



FDG-PET/CT in the evaluation of paraneoplastic neurologic syndromes

Paraneoplastic neurologic syndromes (PNS) are a rare, heterogeneous group of complications associated with malignancy, unrelated to direct tumor invasion or metastasis, that may be immune-mediated. The aim of this article is to provide an overview of PNS and outline the value of 2-deoxy-2- ^{18}F -fluoro-D-glucose PET/CT in the evaluation of patients with a PNS. 2-deoxy-2- ^{18}F -fluoro-D-glucose PET/CT is valuable to identify or exclude an occult malignancy in patients with suspected paraneoplastic syndromes.

Keywords: occult malignancy • paraneoplastic syndromes • PET/CT

Paraneoplastic neurological syndromes (PNS) are a rare, heterogeneous group of complications associated with malignancy, unrelated to direct tumor invasion or metastasis, that may be immune-mediated [1]. The development of PNS may antedate the diagnosis of cancer by several months or years [2,3]. Therefore, early localization of the initiating cancer can play a crucial role in establishing a prompt and accurate diagnosis. The aim of this article is to provide an overview of PNS and outline the value of imaging with a focus on 2-deoxy-2- ^{18}F -fluoro-D-glucose (FDG) PET/CT in the management of PNS.

Overview of PNS

Pathogenesis

PNS are a collection of secondary disorders that are hypothesized to occur in patients with various forms of cancer. PNS have been documented to affect the CNS (e.g., limbic encephalitis, cerebellar degeneration, opsoclonus myoclonus and optic neuritis, among others), the peripheral nervous system (e.g., Guillain-Barré syndrome and autonomic neuropathy, among others), and the neuromuscular junction and muscle (e.g., Lambert-Eaton myasthenic syndrome, dermatomyositis and polymyositis, among others) [4].

The specific pathophysiology underlying the various subtypes of PNS is varied and poorly understood; however, autoimmune phenomena appear to be common. More specifically, antibodies [5] and T cells [6,7] responding to a cancer (often early stage or occult) are thought to develop crossreactivity. This crossreactivity can lead to an attack on homologous ectopic antigens, exclusively expressed by the central and peripheral nervous systems [8,9]. It is believed that an autoimmune response to normal self-antigens occurs because cancer cells process autoantigens in a different fashion, thereby making them reactive targets [10].

Conventional diagnostics

Owing to the heterogeneity of PNS presentations and the mild nature of early symptoms, quick and accurate diagnosis is often difficult. With this difficulty in mind, an international panel of neurologists proposed a rigorous set of clinically diagnostic criteria in 2004 [11]. By utilizing a patient's clinical presentation, cancer workup data, and response to both immunologic and cancer therapies, these criteria try to risk-stratify patients into PNS 'definite' or 'possible' diagnostic categories.

To augment the clinical diagnosis, serum antibodies associated with PNS are routinely

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screened in suspected patients. Of these antibodies, some are fully characterized, and others are only partially characterized, requiring further investigation (e.g., PCA2 and antibipolar cells of the retina, among others). Antibodies that are well characterized attack antigens whose molecular identity is already known and understood. These well-characterized antibodies are specifically pathologic, and are rarely found in patients without cancer and/or PNS [12,13].

While serum antibody screens can add important clinical data to the diagnosis of PNS, there are multiple well-established caveats. First, it has been established that cancer patients without PNS may still demonstrate a positive serum antibody screen for specific PNS-involved antibodies [14,15]. Furthermore, certain antibodies are associated with multiple PNS subtypes, and certain PNS subtypes are associated with multiples types of antibodies. In addition, several PNS antibodies may occur simultaneously in the same patient (e.g., in patients with small-cell lung cancer) [16,17]. Finally, it has been shown that positive antibody screens do not always differentiate between the paraneoplastic and the nonparaneoplastic causes of their associated syndromes. For example, patients with antiampiphysin antibodies typically have the associated stiff-person syndrome, but frequently do not have an associated cancer (and hence do not have PNS) [18,19].

In light of these various shortcomings with serum antibody screens, it is imperative to look for other, more precise methods for diagnosing patients with PNS. Lumbar puncture with the intent of screening the cerebrospinal fluid for paraneoplastic antibodies has been suggested, but in most cases, these antibodies

are found in the serum as well [20]. Other efforts have looked into utilizing electrophysiology for further diagnostic characterization of PNS. However, while certain syndromes (e.g., myasthenia gravis) are associated with characteristic electrophysiological findings, this modality does not allow one to differentiate between the PNS-associated syndromes and their non-PNS counterparts.

Finally, brain MRI can aid in the diagnosis of specific PNS subtypes, such as limbic encephalitis and cerebellar degeneration [21,22]. In the majority of PNS subtypes, however, brain MRI demonstrates normal or nonspecific radiologic changes. Previous studies demonstrated that morphological cross-sectional imaging modalities, such as CT or MRI, have a low yield in the localization of cancer in cases of PNS, since lesions may be small or limited to metastatic lymph nodes [23].

