

# AIDS-Related Central Nervous System Toxoplasmosis With Increased $^{18}\text{F}$ -Fluoroethyl-L-Tyrosine Amino Acid PET Uptake Due to LAT1/2 Expression of Inflammatory Cells

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**Abstract:** We report the case of a 40-year-old woman with a progressive right-sided hemiparesis. Standard MRI revealed a contrast-enhancing brain lesion within the left basal ganglia.  $^{18}\text{F}$ fluoroethyl-L-tyrosine ( $^{18}\text{F}$ -FET) PET showed a distinct tracer uptake (lesion-to-brain ratio [LBR]:  $\text{LBR}_{\text{max}} = 2.03$ ,  $\text{LBR}_{\text{mean}} = 1.68$ ) with a significant larger metabolic lesion volume than contrast-enhancement in MRI, indicating cerebral glioma. Surprisingly, histopathologic analysis demonstrated central nervous system toxoplasmosis with pronounced inflammatory reaction (reactive astrogliosis, microglia activation, macrophage, and T-lymphocyte infiltration), which was associated with strong LAT1/LAT2/CD98 expression. In conclusion, inflammatory brain lesions, such as cerebral toxoplasmosis, represent a potential pitfall of  $^{18}\text{F}$ -FET PET mimicking a brain tumor.

**Key Words:**  $^{18}\text{F}$ -FET PET, brain tumor, CNS toxoplasmosis, MRI, LAT1/LAT2/CD98 expression

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$^{18}\text{F}$ -fluoroethyl-L-tyrosine was used as an unapproved radiopharmaceutical after individual prescription by a nuclear medicine physician according to §13(2b) German Drug Act (AMG) with prior notification of the drug and its indication to the relevant supervisory authority (§67 AMG).

