18F-FDG PET/CT in fever and inflammation of unknown origin

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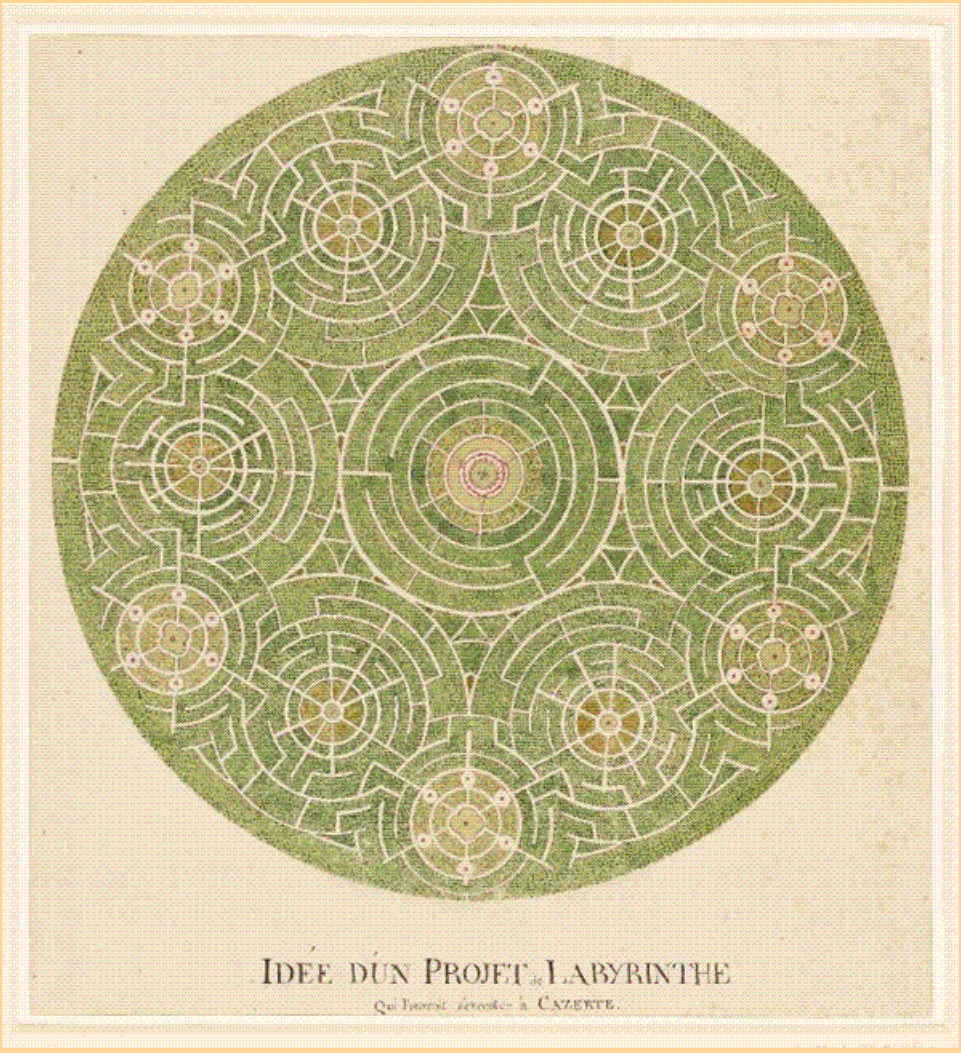

Hans Balink

^{18}F-FDG PET/CT in fever and inflammation of unknown origin

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Cover Design: "idée dún projet de labyrinthe/Qui Pourroit s'executer à Caserta, Italia." Drawn by; anonymous. French, XVIII century. Purchased by the British Museum from Edward Daniel in 1871. Courtesy British Museum, London, United Kingdom. The idea was to be placed blindfolded in one of the peripheral circles; the start in each peripheral circle (when the blindfold was taken off) needed a different approach to reach the centre of the labyrinth. The image represents the heterogeneity and the problematic diagnostic approach for each specific patient with FUO or IUO.

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Aan ‘Jaantje van de polderboer’ en Suzy
(en natuurlijk ook jou pa).

Contents

Introduction and outline of the thesis.

A rationale for the use of ^{18}F-FDG PET/CT in fever and inflammation of unknown origin

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Introduction

In patients suspected for disease, it goes without saying that the initial diagnostic strategies will be based on complaints or cues, gathered from medical history, physical examination and baseline tests. When a diagnosis is not reached after a variety of appropriate diagnostic procedures and the complaints still persist, patients may be defined of having either fever of unknown origin (FUO) or inflammation of unknown origin (IUO).

The definition of FUO has changed over the years. In 1961 Petersdorf and Beeson characterized FUO as an illness for at least 3 weeks' duration, with fever; body temperature higher than 38.3 ˚C (101 ˚F) on several occasions without a diagnosis.[1]
Nowadays FUO can be seen as not having reached a diagnosis after appropriate inpatient or outpatient evaluation.[2]
Although the definition of FUO suggests that the fevers remain of unknown origin, most of the FUOs have a pathophysiological basis. The FUO spectrum may be divided into four general categories: (1) infections, (2) malignancies, (3) non-infectious inflammatory diseases, or (4) miscellaneous disorders including drug-related fever, habitual hyperthermia, and factitious fever. The phrase "non-infectious inflammatory diseases" is semantic for rheumatic diseases, autoimmune diseases, collagen vascular diseases (vasculitides) or vasculitis, connective tissue diseases, and granulomatous diseases. Over the past 40–50 years the proportion of cases of FUO caused by infections and neoplasms has decreased. This is most likely due to the increased detection of solid tumors and abnormal lymph nodes via improved diagnostic properties of ultrasonography and computed tomography (CT).[3]

Remarkably little literature covers unexplained inflammatory syndromes without persisting fever (i.e., inflammation of unknown origin (IUO). A study from 2010 reported that low-grade fever (body temperature between 37.5 and 38.3°C) required the same diagnostic approach as FUO because there was no relationship between body temperature values and the severity of the underlying diseases. In addition the aetiological spectrum was also in line with the causes related to FUO.[4]
In a study from 2009 IUO and FUO patient populations were compared. IUO was defined as; (1) an illness of at least 3 weeks' duration, (2) with signs of inflammation but with temperatures below 38.3°C, C-reactive protein (CRP) > 30 mg/L and/or erythrocyte sedimentation rate (ESR) > age/2 in ♂ or (age + 10)/2 in ♀ on >3 occasions, and (3) uncertain diagnosis despite appropriate investigations after at least 3 days of hospital investigation or 3 outpatient visits. The authors found that the diagnostic yield, case-mix, contribution of stand-alone ^{18}F -FDG PET, and vital outcome were similar in both the FUO and the IUO group.[5] Therefore it has been suggested to delete the 38.3 ˚C limit from the original criteria by Petersdorf and Beeson.[6, 7]
Just as in FUO, the aetiology of IUO may vary from a self-limiting condition to occult malignancy.[8] In short, the aetiology of IUO shows the same variation in diseases as the FUO spectrum and probably requires the same diagnostic approach as FUO.

The search for the origin of FUO (or IUO) is frustrating for both patient and physician because, the diagnostic work may be extensive and may fail to reach a diagnosis in up to 50% of cases.[9] The diagnostic work up includes several non-invasive and invasive procedures that may not only be inappropriate but also expose patients to the risks of these investigational procedures, e.g. lumbar or bone marrow biopsy and gastro-duodenal or colonic endoscopy. In addition, for socio-economic reasons unnecessary use of healthcare resources is perceived as unsatisfactory from the perspective of patient, physician and society in general.

Diagnostic Strategy for FUO and IUO.

In the vast literature that exists on FUO there is no diagnostic gold standard against which other diagnostic tests can be compared. For this reason there is disagreement in the published diagnostic algorithms as to which investigations should constitute a comprehensive diagnostic workup.[3, 10, 11]

In lack of a standardized diagnostic strategy, there is also disagreement whether or not the diagnostic process should be guided by the so-called "potential diagnostic clues" (PDC). These PDC emerge from medical history, physical examination, and baseline tests. PDC are defined as all localizing signs, symptoms, and abnormalities potentially pointing towards a diagnosis. In a review of the literature from 1995 to 2004, the diagnoses obtained in patients with PDC were significantly higher than in patients without PDC (72% versus 30%).[11]

In a prospective multi-centre study however, 15 PDC, on average, were identified per patient, of which 81% proved to be misleading. The remaining 19% of PDC contributed to the final diagnosis, but PDC alone did not directly lead to a diagnosis in any of the patients.[12]

Diagnostic Approaches in FUO and IUO

Although the diagnostic approach in FUO and IUO is not uniform, it will always include a thorough medical history, careful physical examination, laboratory tests (full blood count; haematology and chemistry) blood and urine cultures and a mix of diagnostic imaging techniques. A thorough and repeated medical history is important, including information about alcohol intake and other intoxications, medications, occupational exposures, pets, travel, work environment, familial disorders, previous illnesses and recent contact with persons exhibiting similar symptoms.[13]

The specific findings of a thorough physical examination that have led to a diagnosis in FUO are numerous and diverse. Examples included slight enlargement of the thyroid (thyroiditis), periodontal disease or loose teeth (dental abscess), thickened temporal artery (temporal arteritis), cardiac murmur that changes with position (atrial myxoma), and widespread hyperpigmentation (Whipple's disease). But for instance lymphadenopathy either in children or elderly has not correlated with specific illnesses or a positive biopsy.[14, 15] Although the findings of a thorough physical examination are often misleading, they may help in limiting the list of probable diagnoses. Use of clinical fever curves were reported to be useful as specific fever patterns have been ascribed to many of the causes of FUO.[16]

Unfortunately, in most case series, the height, pattern, or duration of fever did not relate to diagnosis.[9]
In the absence of a consensus on the best/optimal diagnostic strategy for FUO, patients undergo a plethora of diagnostic tests ranging from relatively non-invasive to exploratory laparotomy.

