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Role of F-18 FDG PET/CT imaging in the diagnosis of paraneoplastic neurological syndromes*

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Abstract Paraneoplastic neurological syndromes (PNS) is a series of rare neurologic disorders which happen with an underlying malignancy. It has various clinical symptoms proceding to the diagnosis of tumors. Although the abnormality of anti-neuronal antibodies is suggestive of PNS and tumors, there exist many false positive and false negative cases. The diagnosis of PNS is usually a challenge in clinic. Positron emission tomography/computed tomography (PET/CT) imaging is an anatomical and functional fusion imaging method, which provides the whole-body information by single scan. Fluorodeoxyglucose (FDG) PET/CT imaging can not only detect potential malignant lesions in the whole body, but also assess functional abnormality in the brain. In this review, the mechanism, clinical manifestation, diagnostic procedure and the recent progress of the utility of FDG PET/CT in PNS are introduced respectively.

Key words paraneoplastic neurological syndrome (PNS); fluorodeoxyglucose (FDG); positron emission tomography/computed tomography (PET/CT); anti-neuronal antibody

Paraneoplastic syndromes is a series of rare diseases which impact distant organs and cause their dysfunction in some patients, who have underlying malignant tumors with no metastasis. Among them, paraneoplastic neurological syndromes (PNS) is a heterogeneous group of neurologic disorders caused by indirectly abnormal immune response [1]. Although PNS have the incidence less than 1%, they can lead to severe neurological dysfunction in clinic. The treatment to the primary tumor is crucial to relieve symptoms and prolong the survival period. In clinic, neurological symptoms often appear before the primary tumor, even a few years earlier. PNS have various clinical manifestations. The occurrence of PNS is not necessarily associated with abnormality of paraneoplastic antibodies. Moreover, the paraneoplastic antibodies can increase without neurological symptoms. These problems lead to the difficulty in the diagnosis of PNS in clinic.

Positron emission tomography/computed tomography (PET/CT) can provide functional and anatomy fusion information to evaluate whole-body situation by single scan. ^{18}F-fluorodeoxyglucose (FDG) is a glucose analogue which accumulates significantly higher in tumor cells than normal tissue, its value in the diagnosis of malignant tumors has been widely recognized [2]. Moreover, FDG imaging can also evaluate the level of glucose metabolism in brain tissue [3]. In this review, the mechanism, clinical diagnosis, diagnostic procedure and FDG PET/CT applications in PNS were introduced.

General introduction

PNS occur in almost all types of cancer, especially in small cell lung cancer (SCLC), thymoma, ovarian cancer, teratoma, Hodgkin's lymphoma, testicular cancer, breast cancer, head and neck tumors [1]. SCLC is the most common cancer with PNS in adults, with the incidence of 1%–3%. Neuroblastoma is the most common cancer with PNS in children. The incidence of opsoclonus-myoclonus syndrome (OMS) is 2%–3% [4]. Paraneoplastic lesions can involve any part of the nervous system, such as brain, spinal cord, peripheral nerves, nerve-muscle joints and muscles, therefore PNS present a variety of neurological symptoms. Some neurological disorders such as paraneoplastic encephalomyelitis (PEM), paraneoplastic cerebellar degeneration (PCD), OMS, subacute sensory

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neuron disease and Lambert-Eaton myasthenic syndrome (LEMS) are often associated with the occurrence of cancer, which have been considered as classical PNS. For example, LEMS suggested the existence of SCLC [5].