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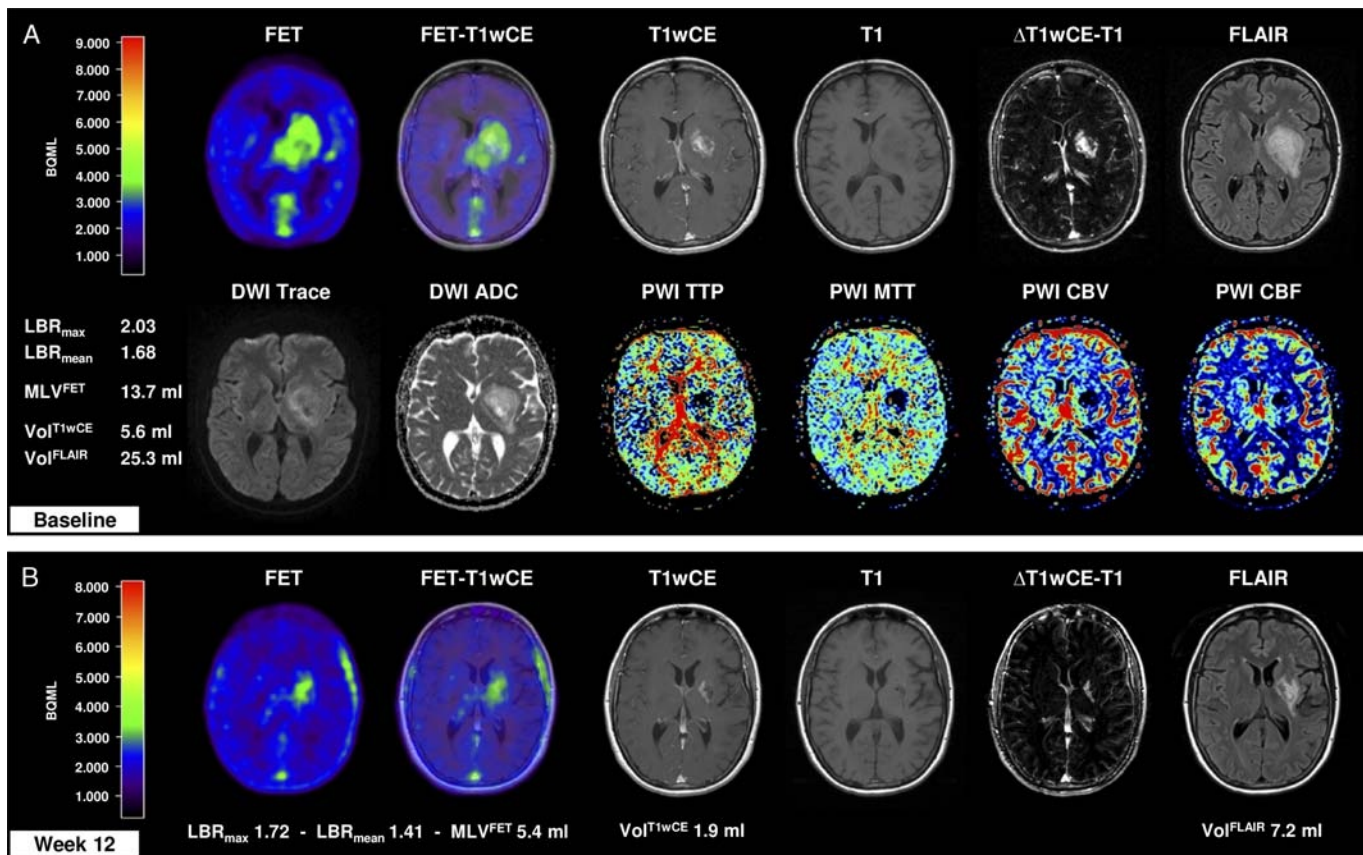
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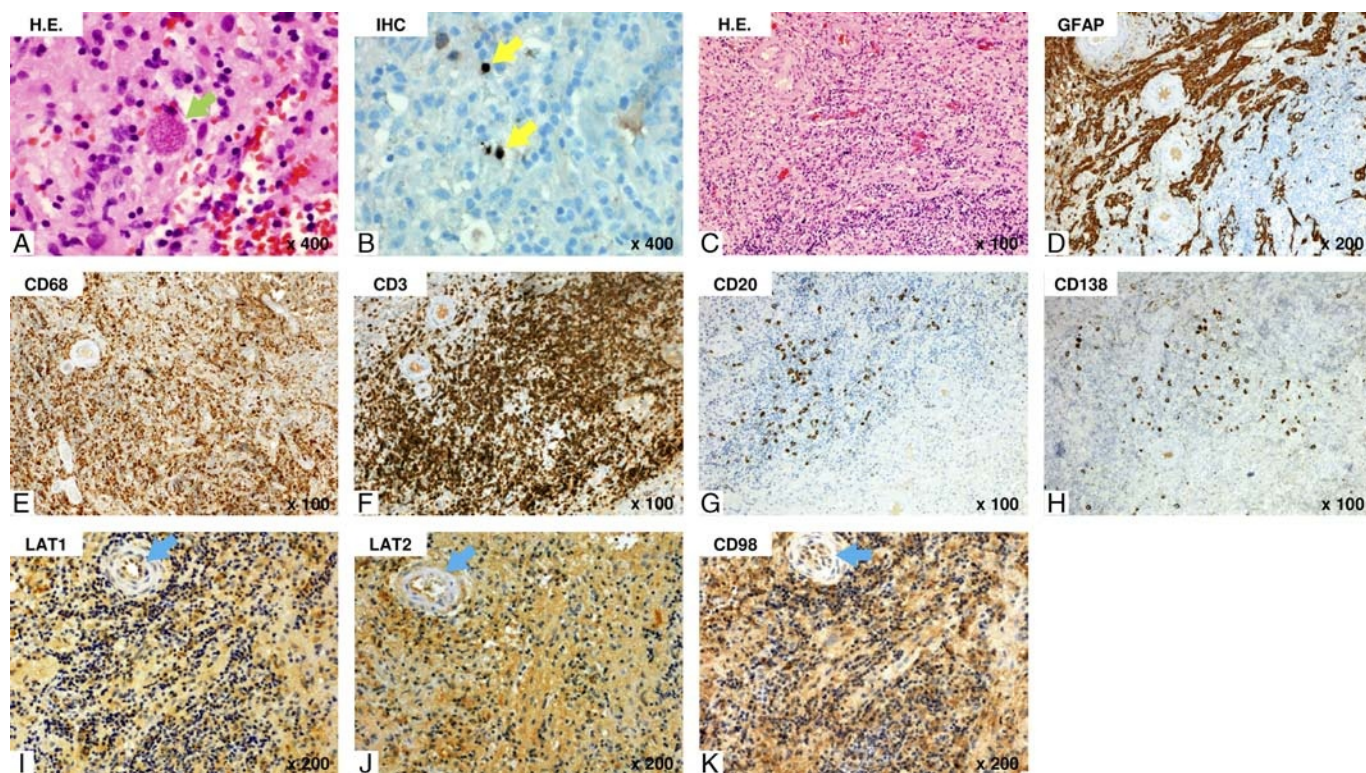
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**FIGURE 1.** We report the case of a 40-year-old woman who presented with progressive right-sided brachiofacial accentuated hemiparesis. **A**, Standard MRI revealed a contrast-enhancing brain lesion with central necrosis (T1wCE,  $\Delta T1wCE-T1$ ) and perifocal edema (FLAIR) within the left basal ganglia and capsula interna. Diffusion- and perfusion-weighted MRI demonstrated no significant diffusion restriction (diffusion-weighted imaging [DWI]/apparent diffusion coefficient [ADC]) or hyperperfusion (perfusion-weighted imaging-time-to-peak/mean transit time/cerebral blood volume/cerebral blood flow [PWI-TTP/MTT/CBV/CBF]). Additional  $^{18}F$ -FET PET (20–30 minutes post-injection) showed a distinct tracer uptake (lesion-to-brain ratio [LBR],  $LBR_{max}$  2.03,  $LBR_{mean}$  1.68; LBR calculation was performed as described previously<sup>1</sup>) with a metabolic lesion volume ( $MLV^{FET}$ ) of 13.7 mL.  $MLV^{FET}$  was larger than contrast enhancement ( $Vol^{CT1wCE}$  5.6 mL, 41%) and smaller than perifocal edema ( $Vol^{FLAIR}$  25.3 mL, 185%), indicating a cerebral glioma. Surprisingly, stereotactic biopsy and histopathologic analysis revealed central nervous system (CNS) toxoplasmosis with a strong inflammatory reaction (Fig. 2). Further laboratory diagnostics was consistent with a newly diagnosis of a human immunodeficiency virus (HIV) infection, leading to an opportunistic cerebral toxoplasmosis as the first symptom and without further signs of AIDS. **B**, Therapy with clindamycin, pyrimethamine/leucovorin, folic acid, and dexamethasone for CNS toxoplasmosis, as well as raltegravir and emtricitabine/tenofovir disoproxil for HIV infection, resulted in continuous clinical improvement. After 12 weeks, MRI and  $^{18}F$ -FET PET showed a treatment response with significant reduction of contrast enhancement, perifocal edema, and  $^{18}F$ -FET uptake ( $LBR_{max}$  1.72,  $LBR_{mean}$  1.41;  $MLV^{FET}$  5.4 mL;  $Vol^{CT1wCE}$  1.9 mL,  $Vol^{FLAIR}$  7.2 mL).



