Review Article

Usefulness of Positron Emission Tomography in Patients with Syphilis: A Systematic Review of Observational Studies

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Abstract

Background: Diagnosis of syphilis is difficult. Follow-up and therapy evaluation of syphilitic patients are poor. Little is known about positron emission tomography (PET) in syphilis. This review was to systematically review usefulness of PET for diagnosis, disease extent evaluation, follow-up, and treatment response assessment in patients with syphilis.

Methods: We searched PubMed, EMBASE, SCOPUS, Cochrane Library, Web of Science, ClinicalTrials.gov, and three Chinese databases (SinoMed, Wanfang, and CNKI) for English and Chinese language articles from inception to September 2016. We also collected potentially relevant studies and reviews using a manual search. The search keywords included the combined text and MeSH terms "syphilis" and "positron emission tomography". We included studies that reporting syphilis with a PET scan before and/or after antibiotic treatment. The diagnosis of syphilis was based on serological criteria or dark field microscopy. Outcomes include pre- and post-treatment PET scan, pre- and post-treatment computed tomography, and pre- and post-treatment magnetic resonance imaging. We excluded the articles not published in English or Chinese or not involving humans.

Results: Of 258 identified articles, 34 observational studies were included. Thirty-three studies were single-patient case reports and one study was a small case series. All patients were adults. The mean age of patients was 48.3 ± 12.1 years. In primary syphilis, increased fluorodeoxyglucose (FDG) accumulation could be seen at the site of inoculation or in the regional lymph nodes. In secondary syphilis with lung, bone, gastrointestinal involvement, or generalized lymphadenopathy, increased FDG uptake was the most commonly detected changes. In tertiary syphilis, increased glucose metabolic activity, hypometabolic lesions, or normal glucose uptake might be seen on PET. There were five types of PET scans in neurosyphilis. A repeated PET scan after treatment revealed apparent or complete resolution of the asymmetry of radiotracer uptake.

Conclusion: PET is helpful in targeting diagnostic interventions, characterizing disease extent, assessing nodal involvement, and treatment efficacy for syphilis.

Key words: Diagnosis; Positron Emission Tomography; Syphilis; Therapeutics

Introduction

Syphilis is a systemic sexually transmitted disease caused by the spirochete *Treponema pallidum*. The World Health Organization estimated that 5.6 million new cases of syphilis occurred among adolescents and adults aged 15–49 years worldwide in 2012, with a global incidence rate of 1.5 cases per 1000 females and 1.5 cases per 1000 males.[1] The estimated 18 million prevalent cases of syphilis in 2012 translated to a global prevalence of 0.5% among females and 0.5% among males aged 15–49 years.[1] Left untreated, syphilis can progress through four stages: primary syphilis, secondary syphilis, latent syphilis, and tertiary syphilis. Primary syphilis is characterized by a chancre (sore or ulcer) at the site of inoculation and painless regional lymphadenopathy.[2] Secondary syphilis can present with variable manifestations of skin lesions as well as systemic expression. Latent syphilis is characterized by positive syphilis serology with no clinical symptoms or signs. The tertiary stage is subdivided into three general

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categories: gummatous syphilis, followed by cardiovascular syphilis and finally neurosyphilis.[3] In particular, tertiary syphilis often mimics cancer, because it frequently presents as a space-occupying lesion in visceral organs.[3,4]

Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) uptake on positron emission tomography (PET) is one of the most valuable imaging methods for establishing tumor extent and size, assessing nodal disease, and detecting distant metastases in head and neck cancer.[5] ^{18}F-FDG accumulation in tissues is proportional to the amount of glucose utilization, and thus increased glucose absorption is observed in most cancers, infections, and inflammatory disorders.[6,7]

Syphilis has often been called "the great imitator". The signs and symptoms may be difficult to distinguish from other diseases.[8] Secondary syphilis can be present without any symptoms, but with generalized lymphadenopathy. Most patients with uncomplicated aortitis are asymptomatic. Diagnosis of neurosyphilis can be difficult, as many patients are asymptomatic or present with nonspecific symptoms. Currently, follow-up and therapy efficacy evaluation of syphilis are poor.[9] Considering that PET is a promising new imaging technique for infectious and inflammatory disorders,[6] the aim of this systematic review was to evaluate PET for diagnosis, disease extent evaluation, follow-up, and treatment response assessment in patients with syphilis.

Methods

Databases and search strategy

The present protocol was registered online at the International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/RPOSPERO, registration number: CRD42016047471). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting systematic reviews were followed.

We first searched the existing literature for systematic reviews and meta-analyses involving studies on PET scans in syphilis. However, no reviews or meta-analyses were found. We then used the combined text and MeSH terms "syphilis" and "positron emission tomography". Two authors (Jian-Hua Chen and Xin Zheng) searched the following electronic bibliographic databases: PubMed, EMBASE, SCOPUS, Cochrane Library, Web of Science, ClinicalTrials.gov, and three Chinese databases (SinoMed, Wanfang, and CNKI). The period for research was from establishment of each database to September 2016. We also collected potentially relevant studies and reviews using a manual search. We assessed both English and Chinese language articles for eligibility.