Pathogenesis

The etiology of PNS is still unclear, but it is generally considered that the abnormal immunological cross-reaction plays an important role in the pathogenesis of PNS. In PNS, tumor cells express some proteins which are normally expressed in nervous system. The immune responses against these proteins act on nervous system, resulting in the occurrence of PNS. Although there is no clear evidence that paraneoplastic antibodies are the risk factors of PNS, these antibodies can be relevant markers. Paraneoplastic antibodies include anti-Hu, anti-Yo, anti-CV2, anti-Ri, anti-Ma2, anti N-methyl-D-aspartate receptor (NMDAR) and anti-amphiphysin antibody [6–9]. Anti-Hu antibody is closely associated with SCLC, relating to limbic encephalitis, PEM, sensory neuron disease and PCD. About half of patients with limbic encephalitis have positive anti-Hu antibody and poor prognosis. Anti-Yo antibody is often associated with breast cancer and ovarian cancer, relating to PCD. Anti-Ri antibody is found in breast cancer, gynecological cancers and SCLC, relating to PCD and OMS. Anti-CV2 (or CRMP5) antibodies are often associated with SCLC and breast cancer, relating to PEM, PCD and perceptual-motor neuron disease. Anti-Ma2 antibody is associated with testicular germ cell tumors and SCLC, relating to the dysfunction of limbic lobe, interbrain and brainstem. Anti-amphiphysin antibody is associated with testicular germ cell tumors and breast cancer, relating to stiff person syndrome and PEM [7–8]. Anti-NMDAR antibody usually occurs in ovarian teratoma and is related to encephalitis [9].

Diagnostic criteria

In 2004, the diagnostic criteria of PNS were proposed by Graus as follow [10]. When neurological abnormalities occur within five years with typical clinical manifestations and tumor lesions, whether paraneoplastic antibodies are abnormal or not, PNS can be diagnosed. When atypical clinical symptoms are relieved or disappeared after the anti-tumor therapy and exclude the spontaneous remission, PNS can also be diagnosed. When the patients with typical or atypical clinical symptoms have positive classical anti-neuronal antibodies, even no obvious sigh of tumors, they should be given long-term follow-up for suspect PNS.

Diagnostic procedure

Anti-neuronal antibody, clinical syndrome and possible underlying malignancy all determined the risk and diagnosis of PNS [6]. Medical imaging methods contribute differently to the screening of malignant lesions. For thoracic lesions, a CT is recommended firstly, which if negative is followed by FDG PET/CT scan. Breast lesion is screened by mammography, followed by MRI. For pelvic lesions, ultrasound is recommended firstly, followed by CT, MRI and PET/CT. FDG PET/CT plays an important role in providing whole-body information. If conventional examinations are negative, FDG-PET/CT is followed. If no paraneoplastic antibodies are found, the patient has a classical PNS and the neurological condition is deteriorating, repeat screening regularly every 6 months up to 4 years in patients is needed.

Diagnostic value of FDG PET/CT in PNS

PET/CT imaging is a kind of fusion imaging combined anatomical CT imaging with functional PET imaging. Functional abnormalities can be found in early stage prior to the structural abnormality, thus PET/CT has a high sensitivity in the detection of malignant lesions. As a glucose analogue, ^{18}F-FDG shows the glucose metabolism in the whole body and brain tissue. Because the energy is entirely provided from glucose metabolism in brain, the brain abnormal FDG uptake is more sensitive than the structural change in diagnosis. To PNS, either PET or PET/CT can improve the tumor diagnostic efficiency by 20% while other routine examinations (eg, whole-body CT scan) showed negative results [11]. In a case of paraneoplastic limbic encephalitis, MRI showed hyper-intensity on the left amygdala and hippocampus on T2-weighted images, whereas FDG PET/CT not only showed the abnormal metabolism in above lesions, but also detected malignant lesion in lung, suggesting the diagnosis of lung cancer [12]. Therefore, FDG PET/CT plays important role in the assessment of neurological lesions and detection of malignant lesions in PNS.

