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BRIEF COMMUNICATION

ASL MRI and 18F-FDG-PET in autoimmune limbic encephalitis: clues from two paradigmatic cases

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Abstract

Background Autoimmune limbic encephalitis (LE) is a neurological condition characterized by seizures and cognitive dysfunction. Fluorine-18 fluorodeoxyglucose (18F-FDG-PET) has recently proved to be an important diagnostic tool in this condition since it may highlight brain metabolism abnormalities in a very early stage of the disease. Two main 18F-FDG-PET patterns have been described: the mixed hypermetabolic/hypometabolic and the neurodegenerative one. Arterial spin labeling (ASL) is an MRI technique showing brain perfusion, rarely used in autoimmune neurological conditions. The aim of the present study was to study patients with LE with both techniques, in order to compare their results.

Methods Two patients with LE underwent to 18F-FDG-PET and ASL MRI scans using the pseudo-continuous arterial spin labeling (PCASL) technique. Areas of altered perfusion and metabolism were analyzed by visual inspection, and findings were compared between the two techniques.

Results In the first patient, a relapsing LGI-1 LE, right hippocampal hypermetabolism was detected by 18F-FDG-PET (mixed hypermetabolic/hypometabolic pattern), while ASL MRI showed right hippocampal increased perfusion. In the second patient, a seronegative LE, 18F-FDG-PET scan detected a left hemispheric hypoperfusion (neurodegenerative pattern) and ASL MRI yielded similar results. The two 18F-FDG-PET patterns of altered metabolism were similarly detected by ASL imaging.

Conclusion ASL and 18F-FDG-PET findings are strongly concordant in LE. ASL imaging was able to detect the two main 18F-FDG-PET patterns previously described in patients with LE.

Keywords Limbic encephalitis · Positron emission tomography · Arterial spin labeling · Neuroimmunology

Limbic encephalitis (LE) is an autoimmune condition characterized by cognitive impairment, seizures, and mood/behavioral disorders. Bilateral medial temporal lobes abnormalities on T2-weighted/FLAIR sequences represent the hallmark of limbic encephalitis and their presence is mandatory for the diagnosis of "definite LE"; however, 18F-FDG-PET can be used to fulfil the radiological criterion if the MRI scans are unremarkable [1]. Two main 18F-FDG-PET metabolic patterns have been described in patients with LE: the "mixed hyper-hypometabolic pattern," which is usually found in younger patients, and it is characterized by occipital hypometabolism, temporal, and orbitofrontal hypermetabolism. The "neurodegenerative" one reminds the patterns seen in neurodegenerative dementias, with areas of cortical hypometabolism, and it is most frequently found in older patients with less striking symptoms and without seizures [2]. Arterial spin labeling (ASL) is an MRI technique requiring no radiations or contrast agents; it magnetically labels inflowing blood, to assess cerebral blood flow and perfusion alterations. ASL and 18F-FDG-PET are closely linked since they examine two strongly coupled aspects in the CNS: perfusion and metabolism [3].

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The role of ASL in autoimmune encephalitis has been reported in single cases [4–7] and, strikingly, most of those cases revealed an overlap of ASL and 18F-FDG-PET findings. This concordance is particularly intriguing because ASL could then represent a feasible contrast- and radiation-free tool to evaluate altered perfusion, and subsequently metabolism, patterns even in early MRI scans.

To prove this hypothesis, we report here two paradigmatic cases of LE that were studied with both 18F-FDG-PET and ASL MRI.

A 54-year-old woman was admitted to our unit for gambling, memory loss with subsequent onset of generalized tonic-clonic seizures. Brain MRI scan revealed T2/FLAIR sequences with bilateral hyperintensities of hippocampus while EEG showed focal slowing on bilateral temporal electrodes with sharp waves. LGI1 antibodies were positive in both serum and CSF. No underlying malignancy was detected. She was treated subsequently with two first-line immunotherapies (high-dose methylprednisolone, intravenous immunoglobulins) with partial improvement of psychiatric symptoms but without seizures control. Complete remission was obtained only after treatment with rituximab. Eight months after treatment, the patient came back to our attention due to encephalitis relapse: her neuropsychological examination showed short-term memory impairment and confabulation; no seizures were reported, and EEG did not reveal epileptic discharges. A new MRI showed increase hyperintensity on T2/FLAIR in the right hippocampus, with contrast enhancement and an increased perfusion area revealed by ASL imaging. 18F-FDG-PET brain scan detected an increased uptake in the right hippocampus (Fig. 1, acquired before rituximab at the time of relapse).