Study selection and data extraction

The inclusion criteria for studies were that the diagnosis of syphilis was based on serological criteria or dark field microscopy and that syphilitic patients must have undergone a PET scan before and/or after antibiotic treatment. The exclusion criteria were articles not published in English or Chinese or not involving humans.

Two independent investigators (Jian-Hua Chen and Xin Zheng) reviewed the study titles and abstracts, and studies that satisfied the inclusion criteria were retrieved for full-text assessment. Consensus was reached through discussion with all of the authors.

We extracted the following data from each selected study: first author, publication year, age, gender, symptoms, cerebrospinal fluid examinations, pre- and post-treatment serum rapid plasma regain (RPR) or venereal disease research laboratory test (VDRL) titers, type of syphilis, pre- and post-treatment PET scans, and pre- and post-treatment computed tomography (CT) and magnetic resonance imaging (MRI) examinations.

Results

Search results

Our initial database search retrieved 258 articles, of which 224 were excluded for not meeting the inclusion criteria [Figure 1]. All 34 observational studies included in the systematic review were published in English. Thirty-three studies were single-patient case reports and one study was a small case series [Table 1]. All patients were adults, 28 (80.0%) were male, 6 (17.1%) were female, and one patient's gender was not reported. The mean age was 48.3 ± 12.1 years. Hoffman *et al*.[10] reported the first syphilitic patient with a PET scan after antibiotic treatment in 1993, and Heald *et al*.[11] reported another case with a PET scan before antibiotic treatment in 1996. All PET scans in the studies were ^{18}F-FDG PET, except for the study by Mimura *et al*.,[12] in which oxygen-15-labeled tracers were used for the PET scan [Tables 2 and 3]. There were three cases of syphilis with HIV coinfection. Five studies provided the

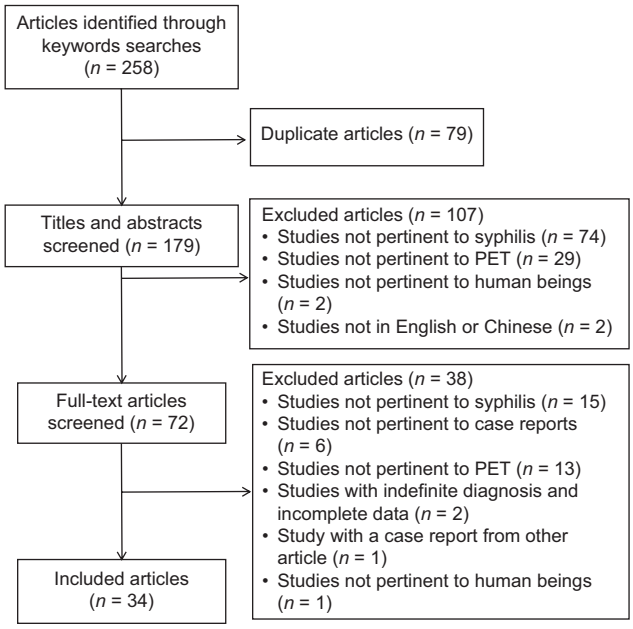

Figure 1: Flow diagram of search strategy for this systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. PET: Positron emission tomography.

Table 1: Laboratory results of all included studies

First author	Publication year	Gender	Age (years)	Symptoms
Scheurkogel[3]	2012	Male	55	Weight loss, night sweats, left upper quadrant pain
Tamura[5]	2008	Male	48	ND
Kösters[7]	2005	Male	42	No complaint
Hoffman[10]	1993	Male	25	Headache, seizure
Heald[11]	1996	Male	23	Diplopia, facial numbness, leg weakness, gait disturbance
				ND
Mimura[12]	1997	Female	41	Amnesic-confabulatory state with hypomanic-expansive features
Pruzzo[13]	2008	Male	59	ND
Kim[14]	2016	Male	49	No complaint
Park[15]	2013	Male	45	Weakness, hair loss, anorexia, weight loss, night sweats
Kim[16]	2011	Female	59	Abdominal pain, weight loss, cough, expectoration
Alrajab[17]	2012	Male	40	Abdominal and chest pain
Fu[18]	2015	Male	50	General fatigue, weight loss
Wang[19]	2011	Male	35	Bone pain in all 4 extremities
Dietrich[20]	2014	Male	70	Eruption, lymphadenopathy, slightly reduced general condition
Baveja[21]	2014	Male	39	Fever, anorexia, malaise, pain in abdomen, dark colored urine
Joseph Davey[22]	2016	Male	50	No complaint
Balink[23]	2013	Female	42	Neck and spine pain
Treglia[24]	2013	Male	40	ND
Fields[25]	2015	Female	55	Sore throat, fever, congestion, cough, pruritic rashes, fatigue, palpitations, tachycardia
De Rango[26]	2013	Female	63	Epigastric pain radiating to back
Ghazy[27]	2011	Female	65	Epigastric discomfort, back pain
Gaslightwala[28]	2014	Male	59	Fever, chills, night sweats, weight loss
Lin[29]	2009	ND	43	Headache, deteriorating mobility, nonsensical speech, behavioral changes
Omer[30]	2012	Male	55	Memory difficulties
Monticelli[31]	2016	Male	62	Low back pain, paraparesis, rashes
Pfender[32]	2015	Male	52	Involuntary irregular movements, emotional instability, and concentration problems
Ranganath[33]	2015	Male	58	Night sweats, blurry vision with floaters, weight loss
Rescigno[34]	2014	Male	50	Blurred vision
Payet[35]	2011	Male	61	Fatigue, night sweats, cervical pain, deafness, rash
Kasanuki[36]	2013	Male	51	Progressive cognitive decline
Spyridonidis[37]	2002	Male	58	Pain in the shoulder and hip, weight loss
Scheid[38]	2005	Male	34	Seizure, generalized cognition slowing
Verjans[39]	2016	Male	56	Progressive memory disturbances
Schöffski[40]	2014	Male	32	Fatigue, weight loss

