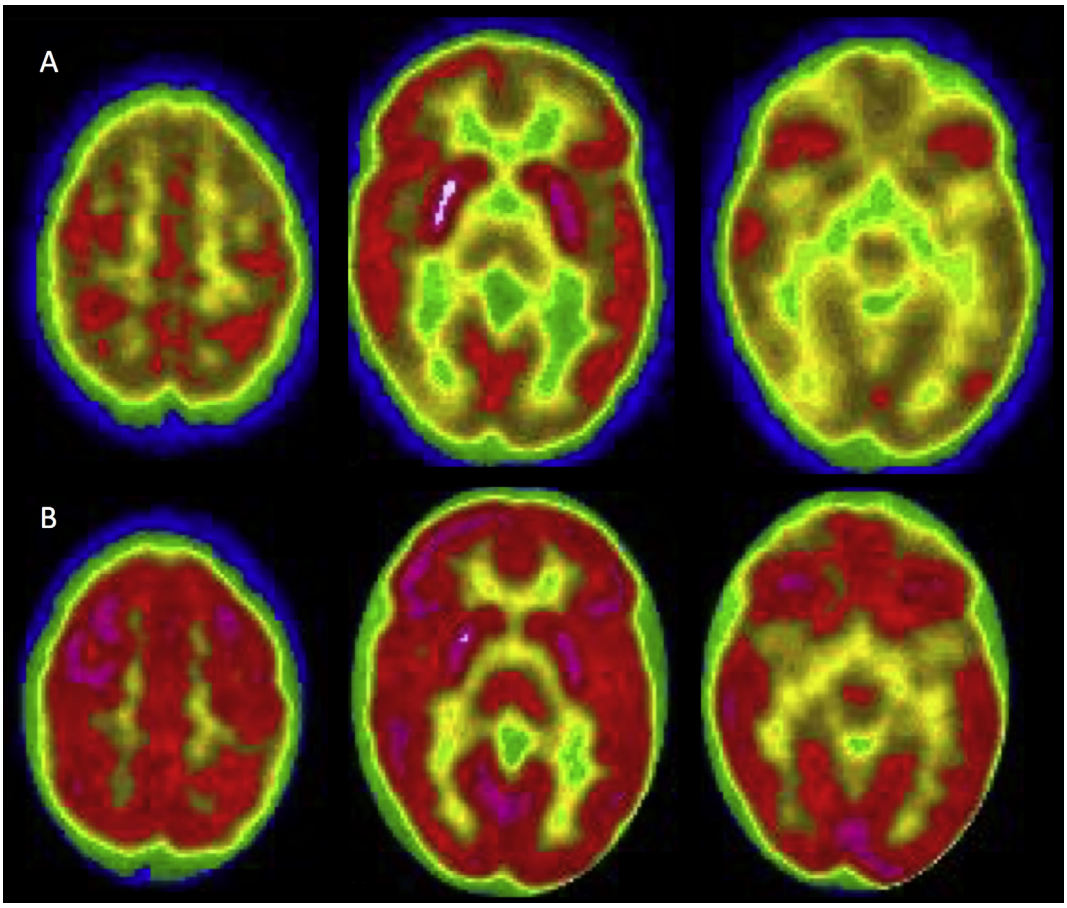

Fig. 1. Cerebral FDG-PET features of patient 1. (A) at initial cerebral FDG-PET time point, patient 1 presented severe clinical status (mRS = 4) with extra-pyramidal syndrome, mutism, and swallowing difficulties. Initial cerebral FDG-PET showed extensive, severe cortical hypometabolism with basal ganglia hypermetabolism. (B) Second cerebral FDG-PET, after treatment showed normalization of cerebral metabolism correlated with good clinical recuperation (mRS = 1).

FDG PET time point and four patients needing intensive care unit management (consciousness alteration in 2 cases, *status dystonicus* with rhadomyolysis and renal failure in 2 cases) (for details see Table 1).

3.2. Ancillary tests

The blood tests were normal in all patients except for patient 4, who had a history of heterozygous sickle cell disease and then presented mild anaemia. Four patients had normal cerebral MRIs. One patient had unilateral hippocampus FLAIR/T2 hyper signal, and another had cerebellum white-matter T2/FLAIR hyper-signal without gadolinium enhancement (see Supplemental Fig. 1). We performed serial MRI in three out of the six patients showing persistent normality in two and stability of the cerebellum hypersignal in another (see Supplemental Fig. 1).