Role of FDG-PET & PET/CT in PNS

In many patients, PNS is diagnosed before the discovery of a primary cancer. In these patients, PET/CT can evaluate patients with suspected PNS to detect an occult malignancy and identify metabolic brain abnormalities confirming PNS. FDG-PET/CT is useful in the diagnosis, therapy assessment and follow-up of patients with many human solid tumors [24–30]. A number of retrospective and prospective trials have agreed on the utility of FDG-PET in the setting of PNS (Table 1), and especially in the event of an unknown primary tumor [31,32] or inflammatory etiology (Figures 1–4). However, differing results have resulted in two recommendations for the application of FDG-PET in PNS: imaging when PNS is clinically suspected, or imaging only in cases of antibody-proven PNS.

Table 1. Studies investigating the value of PET or PET/CT in paraneoplastic syndrome.								
Study (year)	Study type	Sample size (n)	PET or PET/CT	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Ref.
Vaidyanathan et al. (2012)	Retrospective	68	PET/CT	100.0	82.0	42.0	100.0	[23]
Hadjivassiliou et al. (2009)	Prospective	80	PET and PET/CT	75.0	87.0	44.4	98.4	[33]
Patel et al. (2008)	Retrospective	107	PET and PET/CT	80.0	67.0	53.0	88.0	[32]
Younes-Mhenni et al. (2004)	Prospective	20	PET	83.3	25.0	83.3	25.0	[34]
Berner et al. (2003)	Retrospective	30	PET	85.7	91.3	75.0	95.5	[35]
Rees et al. (2001)	Retrospective	43	PET	87.5	74.3	43.8	96.3	[31]
Most studies have found 2-deoxy-2- ¹⁸ F-fluoro-D-glucose PET for paraneoplastic neurological syndromes to have high NPV and moderate sensitivity, with more variation in specificity and PPV results. NPV: Negative-predictive value; PPV: Positive-predictive value.								