A 69-year-old man was admitted to our unit for a 3-month history of relapsing episodes of anterograde amnesia that progressively evolved in a severe amnestic cognitive impairment. The patient never experienced seizures. The EEG revealed bilateral temporal slowing with no epileptiform discharges. Brain MRI scans showed bilateral T2/FLAIR hyperintensities of temporal lobes, with contrast enhancement. ASL MRI showed a left hemisphere hypoperfusion with no temporal hyperperfusion. Total body 18F-FDG-PET scan detected no malignancies, while 18F-FDG-PET brain scans confirmed left hemisphere hypocaptation (Fig. 2, performed while the patient was symptomatic, 3 months from onset). A spinal tap was performed and revealed normal cell count and protein concentration. CSF oligoclonal bands, PCR for neurotropic viruses, cytological, and microbiological analysis resulted negative. No onconeural and neural surface autoantibodies, including antibodies against adenylate-kinase 5, were detected in serum or CSF, and immunohistochemistry on rat brain slices resulted negative. Given the prominent amnestic syndrome without seizure, the typical MRI, and EEG findings, the patient was diagnosed with seronegative LE [8] and he was treated with methylprednisolone and immunoglobulins with partial improvement.

The role of ASL and 18F-FDG-PET in autoimmune encephalitis has been previously reported in patients with NMDAR encephalitis: the pathognomonic occipito-parietal hypoperfusion and hypometabolism has been highlighted by both the techniques in one patient [4], while occipito-parietal hypoperfusion in ASL alone was reported in a pediatric patient with negative brain MRI scan [5]. Regarding autoimmune LE, an overlapping 18F-FDG-PET and ASL right amygdala and hippocampus hyperperfusion/metabolism has been reported in one patient with LGI1 antibodies [6], but the scans were acquired during an autonomic status epilepticus, thus temporal hyperperfusion/metabolism could be related to the underlying epileptic activity and not the encephalitis itself. On the contrary, our patient with LGI1 LE had been seizure-free for 8 months at the time and the EEG did not reveal any epileptiform discharges. We can therefore hypothesize that ASL and 18F-FDG-PET perfusion/metabolism alterations are not related to epileptic discharges, but more strictly to the underlying relapsing autoimmune process. This finding could be indirectly supported by the report of absent ASL and 18-FDG-PET hypermetabolism/perfusion 1

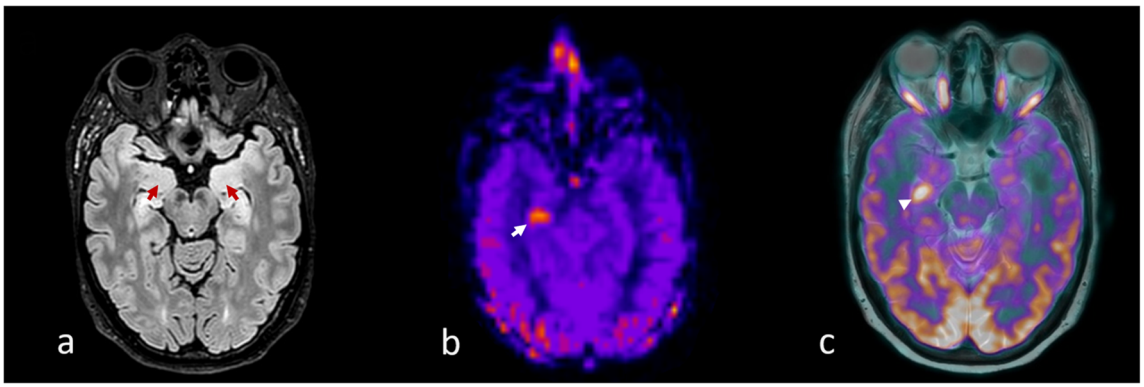

Fig. 1 From left to right: fluid attenuated inversion recovery (a), arterial spin labeling (b), and 18-fluorodeoxyglucose positron emission tomography (c) brain scans in patient 1 showing bilateral hippocampal hyperintensities (red arrows) and right hippocampus increased perfusion (white arrow) and metabolism (white arrowhead) (mixed pattern)