EEG showed in all cases diffuse background slowing associated with more and less diffuse paroxysm (especially slow waves), which predominates in temporal and frontal areas (see Supplemental Fig. 2). Two patients presented the suggestive EEG pattern reported by Kaminska et al. [19] as belonging to the "high severity group": lack of physiological figures of background activity during waking and sleep states, theta and alpha rhythms in non-rapid eye movement sleep (NREM) sleep that predominate in fronto-central areas, and extreme delta-brush pattern (see Supplemental Fig. 2). These patients required management in intensive care unit (for detail see Table 1).

CSF analysis showed normal protein, glucose, and lactate levels in all patients. Pleiocytosis with predominance of lymphocytes was found in 4 cases, and oligoclonal bandings in all cases (IgG for all; IgM and A in 2 cases). All patients showed anti-NMDAR antibody positivity at low titre in serum and with relatively higher titre in CSF, suggesting an intra-thecal synthesis of anti-NMDAR antibodies (for detail see Table 1).

3.3. Initial cerebral FDG-PET

The initial cerebral FDG-PET were performed after a median delay of 3.2 weeks (range: 3 days–5 weeks) after

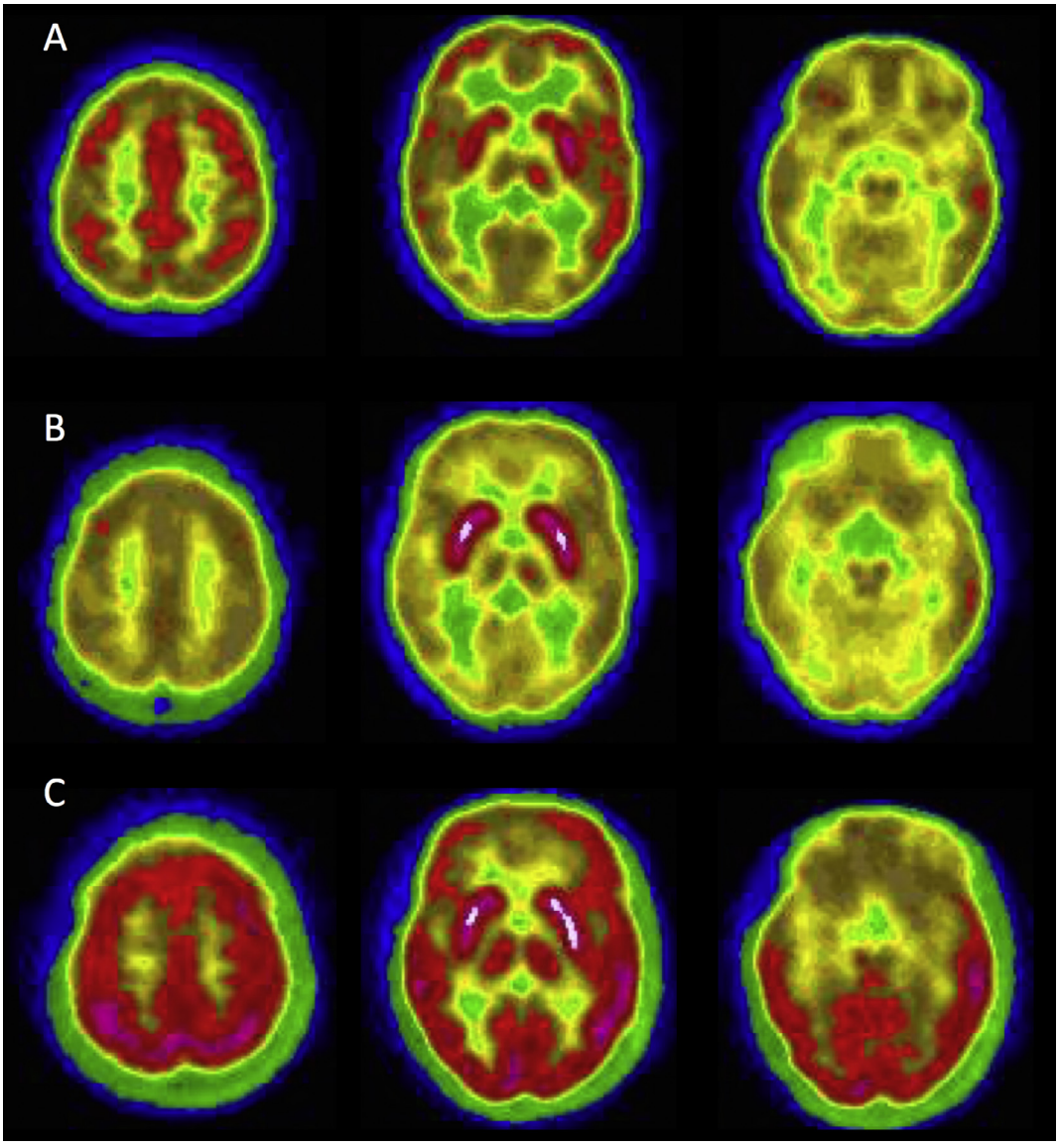

Fig. 2. Cerebral FDG-PET features of patient 6. (A) At initial cerebral FDG-PET time point, patient 6 presented severe clinical status (mRS = 4) with movement disorder (dystonicus status), swallowing troubles and drowsiness. Initial cerebral FDG-PET, showed extensive cortical hypometabolism. (B) Second cerebral FDG-PET, after clinical worsening despite immunotherapy (mRS = 5), showed deterioration of brain metabolism with severe extensive cortical hypometabolism and basal ganglia hypermetabolism. (C) Third cerebral FDG-PET, after intra-thecal methotrexate injection and clinical mild improvement (mRS = 4), showed partial improvement of cortical metabolism but persistent basal ganglia hypermetabolism.

initial symptoms, after a median delay of 1 week after initial MRI (range: 1 day–2 weeks), and before start of immunotherapy. The cerebral FDG-PET were performed during an acute phase of the disease because all patients experienced clinical worsening after the initial FDG-PET.