Noninvasive Procedures

Fundoscopy. Although not widely used in FUO or IUO occasionally the results are reported to be helpful. Retinal abnormalities associated with infections include Roth's spots (white-centred haemorrhages) with infective endocarditis, yellowish-white choroidal lesions with tuberculosis and certain disseminated fungal infections, and active retinitis caused by disseminated toxoplasmosis or cytomegalovirus in immunocompromised patients. Patients with malignancies may have choroidal metastases, usually from a breast or lung malignancy. Leukaemia can cause intraretinal haemorrhages, Roth's spots, and leukemic infiltrates. Various forms of vasculitis produce cotton-wool exudates, intraretinal haemorrhages, and vascular occlusive disease, while sarcoidosis can cause perivascular sheathing ("candle-wax drippings") and choroidal nodules.[17]

Leg Doppler Imaging. Three studies reported a deep vein thrombosis as the cause of FUO in 2% to 6% of patients. Furthermore e.g. Doppler imaging is safe with low costs, high accessibility and it may identify a treatable cause. [18 - 20]

Invasive Diagnostic Procedures

Bonemarrow Aspiration. Not proven to be useful in patients with FUO and anaemia.[21]
A study from 2009 showed that the diagnostic yield of a 'blind' bone marrow biopsy (BMB) in FUO was modest, even after careful patient preselection. Of 280 patients with FUO, the yield of BMB in 130/280 patients after a routine diagnostic work up was 23%.[22]

Percutaneous Liver Biopsy. An early or "blind" liver biopsy can be helpful for the diagnosis of granulomatous hepatitis.[23]
However, as granulomatous hepatitis represents an nonspecific histological reaction to infections, neoplasms or drugs, it is considered a reaction of a group of diseases. Therefore, it cannot be put forward as a final diagnosis.[6]
Only in HIV-infected patients with FUO in combination with hepato-splenomegaly and increased alkaline phosphatase levels, an early liver biopsy has been described as a useful diagnostic technique.[24]

Skin and Muscle Biopsy. The diagnostic yield of these biopsies has only been proven when performed in patients with skin abnormalities and/or abnormal electromyography.[25, 26]

Temporal Artery Biopsy. The only biopsy that may be rewarding (in the absence of prior localising information) is temporal artery biopsy in elderly patients with a high CRP/ESR, although it can be false negative in 15–70% of the cases, which may delay the diagnosis.[27]
Temporal arteritis due to giant cell arteritis (GCA) is an important cause of FUO in patients older than 50 years. In one patient series the contribution of GCA temporal arteritis was as high as 15% of the cases.[28]
In more recent series, patients with increased ^{18}F-FDG uptake in the thoracic aorta and its main branches, suggestive for large vessel vasculitis, also underwent temporal artery biopsies in 39% of these cases. Only half of these patients had a positive temporal artery biopsy.[29]

Bronchoalveolar Lavage (BAL). Mostly performed in patients with an abnormal chest radiography; a myriad of pulmonary problems is associated with abnormal imaging findings (mass, cavitary lesion, infiltrates, etc.). In comparison to BAL, lung fine-needle aspirate (LFNA) is superior for a cytological diagnosis of pulmonary pathology.[30]
BAL was reported useful in advanced HIV infection with alveolar lymphocytosis.[31]

Exploratory Laparotomy. This procedure is standard of care in specific trauma situations with possible multiple life-threatening injuries. However in the setting of FUO/IUO exploratory laparotomy is considered obsolete, and in many hospitals replaced by minimal-invasive laparoscopy.

In general, the abovementioned (non-) invasive investigations have a high specificity, but are hampered by their relatively low negative predictive value. Therefore none of these investigations can reliably exclude malignancy, focal inflammatory disease, or infection. This is an essential limitation and may be overcome with the use of imaging techniques; of which especially ^{18}F-FDG PET/CT seems to be very promising.

Imaging Techniques.

Imaging techniques include anatomical imaging modalities like radiographs, ultrasonography (US), computerized tomography (CT), and magnetic resonance imaging (MRI). Conventional nuclear medicine scintigraphy includes planar/total body scintigraphy and single photon computed tomography (SPECT) and positron emission tomography (PET). All these techniques have specific advantages and disadvantages. In order to understand the evolving role of hybrid ^{18}F-FDG PET/CT in relation to the other imaging techniques, it is important to be aware of their respective advantages and limitations.

Plain-Film Radiography. Chest radiography is not only valuable for disclosing intra-thoracic disorders but also for suggesting intra-abdominal pathology. In most patients with subphrenic, splenic, hepatic, and pancreatic abscesses, an ipsi-lateral finding of atelectasis, an elevated hemi-diaphragm, or a pleural effusion is present, and in a few cases an intra-

abdominal mass is visible on the sub-diaphragmatic part of the film. Plain-film radiography can show typical findings of soft tissue swelling, although they may not be apparent during the early phases of disease. It usually takes 2 to 3 weeks for an osseous lesion to become visible on plain-film radiography because significant loss of bone density must occur before such changes become apparent.[32]

Ultrasonography (US). US is widely available, quick, inexpensive, and not associated with radiation exposure. The spatial resolution may reach below 1mm and US can be used to obtain functional information to a limited extent (e.g., blood flow by Doppler ultrasonography). The disadvantage is that is a regional investigation used in case of specific clues and that the results are operator-dependent. The penetration and reflection of the ultra-sound waves in tissue may be hindered by gas (bowel) or dense structures (bone), and structures deep within the body may be difficult to visualize because the image quality suffers from the longer wavelengths used for deeper imaging. Failure of ultrasound to detect many liver, spleen, and intra-peritoneal abscesses hampers reliance on this examination.[33]

US of the Heart (Echocardiography). Echocardiography can help to diagnose infective endocarditis in demonstrating vegetations. The sensitivity of the trans-thoracic approach is approximately 55–68%, and of the trans-oesophageal approach approximately 90–94%. Furthermore, US may detect other causes of FUO related to the heart such as myxoma, sarcoidosis, or other infiltrative diseases.[34]

Computed Tomography (CT). CT is highly reproducible, has an excellent spatial resolution, and, although more expensive than ultrasonography, is still relatively inexpensive. The examination time is short, generally less than 5–10min. A disadvantage is exposure of the patient to radiation; the substantial radiation to the organs examined (up to 6 mSv), limits its use at frequent intervals. Furthermore, the use of a contrast medium to enhance image contrast may be limited or contraindicated in patients with impaired renal function or previous allergic reactions. Also CT has a lack of functional information. False-negative CT results have occasionally been reported, even with abscesses in solid organs, due to distortions of normal anatomy, small abscess size, or failure to use both oral and intravenous contrast agents.[35]

In neutropenic patients with FUO low-dose multislice CT is useful for the early detection of pneumonia at relatively low cost and limited radiation burden.[36]

Magnetic Resonance Imaging (MRI). MRI is also characterized by a high spatial resolution; it provides excellent structural resolution for visualizing advanced stages of disease. It has some potential to obtain functional information, and causes no radiation exposure. MRI has also become widely available but is prone to movement artifacts because of the relatively long examination time. Furthermore, there are limitations to the scanning of patients with

pacemakers, implants, and other devices, and the procedure is relatively expensive. MRI is (compared to CT) more useful for the evaluation of internal structures such as bone marrow, muscles, tendons, ligaments, cartilage, and small organs such as the prostate gland, testes, cervix, and uterus. [37]

In general radiological techniques, including CT, MRI, and US show anatomical changes and consequently, malignant, infectious, and inflammatory foci cannot be detected in an early phase because of the lack of substantial anatomical changes at this time. Furthermore, after surgery or other therapeutic interventions like radiotherapy, discrimination of active malignant, infectious or inflammatory lesions from morphological sequelae is often difficult. In addition, these techniques usually deliver information from a limited part of the body and the use of total body CT and MRI is not widespread.

Scintigraphic Methods

Functional and metabolic imaging with scintigraphic methods plays an important complementary role in the diagnostic process of patients with FUO. The radiation exposure is dependent on the radiotracer used, and may reach a radiation exposure of an abdominal CT scan (2–6 mSv) which also limits its use at frequent intervals. Conventional planar imaging had the disadvantage of a 2D display which hampers the exact localization of affected sites in most anatomic regions of the body. The introduction of 3D SPECT and more recent hybrid SPECT/CT has overcome this disadvantage.[38]

A wide variety of conventional radiopharmaceuticals/ radiotracers has been tested, but currently only a few radiopharmaceuticals are in general use and/or commercially available for imaging of malignancy, infection and inflammation. These include autologous white blood cells (WBCs (leukocytes)) labelled with ^{99m}Tc or ^{111}In, ^{99m}Tc-labeled bisphosphonates such as methylene diphosphonate or hydroxymethylene diphosphonate, ^{67}Ga-citrate, ^{99m}Tc-antigranulocyte antibodies, ^{99m}Tc-labelled nanocolloids, and ^{99m}Tc- or ^{111}In-labeled proteins, such as human polyclonal immunoglobulin (HIG) or albumin, and
furthermore ^{99m}Tc-labelled or ^{123}I-labelled monoclonal antibodies, cytokines, peptides, antibiotics, antifungal agents and vitamins. [39, 40]
Recently introduced radiolabelled antibodies for the detection of sites of infection were withdrawn from the market because of serious side effects in patients.[41]

The main disadvantage of conventional radiopharmaceuticals is that each (apart from ^{67}Ga), covers only a part of the spectrum of possible diagnoses in the broad setting of FUO and IUO. There are also disadvantages like handling of potentially infected blood products (WBC), high radiation burden, and poor imaging characteristics (WBC, ^{67}Ga) and the long-time span, 2-3 days, between injection and diagnosis (^{67}Ga).

