

Tumefactive Demyelination versus Primary Central Nervous System Lymphoma on ¹⁸F-Fluorodeoxyglucose Positron Emission Tomography Magnetic Resonance Imaging: A Twist in the Tale

Abstract

Demyelinating lesions of the central nervous system (CNS) are classically known to be hypometabolic on ¹⁸F-Fluorodeoxyglucose Positron Emission Tomography (¹⁸F-FDG PET). However, demyelinating lesions may show increased tracer uptake on ¹⁸F-FDG PET and can radiologically mimic neoplasm. Delayed tracer uptake on FDG PET is one of the diagnostic hallmarks of primary CNS lymphoma (PCNSL). Here, we present two cases in which the brain lesions showed increased FDG uptake on delayed integrated PET Magnetic Resonance Imaging (MRI), which were pathologically proven as CNS demyelination. Such demyelinating lesions may also act as “sentinel lesions” and potential harbinger of PCNSL on follow-up.

Keywords: ¹⁸F-fluorodeoxyglucose, delayed uptake, demyelination, positron emission tomography-magnetic resonance imaging, primary central nervous system lymphoma, tumefactive demyelination

Primary demyelinating diseases of the central nervous system (CNS) include several entities such as multiple sclerosis (MS), myelinoclastic diffuse sclerosis, and acute demyelinating encephalomyelitis (ADEM). These lesions have also been synonymously termed as Tumefactive Demyelinating Lesions (TDL), demyelinating pseudotumor, tumefactive MS (TMS), tumor-like demyelinating lesions, or giant plaques in the literature.^[1] Tumefactive demyelinating lesions (TDL), which can be an isolated entity or presenting feature of MS (TMS), may pose a serious diagnostic challenge for a radiologist that frequently prompts biopsy for further evaluation.^[2]

On ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG PET), demyelinating lesions generally tend to be hypometabolic. Maffione *et al.*^[3] have demonstrated increased uptake in TMS. Hypermetabolism has also been described in TDL, primary CNS lymphoma (PCNSL), and glioma.^[4] However, this uptake is significantly more for PCNSL and glioma as compared to TDL.^[4] Most of the literature on FDG PET in PCNSL employs

early imaging; however, Jeanguillaume *et al.*^[5] have demonstrated the role of dual-phase ¹⁸F-FDG PET in picking up additional lesions in PCNSL which were more conspicuous on the delayed phase. We hereby present two cases who presented with CNS lesions showing increased tracer uptake on delayed ¹⁸F-FDG PET magnetic resonance imaging (MRI) and provisionally being diagnosed as PCNSL. However, both were pathologically proven to be CNS demyelination on subsequent biopsy from the lesions.

The first patient was a 10-year-old female child who had presented with a history of multiple episodes of vomiting followed by reduced speech output since the age of 8 years. One month before admission, she had left hemiparesis which transiently improved. She also had right lower motor neuron type of facial palsy, slurring of speech, difficulty in swallowing along with positive cerebellar signs. MRI showed multifocal confluent hyperintensities in the lateral aspect of pons, bilateral middle cerebellar peduncles, dentate nuclei, and peridentate white matter, which showed varying degrees of diffusion restriction with irregular and ring enhancement on

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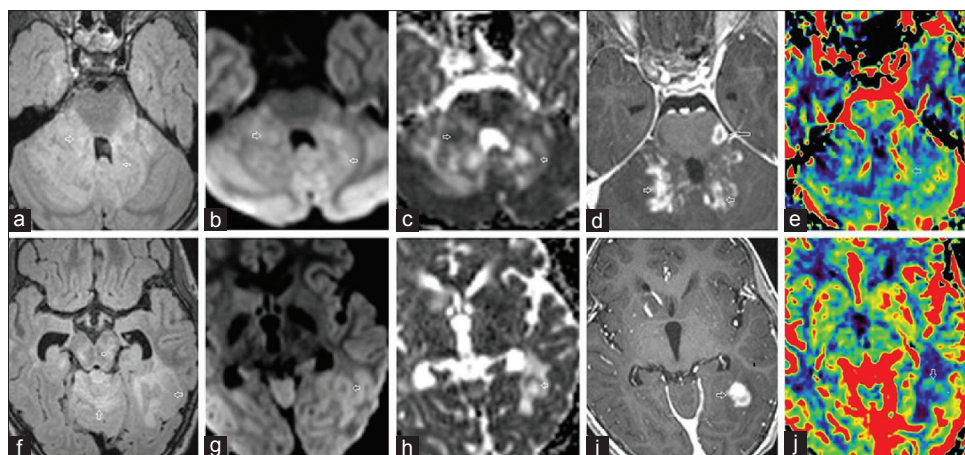