We observed relative alteration of cerebral metabolism in all six patients (all PET data are summarized in Table 2, Figs 1 and 2 and Supplemental Figs. 3–6). We noticed cortical extensive and symmetric relative hypometabolism predominant in posterior areas in all six patients, with:

- Occipital hypometabolism (6/6 patients)
- Frontal hypometabolism (5/6 patients)
- Temporal hypometabolism (4/6 patients)
- Parietal hypometabolism (3/6 patients)

We noticed coexistence of relative hypometabolism and hypermetabolism in four patients, with:

- Basal ganglia relative hypermetabolism (4/6 patients)
- Asymmetric, anterior cortical relative hypermetabolism (2/6 patients: one with temporal and another with frontal relative hypermetabolism).

Table 1
Individual patient data concerning clinical features, ancillary tests, treatment, and outcome (✓ = Yes; ✗ = No or normal).

Case	1	2	3	4	5	6
Age/Gender	10/F	17/F	14/F	3/M	11/F	5/M
First symptoms	Generalized seizure	Behaviour troubles Hallucination	Behaviour troubles	Focal seizure	Movement disorder	Behaviour troubles
Delay before hospitalization	2 weeks	2 weeks	1 month	1 day	1 day	2 weeks
Delay before PET-FDG	5 weeks	2 weeks	4 weeks	5 weeks	3 days	3 weeks
Delay before treatment	6 weeks	3 weeks	6 weeks	5 weeks	3 days	3 weeks
Behavioural disorder	✓	✓	✓	✓	✓	✓
Movement disorder	✓	✓	✓	✓	✓	✓
Parkinsonism	✓	✗	✓	✗	✗	✗
Seizure	✓	✓	✓	✓	✓	✓
Speech disorder	✓	✓	✓	✓	✓	✓
Swallowing difficulties	✓	✓	✗	✗	✓	✓
Loss of Consciousness	✗	✓	✓	✓	✓	✓
Hypoventilation	✗	✓	✗	✗	✗	✗
Other symptoms				Hemiparesis	Dystonic' status	Dystonic' status
Initial MRI	Normal	Normal	Cerebellum hyper T2	Normal	Normal	Left hippocampus FLAIR hypersignal
EEG background	Diffuse slowing	Diffuse slowing	Diffuse slowing	Diffuse slowing	Diffuse slowing	Diffuse slowing
EEG inter-ictal abnormalities	Temporal bilateral slow waves	Frontal high amplitude slow wave NREM sleep: fronto-central alpha rhythms; "extreme delta brush" pattern	Left temporal slow waves	Bilateral fronto temporal slow waves	NREM sleep: fronto-central alpha rhythms; "extreme delta brush" pattern	Diffuse poly-spikes and waves
CSF protein level	Normal	Normal	Normal	Normal	Normal	Normal
CSF cytology	Normal	Pleiocytosis	Pleiocytosis	Normal	Pleiocytosis	Pleiocytosis
CSF oligoclonal bands	IgG	IgG	IgG	IgG	IgG, M, A	IgG, M, A
Associated neoplasm	✗	✗	✗	✗	✗	✗

Notably, all patient experienced clinical worsening after the initial FDG-PETs.