^{67}Ga-citrate was until recently the most used radiopharmaceutical for imaging in patients with FUO/IUO and was considered the "gold standard," because of its ability to detect both acute and chronic infectious and inflammatory conditions and some neoplasms.[42, 43]
The clinical application is limited though, the specificity is decreased due to hepatobiliary excretion and the accordingly rather high physiological bowel activity and excretion. Also physiological uptake in active cortical bone remodelling hampers the accuracy.[44, 45]
Besides, optimal imaging requires delayed imaging up to 72 hours after the injection. The unfavourable imaging characteristics, the long physical half-life (78 hours), and the high-energy gamma radiation (93–889 keV), causes a high radiation burden to the patient.[46]

As for *ex vivo-labelled autologous leukocytes*, the usefulness in many acute and several chronic infections and inflammatory diseases is widely established. Albeit, the use of leukocyte scintigraphy in patients with FUO is scarcely reported. The number of patients with FUO who are eventually diagnosed with malignant disease are nowadays rather small (usually less than 10% of cases in modern FUO populations in Western countries).[46]
A good accuracy for diagnosing malignant disease is therefore an important requirement of any diagnostic approach (i.e., imaging technique) in FUO and IUO patients. In a retrospective study of 208 patients with ^{111}In-granulocyte scintigraphy, 25 patients had malignant neoplasms. Among these, pathological uptake of ^{111}In activity in malignancy was observed in only 10/25 patients.[47]
In a study of 117 patients with known various malignancies ^{111}In-leukocyte scintigraphy was performed in order to diagnose localized infectious disease. The accuracy for infection as comorbidity of malignancy was 91%. However, no uptake was observed in primary or secondary tumours, with the exception of accumulation of labelled leukocytes at the site of an osteolytic metastasis in one case.[48]

Positron Emission Tomography (PET)/ComputedTomography (CT).
The most widely used PET tracer is the glucose analogue 2-deoxy-2-(^{18}F) fluoro-glucose (^{18}F-FDG). ^{18}F-FDG PET imaging in the oncology setting is based on the increased glycolytic rate in malignant cells, and overexpression of glucose transporters (GLUT-1 and -3). Intracellularly FDG is phosphorylated to FDG-6-phosphate by hexokinase. Because FDG-6-phosphate is not a suitable substrate for the glycolytic enzymes that follow, FDG-6-phosphate continues to accumulate intracellularly. Similarly many infective and inflammatory conditions can be imaged with PET due to the increased accumulation of ^{18}F-FDG by inflammatory cells and granulation tissue, as these cells use glucose as an energy source.[49]

Increased ^{18}F-FDG uptake is present in all activated leukocytes (granulocytes, monocytes as well as lymphocytes) enabling imaging of acute and chronic inflammatory processes. In the recognition that ^{18}F-FDG shows increased uptake in not only malignant cells, but also in cells involved in infectious and inflammatory processes, the possible advantages of PET over

other diagnostic procedures in identifying FUO aetiology were already understood several years ago. In less than 15 years its use in this field was evaluated in several studies.[10, 50-56]
In these eight studies the overall percentage of finding a final diagnosis was 67%. Stand-alone ^{18}F-FDG PET had a mean overall helpful contribution in the diagnostic approach of 39 % of the cases. PET scans were considered as "helpful contribution" when the PET study demonstrated a focal localized disease process, confirmed by other investigations, as being the cause of FUO.

Related to the broad range of conditions that may cause FUO and IUO it is essential to optimize both the scan procedure and the patient preparation.
(I) High myocardial uptake of ^{18}F-FDG is frequently observed and has been reported to result in both false-positive and false-negative findings.[57, 58]
As the cause or the focus for FUO or IUO may be localized in or near the heart, this physiologic cardiac uptake may hamper for instance diagnosis of endocarditis or myocardial sarcoidosis. A fat-allowed, carbohydrate-restricted diet starting the day before ^{18}F-FDG administration has proven to suppress myocardial ^{18}F-FDG uptake satisfactorily.[59]
Another reported method is infusion of heparin and triglycerides which elevates bloodlevels of free fatty acids (FFAs) and accordingly decreases myocardial glucose uptake. Heparin displaces lipoprotein lipase in capillaries so that triglycerides are cleaved to yield FFAs, which are the preferred substrate of the myocardium. [61]
(II) In patients with FUO/IUO it is important to perform a whole-body PET/CT investigation, including the brain, otherwise a cerebral lymphoma or a rare occult prolactinoma may be missed. [61]
(III) Cold-stimulated ^{18}F-FDG uptake by brown adipose tissue (BAT) in humans is more pronounced during fasting. To prevent increased ^{18}F-FDG uptake in BAT, which may hamper the interpretation of the PET images, patient preparation in rooms at comfortable warm temperature is advised.[62]
(IV) Steroids as a treatment for disease should preferably not be started before ^{18}F-FDG PET/(CT) has been performed; of course as much as clinically possible. After corticosteroid administration/immunosuppressive therapy normalisation of ^{18}F-FDG uptake in inflammatory lesions is described and thereby hampering the establishment of an accurate diagnosis.[63, 64]

Already in 2003 it was recognized that in patients presenting with FUO or with a marked inflammatory syndrome (IUO), the presence of diffuse and intense arterial ^{18}F-FDG uptake (with stand-alone PET) may efficiently guide clinicians by suggesting the diagnosis of large vessel vasculitis. Atypical presentations of large vessel vasculitis are a real diagnostic dilemma often leading to repeated and extensive work-ups. In such circumstances, metabolic imaging may be a powerful diagnostic tool that may avoid a lot of unpleasant examinations.[65]

The development of hybrid PET/CT was a milestone in medical imaging. As PET imaging is able to reveal functional alterations (with high spatial resolution) that precede the morphological changes, the integration of anatomical and morphological images allows improved interpretation of both abnormal ^{18}F-FDG uptake and suspicious morphological findings. The synergy of the anatomic-metabolic information of hybrid PET/CT imaging allows both localization and characterization of tissues with increased metabolism, providing in this way a significant contribution in the process of finding pathological processes.

With a maximum of 333 MBq ^{18}F-FDG injected, in combination with a CT with contrast medium, the radiation exposure could remain below 10 mSv in the first generation of PET/CT systems. The new generation PET/CT systems require less ^{18}F-FDG injected. In addition, in patients with impaired renal function or previous allergic reactions to the use of intravenous contrast medium, a PET/CT study without contrast medium will still have diagnostic value.

In conclusion, compared to stand-alone PET, hybrid ^{18}F-FDG PET/CT is expected to augment the accuracy in the workup of FUO and IUO.

Outline of this thesis

Although the rationale for the use of ^{18}F-FDG PET/CT in patients with FUO/IUO has been established several issues remain to be studied. Some of these issues are formulated below and are the subject of this thesis:

Is there an optimized dietary preparation for patients to reduce possible interfering cardiac ^{18}F-FDG uptake?

How does ^{18}F-FDG PET/CT contribute to the identification of the aetiology of FUO?

How does ^{18}F-FDG PET/CT contribute to the identification of the aetiology of IUO?

Do specific clinical and laboratory parameters improve the effectiveness of ^{18}F-FDG PET/CT for diagnosing large vessel vasculitis (LVV) (i.e. a specific population of patients with IUO)?

The American College of Rheumatology 1990 criteria for vasculitis, based on late LVV effects like arterial stenosis and/or occlusion, most likely cause underdiagnosis of LVV. Should these criteria be optimized based on available ^{18}F-FDG-PET/CT data in patients with LVV in giant cell arteritis (GCA) and Takayasu arteritis (TA)?

What is the role of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in patients with FUO/IUO as predictors for ^{18}F-FDG-PET/CT? What is the additional value of ^{18}F-FDG-PET/CT to these classical markers of disease in establishing a diagnosis?

Is a diagnostic work-up/strategy with ^{18}F-FDG PET/CT in patients with IUO cost-effective compared to a work-up/strategy without ^{18}F-FDG PET/CT?

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Suppression of ^{18}F-FDG myocardial uptake using a fat-allowed, carbohydrate-restricted diet

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Abstract

Objective. Patients prepared by the generally used fasting protocol show variable myocardial ^{18}F-FDG uptake, which may result in difficult interpretation of mediastinal ^{18}F-FDG uptake. This retrospective study describes the effect of a one-day fat-allowed, carbohydrate-restricted diet on myocardial ^{18}F-FDG uptake.

Subjects and Methods. 100 patients on a carbohydrate-restricted diet from the Medical Center Leeuwarden (MCL) and 100 patients from the University Medical Center of Utrecht (UMCU), without any diet preparation, were included. A visual uptake categorical scale was used, (0); myocardial uptake is less compared to the liver, (1); myocardial uptake comparable to the liver, (2); myocardial uptake considerably higher compared to the liver.

Results. After a carbohydrate-restricted diet 68% of patients had a homogeneously low myocardial uptake of ^{18}F-FDG (0), and 16% a moderate myocardial uptake (1)) whereas 18% had homogeneously intense myocardial uptake (2). Without a carbohydrate-restricted diet 69% of patients showed a homogeneously intense myocardial uptake (2), 16% a moderate myocardial uptake(1), and 15% a homogeneously low myocardial uptake (0).

Conclusion. A fat-allowed, carbohydrate-restricted diet, starting the day before the ^{18}F-FDG administration, suppresses myocardial ^{18}F-FDG uptake satisfactorily

Introduction

Positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is widely used to stage malignant diseases and to evaluate metabolic changes in tumours after therapy, at a cellular level. The generally accepted patient preparation protocols for ^{18}F-FDG PET/(CT) involve fasting for approximately 6 hours (4-12 hours).

The purpose of fasting is to produce lower levels of serum glucose and insulin, enabling optimal uptake of ^{18}F-FDG, a glucose analog, in pathology characterized by increased glycolysis. In the fasting state, oxidation of fatty acids is the most predominant energy source available to the myocyte, supplying over half of the myocardial energy. The presence of insulin may lead to increased expression of insulin-sensitive glucose transporters (predominantly GLUT4), increased glucose oxidation rates supplying more than half of the myocardial energy, thus shifting the balance away from fatty acid metabolism to glucose metabolism. Consequently, myocardial uptake of ^{18}F-FDG may vary greatly with increasing insulin levels.[1]

Furthermore, marked variability of regional myocardial uptake over time was reported in patients who had their whole-body PET/CT's at multiple time points, each time after 6 hours fasting.[2]

High myocardial ^{18}F-FDG uptake, usually mainly in the left ventricle, is unwanted since it may hamper image reading in the thoracic and upper abdominal area. High physiologic myocardial FDG uptake has been reported to result in both false-positive and false-negative findings. [3,4]

A patient preparation method that minimizes myocardial ^{18}F-FDG uptake is expected to facilitate mediastinal staging and detection of focal lung pathology in proximity of the left ventricle of the heart. Since prolonged fasting did not seem to influence physiological ^{18}F-FDG uptake in the myocardium, perhaps because the energy balance was not shifted away from glucose metabolism enough, we hypothesized that prescribing a low-carbohydrate diet may lower myocardial ^{18}F-FDG uptake by a proper shift of the myocardial energy balance in the proper direction, as was previously described by Lum et al. [5]

Therefore, we included a 24 hour low-carbohydrate diet in the patient preparation protocol, at implementation of PET/CT in our institution in 2005. In this retrospective study myocardial ^{18}F-FDG uptake in patients from our hospital on such a low-carbohydrate diet was compared to patients from another hospital without such a diet preparation.