First author	Pretreatment					Posttreatment	
	CSF WBC	CSF Pro	Serum RPR/VDRL	CSF RPR/VDRL	Serum FTA-ABS	Serum RPR/VDRL	RPR/VDRL
Scheurkogel[3]	ND	ND	Positive	ND	ND	ND	ND
Tamura[5]	ND	ND	1:64	ND	ND	ND	ND
Kösters[7]	190 cells/mm^3	471 mg/L	1:128	1:4	ND	ND	ND
Hoffman[10]	14 cells/mm^3	710 mg/L	1:64	Negative	Positive	ND	ND
Heald[11]	Increased	ND	1:128	ND	ND	1:16	ND
	Increased	ND	Positive	ND	ND	ND	ND
Mimura[12]	37 cells/mm^3	500 mg/L	1:64	1:64	Positive	ND	ND
Pruzzo[13]	ND	ND	Positive	ND	ND	Negative	ND
Kim[14]	ND	ND	1:128	ND	Positive	Decreased	ND
Park[15]	80 cells/mm^3	400 mg/L	1:32	Positive	ND	1:8	ND
Kim[16]	ND	ND	Positive	ND	Positive	ND	ND
Alrajab[17]	Normal	Normal	1:64	Negative	ND	ND	ND
Fu[18]	ND	ND	ND	ND	ND	ND	ND
Wang[19]	ND	ND	Positive	ND	ND	ND	ND
Dietrich[20]	ND	ND	1:128	Positive	ND	ND	ND

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Table 1: Contd...

First author	Pretreatment					Posttreatment	
	CSF WBC	CSF Pro	Serum RPR/VDRL	CSF RPR/VDRL	Serum FTA-ABS	Serum RPR/VDRL	RPR/VDRL
Baveja[21]	ND	ND	1:16	ND	ND	ND	ND
Joseph Davey[22]	ND	ND	1:256	ND	1:16	1:16	ND
Balink[23]	ND	ND	1:64	ND	ND	1:32	Negative
Treglia[24]	ND	ND	Positive	ND	ND	ND	ND
Fields[25]	Normal	Normal	Negative	Negative	Positive	ND	ND
De Rango[26]	ND	ND	1:8	ND	ND	1:4	ND
Ghazy[27]	ND	ND	Positive	ND	ND	ND	ND
Gaslightwala[28]	ND	ND	1:512	ND	ND	ND	ND
Lin[29]	ND	ND	ND	ND	ND	ND	ND
Omer[30]	Increased	Increased	Positive	Positive	ND	ND	ND
Monticelli[31]	352 cells/mm^3	3880 mg/L	>1:152	Positive	ND	>1:16	ND
Pfender[32]	396 cells/mm^3	1019 mg/L	ND	1:4	ND	ND	ND
Ranganath[33]	50 cells/mm^3	850 mg/L	1:2048	1:16	ND	ND	1:1
Rescigno[34]	Increased	Increased	1:2048	1:16	ND	ND	ND
Payet[35]	86 cells/mm^3	920 mg/L	1:256	1:2	ND	ND	ND
Kasanuki[36]	ND	ND	Positive	Positive	ND	ND	ND
Spyridonidis[37]	ND	ND	1:1024	1:128	1:6400	1:128	ND
Scheid[38]	22 cells/mm^3	952 mg/L	1:8	1:4	ND	ND	ND
Verjans[39]	80 cells/mm^3	1094 mg/L	1:64	1:8	ND	ND	ND
Schöffski[40]	ND	ND	1:16	ND	ND	ND	ND

CSF: Cerebrospinal fluid; ND: Not done or no data available; RPR: Rapid plasma regain; VDRL: Venereal disease research laboratory test; FTA-ABS: Fluorescent treponemal antibody absorbed; WBC: White blood cell.

maximum standardized uptake value (SUV_{max}), and the mean pretreatment SUV_{max} was 6.99 ± 2.47 (range: 3.60–10.30).