3.4. Treatment / Evolution

The first line of treatment was initiated less than 4 weeks after first symptom (median: 3.9). We used intravenous steroids (30 mg per kg for 5 days) for 2 patients, intravenous immunoglobulins (IgIV, 1 g per kg in 5 days) and plasma exchange for all patients. This first-line of treatment had only partial efficiency or inefficiency. For all patients, we used rituximab (375 mg per m^2) as second line of treatment with significant clinical improvement for 5/6 patients. One patient (case 5) did not respond to rituximab and was included in methotrexate intra-thecal injection protocol [20]. Total follow-up was 57 months after the first symptom (range: 11–71) and median mRS at the end of follow-up was 1 (range: 1–4). All patients had EEG follow-up with normalization in five patients after clinical improvement and persistent background activity slowing for one patient with poor clinical outcome (case 6). During follow-up, no patients experienced relapse or exhibited associated neoplasm.

3.5. Cerebral FDG-PET follow-up

Serial cerebral FDG-PETs were performed in five patients with a median follow-up of 5 months (range: 2–5 months; see Table 2 and Supplemental Figs. 3–6). The cerebral FDG-PET follow-up were performed after the end of first line of treatment. We noticed:

- Cerebral FDG-PET metabolism and clinical improvement in five patients (including three with sub-normalization of brain metabolism)

Table 2
Detailed cerebral FDG-PET data (N = normal; ↓ = hypometabolism; ↑ = hypermetabolism; L = left; R = right; mid = middle; inf = inferior; temp = temporal; occ = occipital; SMA = supplementary motor area; hipp = hippocampus; sup = superior; par = parietal). Percentage of metabolic changes between two exams calculated as follow for each region: (uptake ratio of 2nd [or 3rd] PET scan – uptake ratio of 1st [or 2nd] PET scan)/(uptake ratio of 1st [or 2nd] PET scan). Between commas is the percentage of changes and the corresponding region.

Patients	Cerebral Area				
	Frontal	Temporal	Parietal	Occipital	Basal Ganglia
Case 1 – initial TEP	↓	↓	↓	↓	↑
Case 1 – second TEP	N/↑	N	N	N	N
(5 month after)	(+8%; L mid frontal)	(+8,1%; L inf temp)	(+7,8%; angular)	(+17,7%; L inf occ)	(−15,7%; R pallidum)
Case 2	↓	N	N	↓	↑
Case 3 – initial TEP	↑	↓	↓	↓	N
Case 3 – second TEP	N/↑	N	N	N	N
(2 month after)	(−19,3%; L SMA)	(+17,1%; L temp pole)	(+12,5%; L precuneus)	(+41,9%; L calcarine)	
Case 4 – initial TEP	↓	↑	N	↓	↑
Case 4 – second TEP	↓	N	N	N	N
(2 month after)		(−22,5%; L mid temp)		(+36,4%; L calcarine)	(−14,3%; L caudate)
Case 4 – third TEP	N	N	N	N	N
(5 month after)	(+6%; L SMA)				
Case 5 – initial TEP	↓	↓	N	↓	↓
Case 5 – second TEP	↓	↓	N	N	↓
(4 month after)		(+35,1%; R hipp)		(+131,4%; L calcarine)	
Case 6 – initial TEP	↓	↓	↓	↓	N
Case 6 – second TEP	↓	↓	↓	↓	↑
(3 month after)	(−5% L SMA)	(−5,9%; R heschel)	(−7,9%; R sup par)	(−6,4%; R sup occ)	(+28,8%; L putamen)
Case 6 – third TEP	↓	N	N	N	↑
(5 month after)	(+18%; L pre-central)	(+6,1%; L sup temp)	(+30,7%; L sup par)	(+35,7%; L sup occ)	

- Cerebral FDG-PET metabolism and clinical initial worsening in one patient (case 6) before secondary improvement.