Figure 1: Magnetic resonance imaging findings in biopsy-proven demyelination (Patient 1); (a) Axial FLAIR image showing multifocal confluent hyperintensities in the lateral aspect of pons, bilateral middle cerebellar peduncles, dentate nuclei, and the peridentate white matter (arrows); (b and c) Axial DWI and ADC maps showing patchy areas of diffusion restriction within the lesions (arrows); (d) Axial postcontrast T1 image showing irregular enhancement of the dentate and peridentate lesions (short arrows) with ring enhancement of the lesion in the left lateral pons (long arrow); (e) CBV map (T2 perfusion) showing elevated perfusion within the lesions in the dentate nuclei (arrows); (f) Axial FLAIR image showing patchy hyperintensities in the midbrain, superior vermis and cerebellar hemispheres and in the left temporal lobe (arrows); (g and h) Axial DWI and ADC maps showing ring like diffusion restriction within the left temporal lobe lesion (arrow); (i) Axial post contrast T1 image showing heterogeneous peripheral enhancement of the lesion in the left temporal lobe (arrow); (j) CBV map (T2 perfusion) showing elevated perfusion within the periphery of the lesion (arrow)

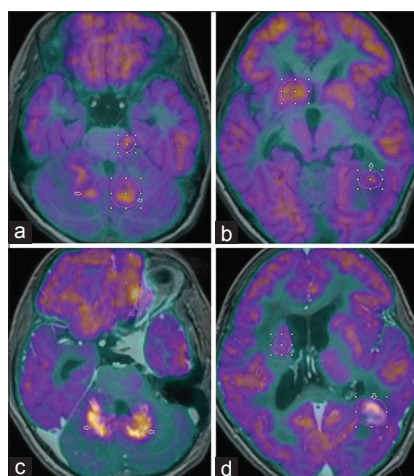


Figure 2: Positron emission tomography-magnetic resonance images of Patient 1; (a and c) Axial positron emission tomography-magnetic resonance imaging images at 45 min (a) and 270 min (c) following ^{18}F -fluorodeoxyglucose injection showing abnormal increase in fluorodeoxyglucose uptake in the bilateral dentate nuclei lesions with further mild increase on the delayed scans (SUV_{max} at 45 min = 7.3; SUV_{max} at 270 min = 9.1) (arrows); (b and d) Axial positron emission tomography-magnetic resonance images at 45 min (b) and 270 min (d) following ^{18}F -fluorodeoxyglucose injection showing abnormal fluorodeoxyglucose uptake in the left temporal lobe lesion further mild increase on the delayed scans (SUV_{max} at 45 min = 6.5; SUV_{max} at 270 min = 8.3) (arrows). SUV_{max} : Maximum standard uptake value

postcontrast study [Figure 1]. The patient underwent ^{18}F -FDG PET-MRI in the Siemens mMR Biograph scanner with a routine scan at 45 min (after tracer injection) and a delayed scan repeated at 270 min. The early scan showed abnormal increase in tracer uptake at the periphery of the lesions with further increase in the delayed scan [Figure 2]. A provisional diagnosis of PCNSL was made. However, biopsy from the posterior fossa lesion showed predominant foamy histiocytes positive for CD68,

admixed with few CD3-positive T-cells. There was no evidence of CD20-positive B-cells, atypical or neoplastic cells. The above-mentioned features were compatible with inflammatory demyelinating pathology. During hospital stay, there was worsening of her cerebellar signs with reduced speech output, despite on intravenous (IV) methylprednisolone.