Positron emission tomography in primary and secondary syphilis

In one patient with anal and rectal syphilis, PET demonstrated increased FDG uptake in the distal rectum, anus, and regional lymphadenopathy.[13] In another case with oropharyngeal and gastric syphilis, PET showed increased FDG accumulation in the oropharynx and lymph nodes of the cervical regions.[5] Two cases of secondary syphilis presented with generalized lymphadenopathy, and one of them also had asymptomatic neurosyphilis.[14,15] Three cases were syphilis with pulmonary involvement,[16-18] one was syphilitic osteomyelitis,[19] one was syphilitic aortitis,[20] and one was syphilitic hepatitis.[21]

Regarding pulmonary involvement, hypermetabolic activity nodules in the lung could be detected by PET.[17,18] Kim *et al*.[16] described that there was no significant hypermetabolism in small pulmonary nodules, while hypermetabolic enlarged nodes were only present in the inguinal regions. In syphilitic bone destruction, PET images demonstrated multiple foci of increased FDG uptake in all extremities, corresponding to the osseous destruction observed on the concurrent CT images.[19] In secondary syphilis presenting with generalized lymphadenopathy, PET showed intensely increased FDG uptake with enlarged lymph nodes in the submandibular areas, neck levels, axillary and inguinal regions, and retroperitoneal, hilar, mediastinal, internal, and external iliac areas.[14,15]

Positron emission tomography in latent syphilis

Joseph Davey *et al*.[22] reported one case with latent syphilis presenting as generalized lymphadenopathy and probable aortitis. In that case, the PET scan confirmed increased glucose metabolism in the inguinal regions and along the ascending aorta and aortic arch, being compatible with aortitis.

Positron emission tomography in tertiary syphilis

Six cases were diagnosed as cardiovascular syphilis and presented with aortitis and thoracic aneurysm.[7,22-24,26,27] Two patients were diagnosed as gummatous syphilis of the adrenal gland,[3] and hepatic gummas and syphilitic episcleritis.[28] Twelve patients were diagnosed as neurosyphilis.[12,29-36,38,39] One was diagnosed as tertiary syphilis with bone, adrenal gland, liver, and skin involvement.[37]

In syphilitic aortitis, PET showed marked radiotracer enhancement along the ascending aortic wall or in the thoracoabdominal aorta with involvement of the brachiocephalic and left carotid arteries.[7,23-25] In syphilitic thoracic aneurysm, PET showed increased glucose metabolic activity, or no enhanced uptake.[26,27] PET in gummatous syphilis with adrenal gland involvement showed high uptake of FDG in lesions.[27] Scheurkogel *et al*.[3] reported a case of syphilis with liver involvement as a lesion with photopenia at the center of the mass, indicating an area of central necrosis. In tertiary syphilis with bone involvement, PET showed increased uptake of FDG at the bone.[37]

There were five types of PET scans in neurosyphilis. The first type of PET revealed a focus of intensely increased

Table 2: PET scan in the included studies

First author	Type of syphilis	Pretreatment		Posttreatment	
		PET	SUV_{max}	PET	SUV_{max}
Scheurkogel[3]	Gummatous syphilis of the adrenal gland	High uptake in the periphery of the adrenal lesion with central photopenia	ND	ND	ND
Tamura[5]	Oropharyngeal and gastric syphilis	Increased FDG accumulation in the oropharyngeal region and lymph nodes of both cervical regions	ND	ND	ND
Kösters[7]	Syphilitic aortitis with HIV coinfection	Increased FDG uptake in the ascending aorta	ND	Normal	ND
Hoffman[10]	Syphilitic gumma with HIV coinfection	ND	ND	Hypometabolic lesion with Grade 2 FDG uptake in the right parietal region	ND
Heald[11]	Neurosyphilis with positive toxoplasmosis serology presented as syphilitic gumma	A spherical region of hypometabolism in the right cerebellum	ND	ND	ND
Heald[11]	Neurosyphilis presented as syphilitic gumma	Hypometabolism change	ND	ND	ND
Mimura[12]	Paretic neurosyphilis	Hypometabolism in the bilateral medial frontal cortices and the temporoparietal regions, bilateral ventricular dilatations, and hypometabolism in the medial temporal cortices*	ND	Focal hypometabolism	ND
Pruzzo[13]	Anal and rectal syphilis	Increased FDG uptake in the distal rectum, anus, and regional lymphadenopathy	7.9 (4.4–10.3)	ND	ND
Kim[14]	Generalized enlarged lymph, lymphadenopathy	Enlarged lymph nodes with intensely increased FDG uptake in both submandibular areas, right neck level III, left internal and external iliac areas; multiple enlarged lymph nodes with mildly increased FDG uptake at the right neck level III, mediastinum, bilateral axillae, hepatic hilum, left internal iliac area, bilateral external iliac area, and bilateral inguinal area	6.22–7.12	ND	ND
Park[15]	Secondary syphilis with generalized lymphadenopathy and asymptomatic neurosyphilis	Multiple hypermetabolic lymph nodes in both sides of the neck, axilla, supraclavicula, porta hepatic, aortocaval, external iliac, inguinal area, tonsil and adenoid	ND	Complete interval resolution	ND
Kim[16]	Secondary syphilis with pulmonary involvement	Hypermetabolic enlarged nodes in both inguinal regions, along both iliac vessels and the portacaval space; no significant hypermetabolism in the small pulmonary nodules	10	Decreased FDG uptake in the right Inguinal lymph node	5.2
Alrajab[17]	Secondary syphilis with pulmonary involvement	Intense FDG uptake in the right middle lobe pulmonary nodules	ND	ND	ND
Fu[18]	Secondary syphilis	Abnormal FDG activity in the tonsils, right lung, cervical, axillary and inguinal lymph nodes	4.6–8.8	Significant interval improvement	4.9
Wang[19]	Syphilitic osteomyelitis	Regions of intense FDG activity in all extremities	ND	ND	ND
Dietrich[20]	Syphilitic aortitis in secondary syphilis	A maximum isotope uptake of the descending aorta	ND	ND	ND

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Table 2: Contd...