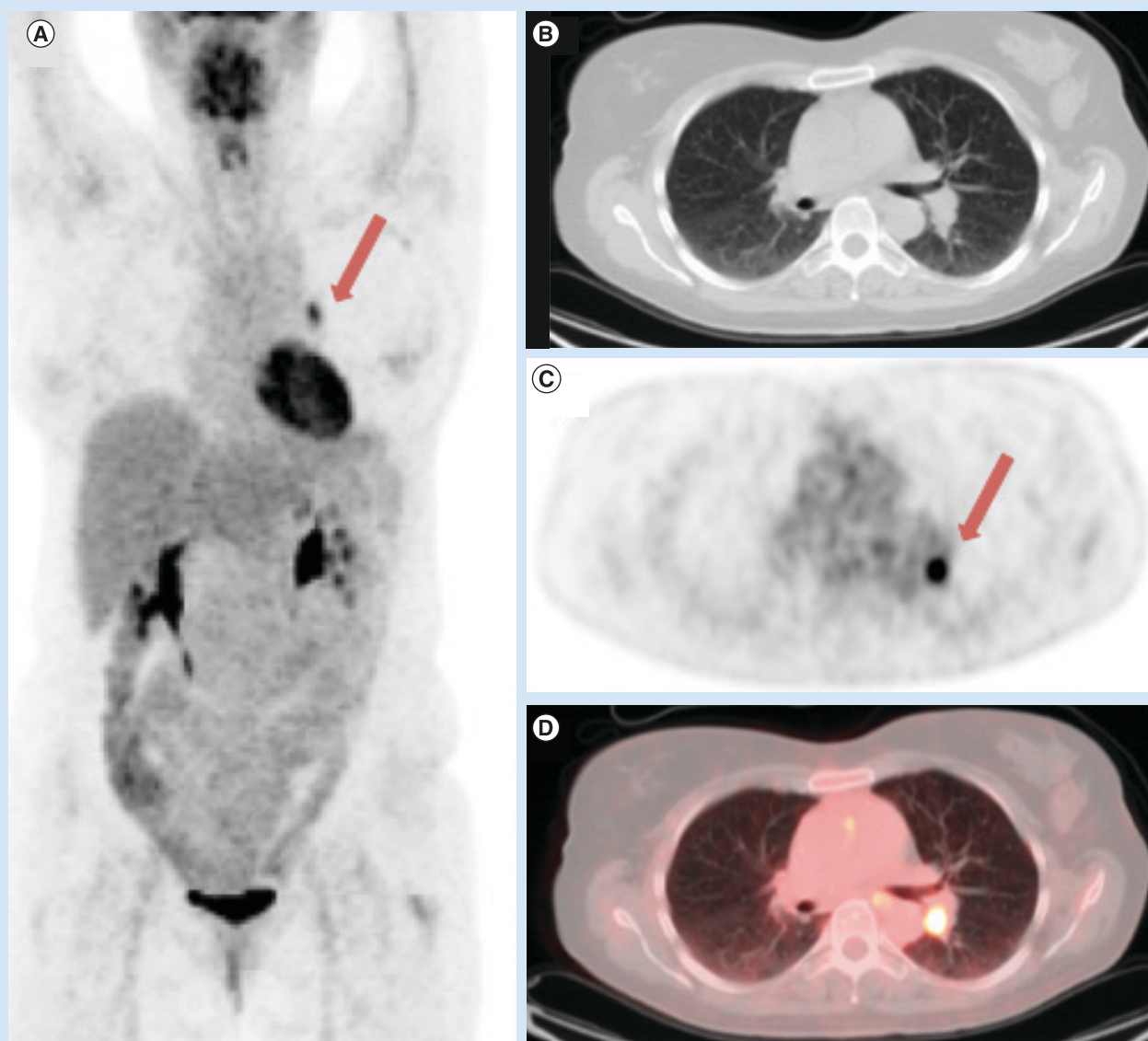


Figure 1. Small cell lung cancer. Demonstrates a 48-year-old woman with a history of sensory ataxia and spinal degenerative joint disease, who presented with progressive sensation loss and ataxia. The patient's symptoms started approximately 1 year prior with numbness and tingling of her right hand, which progressed slowly to involve her left hand as well. Her symptoms continued to progress and eventually to involve both her legs, as well as her trunk. (A) Anti-Hu antibody was positive. 2-deoxy-2- ^{18}F -fluoro-D-glucose PET/CT maximum-intensity projection, (B) axial CT, (C) PET and (D) fused, demonstrates a small focus of soft tissue density with intense 2-deoxy-2- ^{18}F -fluoro-D-glucose uptake in the left hilum (arrow), most consistent with lung cancer. She underwent a left lower lobe lobectomy and thoracic lymphadenectomy. Pathology revealed small cell lung cancer. By this time, she had profound motor and sensory deficits, and required a wheelchair. She received four cycles of adjuvant chemotherapy initially with cisplatin plus etoposide (one cycle), which was switched to carboplatin plus etoposide due to concern of worsening neuropathy. Her neuropathy slowly improved.

Rees *et al.* [31] retrospectively reviewed the records of 43 unselected patients with suspected PNS referred for FDG-PET scanning to determine the value of this technique when conventional imaging was negative. Of these, 16 patients had PET scans consistent with malignancy (37%) and 27 had negative scans. All but one of the patients with a negative PET result

remained free of malignancy on prolonged follow-up. They concluded specifically that FDG-PET was useful for detecting small lesions in the setting of suspected PNS, and that false-positive or -negative studies do not occur at a clinically problematic rate.

Berner *et al.* found a high specificity and negative-predictive value (NPV) and determined that FDG-PET