**FIGURE 2.** Neuropathological workup led to the diagnosis of CNS infection by *Toxoplasma gondii* in hematoxylin-eosin staining (A, *Toxoplasma bradyzoites* encased in a cyst, green arrow) and immunohistochemistry (B, *Toxoplasma tachyzoites*, yellow arrows). Hematoxylin-eosin staining demonstrated a distinct inflammatory process (C) with GFAP<sup>+</sup>-reactive astrogliosis (D), CD68<sup>+</sup>-microglia activation and CD68<sup>+</sup>-macrophage infiltration (E), CD3<sup>+</sup>-T-lymphocytic infiltration (F), and less pronounced CD20<sup>+</sup>-B-lymphocytic (G) and CD138<sup>+</sup>-plasma cellular (H) staining. Of note, the system L-amino acid transporter LAT1/LAT2 (light chain) and CD98 (heavy chain) (I–K), which are known to specifically mediate <sup>18</sup>F-FET uptake into cells, were immunohistochemically strongly expressed in immune-reactive astrocytes, microglia and macrophages, T lymphocytes, and vascular endothelial cells (I–K, blue arrows). Here we present a novel case of an AIDS/HIV-associated solitary cerebral toxoplasmosis lesion<sup>2</sup> mimicking cerebral glioma in <sup>18</sup>F-FET PET because of a strong LAT1/LAT2/CD98 expression of resident and immigrated inflammatory activated immune cells mediating a nontumoral tracer uptake. <sup>18</sup>F-FET uptake by nonneoplastic tissue is considered as a rare phenomenon. Similar “pitfalls” of <sup>18</sup>F-FET PET were reported for various inflammatory and ischemic brain lesions, intracerebral hematoma, and cortical epileptic activity.<sup>1,3–9</sup> As LAT transporters are expressed in the endothelium, <sup>18</sup>F-FET uptake mainly occurs independent of blood-brain barrier disruption, as indicated by contrast enhancement and perifocal edema in MRI.<sup>1</sup> Therefore, <sup>18</sup>F-FET PET may show increased uptake in both contrast- and non-contrast-enhancing inflammatory brain lesions, but not in perifocal edema, which offers important additional information to standard MRI alone. In conclusion, etiologically distinct brain lesions may induce an increase in cerebral amino acid transport. In order to avoid misinterpretation and/or overtreatment, these “pitfalls” have to be closely matched with clinical and additional technical information whenever <sup>18</sup>F-FET PET images are available.