First author	Type of syphilis	Pretreatment		Posttreatment	
		PET	SUV_{max}	PET	SUV_{max}
Baveja[21]	Syphilitic hepatitis in secondary syphilis	Retroperitoneal, hilar, mediastinal, axillary, inguinal, and external iliac lymph nodes	ND	ND	ND
Joseph Davey[22]	Coinfection of syphilitic aortitis and HIV	Generalized lymphadenopathy, more prominent in the bilateral linguinal regions with increased glucose metabolism, mild asymmetrically increased activity along the ascending and arch of aorta	3.6	Apparent resolution of increased metabolic activity along the aorta and the inguinal lymph nodes	ND
Balink[23]	Syphilitic aortitis with HLA-B27 positive AS	Moderately increased FDG uptake in the ascending aorta wall	ND	Evidently decreased FDG uptake in the ascending aorta wall	ND
Treglia[24]	Syphilitic aortitis	An increased FDG uptake along the ascending aortic wall	ND	Decrease of FDG uptake in the ascending aorta wall	ND
Fields[25]	Cardiovascular syphilis and cervical lymphadenopathy	Hypermetabolic lymph nodes prominent and symmetric in the peritonsillar area but were not enlarged; bilateral inguinal hypermetabolic nodes; diffuse uptake in the thoracoabdominal aorta with involvement of the brachiocephalic and left carotid arteries	ND	Complete resolution of aortic vasculitis	ND
De Rango[26]	Cardiovascular syphilis	Marked radiotracer enhancement at the periaortic level D8–D9	ND	ND	ND
Ghazy[27]	Syphilitic aneurysm of the descending aorta	No enhanced uptake denoting any inflammatory activity	ND	ND	ND
Gaslightwala[28]	Hepatic gummas and syphilitic episcleritis	Multiple intensely hypermetabolic hepatic lesions	ND	ND	ND
Lin[29]	Neurosyphilitic gumma	An intensely FDG avid lesion at a metabolic activity similar to contralateral cortex, with a small central photon-deficient area corresponding to the abnormality seen on MRI	ND	ND	ND
Omer[30]	Neurosyphilis	A focus of intensely increased FDG uptake limited to the head of right hippocampus on a background of globally decreased FDG uptake	ND	Normal	ND
Monticelli[31]	Cauda equina radiculitis	No pathological glucose uptake	ND	ND	ND
Pfender[32]	Neurosyphilis with movement disorder	A markedly asymmetric radiotracer uptake with higher uptake in the left striatum	ND	Asymmetry of striatal radiotracer uptake had disappeared	ND
Ranganath[33]	Neurosyphilis with primary squamous cell carcinoma history of the neck with nodal involvement	Hypermetabolic enlarged symmetric bilateral nymph nodes in the cervical, axillary, hilar, tracheobronchial, portocaval, iliac, and inguinal regions	ND	ND	ND
Rescigno[34]	Neurosyphilis presented as uveitis	Mild to moderate diffusely lymphadenopathy in the neck, axillae, mediastinal, and inguinal regions	ND	ND	ND
Payet[35]	Neurosyphilis present with cervical syphilitic spondylodiscitis, cervical and axillary lymphadenopathy	Abnormal FDG uptake in cervical lymph nodes	ND	ND	ND
Kasanuki[36]	Neurosyphilis with dementia	Occipital hypometabolism	ND	ND	ND

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Table 2: Contd...

First author	Type of syphilis	Pretreatment		Posttreatment	
		PET	SUV_{max}	PET	SUV_{max}
Spyridonidis[37]	Tertiary syphilis with bone, adrenal gland, liver, and skin involvement	Increased uptake of FDG at the left femur	ND	ND	ND
Scheid[38]	Neurosyphilis with dementia	A focal hypometabolism in the left medial temporal lobe and a circumscribed area of increased tracer uptake in the left upper lung	ND	ND	ND
Verjans[39]	Neurosyphilis with dementia	Severe hypometabolism in the inferior temporal gyrus, spreading anteriorly (anterior temporal and orbitofrontal areas) and into precuneus and intraparietal sulcus	ND	ND	ND
Schöffski[40]	Syphilitic granulomas together with seminoma testis and neurofibromatosis type I	Multiple hypermetabolic lesions in right scrotum, omentum, peritoneum, neuroforamen C5/C6, sternum, ribs, both lungs and mediastinum	ND	Complete regression of all hypermetabolic foci, except for known sites of neurofibroma	ND

*A PET study using oxygen-15 labeled tracers. SUV_{max}: Maximum standardized uptake value; ND: Not done or no data available; HLA-B27 AS: A human leukocyte antigen B27 positive ankylosing spondylitis; PET: Positron emission tomography; FDG: Fluorodeoxyglucose; MRI: Magnetic resonance imaging.