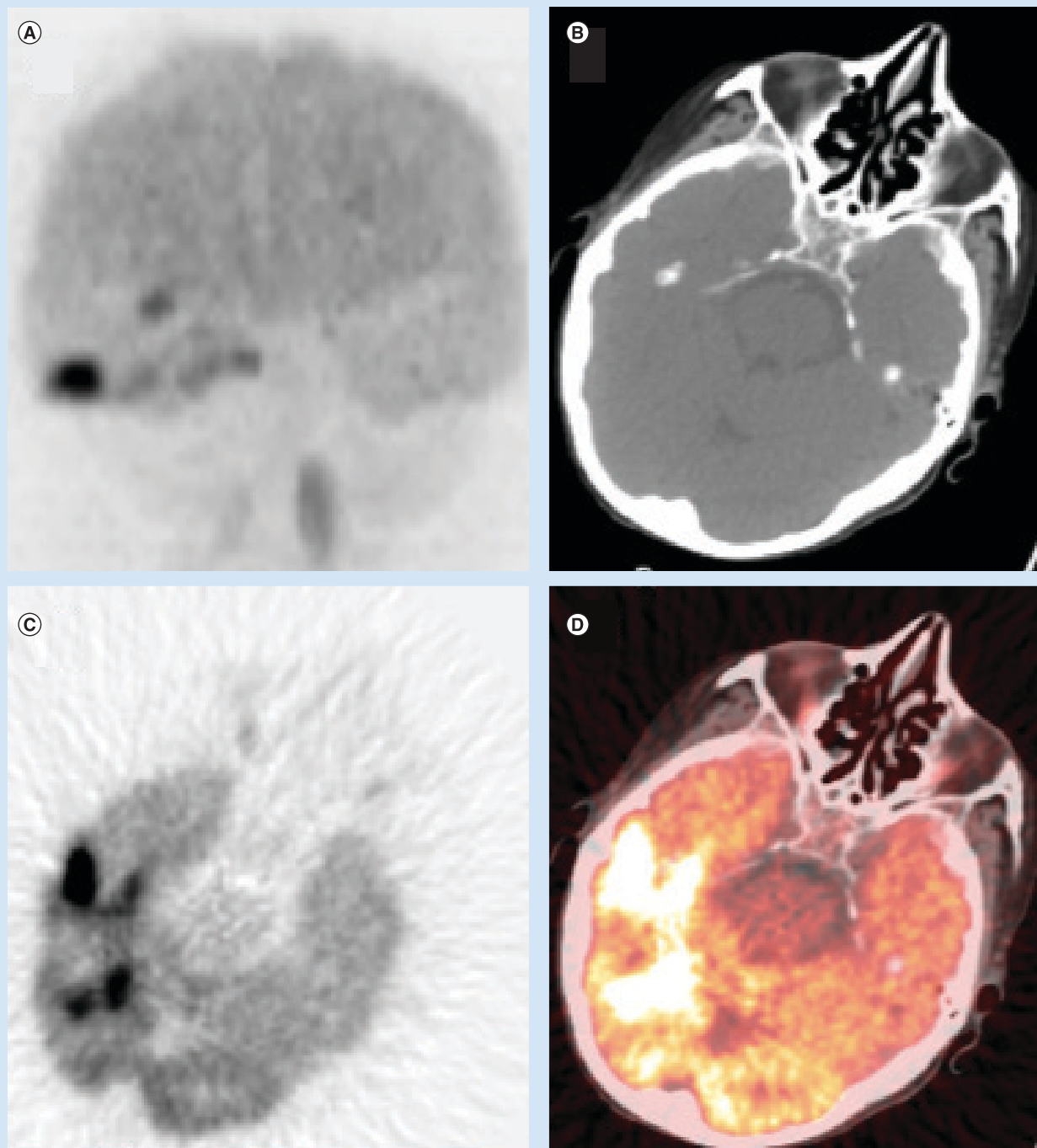


Figure 2. Granulomatous angiitis. Demonstrates a 73-year-old woman with history of cognitive decline over a few months. (A) 2-deoxy-2-¹⁸F-fluoro-D-glucose PET/CT maximum-intensity projection, (B) axial CT, (C) PET and (D) fused, ordered for suspicion of paraneoplastic syndrome demonstrates multiple focal intense right cerebral 2-deoxy-2-¹⁸F-fluoro-D-glucose-avid lesions, most prominent in the right inferior temporal lobe but also involving the right insula and temporal lobe. There is also relative sensorimotor cortical and occipital lobe sparing with otherwise diminished relative brain metabolic activity. These findings are suspicious for either an infectious/inflammatory process, possibly a granulomatous process (sarcoid or tuberculosis) given correlative calcified anterior mediastinal and pulmonary nodules (not shown). Brain biopsy was read as showing granulomatous angiitis.

is helpful in the diagnosis of patients with suspected PNS (Figures 5 & 6) [35]. In this study, out of 30 patients with suspected PNS, seven showed malignancy (23%). Six out of the seven were positive by PET (sensitivity: 86%). PET correctly ruled out underlying malignancy in 21 out of 23 patients (specificity: 91%). McKeon

et al. [36] studied 56 patients with clinically suspected PNS who underwent PET/CT after negative standard evaluations. These investigators demonstrated that the use of PET/CT increased the diagnostic yield for cancer by 18% in patients with suspected PNS for whom results of standard oncologic tests were negative.