Evaluation on nervous lesions

As a kind of functional imaging, FDG PET show the change of brain glucose metabolism which occurs before the anatomical changes. FDG PET imaging would be more sensitivity to detect brain lesions than MRI. In a case with positive anti-Ma2 antibody, MRI showed hyper-intensity in the former central temporal gyrus with no contrast-enhancement, whereas PET displayed increased FDG uptake in more areas including deep cerebellar, inferior rectus and superior oblique muscle. This patient was eventually diagnosed as testicular seminoma with the help of PET imaging [13]. There were many relevant studies and case re-

ports about paraneoplastic limbic encephalitis, a classical PNS. FDG PET could show abnormal high metabolism in temporal lobe limbic system, whereas MRI imaging failed [14]. In a case of limbic encephalitis and increasing anti-Ma2 antibody, MRI imaging showed that the hyper-intensity in the left medial temporal lobe did not change in T2-weighted images, whereas the FDG uptake increased gradually in PET imaging [15]. Ances *et al* [16] detected three cases of cerebral glucose metabolic abnormalities among seven cases of limbic encephalitis patients, including one case of increased metabolism of brain stem and reduced metabolism of occipital lobe, two cases of increased metabolism of cerebella. In a case of PCD, the abnormally high metabolism in cerebellum reduced after treatment, indicating the role of FDG PET in the assessment of PNS. Till now, the mechanism of glucose metabolism in PNS lesions has not been declared. Some studies thought high metabolic areas might represent epileptic foci and some explained high metabolism with inflammation [17].

Meanwhile, some other studies found abnormally reduced glucose metabolism in brain lesions in PNS [18]. Clapp *et al* [19] reviewed 102 patients of suspected or confirmed PNS undergoing FDG PET brain imaging. 67 cases showed reduced cerebral glucose metabolism in different areas, including diffuse cerebral cortex (36 cases), cerebellum (10 cases), basal ganglia (10 cases), frontal (9 cases), temporal lobe (1 case) and occipital lobe (1 case), especially cortical sensorimotor cortex. In this study, 62.9% of cases had abnormal FDG uptake, whereas MRI showed no abnormality, revealing the great value and advantage of FDG PET in the diagnosis of brain disorders of PNS. When PNS involved the neuron-muscle joint and caused some diseases such as LEMS and gravis myasthenia, FDG PET/CT could not show abnormality in the peripheral nervous lesions. In some patients with dermatomyositis or polymyositis, diffused slightly increased FDG uptake in muscle could be shown, relating to the possibility of inflammatory reaction [6].

Evaluation on malignant lesions

Evaluation by FDG PET

When positive paraneoplastic antibodies strongly suggested malignant tumors, FDG PET has a great value to detect the potential malignant lesions [20]. Linke *et al* [21] evaluated 13 cases with positive antibody using PET. The tumor detective rate by PET was 90% (10/13), that of CT was only 30% (4/13) and that of PET with CT was 100%. In a prospective study about 20 patients with positive paraneoplastic antibodies but normal CT or MRI results, PET imaging showed abnormalities in 18 cases, including 13 cases of lesions in mediastinum, 2 in lung, 2 in breast, 1 in parotid gland and 7 in cervical, supraclavicular, axillary lymph nodes. Finally, 8 cases of SCLC, 2 of breast cancer, 2 of lung adenocarcinoma, 1 of ovarian cancer axillary lymph node metastases, 1 of malignant thymoma were diagnosed, showing that FDG PET could improve the detective efficiency in cancer [22].

Although positive paraneoplastic antibodies suggest the existence of PNS, there were some false positive or false negative cases. Hadjivassiliou *et al* [23] evaluated 80 suspected PNS cases whose CT were negative in six years. The diagnostic positive rate of PET was 23% (18/80), true positive rate was 61% (11/18), and false negative rate was 5% (3/62). The positive rate of PET in the diagnosis of classical PNS was 41%, higher than that in non-classical PNS (21%). The diagnostic sensitivity of PET was 75% and specificity is 87%, whereas the true positive rate of antibody was only 50% (7/14). Patel *et al* [24] studied 104 suspected PNS cases, including 73 cases of positive antibody and 31 cases of negative antibody. In the 10 cases finally diagnosed as cancer, PET diagnosed eight cases and CT diagnosed three cases. Moreover, 5 patients were shown abnormal only by PET imaging. The diagnostic sensitivity, specificity, positive predictive value, and negative predictive values of PET were 80%, 67%, 53% and 88%, respectively. Two cases of false negative PET findings were tuberculosis and uterine adenocarcinoma. Therefore, the efficacy of FDG PET in the diagnosis of PNS, especially in the diagnosis of malignant tumors, is higher than that of paraneoplastic antibodies. According to the guideline by European Federation of Neurological Societies in 2011, when the patients were suspected PNS but routine examinations were negative, regardless of the antibody positive or not, whole-body FDG PET imaging was recommended [6].