Table 3: Radiography/CT/CTA/DSA and MRI of all included studies

First author	Type of syphilis	Pretreatment X-ray/CT/CTA	Pretreatment MRI	Posttreatment X-ray/CT/CTA/DSA	Posttreatment MRI
Scheurkogel[3]	Gummatous syphilis of the adrenal gland	Abdominal CT: A 7 cm × 8 cm × 6.5 cm rim-enhancing mass in the left adrenal gland with central necrosis	ND	ND	ND
Tamura[5]	Oropharyngeal and gastric syphilis	ND	ND	ND	ND
Kösters[7]	Syphilitic aortitis with HIV coinfection	CXR: Normal	ND	ND	ND
Hoffman[10]	Syphilitic gumma with HIV coinfection	Head CT: A contrast-enhancing right parietal occipital lesion	Head MRI: A large mass in the right parietal occipital region with edema and minimal mass effect	ND	Almost complete resolution of the mass
Heald[11]	Neurosyphilis presented as syphilitic gumma	Head CT: Right cerebellar mass	Head CT: Right cerebellar mass hemorrhage in the right cerebellum	Decreased size of hyperdense lesion of the right brachium	Resolved of the lesion
	Neurosyphilis presented as syphilitic gumma	ND	Head MRI: Enhancing lesion in right parietal occipital region	ND	Frontotemporal cortical atrophy
Mimura[12]	Paretic neurosyphilis	ND	Head MRI: Frontotemporal cortical atrophy and severe ventricular dilatation; hippocampal and parahippocampal gyri atrophy	ND	Frontotemporal cortical atrophy
Pruzzo[13]	Anal and rectal syphilis	ND	ND	ND	ND
Kim[14]	Generalized lymphadenopathy	CXR: Normal	ND	Abdominal CT: Decreased size of the lymph nodes seen on PET	ND

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Table 3: Contd...

First author	Type of syphilis	Pretreatment X-ray/CT/CTA	Pretreatment MRI	Posttreatment X-ray/CT/CTA/DSA	Posttreatment MRI
Park[15]	Secondary syphilis with generalized lymphadenopathy and asymptomatic neurosyphilis	Abdomen CT: Several enlarged lymph nodes in porta hepatitis; gastrohepatic, perigastric, aortocaval areas; splenic hilum; and mesenteric and both inguinal areas	ND	ND	ND
Kim[16]	Pulmonary syphilis	Abdominal CT: Several gallbladder stones and diffuse wall thickening of the gallbladder, especially with irregular thickening in its neck several enlarged lymph nodes in both inguinal regions, along both iliac vessels and in the portocaval space Chest CT: Multiple, small, well-defined nodules in the right upper lobe and both lower lobes	ND	Complete disappearance of the pulmonary nodules with a further reduction in the size of the involved lymph nodes	ND
Alrajab[17]	Secondary with pulmonary involvement	CXR: Right lower lung field opacity Chest CT: A cluster of three small subpleural nodules on the lateral aspect of the right middle lobe and a smaller left lower lobe and right lower lobe subpleural nodules	ND	ND	ND
Fu[18]	Secondary syphilis	ND	ND	ND	ND
Wang[19]	Syphilitic osteomyelitis	X-ray demonstrated extensive, mixed lytic and sclerotic lesions in all limbs accompanied with soft-tissue involvement	ND	ND	ND
Dietrich[20]	Syphilitic aortitis in secondary syphilis	CXR: An enlarged aortic contour Chest CT: Thickening of the aortic wall and aortic sclerosis in the transverse plane	ND	ND	ND
Baveja[21]	Syphilitic hepatitis in secondary syphilis	ND	MRCP: Hepatomegaly	ND	ND
Joseph Davey[22]	Coinfection of syphilitic aortitis and HIV	ND	ND	ND	ND
Balink[23]	Syphilitic aortitis with HLA-B27 positive AS	ND	Thorax MRI: Diffuse increased signal of the wall of the ascending aorta with a wall thickness of 4 mm, no signs of active	ND	ND
Treglia[24]	Syphilitic aortitis	ND	ND	ND	ND
Fields[25]	Cardiovascular syphilis Cardiovascular syphilis	ND	ND	ND	ND
De Rango[26]	Cardiovascular syphilis	CTA revealed a saccular aneurysm of thoracic aorta with localized dissection and thickening of the aortic wall	ND	Aneurysm exclusion	ND

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Table 3: Contd...

First author	Type of syphilis	Pretreatment X-ray/CT/CTA	Pretreatment MRI	Posttreatment X-ray/CT/CTA/DSA	Posttreatment MRI
Ghazy[27]	Syphilitic aneurysm of the descending aorta	CXR: A widened mediastinum Chest CT: A monstrous aneurysm of the thoracic descending aorta with thickened wall and intraluminal thrombotic bedding, compressing the esophagus and heart	ND	DSA: The aneurysm was successfully treated by endovascular stent	ND
Gaslightwala[28]	Hepatic gummas and syphilitic episcleritis	ND	ND	ND	ND
Lin[29]	Neurosyphilitic gumma	ND	Head MRI: A rim-enhanced lesion in the left temporal lobe lesion with significant midline shift and edema	ND	ND
Omer[30]	Neurosyphilis	Head CT: Right frontal gliosis related to prior trauma	Head MRI: Bilateral mesial temporal high T2 signal intensity, high T2 signal intensity and atrophy within the right frontal area consistent with the gliosis	ND	Marked improvement in the previously bilateral hyperintensities which were replaced by atrophy
Monticelli[31]	Cauda equina radiculitis	ND	Hyperintense thickening of the cauda equina roots on T2, marked and diffuse enhancement of the cauda equina roots on T1	ND	ND
Pfender[32]	Neurosyphilis	ND	Head MRI: No focal lesions on FLAIR and DWI MRA: A focal (<50%) stenosis of the M1 segment of the left middle cerebral artery	ND	ND
Ranganath[33]	Neurosyphilis with primary squamous cell carcinoma history of the neck with nodal involvement	ND	ND	ND	ND
Rescigno[34]	Neurosyphilis presented as uveitis	ND	Orbits MRI: Mild optic nerves	ND	ND
Payet[35]	Cervical syphilitic a spondylodiscitis associated with neurosyphilis; cervical and axillary lymphadenopathy	Cervical spine CT revealed C2–C3 spondylodiscitis	Cervical MRI: High signal intensity of the C2–C3 disc and C2 bodies with anterior lesions of surrounding tissues from C1 to C3 on T2 and low signal intensity on T1 of the vertebral body of C2 and gadolinium enhancement in the C2 lower plate and C2–C3 disc	ND	Cervical MRI: Marked improvement
Kasanuki[36]	Neurosyphilis with dementia	ND	Head MRI: Normal Head MRI: Notable bilateral hippocampal atrophy	ND	ND