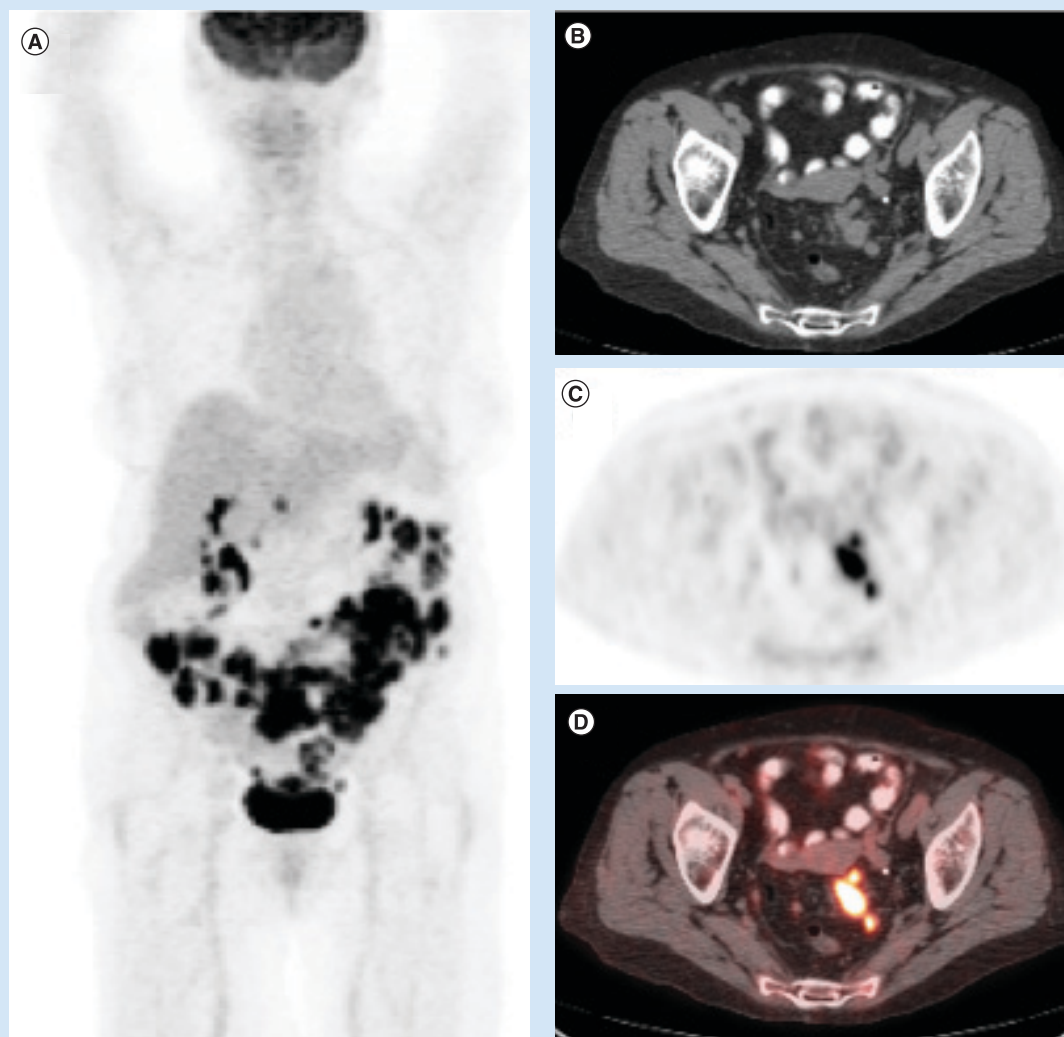


Figure 3. Primary peritoneal and papillary renal cell carcinomas. Demonstrates a 71-year-old lady who developed progressive unsteadiness of gait and difficulty with her balance over 4–5 months, progressive in nature, to the point of having difficulty with walking, as well as some slurring of her speech. She initially presented for neurology evaluation. She had no evidence of cerebrovascular disease. Her symptoms were suspicious for paraneoplastic cerebellar degeneration and 2-deoxy-2-¹⁸F-fluoro-D-glucose PET/CT scan was requested. (A) Maximum-intensity projection, (B) axial CT, (C) PET and (D) fused, demonstrated intense 2-deoxy-2-¹⁸F-fluoro-D-glucose activity, which fused to both ovaries, the superior uterus, numerous intraperitoneal masses and omental caking. Patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, resection of the terminal ileum, cecum, ascending colon and appendix, with ileal–ascending colon re-anastomosis, transverse colon resection with re-anastomosis and rectosigmoid resection with re-anastomosis. She also had a radical right nephrectomy for suspicious renal mass. Pathology revealed high-grade carcinoma with serous features with widespread metastasis. In view of the absence of tumor involvement of the entirely submitted ovaries and fallopian tubes and extensively sampled endometrium, the tumor was read as representing a primary peritoneal carcinoma. Renal specimen showed papillary renal cell carcinoma.