The second patient was a 37-year-old female who presented with paresthesia of the face and decreased vision in the left eye for 4 months, which was followed by initially left and then right hemiparesis over the next 2 months. Before admission, she also had urinary incontinence and reduced speech output for 1 month. MRI showed large confluent hyperintense lesions in the bilateral cerebral hemispheres with involvement of corpus callosum splenium and posterior aspect of right basal ganglia. Peripheral diffusion restriction with incomplete “open ring enhancement” was seen in the centrum semiovale lesions. There was expansion of the spinal cord with multiple peripherally enhancing intramedullary lesions [Figure 3]. This patient also underwent ^{18}F -FDG PET-MRI with initial and delayed scans being performed. There was abnormal increased in tracer uptake at the periphery of the lesions in the centrum semiovale and left periventricular region with the delayed scan showing significant increase in maximum standard uptake value (SUV_{max}) of the above-mentioned lesions [Figure 4]. Similar to the first case, initially, PCNSL was diagnosed based on the PET-MRI findings. However, biopsy from the left centrum semiovale lesion showed extensive reactive changes of the glial cells admixed with numerous scattered CD68-positive foamy macrophages. There was perivascular and diffuse infiltration of parenchyma with predominant

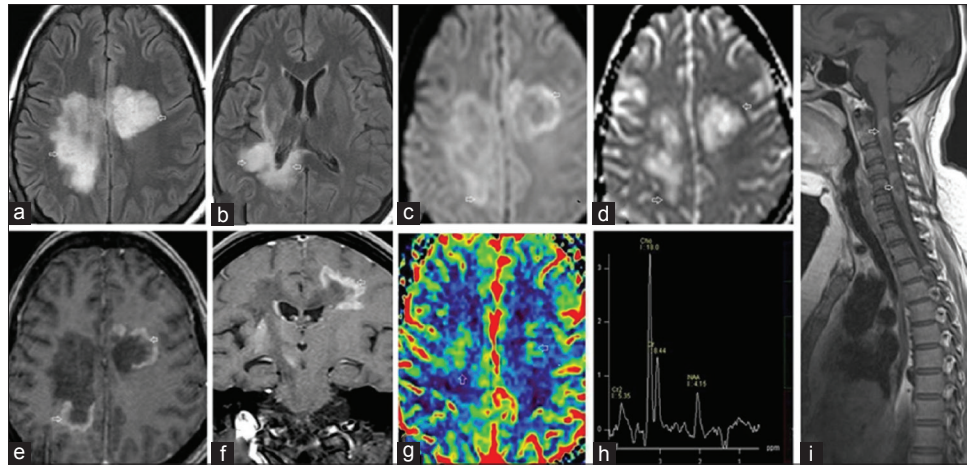


Figure 3: Magnetic resonance imaging findings in a case of pathologically proven demyelination (Patient 2); (a and b) Axial FLAIR image showing large confluent hyperintense lesions in the bilateral centrum semiovale (arrows in a) and in the right posterior periventricular white matter with involvement of the right half of corpus callosum splenium and posterior basal ganglia (arrows in b); (c and d) Axial DWI and ADC maps showing peripheral diffusion restriction at the margins of the centrum semiovale lesions (arrows); (e and f) Axial (e) and coronal (f) postcontrast T1 images showing peripheral incomplete "open ring" type of enhancement of the centrum semiovale lesions (arrows); (g) CBV map (T2 perfusion) showing foci of elevated perfusion within the lesions in the centrum semiovale (arrows); (h) Single Voxel MR Spectroscopy (TE-144 ms) from the left centrum semiovale lesion showing an elevated Choline peak, reduced NAA peak with increased Cho/Cr and Cho/NAA ratios. Note is also made of an inverted lactate peak; (i) Sagittal T1 postcontrast image of spine showing cord expansion with multiple peripherally enhancing intramedullary lesions in the cervical region