Contd...

Table 3: Contd...

First author	Type of syphilis	Pretreatment X-ray/CT/CTA	Pretreatment MRI	Posttreatment X-ray/CT/CTA/DSA	Posttreatment MRI
Spyridonidis[37]	Tertiary syphilis with bone, adrenal gland bone, adrenal gland liver, and skin involvement	Radiograph of the left hip: Osteolysis and periosteal reaction Abdominal CT: A low density nodule in the liver and a lesion in the right adrenal gland	ND	ND	ND
Scheid[38]	Neurosyphilis with dementia	Noncontrast head CT: Normal Thoracic CT: A hyperdense lesion in the left superior pulmonary lobe	Head MRI: A contrast-enhancing lesion on T1 and hyperintense signal alteration in the left medial temporal lobe on FLAIR and T2 images	ND	Atrophy of left medial temporal lobe structures
Verjans[39]	Neurosyphilis with dementia	ND	Head MRI: Moderate hippocampal atrophy and mild global atrophy	ND	ND
Schöffski[40]	Syphilitic granulomas together with seminoma testis and neurofibromatosis type I	ND	ND	ND	ND

ND: Not done or no data available; CXR: Chest X-ray; CT: Computed tomography; CTA: CT angiography; MRI: Magnetic resonance imaging; MRA: Magnetic resonance angiography; FLAIR: Fluid-attenuated inversion recovery; DWI: Diffusion-weighted imaging; MRCP: Magnetic resonance cholangiopancreatography; PET: Positron emission tomography; HLA-B27 AS: A human leukocyte antigen B27 positive ankylosing spondylitis.

FDG uptake with or without a background of globally decreased FDG uptake.[30,32] The second type of PET showed a focal hypometabolic mass.[11,38] The third type of PET produced patchy severe hypometabolism, usually involving the medial frontal cortex, temporal parietal area, inferior temporal gyrus, anterior temporal lobe, orbitofrontal lobe, posterior gyrus cingulum/precuneus, medial temporal lobe, intraparietal sulcus, or occipital lobe.[12,36,38,39] The fourth type of PET in neurosyphilis only presented as generalized lymphadenopathy and demonstrated hypermetabolic enlarged lymph nodes in the symmetric bilateral cervical, axillary, hilar, tracheobronchial, protocaval, iliac, or inguinal regions, without abnormal FDG uptake in the brain.[33-35] The fifth type of PET in neurosyphilis revealed no pathological glucose uptake anywhere in the whole body scan.[31] In neurosyphilitic gumma, PET may demonstrate an intensely FDG avid lesion or a hypometabolic lesion.[10,29]

Positron emission tomography in targeting diagnostic interventions

Three cases with syphilitic aortitis and one case with anal and rectal syphilis were incidentally diagnosed by PET.[7,13,14,20] There were three cases, in which PET was used to rule out paraneoplastic limbic encephalitis or malignancy.[31,38,40] In one case with aortic aneurysm, PET was carried out to exclude active vasculitis.[27] In ten case reports, other diseases such as malignancy or Alzheimer's disease were first considered, until the PET findings of intensely hypermetabolic lesions, indicative of inflammatory processes, led to the suspicion of syphilis, which was then confirmed by a biopsy or serological tests.[3,14,19,23,26,28-30,33-39]

There were 32 patients with positive PET findings and positive VDRL and/or RPR results, one patient with positive PET findings and negative VDRL/RPR results, and two patients with negative PET findings and positive VDRL/RPR results. Compared with nontreponemal tests for VDRL/RPR, the sensitivity of PET in identifying syphilis was 94.3% versus 97.1%.