The quantification method of brain metabolism changes showed similar evolution. These data are detailed in Table 2.

4. Discussion

We report a series of 6 young patients suffering from anti-NMDAR encephalitis. Our patients exhibited classical features of this entity: rapidly progressive encephalitis with seizures, movement disorders, language difficulties, and behavioural changes [2,6,9,10]. The clinical course was severe with 4 patients requiring management in intensive care because of drowsiness or *status dystonicus*. We described only non-paraneoplastic cases, as often reported in children [21]. IgIV, plasma exchange and intravenous steroid pulse remained incompletely efficient for our patients. Rather, Rituximab showed good efficacy in our series, as suggested by previous studies [22,23].

Paradoxically in anti-NMDAR encephalitis, despite patient's severe clinical status, MRI [10,24] and CSF analysis [12] may be normal. In our series, four patients had normal MRI and the persistent normality of serial MRI argues against delayed appearance of MRI lesion. Aiming to improve diagnosis accuracy, advanced MRI markers have been studied in anti-NMDAR encephalitis with better sensitivity than standard sequences. Thus, diffusion tensor imaging and functional MRI showed alterations of functional connectivity and impairment of white matter integrity [11]. Similarly, some studies suggest potential role of cerebral FDG-PET for evaluation of autoimmune encephalitis [14]. Currently, about 40 cases of anti-NMDAR encephalitis with cerebral FDG-PET data have been published [5,24–43]; but paediatric population remains unexplored with only 4 cases reported [26,31,37]. In this study, we confirm the feasibility of cerebral PET-FDG in children even the younger (3 year old). Our data suggest also a good sensitivity of cerebral PET-FDG in this population (all our six patients had metabolism alteration), similarly to previous report in adults [24]. Nevertheless, the indication of cerebral PET-FDG in children has to be considered carefully in regards of inherent risk due to ionizing radiation [44]. For example, initial cerebral FDG-PET could be perform during the same time that the whole-body FDG-PET used of paraneoplastic screening, in order to avoid additional dosimetric exposure. But, tumours are rarely associated with autoimmune encephalitis in paediatric population (mostly mature ovarian teratoma) [6,9]. Moreover, FDG-PET is not recommended for the research of such tumour [45]. Then, if FDG-PET is recommended in adult with suspected autoimmune encephalitis [45], no such guidelines exist in paediatric population. In conclusion, anti-NMDAR encephalitis diagnosis is based on the association of suggestive clinical, electrophysiological and imaging features; and the crucial need of immunological confirmation.

We reported some particular patterns of metabolism alteration: extensive cortical symmetric relative hypometabolism predominant in occipital, basal ganglia relative hypermetabolism, and cortical asymmetric anterior (frontal or temporal) focus of relative hypermetabolism. Contrary to adult patients, we highlight the frequent basal ganglia metabolism impairment in our series, confirming similar suggestion in previous studies [5,24,35,36]. This relative hypermetabolism is consistent with the high prevalence of movement disorders and parkinsonism features in young patients (e.g. all patients in our series) [2]. Moreover, previous studies reported decreased levels of N-acetyl aspartate in basal ganglia using MR-spectroscopy [46,47].

We also found a good correlation between the degree of brain metabolism alteration (extensive cortical hypometabolism) and the clinical severity (high mRS) in our series. Moreover, we reported serial cerebral FDG-PET in five patients with brain metabolism improvement in parallel to the favourable clinical outcome.

Nevertheless, the pathophysiological substratum of such brain metabolism changes remains currently speculative. Concerning relative hypermetabolism, we could suggest some mechanisms: epileptic/spiking activity, inflammation processes, enhancement of excitatory synaptic transmission, or "windowing" effect. Firstly, sustained spiking activity could lead to cortical hypermetabolism focus in FDG-PET scan [48,49], but because we did not dispose of EEG monitoring during FDG-PET scan, we cannot assess the impact of such activity in our series. Secondly, it was also reported that focal FDG uptake could directly reflect brain inflammation processes [51]. However, because anti-NMDAR encephalitis are not mainly mediated by complement or cytotoxic T-cell mechanisms [2], a such explanation seems to us less probable. Thirdly, anti-NMDAR antibodies lead to NMDAR internalization and altered synaptic functions [3]. In parallel to basal ganglia relative hypermetabolism in our series, NMDARs are well-known to modulate glutamate, acetylcholine and γ-aminobutyric acid (GABA) synaptic transmissions in these structures [50]. Some authors proposed that anti-NMDAR antibodies could diminish the GABAergic transmission leading to disinhibition of excitatory pathways in basal ganglia [2]. We hypothesized that such mechanism could be one explanation of movement disorders/parkinsonism features as well as FDG-PET relative hypermetabolism in basal ganglia. Finally, without absolute quantitative data, we recall the possibility of a "windowing" effect due to the relative preservation of metabolism in some structures (e.g. basal ganglia)