Evaluation by FDG PET/CT

Because FDG PET/CT can provide the information of glucose metabolism and morphology, it has been widely applied to improve the diagnostic accuracy in tumors. 66 cases with PNS were analyzed retrospectively and compared the diagnostic value between PET/CT and enhanced CT [25]. PET/CT diagnosed 10 cases of malignant tumors, including bronchial cancer, breast cancer, cervical cancer, ovarian cancer, bladder cancer, tonsil cancer and lymph node metastasis, except for one case of false positive diagnosis of thymoma, whereas enhanced CT could not diagnose cervical cancer, tonsil cancer and ovarian cancer lymph node metastasis. The diagnostic sensitivity and specificity of PET/CT was 100% and 90%, and that of enhanced CT was 78% and 88% respectively. PET/CT showed the advantage in the diagnosis of neck and gynecological tumors, lymph node metastasis without abnormal sizes. Another advantage of PET/CT was the ability to detect multiple lesions by one scan. In the same study, two cases of double primary tumors were diagnosed, one case of lung adenocarcinoma and tonsil cancer, and another case of bronchial cancer and bladder cancer. PET/CT had the positive rate of 26% (18/68), the

sensitivity of 100% and specificity of 82% [26]. Matsuhisa *et al* [27] used FDG PET/CT imaging to evaluate 27 PNS suspected patients and showed its diagnostic sensitivity was 83% (5/6). In 7 patients with positive antibodies, one false positive case was found no abnormal FDG uptake or malignant tumor. A 42-year-old female who presented progressive neurological symptoms without positive antibody was evaluated by PET/CT imaging. The abnormality was found in the right breast, which was diagnosed as invasive ductal carcinoma. Her neurological symptoms disappeared after anti-tumor treatment [28]. Conversely, some early studies showed that the diagnostic accurate and sensitivity of PET/CT in PNS were not high. In a retrospective study of suspected PNS cases, the positive rate of PET/CT was only 22% (10/46), true positive rate was 8.7% (4/46), and the diagnostic sensitivity was 40% [29]. The reason might be related to the difference of samples, small number cases or lack of experience.

Limitations of FDG PET/CT

Because FDG accumulates physically in maxilla, vagina, uterus, ovaries, testicles and bladder, the diagnostic efficiency is limited in these organs. The diagnosis of the urinary lesions can be affected by the high uptake of FDG in the urine [30]. To solve these problems, the combination of other examinations such as enhanced CT or MRI can improve the diagnostic efficiency. In addition, focal delayed imaging is also helpful to the differentiation. Some tumor positive imaging agents were also expected to be used to improve the diagnosis of tumors, such as ^{68}Ga-DOTA, ^{68}Ga-octreotide, ^{18}F-FMT, 11C-FLT, and ^{18}F-galacto-RGD [2].

Conclusion

PNS have various clinical manifestations and neurological symptoms which usually appear before the diagnosis of tumors, causing the difficult diagnosis in clinic. Although paraneoplastic antibodies are suggestive of PNS, there exist many false-positive and false-negative cases. The advantage of FDG PET/CT in the diagnosis of PNS is not only in the detection of potential malignant lesions in the whole body, but also in the early evaluation of brain lesions with abnormal metabolism prior to morphological change. Therefore, when the patients are suspected of PNS but routine examinations can not find malignant lesions, regardless of antibody positive or not, FDG PET/CT should be considered as an important tool in the diagnosis or follow-up. With the development of novel tumor imaging agents and the optimization of imaging technology, the diagnostic efficacy of PNS is expected to improve greatly.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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