Positron emission tomography in characterizing disease extent

The majority of the case reports found that a PET scan was useful for characterizing the disease extent, especially in generalized lymphadenopathy, syphilitic aortitis, and neurosyphilis with dementia,[3,7,12,14,20,22-25,28,30,32,33,38,39] with the exception being cases in which the PET scan showed no pathological glucose uptake.[27,31]

Positron emission tomography in follow-up and treatment response assessment

Eleven case reports described that a repeated PET scan after antibiotic therapy revealed apparent or complete resolution of the asymmetry of radiotracer uptake, in accordance with decreased RPR titer and/or disappearance of clinical symptoms and signs.[7,12,16,18,21-25,30,32,40] Two cases of neurosyphilis with dementia showing no clinical improvement after treatment were not reexamined by a PET scan.[36,39]

Discussion

Little is known about PET scans in syphilitic patients. This study was a comprehensive systematic review on PET in syphilis worldwide. We found that PET is prospective for diagnosis, follow-up, and therapy evaluation in disseminated syphilis.

Our results showed that hypermetabolic activity nodules in the lung could be detected on PET in pulmonary syphilis.[17,18] Although PET had high overall sensitivity and specificity in pulmonary lesions, it had low accuracy in smaller subcentimeter lung lesions.[16,41] We should also remember that increased glucose metabolism in lesions on PET occurred in a large variety of primary lung tumors and metastases as well as in inflammatory diseases such as tuberculosis, fungal infection, and sarcoidosis.[16,40] Our findings further demonstrated that PET could provide positive results in gastrointestinal syphilis with increased FDG accumulation in the infected region and with regional lymphadenopathy.[5,13,28]

The findings of this systematic review implied that PET could identify syphilitic aortitis at an early asymptomatic stage.[7,14,22] PET could detect early inflammation of the vessel wall because the activated inflammatory cells were characterized by increased FDG uptake.[24] Large-vessel vasculitis could be diagnosed by ^{18}F-FDG PET at an earlier stage compared with conventional imaging techniques, such as CT or MRI.[23] PET might also be helpful in the distinction of syphilitic aortitis from large-vessel vasculitis.[23] Giant-cell arteritis usually showed homogeneous/smooth linear or long segmental patterns of FDG uptake in the thoracic aorta and its main branches.[42] Takayasu's arteritis affected the aorta and its branches but might show a more focal and localized inhomogeneous pattern of FDG uptake and had a more aggressive clinical course.[43,44] The localization of the increased metabolic activity seemed to be present in the ascending aorta in syphilitic aortitis, consistent with postmortem examinations.[23] The ascending aorta and transverse aortic arch were the most commonly affected blood vessels in syphilitic aortitis.[24]

The findings of this systematic review also implied that PET should have some priority over head MRI while central nervous system involved, especially when the latter has demonstrated no focal lesions on fluid-attenuated inversion recovery and diffusion-weighted imaging. Our results demonstrated that PET in neurosyphilis is somewhat complicated. There are five types of PET patterns ranging from hypermetabolic to hypometabolic foci or no significant glucose uptake in the brain.[31,34,35,39,44,45] The latter is often seen in syphilitic cauda equina radiculitis, syphilitic retinitis, and syphilitic spondylodiscitis.[31,34,35] Gummatous neurosyphilis may demonstrate intense FDG avidity on PET. A global reduction in glucose consumption particularly in the frontal or temporal areas and precuneus/posterior cingulate with sparing of the basal ganglia and thalamus in neurosyphilis with dementia can usually be found on PET.[12,36,38,39,44]

From this systematic review, it appeared that there is no definable influence on PET results of the presence or absence of HIV coinfection. In syphilitic patients with lymph node, lung, anus, and rectum involvement, the SUV_{max} ranged from about 3.60 to 10.30.[13,14,16,18,22] This systematic review told us that metabolic findings on PET should be always interpreted with caution. It was important to suspect inflammatory or infectious diseases even in cancer patients to avoid a false-positive interpretation.[5]

This systematic review indicated that no clinical symptoms or no serologic evidence for active infection were not always equal to no inflammatory pathological processes.[7,14,22] Follow-up of syphilis was usually achieved by assessing the clinical and serological response to treatment.[9] Globally, however, many studies have confirmed that follow-up was poor.[46,47] About 15% of patients with early syphilis and no HIV infection did not have a 4-fold decrease in titer at 6 months, and in late syphilis, the serological response was often absent.[9] In some patients, serological tests might remain positive for life following effective treatment, and a positive treponemal test did not distinguish between active infection and infection that has been previously treated.[1,9] Thus, it was important to have one proper assessment that could prevent unnecessary retreatment. Our results showed that PET is helpful not only for diagnosis, but also in follow-up and assessment of antibiotic treatment response. PET adequately enabled imaging of the therapeutic response and might be superior to morphologic imaging.[44] Utilization of PET in syphilis should be combined with serological tests or dark field microscopy, and its positive effect might be maximized by repeating the examination during follow-up to assess the response to antibiotic therapy.

There were some limitations to this systematic review as follows. The major limitation was the small sample size, which was related to the lack of experience with PET in syphilis among clinicians. It could be difficult to differentiate active inflammation (infectious or not) from cancer when high FDG uptake was observed without serological tests. Our exclusion of non-English or non-Chinese studies might neglect some information that could make our results more concrete.

In conclusion, this systematic review suggested that ^{18}F-FDG PET is useful for diagnosis, disease extent evaluation, follow-up, and treatment efficacy assessment in patients with disseminated syphilis.[24,33] PET may shed light on the follow-up of syphilis besides the clinical and serological response to treatment, which currently remains a puzzle. Further prospective cohort studies and clinical trials are warranted.

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Conflicts of interest
There are no conflicts of interest.

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