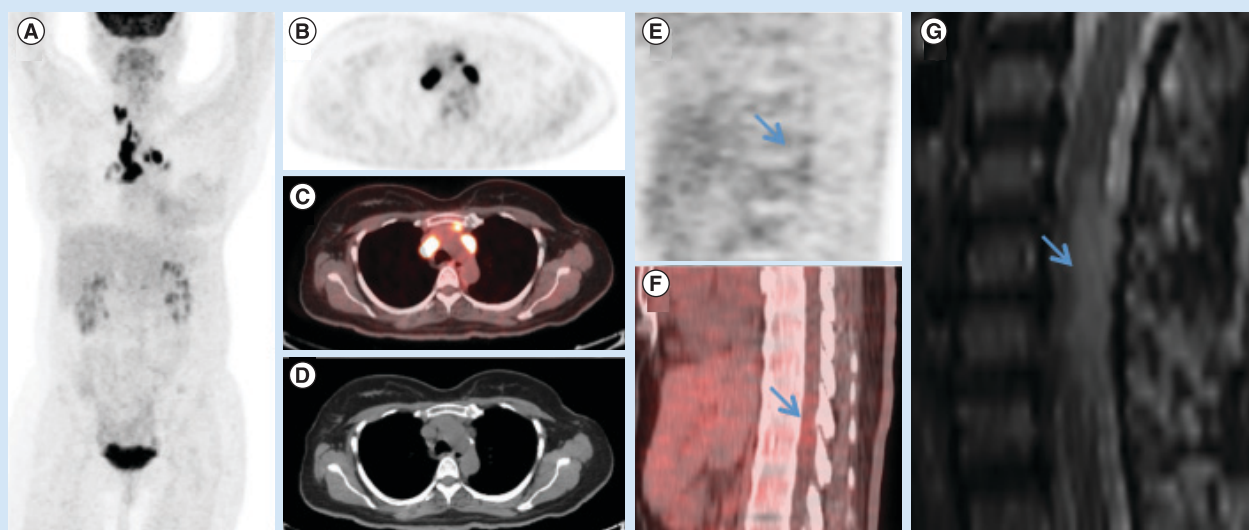


Figure 4. Neurosarcoidosis. Demonstrates a 56-year-old woman with a history of diabetes, hypertension, hyperlipidemia and myelopathy of unclear etiology, with worsening numbness that started in her groin and pelvic region and progressed to involve her lower extremities. The patient has had good response to steroid treatment. Extensive prior workup including rheumatologic evaluation and lumbar puncture with no clear etiology. PET/CT was ordered to evaluate for neoplastic process. (A) MIP, (B) axial CT, (C) PET and (D) fused images demonstrate intense 2-deoxy-2-¹⁸F-fluoro-D-glucose activity with mediastinal, paratracheal, hilar and right supraclavicular lymph adenopathy. (E & F) There is also increased 2-deoxy-2-¹⁸F-fluoro-D-glucose activity within the spinal canal of the mid/lower cervical spine (arrow), which correlates to (G) the T₂ hyperintensity and cord expansion on the MRI. Right-node biopsy was consistent with sarcoidosis. Final diagnosis was of steroid-responsive myelopathy related to neurosarcoidosis.

Linke *et al.* [37] showed that the integration of PET and CT scanning increases sensitivity and accuracy of tumor diagnosis. In this study, CT was positive for malignancy in three of ten patients (sensitivity of 30%), which FDG-PET detected in nine of ten (sensitivity of 90%), and the difference between the two techniques was significant ($p < 0.01$). The combination of both methods demonstrated a sensitivity of 100%. Nevertheless, Titulaer *et al.* stated a negative PET/CT does not rule out underlying cancer and repeat PET/CT scanning after a 3–6-month interval can be fruitful [38].

Patel *et al.* note that FDG-PET was more sensitive than CT for detecting an unknown primary tumor for patients with suspected PNS [32]. Vaidyanathan *et al.* showed that PET/CT is a highly sensitive and specific imaging technique in the assessment of PNS and adds confidence to clinical possibility [23]. In that retrospective study, they showed that PET/CT had 100% sensitivity, 82% specificity, 42% positive-predictive value (PPV) and 100% NPV in detecting malignant involvement of the PNS. On the other hand, clinical risk scoring on its own was 50% sensitive, 70% specific, 18% PPV and 91% NPV. On combining the two methods, the additive sensitivity was 100%, specificity was 84%, PPV was 36% and NPV was 100%.

FDG-PET useful for clinically suspected PNS for antibody-proven PNS

Younes-Mhenni *et al.* recommend a more restricted role for FDG-PET. Finding only moderate sensitivity and PPV, with poor specificity and NPV, they concluded that FDG-PET for PNS is only indicated for patients with well-defined PNS antibodies, in specific settings (e.g., unknown primary or difficult-to-biopsy lesions). They stated PET should be reserved for patients with well-characterized paraneoplastic antibodies when conventional imaging fails to detect primary malignancy [34].

On the contrary, Hadjivassiliou *et al.* found a high specificity and NPV and agreed with the utility of FDG-PET for clinically suspected PNS, without a need for positive PNS antibodies before imaging [33]. In this study, the prevalence of abnormal PET in 80 patients clinically suspected for PNS was 18 out of 80 (23%). Biopsy-proven cancer was confirmed in 44% of patients with abnormal PET as opposed to less than 2% of patients with a normal PET. According to their results, the presence of PNS antibodies should not be a prerequisite for performing a PET scan; however, the presence of PNS antibodies increases the chances of the PET scan detecting a tumor. Additionally, Matsuhisa *et al.* showed that PET/CT was a useful screening method for patients

with clinically suspected PNS who do not demonstrate well-characterized paraneoplastic antibodies. They retrospectively studied the utility of FDG-PET/CT in 27 patients with suspected PNS and found that FDG-PET/CT detected malignancy in 19% of the cases [39].