Materials and Methods

Subjects

Hundred patients on a low carbohydrate diet from the Medical Center Leeuwarden (MCL) and 100 patients from the University Medical Center of Utrecht (UMCU), without any diet preparation, were included in this retrospective study. The included patients had their PET/(CT) scans in the fourth quarter of 2008.

All patients were scanned for oncological reasons, primarily lung cancer, head and neck cancer and lymphoma. Patients with diabetes mellitus, and renal diseases were excluded, as most of these patients do not receive a standard patient preparation protocol, and usually already have an adapted diet. Also patients with known coronary artery disease and sarcoidosis were excluded as these heart conditions are known to interfere with myocardial FDG uptake.

Diet protocol

In the MCL out-clinic patients had a confirmation telephone call from the technologist two days before scanning, to outline the diet instructions, and a menu of permitted and non-permitted foods was given (Appendix 1). Clinical patients were instructed via the nursing staff. These diet instructions were then followed for 24 hours prior to scanning.

Appendix 1. Foods permitted and not permitted one day prior the ^{18}F-FDG scanning for patients prepared with a low-carbohydrate, fat/protein-permitted diet.

Permitted

- Fatty unsweetened chicken, turkey, fish, meat, meat-only sausages, fried eggs, bacon, butter/margarine
- Liquids (coffee,tea) without sugar
- Milk products with a maximum of 3 portions per day (milk, yoghurt, cheese)
- Vegetables (e.g. green salad, no beans)
- Sugar substitutes

Not-Permitted

- Bread, bagels, cereals, soup with vermicelli, potatoes, rice, cookies, toast, crackers, muffins, peanut butter, jam/confiture, nuts, fruit juice, candy, chewing gum, mints, cough drops, beans, alcohol

Scanning procedure

In MCL a Biograph 6 LSO HI-REZ hybrid PET/CT scanner was used, with CT based attenuation correction (Siemens Medical Systems Inc, Hoffman Estates, IL, USA. Patients had a carbohydrate restricted one day before the PET/CT investigation. A solution containing 0.2% locust bean gum and 2.5% mannitol was used as an oral contrast agent, in order to provide a useful bowel distension (optimal imaging of the intestinal tract), while avoiding contrast material induced PET artifacts. [6]

Patients were fasting for 6 h prior to the injection of 3.7 MBq (0.1 mCi)/kg bodyweight of ^{18}F-FDG, with a maximum of 333 MBq(9 mCi). Blood glucose levels were measured before administration. Ninety minutes after the ^{18}F-FDG administration, the data acquisition of the diagnostic CT was started, with intravenous administration of 120 ml of Optiray 300. Followed by a 3-dimensional PET, with the patient in the same supine position, the field of investigation ranged from the base of the skull to mid-thigh in (patient length dependent) six to nine 3-minute bed positions. The total imaging time of a PET/CT study lasted approximately 30 minutes. CT parameters; 95 kV (Q ref. mAs care dose 4D), slice thickness varying from 0.6 - 5.0 mm, collimation 6 x 1 mm, pitch 1.33.

PET images were reconstructed iteratively using ordered-subset expectation maximization software.

In UMCU a Philips Allegro PET scanner was used with attenuation correction by a Germanium-68 transmission scan. (Philips Medical Systems Inc, Cleveland, Ohio, USA).

Patients were fasting for 6 h prior to the injection of 3.7 MBq (0.1 mCi)/kg bodyweight of ^{18}F-FDG. Blood glucose levels were measured before administration. Sixty minutes after the FDG administration, the data acquisition of the 3-dimensional PET was started, with the patient in supine position, the field of investigation ranged from sub-cranial to above the knees in ten 3-minute bed positions. Including 12 transmission frames of 38 seconds, the total imaging time of a PET/CT study lasted approximately 40 minutes. PET images were reconstructed with 3D RAMLA.

Quantification of ^{18}F-FDG uptake and image analysis.

As a consequence of the use of different PET hardware and acquisition protocols in the two hospitals, comparison of measurements of the standardized ^{18}F-FDG uptake value (SUV) of the myocardium was deemed unreliable. Also assessment of only the intensity of the myocardial ^{18}F-FDG uptake based on a qualitative visual uptake scale was not considered as reliable enough. For this reason a visual uptake categorical scale was used, comparing the myocardial ^{18}F-FDG uptake to liver uptake. Myocardial ^{18}F-FDG uptake was divided in three categories (figure 1).

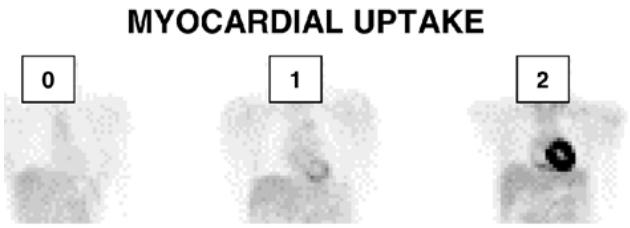

Figure 1. Myocardial uptake levels compared to the liver, in categories 0, 1 and 2.

- **0** Myocardial uptake is less compared to the liver (homogeneously minimal)
- **1** Myocardial uptake comparable to the liver (mostly mild or moderate uptake)
- **2** Myocardial uptake considerably higher compared to the liver (homogeneously intense)

Visual assessment was conducted as a triple-observer analysis, when all three observers agreed on the category of the myocardial uptake, the categorization was definitive.
In case of disagreement all three observers discussed until agreement on the category was reached, in a consensus reading,

Statistical analysis was performed using a statistical software package SPSS 15.0 for Windows Release 15.0 and using a χ-square test.

Results

Table 1 shows the Characteristics of the two study populations, 100 patients on a carbohydrate-restricted diet from the Medical Center Leeuwarden (MCL) and 100 patients from the University Medical Center of Utrecht (UMCU), without diet preparation.

Table 1. Patient characteristics of the two study populations.

Characteristic	MCL	UMCU
Mean age (years)	64	58
Mean serum glucose (mmol/l)	5.7	5.8
Sex	66 Male 34 Female	67 Male 33 Female
Mean Body Mass Index	24,75	24,04

Table 2 shows the results as percentages for the 100 patients with a carbohydrate-restricted diet and the 100 patients without a carbohydrate-restricted diet, per category of myocardial uptake. The diet-related difference in ^{18}F-FDG myocardial uptake is statistically significant (X^2 =63,837;p<0.0001)

Table 2. Correlation of Myocardial 18F-FDG Uptake and Diet

Parameter	Category		
	0	1	2
Without low-carbohydrate diet (%)	15	16	69
With low-carbohydrate diet (%)	68	14	18

Table 3 shows that no difference was found between both sexes in the beneficial effect of lowering the myocardial uptake of a carbohydrate-restricted.

Table 3. Correlation of Myocardial ^{18}F-FDG Uptake and Diet Analyzed by Sex

Parameter	Sex	Category		
		0	1	2
Without low-carbohydrate diet (%)	Male	18	13.4	68.6
	Female	9.1	21.2	69.3
With low-carbohydrate diet (%)	Male	62.1	18.2	19.7
	Female	79.4	5.9	14.7

Table 4 shows that weight, expressed in body mass index (BMI), did not attribute to the degree of myocardial ^{18}F-FDG uptake. With reference to age, patients were divided in categories of 5 years each. No difference in myocardial uptake was found between the different age categories.

Table 4. Correlation of Myocardial ^{18}F-FDG Uptake and Diet Analyzed by Body Mass Index

Parameter	Category	Body mass index			
		14–20	20–26	26–32	32–38
Without carbohydrate-restricted diet (%)	0	1	6.2	5.2	1
	1	5.2	6.2	3.1	2.1
	2	15.5	33	19.6	2.1
With carbohydrate-restricted diet (%)	0	7.1	46.4	10.7	6
	1	0	4.8	3.6	1.2
	2	2.4	13.1	3.6	1.2

Discussion

These results show that a fat-allowed, carbohydrate-restricted diet, starting the day before the ^{18}F-FDG administration, suppresses myocardial ^{18}F-FDG uptake satisfactorily. 68 % of patients have a homogeneously low myocardial uptake of ^{18}F-FDG after a carbohydrate-restricted diet, compared to only 15 % of patients without such a diet.

The use of a fat-allowed, carbohydrate-restricted diet in patient preparation prior to ^{18}F-FDG scanning may have some advantages.