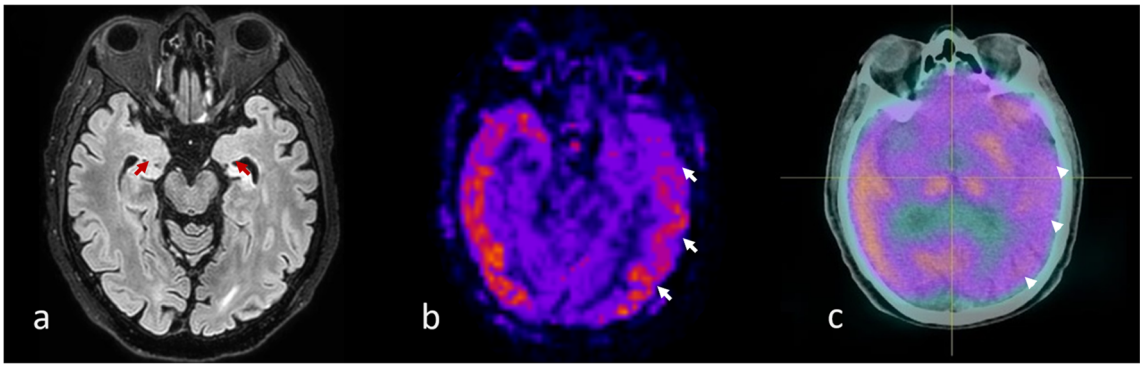

Fig. 2 From left to right: fluid attenuated inversion recovery (a), arterial spin labeling (b), and 18-fluorodeoxyglucose positron emission tomography (c) brain scans in patient 2 showing bilateral hippocampal hyperintensities with atrophy (red arrows), left hemispheric decreased perfusion (white arrows), and metabolism (white arrowheads) (neurodegenerative pattern)

month after treatment in another patient with LGI1 antibodies [7]. Unfortunately, we were unable to repeat the scan after treatment to confirm this hypothesis that is particularly relevant because it could imply that ASL may be used to monitor disease activity. Finally, no previous data regarding ASL and 18F-FDG-PET scans have been reported in patients with seronegative LE.

The clinical features of our two patients perfectly fit with the two typical patterns of 18F-FDG-PET captation: the patient with LGI1 antibodies was an adult with cognitive dysfunction and seizures: her 18F-FDG-PET and ASL scans unsurprisingly showed a "hypermetabolic pattern." On the other hand, the seronegative patient was older, had milder, predominantly cognitive symptoms, and did not experience any seizures: his 18F-FDG-PET and ASL scans showed a "neurodegenerative pattern." This paradigmatic concordance of ASL and 18F-FDG-PET findings have never been reported so far in patients with autoimmune LE and it is particularly relevant because it represents a proof-of-concept that ASL scans may be used to evaluate the well-known metabolic patterns of LE even in the early MRI scans, when total body and brain 18F-FDG-PET scans have not been performed yet.

Our report is obviously limited by the very small sample size: autoimmune LE is a rare condition and further studies with larger cohorts are required to achieve more conclusive data about sensitivity and specificity of ASL MRI and 18F-FDG-PET imaging and to assess their application in diagnosis and follow-up.

Availability of data and material Data are available upon reasonable request to the corresponding author.

Declarations

Ethics approval Not available.

Consent to participate Patients gave their written informed consent for publication.

Consent for publication Patients gave their written informed consent for publication.

Conflict of interest The authors declare no competing interests.

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