FDG-PET & altered brain glucose metabolism:

The metabolic abnormalities depicted on PET/CT typically correlate with clinical symptoms. Both qualitative and quantitative analysis of brain glucose metabolism may be helpful in evaluating PNS, especially in patients with a normal MRI. In many patients with paraneoplastic limbic encephalitis, FDG-PET shows hypermetabolism in the temporal lobes with negative findings on MRI or T2-hyperintense mesiotemporal lesions. In the literature, focal hypermetabolism on PET was attributed to seizure activity [40,41], or an underlying inflammatory process [42–44]. Patients with PNS may demonstrate abnormal hypometabolism

on brain FDG-PET/CT before MRI demonstrates cerebellar atrophy [45].

Conclusion

In conclusion, FDG-PET/CT offers value in investigating suspected PNS to identify or exclude occult malignancy, with a greater likelihood of cancer detection in cases of antibody-proven PNS.

Future perspective

FDG-PET/CT is valuable in excluding occult malignancy in patients with suspected PNS. It may help in identifying the malignancy in antibody-proven PNS. The value of novel radiopharmaceuticals, such as ^{11}C -choline and ^{68}Ga -DOTA, in identifying the occult malignancies is currently unknown in patients suspected or antibody-proven PNS and further studies will be conducted in the next few years. In addition, future novel radiopharmaceuticals targeting the immune system will help elucidate the biologic mechanisms of PNS.

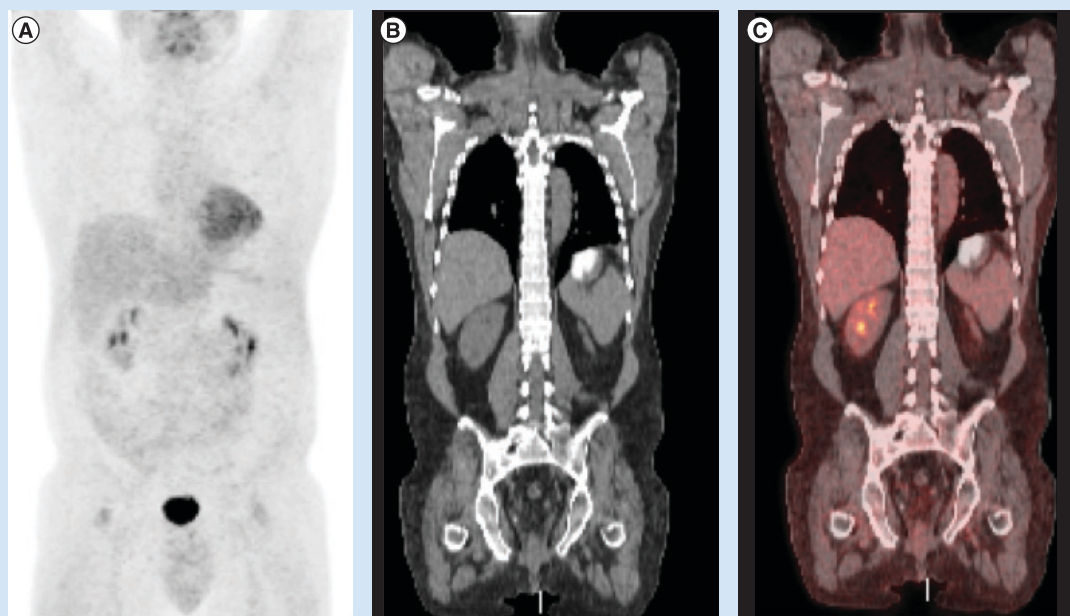


Figure 5. Amyotrophic lateral sclerosis with negative PET/CT. Demonstrates a 50-year-old male with weakness and numbness in the lower legs, progressing over 2 years. The patient was in his usual state of health until November 2010, when while lifting a heavy object, he heard a pop in his lower back and developed excruciating pain radiating to his legs. He received treatment with multiple spinal injections and underwent microdissection. However, after the surgery he started developing weakness with numbness/tingling involving his left toes, which have progressed cranially involving his left knee. Diagnostic MRIs were negative. Subsequently, a sural nerve biopsy showed borderline neuropathic changes with increased rate of myelin remodeling. A trial of high-dose anti-inflammatory did not show improvement. Despite multiple courses intravenous immunoglobulin treatment, his symptoms progressed rapidly to the proximal thighs bilaterally. PET/CT scan was considered in order to evaluate for possible malignancy/paraneoplastic syndrome. (A) Maximum-intensity projection, (B) coronal CT and (C) coronal fused images showed no evidence of 2-deoxy-2- ^{18}F -fluoro-D-glucose-avid disease. Subsequently, a genetic study for familial amyotrophic lateral sclerosis showed positive for *SOD1* mutation.