Firstly, a more accurate recognition of pathology in the mediastinum, and of focal lung pathology in close proximity to the myocardium. In a case report describing a patient who had two sequential ^{18}F-FDG examinations for the characterization of a solitary pulmonary nodule (SPN), because the patient by mistake had eaten a meal just before the first examination, images initially showed high myocardial uptake, and the SPN was almost missed due to low focal uptake. After proper preparation images showed low myocardial uptake whereas the SPN showed high focal uptake.[4]

Probably competition of ^{18}F-FDG between myocardium and surrounding tissues plays an important role. This hypothesis is corroborated by the observation that in patients with lymphoma showing intense focal uptake in mediastinal lymphadenopathy, myocardial ^{18}F-FDG uptake is usually low and increases after successful chemotherapy. [7] Competition may also be the basis for the observation that in patients with diffuse high bone marrow uptake, significant ^{18}F-FDG uptake is rarely seen in the myocardium.[8]

A second advantage, is that lower myocardial ^{18}F-FDG uptake may increase accuracy in the detection of myocardial pathology, for instance myocardial sarcoidosis. In our own experience low myocardial uptake made it possible to recognize pericarditis in a patient who was referred for fever of unknown origin (FUO) (Figure 2). [9]

And as a third advantage, this adapted method of patient preparation may permit the detection of biologically active coronary artery disease (CAD). In a retrospective study of 32 patients treated for malignancy underwent ^{18}F-FDG PET/CT and concomittant cardiac catherization. They were instructed to eat a low-carbohydrate, high-fat meal the night before and to not eat or drink the morning of the ^{18}F-FDG PET/CT procedure, except for a vegetable oil drink (ClearScan; E-Z Em Inc.) ^{18}F-FDG uptake was identified in 1 or more coronary segments in 15 patients. A trend towards significance in correlation between ^{18}F-FDG uptake in the vessel and presence of angiographic disease was observed. (p=0.07;80 vessels examined).[10]

Several methods to decrease myocardial ^{18}F-FDG uptake have been investigated. Caffeine is known to elevate free fatty acid blood levels, creating a shift from glucose to free fatty acid metabolism in myocytes.[11]

However, no influence of caffeine on the uptake of ^{18}F-FDG in the myocardium was found. (Abstracts Eur J Nucl Med Mol Imaging 2004;31:S205 and S484). Other investigated factors like age and fasting time did not seem to influence ^{18}F-FDG physiologic uptake in the myocardium. [1]

Myocardial ^{18}F-FDG uptake was found to be lower in patients receiving bezafibrate and levothyroxine and higher in patients receiving benzodiazepines. The authors suggested manipulation of these drugs to optimize ^{18}F-FDG PET/CT imaging. [12]

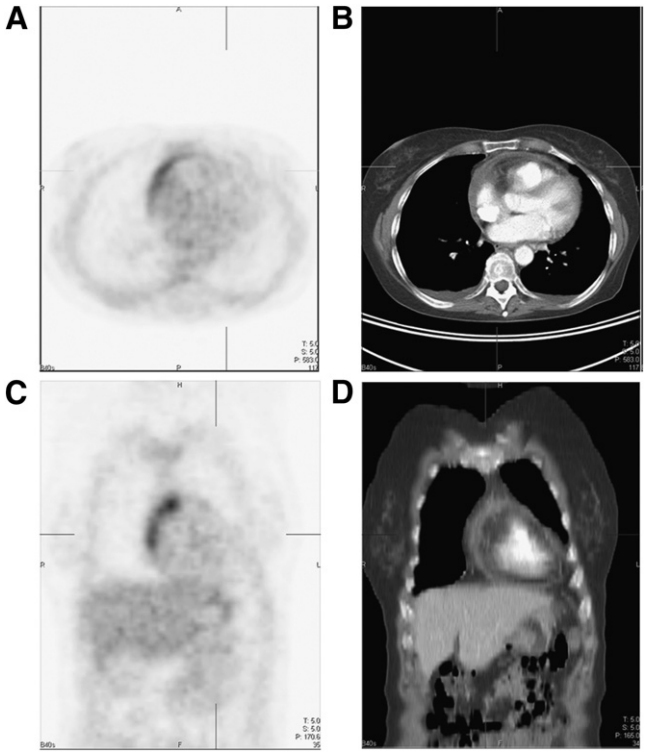

Figure 2. Transverse ^{18}F-FDG PET slice (A), corresponding transverse CT slice (B), coronal ^{18}F-FDG PET slice (C), and corresponding coronal CT slice (D). The irregular increased ^{18}F-FDG uptake in ventral portion of pericardium adjacent to right ventricular wall would not have been recognized in the otherwise moderate to high ^{18}F-FDG uptake ventral in right ventricular wall. Both transverse and coronal CT slices show thickened pericardium ventral in right ventricular wall, up to 8 mm.

Our results are concordant with those of Williams and Kolodny, who found an obvious suppression of myocardial standardized uptake value (SUV) after patient preparation with a high-fat, low-carbohydrate diet, eaten as a meal 3-6 hours before FDG injection.[13]
The average SUV_{max} in the myocardium for the fasting group was 8.8 ± 5.7 and the average SUV_{max} after the high-fat, low-carbohydrate diet was 3.9 ± 3.6. In a later study the same group included abstaining from carbohydrates the night before the scan and not eating or drinking the morning of the procedure, except for a vegetable oil drink (ClearScan). [10]

The underlying mechanism of suppression of myocardial ^{18}F-FDG uptake is likely the result of the Randle cycle, which has established that fatty acid loading suppresses glucose metabolism in a variety of tissues including myocardium. [14]

Furthermore, a report described that elevated blood levels of free fatty acids (FFA's) also decreased myocardial glucose uptake The change was effected by infusing heparin and triglycerides. Heparin displaces lipoprotein lipase in capillaries so triglycerides are clieved to yield FFA's, which are the preferred substrate of the myocardium.[15]

The suppression of myocardial ^{18}F-FDG uptake is further supported as FFA's are also reported to inhibit GLUT-4 expression in cardiac muscle. [16]

In support of the mechanism of the Randle cycle operating in myocardium is also a recent study performed in rodents, which were divided in three diet groups; low (0,1 % of total energy), intermediate (52 %) and high (78%) carbohydrate content. A diet of four weeks carbohydrate restriction resulted in marked and reproducibly reduced myocardial ^{18}F-FDG uptake, whereas glucose, insulin and glucagon did not differ among the three rodent groups. Ketone bodies were measured six-fold to seven-fold increased, and provided an alternative substrate to glucose. [17]

The optimal composition of a preparatory diet is not yet defined, probably the allowance of oil and butter to fry or bake fish and meat and allowing eating of (usually full-fat Dutch) cheese in our patient preparation is probably just as effective in suppressing the myocardial ^{18}F-FDG uptake. The use of a vegetable oil drink has advantages though, compliance is increased and exact intake is known. Patient compliance related to any diet is a known problem, probably also in our patient group. Eighteen of the 100 patients had a diffuse high myocardial uptake despite the carbohydrate-restricted diet. Although we did not use a questionnaire, non-compliance to the diet is a probable cause in at least some of them. In 2 of these 18 patients a probable explanation was found by serendipity, one outpatient could not be reached by telephone, another inpatient had a normal diet the day before PET/CT imaging due to miscommunication.

A possible influence of medication on the ^{18}F-FDG myocardial uptake, like lipid-lowering drugs, was not evaluated. Medication was not mentioned on the PET/CT request, and in this retrospective study patient referral was also from surrounding hospitals for both MCL and UMCU, making retrieval of patient medication problematic.

Conclusion

A fat-allowed, carbohydrate-restricted diet, starting the day before the ^{18}F-FDG administration, suppresses myocardial ^{18}F-FDG uptake satisfactorily.

There have been only a few retrospective studies using a carbohydrate-restricted diet in the patient preparation for ^{18}F-FDG imaging, and to our knowledge this is the first study that

compares the effect of a fat-allowed and carbohydrate-restricted diet on myocardial FDG uptake in daily routine in large patient groups between two hospitals. Because retrospective studies may potentially suffer from various forms of bias, of which selection bias probably is the most important, future prospective randomized studies are needed.

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^{18}F-FDG PET/CT in the Diagnosis of Fever of Unknown Origin

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Abstract

Objective: The utility of Fluorine-18 fluorodeoxyglucose positron emission tomography/CT in identifying the causal source was assessed in this retrospective study.

Methods: A total of 68 patients (33 men, 35 women; age range, 23–91 years) with fever of unknown origin (FUO) underwent a positron emission tomography/computed tomography (PET/CT) scan. PET/CT was considered helpful when abnormal results allowed an accurate diagnosis, based on histopathology, microbiologic assays, or clinical and imaging followup.

Results: PET/CT demonstrated suspected pathologic foci of Fluorine-18 fluorodeoxyglucose (F-18 FDG) uptake in 41 patients (60%), in 38 of these 41 patients (93%) F-18 FDG PET/CT helped in identifying the causal source, including infection in 25 patients, inflammation in 11 patients, a benign neoplasm in 1 patient, and in 1 patient rejection of a pancreas transplant. In 27 negative F-18 FDG PET/CT studies, no focal pathologic disease was diagnosed in the follow-up. In 6 of these 27 patients, a systemic disease without a focal manifestation was the cause for FUO. In the remaining 21 patients, fever and other signs subsided during follow-up.

Conclusion: Overall 56% of the F-18 FDG PET/CT studies contributed in the identification of the source in patients with FUO, and elevated erythrocyte sedimentation rate and C-reactive protein (positive predictive value 93%). When systemic diseases are excluded ^{18}F-FDG PET/CT has a high negative predictive value for focal etiologies of FUO (negative predictive value 100%).

Introduction

Fever of unknown origin (FUO) remains a major medical problem. The diagnostic work-up in patients with FUO remains challenging with up to 51% of cases undiagnosed.[1] FUO was defined in 1961 by Petersdorf and Beeson as recurrent fever of 38.3°C or higher and lasting 2 to 3 weeks or longer, without a diagnosis after 1 week of hospital evaluation.[2] FUO is nowadays generally interpreted as no diagnosis after appropriate inpatient or outpatient evaluation.[3]

More than 200 causes for FUO are reported.[4] Infections and noninfectious inflammatory diseases represent the main causes of FUO, followed by malignancy.[5,6]

Despite the major advances in investigative techniques, the overall mortality from FUO-related causes is 12% to 35%.[7] Early identification and precise localization of the cause for FUO are important for guiding further invasive diagnostic procedures and subsequently prompt initiation of appropriate treatment, with a significant impact on patient care.[8,9]

Conventional imaging modalities (computed tomography, ultrasound, and magnetic resonance imaging) are used for the localization of infectious or inflammatory foci. In the early stages of disease, morphologic changes or abnormalities may be absent, which causes anatomic imaging modalities to have a rather low sensitivity. In addition, these techniques usually deliver information from a limited part of the body and the use of total body CT and MRI is not widespread. Moreover, when after surgery or other therapeutic interventions morphologic changes are found, differentiation of inflammation from residual changes is limited.