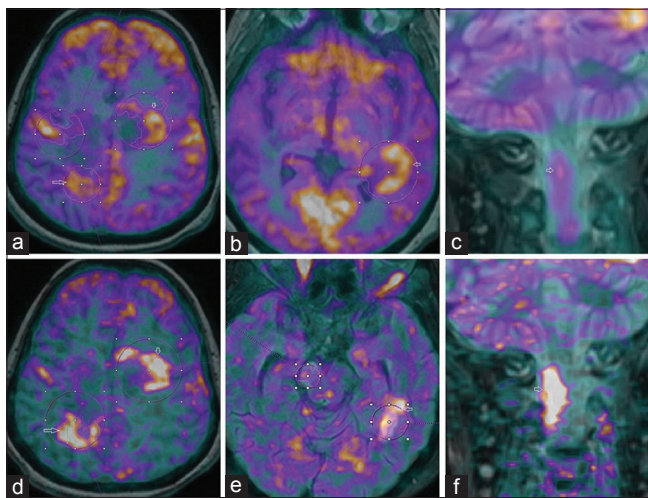


Figure 4: Positron emission tomography-magnetic resonance images of Patient 2; (a and d)-Axial positron emission tomography-magnetic resonance images at 45 min (a) and 270 min (d) following ^{18}F -fluorodeoxyglucose injection showing abnormal fluorodeoxyglucose uptake along the margins of the bilateral centrum semiovale lesions with significant increase in tracer uptake on the delayed scans-left (SUV_{max} at 45 min - 7.5; SUV_{max} at 270 min - 12.4) (short arrow), Right (SUV_{max} at 45 min - 6.8; SUV_{max} at 270 min - 11.8) (long arrow); (b and e) Axial positron emission tomography-magnetic resonance images at 45 min (b) and 270 min (e) following ^{18}F -fluorodeoxyglucose injection showing abnormal fluorodeoxyglucose uptake in the left periventricular lesion with mild increase in uptake on delayed scan (SUV_{max} at 45 min - 7.5; SUV_{max} at 270 min - 8.6) (arrows); (c and f) Coronal positron emission tomography-magnetic resonance images at 45 min (c) and 270 min (f) following ^{18}F -fluorodeoxyglucose injection showing mild fluorodeoxyglucose uptake in the cervical cord lesion with marked increase in uptake on delayed scan (SUV_{max} at 45 min - 4.9; SUV_{max} at 270 min - 10.2) (arrows). SUV_{max}: Maximum standard uptake value

T-lymphocytes, staining positively for CD3 and CD20. No atypical cells or neoplastic/immature lymphocytes were noted. The above findings were consistent with the diagnosis of active demyelination. The patient was given

IV methylprednisolone and plasma exchange therapy to which she responded well and had improvement in her clinical outcome at the time of discharge.

Both of these patients were provisionally diagnosed as PCNSL in view of increased FDG uptake in the delayed scan, which is one of the hallmarks to differentiate inflammatory versus neoplastic pathology. It was also interpreted as false low uptake of FDG as opposed to that normally seen in PCNSL due to drug interference (both of these patients were on IV and oral steroids).

PCNSL has a very high cellular density with increased glucose metabolism and usually show intense uptake of ^{18}F -FDG, SUV_{max} being about 2.5 times higher than the average SUV in the normal gray matter.^[6] TDL can be found in 2.8% of MS patients. They may also be seen in patients without preexisting MS history, although they usually develop typical MS features in the near future.^[2] Delayed uptake of FDG on PET-MRI has been classically described in neoplastic etiology, including PCNSL;^[5] however, both our cases with the above findings were pathologically proven to be demyelination. It should be kept in mind that PCNSL can be preceded by sentinel lesions indistinguishable from the demyelination of MS or ADEM, and steroid treatment before biopsy may obscure diagnosis of PCNSL.^[7] These antecedent demyelinating "sentinel lesions" can act as a potential harbinger for the development of PCNSL in the future, although the pathogenesis remains unclear.^[8]

Although delayed uptake of ^{18}F -FDG on PET-MRI has been described in neoplastic etiology including PCNSL, the differential diagnosis of demyelination must be kept in mind as is evident in both our cases. Combination of the

spectrum of clinical findings, MRI (routine and advanced sequences), and nuclear imaging is likely to pave the path in arriving at diagnosis while facing similar cases in the future.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflict of interest

There are no conflicts of interest.

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