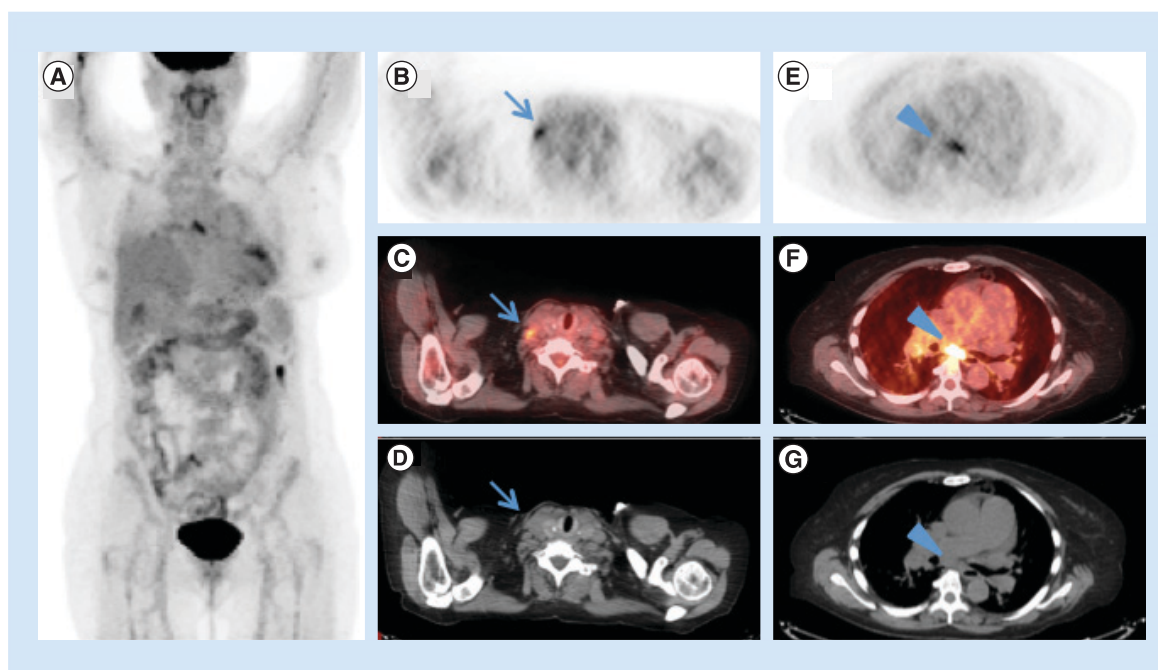


Figure 6. False-positive scan. A 72-year-old woman presented with 10–12 weeks history of progressive shortness of breath, fatigue and generalized weakness. Her symptoms improved with a diuretic and she was discharged home with oxygen. She returned to the hospital with worsening symptoms and proximal lower extremity weakness. She was found to have mild noninflammatory proximal myopathy on electromyography and clinical exam. PET/CT was ordered to evaluate for paraneoplastic syndrome. (A) Maximum-intensity projection, (B & E) axial PET, (C & F) fused and (D & G) CT demonstrated 2-deoxy-2-¹⁸F-fluoro-D-glucose-avid right level IV cervical (arrow) and subcarinal (arrowhead) adenopathy. Biopsy of both nodes revealed benign lymphoid tissue.

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Executive summary

- Paraneoplastic neurological syndromes (PNS) are a rare, heterogeneous group of complications associated with malignancy that may be immune-mediated.
- 2-deoxy-2-¹⁸F-fluoro-D-glucose-PET/CT offers value in investigating suspected PNS to exclude occult malignancy, with very high negative-predictive value.
- 2-deoxy-2-¹⁸F-fluoro-D-glucose-PET/CT has a greater likelihood of cancer detection in cases of antibody-proven PNS.

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- Retrospective study involving 104 patients with paraneoplastic neurologic syndromes (PNS); 73 patients had at least one positive result for paraneoplastic antibody, and 31 had antibody-negative PNS. Malignancy was confirmed pathologically in ten patients, of whom eight had positive PET results. There were two cases of confirmed malignancy (fallopian tube adenocarcinoma and spindle cell uterine carcinoma), for which PET results

- were negative. Two patients with positive PET results declined biopsy. All patients with confirmed malignancy had positive results for at least one paraneoplastic antibody. One patient with positive results for PNS antibody and negative PET results was diagnosed as having small-cell carcinoma on a follow-up PET scan after 27 months. PET had sensitivity, specificity, positive-predictive value and negative-predictive value of 80, 67, 53 and 88%, respectively.
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