Conventional methods of nuclear medicine (bone scintigraphy, labeled leukocyte scintigraphy WBC, or scintigraphy with gallium citrate (^{67}Ga) or antigranulocyte antibodies) offer a wholebody examination, but each investigation covers only a part of the spectrum of possible diagnoses in the broad setting of FUO. There are also disadvantages like handling of potentially infected blood products (WBC), high radiation burden, and poor imaging characteristics (WBC, ^{67}Ga) and the long-time span between injection and diagnosis (^{67}Ga).[10]

Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) is well established as a marker of malignant disease due to the increased glycolytic activity of malignant cells. Furthermore, activated inflammatory cells are also known to have increased glucose utilization, which makes ^{18}F-FDG-PET useful also in the demonstration of infectious and inflammatory processes and a serious candidate in the FUO diagnostic work-up. ^{18}F-FDG PET has several advantages over conventional scintigraphy; rapid reporting (scanning can be completed in approximately 2 hours from the injection), superior imaging quality and resolution (5–8 mm for PET vs. 10–15 mm for SPECT), higher lesion-to-background ratios at early time points, and lower physiological uptake in organs, resulting in optimal imaging conditions.[11] ^{18}F-FDG-PET was reported to be helpful for FUO diagnosis in 16% to 69% of the cases, and on average in 39% of the cases[9,12–15] (Table 1).

Hybrid PET/computed tomography (CT) could theoretically augment the accuracy in the work-up of FUO as a result of the expected complementary anatomic-metabolic information. However, only a limited number of studies have been published on the performance of ^{18}F-FDG PET/CT in the diagnosis of FUO.[16–18]

The primary purpose of this retrospective study was to evaluate the contribution of hybrid ^{18}F-FDG-PET/CT in the diagnosis of 68 patients with classic fever of unknown origin, and secondary to compare our results to other reports in the literature.

TABLE 1. Helpful Contribution of PET in Classical FUO

Author	Study Design/Technique P/R.	Patients Number	PPV/NPV	Helpful/Contribution Number/(%)	Final Dx Number/(%)
Meller	P.		92%/75%	11 (55%)	18 (90%)
	DHC-PET vs.	20			
	Ga-citrate	18			
Blockmans	P.		NA	24 (41%)	38 (66%)
	Full-ring PET vs.	58			
	Ga-citrate	40			
Lorenzen	R. Full-ring PET	16	92%/100%	11 (69%)	13 (81%)
Bleeker-Rovers (2004)	R. Full-ring PET	35	87%/95%	13 (37%)	19 (54%)
Kjaer	P.	19	30%/67%	16%	63%
	Full-ring PET vs.				
	In-111 granulocyte			26%	
Buysschaert	P.	74	NA	19 (26%)	39 (53%)
	Full-ring PET				
Bleeker-Rovers (2007)	P. multicenter Full-ring PET	70	70%/92%	24 (33%)	37 (51%)
Jaruskova	R.	124	NA	45 (36%)	51 (84%)
	Full-ring PET and (PET/CT)	FUO = 94			
PET	Total number patients	386		Overall helpfulness of PET 39% (mean)	Overall final diagnosis 67% (mean)

Legends: DHC: dual-headed coincidence camera; NPV: negative predictive value; PPV: positive predictive value; CECT: contrast-enhanced CT; NA: not applicable.

PATIENTS AND METHODS

Patient Population

All 68 patients (33 men, 35 women; age range, 23–91 years) were referred for ^{18}F-FDG-PET/CT by the Departments of Internal Medicine and Rheumatology between June 2005 and October 2008, for the investigation of prolonged fever or FUO. Patients from 3 surrounding community hospitals (without a PET or PET/CT camera) were also included.

HIV-positive patients, or patients with AIDS, were not included, as the diagnostic and therapeutic approach is conceptually different in this category of immunocompromised patients.[4] Patients with recent surgical procedures were not included.

Files of patients from our own hospital were extracted from the digital hospital information system. Treating/referring physicians of patients from the 3 other community hospitals were asked for information concerning the final diagnosis and how this definitive diagnosis was arrived at; including both invasive and noninvasive procedures, such as biopsy/surgery, serology, or cultures (blood, urine, or tissues). The time point for requesting a ^{18}F-FDG PET/CT was chosen by the referring physician. Follow-up was obtained for all patients, also for those with a negative ^{18}F-FDGPET/CT finding.

PET/CT Acquisition and Processing

A Biograph 6 LSO HI-REZ hybrid PET/CT scanner was used (Siemens Medical Systems Inc., Hoffman Estates, IL). Patients had a carbohydrate restricted diet one day before the PET/CT investigation, to decrease the uptake in the myocardium.[19] A solution containing 0.2% locust bean gum and 2.5% mannitol was used as an oral contrast agent, to provide useful bowel distension (optimal imaging of the intestinal tract), while avoiding contrast material induced PET artifacts.[20] Patients were fasting for 6 hours prior to the injection of 4 MBq (0.1 mCi)/kg body weight of ^{18}F-FDG, with a maximum of 333 MBq (9 mCi). Blood glucose levels were measured before administration. The data acquisition of the diagnostic CT was started 90 minutes after the ^{18}F-FDG administration, with intravenous administration of 120 mL of Optiray 300. Followed by a 3-dimensional PET, with the patient in the same supine position, the field of investigation ranged from subcranial to above the knees in (length dependent) 6- to 9 3-minute bed positions. The total imaging time of a PET/CT study lasts approximately 30 minutes. Attenuation correction was based on CT. CT parameters: 95 kV (Q ref. mAs care dose 4D), slice thickness varying from 0.6 to 5.0 mm, collimation 6x1 mm, pitch 1.33.

PET images were reconstructed iteratively using orderedsubset expectation maximization software. PET, CT, and fused PET/CT images were available for review and were displayed as noncorrected and attenuation-corrected images and also in a rotating maximum-intensity projection view.

Interpretation and Analysis of PET/CT Images

The initial PET reading at the Department of Nuclear Medicine and the CT reading at the Radiology department were done the same day of the investigation. The combined reading session of the fused PET and CT images was held in the morning after the PET/CT investigation, by both the radiologist and the nuclear physician at the Department of Nuclear Medicine. Both readers had knowledge of the patient's clinical history and results of previous imaging studies.

Any focal or diffuse ^{18}F-FDG uptake, with intensity higher than that of surrounding tissues, and in correlation with the corresponding CT slices, localized to an area that did not correspond to the physiologic biodistribution of the radiopharmaceutical was considered as pathologic. A negative study showed only ^{18}F-FDG activity in areas of the physiologic tracer biodistribution and no sites of increased uptake.

True negative (TN) - a normal study with further investigations or clinical follow-up excluding focal inflammation or malignancies.

False negative (FN) - was defined as a normal study and when a focal inflammation or malignancy was subsequently detected by other diagnostic modalities, or when the patient had a favorable response on the administered treatment.

True positive (TP) - a study demonstrating a focal localized disease process, confirmed by further investigations, as being the cause of FUO.

False positive (FP) - a study demonstrating a focal localized disease process, which could not be confirmed as being the cause of the FUO.

RESULTS

From June 2005 to October 2008, 68 patients with FUO were evaluated (33 men, 35 women; age range, 23–91 years). In all patients, glucose levels measured were below 180 mg/dL.

Initially 70 patients were evaluated; 2 patients were excluded from follow-up. One patient, showing a FDG positive mediastinal mass, died before a clinical diagnosis could be made. One other patient showed 6 years after breast cancer treatment unexpected multiple lymph node, skeletal, soft tissue, and adrenal metastases on ^{18}F-FDG PET/CT, confirmed by histopathology. As a urinary tract infection was suspected, and accordingly treated with antibiotics, it was unclear whether tumor fever or the urinary tract infection was the cause for the fever.

In 44 patients, a final diagnosis could be made; based on histopathology in 12 patients, on microbiologic or serologic assays in 4 patients, on microbiologic assays after biopsy surgery in 10 patients, and on imaging follow-up and/or clinical diagnostic criteria defined by the treating physicians in 18 patients. The final diagnosis included a focal infectious process in 25 patients (37%), noninfectious inflammatory processes in 14 (21%), a neoplasm in 2 (3%), (1 malignant and 1 benign, with the note that in 1 patient with diverticulitis an unexpected sigmoid carcinoma was histopathologically proven after colonoscopy), and miscellaneous diagnoses in 3 patients (4%), such as a rejected pancreas transplant in 1 and drug-induced fever in 2.

Out of 68 ^{18}F-FDG PET/CT studies, 41 patient studies (60%) demonstrated foci of pathologic ^{18}F-FDG uptake, suggestive of an underlying disease process representing the causal source for the FUO. In 38 of these 41 positive studies (93%), PET/CT led to the causal source of the FUO, and was therefore defined as TP, which included localized infection in 25 patients, inflammation in 11 patients, a benign neoplasm in 1 patient, and rejection of a pancreas transplant in 1 patient (Table 3).

Hybrid PET/CT results were helpful in localizing and establishing the diagnosis of abscesses in several locations, including the abdomen, in the spine, kidney, and liver, and also pinpointed an infected collection at the tip of a dynamic hip screw. Coregistered CT images were very useful in recognizing the focus of increased ^{18}F-FDG uptake as an abscess, but on the other hand, CT alone could not further distinguish between cystic necrosis, a specific intra-abdominal collection or even hemorrhage.

After hip prosthesis surgery, inflammatory changes may be indistinguishable from infection and may persist for years.[21] Therefore, at the initial PET reading not much attention was given to the increased uptake around the dynamic hip screw, which was placed 3 years earlier. The interpretation changed when at the tip of the osteosynthesis material, located just caudal to the metal artifacts on the CT images, a thin line suggestive of a small abscess was noticed, which coincided with a rim of linear increased ^{18}F-FDG uptake.

In the case of the focal Bartonella henselae infection, the distribution of pathologic foci in the spleen, liver, abdominal soft tissue (and not in the lymph nodes) was for the referring physician reason to reconsider cat scratch disease and to perform Bartonella serology.

One patient revealed ring-shaped pathologic ^{18}F-FDG uptake at the proximal anastomosis of the aortic bifurcation graft that was implanted 6 years earlier. A previously performed abdominal CT was considered normal. Only at the time of the reading session of the fused PET and CT images, the presence of gas in the ventral wall of the proximal anastomosis appreciated.