contrasting with the severe and extensive cortical hypometabolism.

Concerning the cortical hypometabolism, we could also hypothesized some mechanisms: consequence of neuronal damage, synaptic transmission alteration, or cortico-striatal diaschisis [52]. The hypothesis of neuronal death seems to us unlikely because anti-NMDAR antibodies lead essentially to receptors internalization, usually MRI scans do not revealed diffuse T2/FLAIR hyper intense signals, and serial cerebral FDG-PET scans improve in parallel to favourable clinical outcome after treatment.

We found more rarely, than previous reports in adults, the antero-posterior gradient with fronto-temporal hypermetabolism and parieto-occipital hypometabolism [25,32,35,42]. This difference may reflect different pathobiology of the disease as well as particular cerebral FDG uptake in paediatric population and its progressive change with age. Four studies had recently described normal cerebral metabolism in childhood [15,17,53,54], reporting linear and differential regional increase of FDG uptake with the age. For example, one study [15] reported that:

- Putamen and caudate nuclei have constantly the maximum FDG uptake;
- Children under 7 years have more intense FDG uptake in parietal and occipital lobes than in frontal;
- Children between 7 and 10 years have frontal lobes FDG uptake becoming more intense than parietal and occipital lobes;
- Children over 10 years have thalamic FDG uptake becoming more intense than parietal and occipital lobes (but less than frontal lobes).
- Temporal lobes have constantly the lowest FDG uptake of cortex.

Therefore, in order to avoid misinterpretation, practitioners should be aware of these regional changes in cerebral metabolism patterns with the age.

Finally, our study has some limitations: few patients, retrospective design, no absolute quantification, and no comparison to healthy children. The lack of absolute quantitative data is due to ethical consideration (need of arterial sample). Furthermore, for dosimetric reason, we do not disposed of age-adjusted control group in paediatric population, avoiding colour-coded voxel based comparisons. Consequently, we reported only relative metabolism changes and quantification of brain metabolism changes during disease course. On the other hand, a classical bias due to potential treatment effect on cerebral metabolism is limited in our series because cerebral FDG-PET were performed out of corticosteroids course and without sedation.

In conclusion, we reported specific patterns of brain metabolism change (extensive cortical hypometabolism, relative basal ganglia hypermetabolism) in paediatric anti-NMDAR encephalitis. Further studies comparing cerebral FDG-PET with advanced MRI markers and immunological data would be interesting. Moreover, the development of more specific ligands for cerebral PET, especially those of neuro-inflammation, may improve its accuracy.

Disclosure forms

The authors have no financial or personal relations that could pose a conflict of interest.

Authors contributions

S. Lagarde contributed to clinical, immunological and PET data collection, data interpretation and manuscript writing.

A. Lepine, E. Caietta, M. Milh, B. Chabrol contributed to evaluation of patients, clinical data collection, data interpretation, and manuscript writing.

F. Pelletier contributed to immunological data collection and analysing.

J. Boucraut contributed to immunological data collection, data interpretation, and writing manuscript.

E. Guedj contributed to PET data collection, data interpretation, and writing manuscript.

Acknowledgement

Thanks to Gary BURKHART for complete revision of the manuscript's English language. We are grateful to Pr Honnorat and his team (French Reference Centre on Paraneoplastic Neurological Syndrome, Hospices Civils de Lyon, Hôpital Neurologique, Lyon, France) that confirmed the immunological diagnosis; and Dr Deiva (National Referral Centre for Neuro-Inflammatory Diseases in Children, University Paris-Sud, Le Kremlin-Bicêtre, France), that made useful recommendations to support some patient.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.braindev.2015.10.013.

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