In another patient, the diagnosis of pericarditis would probably not have been made without the carbohydrate restricted diet during the 2 days prior to the PET/CT. The irregular increased ^{18}F-FDG uptake in the ventral portion of the pericardium adjacent to the right ventricular wall (showing thickening on CT initially missed by the radiologist) would not have been recognized in the otherwise moderate to high ^{18}F-FDG uptake in the myocardium (Fig. 1). Echocardiography 4 weeks after antibiotic therapy revealed no signs of pericarditis, and the temperature of the patient was normalized.

The patient with proven systemic candidiasis had 3 lung foci, of which the CT images were not suspicious for malignancy. The patient was accordingly successfully treated with fluconazol.

About 14 patients (21%) had a final diagnosis of noninfectious inflammatory disease. PET/CT was contributory in making the diagnosis in 11 of 14 patients.

In 3 of 14 patients, the intense linear ^{18}F-FDG uptake was localized by CT to the large thoracic, abdominal, brachiocephalic, and subclavian arteries, contributing to the diagnosis of large vessel arteritis/vasculitis. In 1 additional patient, a ring-shaped pathologic ^{18}F-FDG uptake was anatomically shown by CT to be confined to the wall of the aortic arch, in particular in the lateral wall and perivascular space adjacent to the truncus pulmonalis. “Atypical” Cogan syndrome was diagnosed on the basis of sensorineural deafness and large-vessel vasculitis of the aortic arch with improvement on steroid treatment (Fig. 2).[22]

In another patient who had an endovascular aneurysm repair due to inflammation of unknown origin, (HIV and Treponema pallidum serology negative) and inserted 12 months earlier, circular pathologic uptake around the prosthesis was demonstrated. On the corresponding CT slices, the pathologic uptake was located in the wall of the large saccular aneurysm, instead of the aortic prosthesis. As the uptake was regular without focal increased uptake, infection was considered less likely and the diagnosis of recurrent aseptic inflamed aneurysm was made. Immediate institution of corticosteroid treatment led to fast resolution of fever and symptoms (Fig. 3A and B).

Based on the ^{18}F-FDG PET images, diverticulitis of the sigmoid was suspected in 1 patient. CT slices revealed signs of diverticulosis at the same location, but also the suggestion of a small intraluminal process. More scrutinous inspection of the PET images revealed a focus with more intense uptake in close proximity; taken in consideration that some misalignment due to bowel movement is highly likely. After colonoscopy and sigmoid resection, carcinoma

of the sigmoid was confirmed by histopathology. The patient with a "hot" pituitary on the PET/CT images had, according the following laboratory tests, a prolactinoma with secondary adrenal cortex insufficiency and treatment with Dostinex and hydrocortisone resolved the fever and the clinical condition of the patient improved.

In 3 of the 41 patients, the positive ^{18}F-FDG PET/CT studies did not contribute to the final diagnosis and lacked impact on patient management, and were therefore defined as FP. One patient showed irregular linear ^{18}F-FDG uptake at the site of a pacemaker lead, but revealed no signs of infection at surgical exploration. Suspicion of infected renal cysts was not confirmed in an additional patient; as blood and urine cultures were negative and the temperature normalized; further investigations were not undertaken. In 1 patient, an ^{18}F-FDG-avid focus was localized at the site of the right ovary, which had a strange configuration on CT images, possibly a cyst. At the time of the abdominal ultrasonography, the temperature was normalized, and both ovaries had a normal appearance. A corpus luteum cyst was therefore the most probable cause for the focal increased ^{18}F-FDG uptake.

PET/CT showed no focal abnormal ^{18}F-FDG uptake in 27 patients. In 6 of them, eventually nonavid ^{18}F-FDG (systemic) diseases could be established, as causal source of the fever. Of these, 2 patients had drug fever, 1 patient had chronic lymphatic leukemia, 1 patient had a skin disease (Sweet syndrome, secondary to a myelodysplastic syndrome),[23] 1 patient had bilateral temporal arteritis, and 1 patient had Churg Strauss syndrome.[24] All studies in these 6 patients were categorized as true negative (TN).

In the other 21 of 27 patients, the fever resolved spontaneously without the use of antibiotics, and there was no evidence of any focal inflammatory, infectious, or malignant process during a clinical follow-up period varying from 4 to 24 months; consequently, these studies were considered as true-negative (TN) and no false-negative (FN) studies were noted.

In 6 of the 27 TN patients in our study population, normal laboratory values for erythrocyte sedimentation rate, C-reactive protein (CRP), and white blood cell count were found. In all of these 6 patients, no focal abnormalities were demonstrated on ^{18}F-FDG PET/CT images and subsequently at follow-up the temperature normalized spontaneously, without any intervention.

TABLE 3. Final Diagnosis in Patients With FUO and Results of FDG PET/CT Classified

Category	Total Cases (%)	No. Cases	True Positive	True Negative	False Positive
Infection	25 (37%)				
Pyelonephritis with extracapsular infiltration		1	1		
Pancreatitis		1	1		
Abdominal abscesses		1	1		
Diverticulitis (in 1 an accidental sigmoid carcinoma)		2	2		
Systemic/focal candidiasis		1	1		
Spondylodiscitis		1	1		
Vertebral abscess		1	1		
Infected vascular graft		3	3		
Psoas phlegmon		1	1		
Infected renal cysts		1	1		
Arthritis		1	1		
Pneumonia		3	3		
Pericarditis		1	1		
Infection after oesophagus varices treatment		1	1		
Liver abscess		1	1		
Focal *Bartonella* infection		1	1		
Infected spleen infarction		1	1		
Infected hip osteosynthesis material		1	1		
Osteomyelitis		2	2		
Neoplasm	2 (3%)				
Chronic lymphatic leucemia		1		1	
Pituitary macroadenoma (prolactinoma)		1	1		
Noninfectious inflammatory disease (NIID)	14 (21%)				
Polymyalgia rheumatica		1	1		
Arthritis psoriatica		1	1		
Morbus Sweet		1		1	
Bilateral arteritis temporalis		1		1	
Inflammatory aneurysm abdominal aortae		1	1		
Morbus Wegener		1	1		
Sarcoidosis		1	1		
Cryptogenic organizing pneumonia (COP)		1	1		
Atypical Cogan syndrome		1	1		
Severe gout		1	1		
Large-vessel arteritis		3	3		
Churg-strauss vasculitis		1		1	
Miscellaneous	3 (4%)				
Rejection pancreas transplant		1	1		
Drug fever		2		2	
No diagnosis	24 (35%)			21	3

No false negative cases reported.

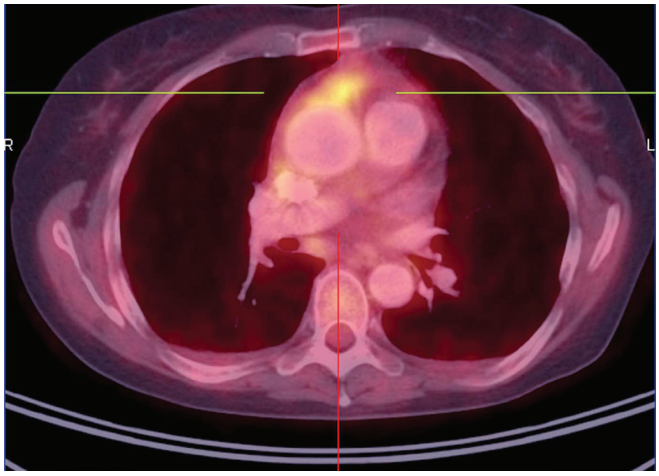

FIGURE 1. Transverse fused PET/CT slice. This case of pericarditis could probably not have been diagnosed without the carbohydrate restricted diet 1 day before the PET/CT. The irregular increased FDG uptake in the ventral portion of the pericardium adjacent to the right ventricular wall would not have been recognized in the otherwise moderate to high FDG uptake ventral to the right ventricular wall.

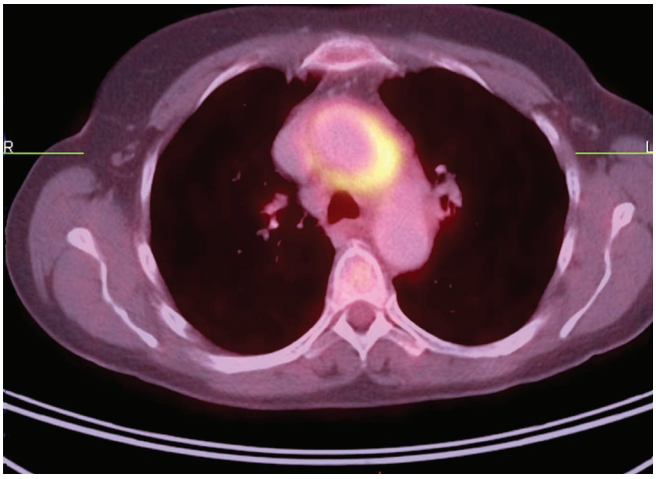

FIGURE 2. Transverse fused PET/CT slice, showing ringshaped pathologic ^{18}F-FDG uptake, which was anatomically shown by CT to be confined to the wall of the aortic arch, in particular in the lateral wall and perivascular space adjacentto the truncus pulmonalis. Atypical Cogan syndrome was diagnosed on the basis of sensorineural deafness andlarge-vessel vasculitis of the aortic arch with improvement on steroid treatment.

DISCUSSION

The utility of hybrid ^{18}F-FDG-PET/(diagnostic, contrast enhanced) CT in patients with FUO was evaluated in a retrospective series. In 27 negative PET/CT studies, no focal pathologic disease was diagnosed in the follow-up. In 6 of these 27 patients, a systemic disease without a focal manifestation was the cause for FUO (drug fever, chronic lymphatic leukemia, Sweet syndrome, secondary to a myelodysplastic syndrome, bilateral temporal arteritis, Churg Strauss syndrome). Due to the systemic nature of these diseases and the spatial resolution limited to 6 to 7 mm of the PET camera, the PET findings in these 6 patients were considered as true negative (TN).

These results confirm the high negative predictive value of ^{18}F-FDG imaging for assessment of FUO. ^{18}F-FDG PET/CT allows exclusion of a focal etiology of FUO with a high degree of certainty. When systemic diseases are excluded by other diagnostic tests, a negative PET/CT (in combination with negative first-level diagnostic tests, such as routine laboratory tests, urine and blood cultures, and serology) may avoid the need for further futile investigations.[9,12]

Overall 56% of the PET/CT studies contributed to the final causal diagnosis. In 93% of positive PET/CT studies, the images were contributory either by identifying the etiology of the FUO or by guiding further management, including invasive therapeutic procedures. The final causal diagnosis for FUO in our patient population included focal or systemic infection in 37% of patients, an inflammatory process (noninfectious inflammatory diseases) in 21%, a neoplasm in 3%, and rejection of a pancreas transplant in 1 patient and drug fever in 2 patients. In 2 patients, malignancy was demonstrated as a coincidental finding, rather than the actual cause of the fever.

The spectrum of etiologies and the distribution are rather similar to those in previously reported studies.[12,15]

The concept that with ^{18}F-FDG it is possible to detect infectious and inflammatory diseases as well as malignancy (the consequence of the relative nonspecificity of focal pathologic uptake of the tracer) can be considered as a powerful advantage in the diagnostic work-up of FUO patients, as reported by several authors. In a retrospective study by Bleeker-Rovers et al, the utility of FDG PET was evaluated in 35 patients with FUO, 37% of the ^{18}F-FDG PET scans were helpful. In the same study, 65% of the scans were clinically helpful in 48 patients suspected of focal infection or inflammation.[9] Meller et al found ^{18}F-FDG coincidence imaging

TABLE 2. Helpful Contribution of PET/CT in Classical FUO

Author	Study Design/Technique P/R.	Patients Number	PPV/NPV	Helpful/Contribution Number/(%)	Final Dx Number/(%)
Federici	R. Full-ring PET/CT	14	NA	7 (50%)	10/14 (70%)
Keidar	P. Full-ring PET/CT	48	. . ./100%	22 (46%)	28 (60%)
Ferda	R. Full-ring PET/CECT	48	NA	37 (77%)	44 (92%)
Present study	R. Full-ring PET/CECT	68	93%/100%	38 (56%)	47 (69%)
PET/CT	Total number patients	178		Overall helpfulness of PET/CT 57% (mean)	Overall percentage final diagnosis 72% (mean)

helpful in 55% of 20 patients with FUO. Blockmans et al demonstrated in a prospective study that ^{18}F-FDG PET was helpful in 41% of 58 patients with FUO.[14] Jaruskova and Belohlavek included 124 patients in a retrospective study (94 patients 76% with FUO and 24% patients with a clinical suspicion of a postsurgical infection). In 8 patients (16%), PET findings were FP. Patients underwent either ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT scanning, 36% of the studies were considered helpful. Unfortunately, the incremental value of PET/CT compared with stand-alone PET was not highlighted.[10] Kjaer et al found in a prospective comparison with In-111 granulocyte scintigraphy ^{18}F-FDG PET helpful in 16% of 19 patients and in 26% of patients with In-111 granulocyte scintigraphy. Both the rather small patient population and the used BSO PET camera (with a lower spatial resolution compared with the LSO PET camera) could be possible explanations for the rather low ^{18}F-FDG PET contribution.[25] Lorenzen et al found that in a small patient group of 16 patients, 11 PET studies (69%) were helpful.[26] In approximately 40%, of the total number of patients in these reports, stand-alone ^{18}F-FDG PET contributed to the final diagnosis (Table 1).

A negative aspect of ^{18}F-FDG PET is the limited anatomic information provided. In the oncologic setting, it is already demonstrated that hybrid ^{18}F-FDG-PET/CT imaging increases the diagnostic impact if ^{18}F-FDG PET, mainly by improving the specificity of the method; in particular, by decreasing the rate of false-positive cases but also by CT-guiding to the target lesion.[27] Also in our series, the number of false positive cases was low, probably related to the combined reader sessions by both the nuclear medicine physician and the radiologist.

Federici et al concluded in a retrospective study of 14 patients that ^{18}F-FDG PET/CT was essential to the diagnosis in 23% of the patients. In their opinion, PET/CT should be performed as a second level test, especially when conventional CT is normal or is unable to discriminate between active and silent lesions.[16]

In a recent prospective study by Keidar et al identified the underlying cause of a fever in 46%, and contributed to the diagnosis or exclusion of a focal pathologic etiology of the febrile state in 90% of 48 patients.[17] They suggested that ^{18}F-FDG PET/CT, as a noninvasive single imaging modality, may in the future be used as one of the initial diagnostic investigations in patient with FUO.

Ferda et al retrospectively investigated 48 patients with FUO with ^{18}F-FDG PET/2 phase contrast enhanced CT. They found only one false negative and one false positive case.

In only 4 of 48 patients (8%), eventually no diagnosis was found, which is a substantially lower percentage compared with all other reports.

Comparison of these studies is difficult because of the heterogeneity of the patient population, differences in PET and CT techniques (including the specific preparation of the patient), and use of contrast material.[15]

Due to the retrospective character of this study, several limitations need to be mentioned; a comparison between stand-alone ^{18}F-FDG PET results and ^{18}F-FDG PET/CT was not considered as reliable. No structured diagnostic work-up or protocol was used, the

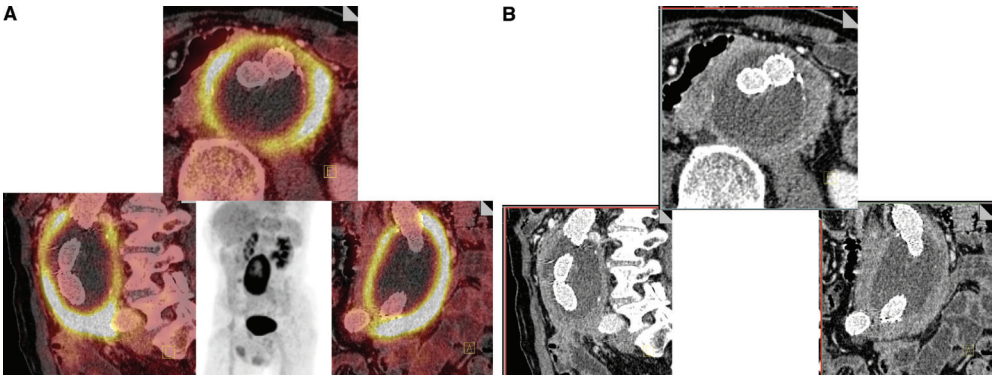

FIGURE 3. A, B, In a patient who had an endovascular aneurysm repair due to inflammation of unknown origin, (HIV and treponema pallidum serology negative) and a prosthesis was inserted 12 months earlier, circular pathologic uptake around the prosthesis was demonstrated. On the corresponding CT slices, the pathologic uptake was located in the wall of the large saccular aneurysm, instead of the aortic prosthesis. As the uptake was uniform without focal increased uptake, infection was considered less likely and the diagnosis of recurrent aseptic inflamed aneurysm was made. Immediate institution of corticosteroid treatment led to rapid resolution of fever and symptoms.

involved referring physicians decided at which point in time during the diagnostic work-up a PET/CT was needed.

Calculation of sensitivity and specificity of ^{18}F-FDG PET/CT in patients with FUO is difficult.

A final diagnosis is not established in all patients. In our study, in 6 patients with negative PET/CT, a variety of systemic diseases were found that could not be diagnosed with ^{18}F-FDG PET.

Obvious disadvantages of ^{18}F-FDG PET and PET/CT are the relatively high cost and the currently limited availability. However, when the number of PET/(CT) systems further increases, the high diagnostic yield of ^{18}F-FDG PET and PET/CT may very well become a clinically significant and also cost-effective modality, since adequate early diagnosis limits the number of other (noncontributing and/or invasive) tests required and the time to diagnosis and thereby the duration of hospitalization.[12]

Our study confirms that the complementary information of a hybrid ^{18}F-FDG PET investigation with a diagnostic CT (including the use of an i.v. contrast agent, bowel preparation with an oral contrast agent, and a carbohydrate restricted diet for 1 day to minimize the myocardial ^{18}F-FDG uptake) leads to an improvement in the diagnostic impact, compared with a stand-alone ^{18}F-FDG PET investigation (Tables 1 and 2). Not only by improving the specificity, but also the possibility of a false positive study is diminished by guiding the exact localization for a biopsy, which minimizes the risk of a sample error.

Furthermore, this study confirms the results by Bleeker-Rovers et al that ^{18}F-FDG PET/(CT) is not helpful in patients with fever and normal erythrocyte sedimentation rate and CRP.

CONCLUSION

These results from a retrospective study confirm that dedicated hybrid ^{18}F-FDG PET/CT scanning has a high positive predictive value (93%) and high negative predictive value (100%) for focal etiologies in the differential diagnosis of patients with classic FUO and elevated ESR and CRP. When systemic diseases are excluded by other diagnostic tests, a negative PET/CT (in combination with negative first-level diagnostic tests, such as routine laboratory tests, urine and blood cultures, and serology) may avoid the need for further investigations.

The synergy of combined anatomic-metabolic information is of incremental value in the diagnostic work-up of FUO. Compared with stand alone PET the number of false-positive cases can be reduced, and on the other hand, CT-guided biopsies can be more targeted.

Further, larger well-designed, prospective, studies are needed to validate and to implement the strategy of using this hybrid imaging modality as an initial diagnostic investigation in patients presenting with FUO.

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The diagnostic utility of ^{18}F-FDG PET/CT in inflammation of unknown origin

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Abstract

Objectives: The goal of this multicenter retrospective study was to evaluate the contribution of ^{18}F-FDG PET/CT in the diagnosis of patients with inflammation of unknown origin (IUO). Secondly, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were assessed as possible predictors for the outcome of ^{18}F-FDG PET/CT.

Methods: IUO was defined as prolonged and perplexing inflammation; with repeated CRP levels more than 20 mg/l or ESR more than 20 mm/h, body temperature below 38.3 ºC and without a diagnosis after a variety of conventional diagnostic procedures.

A total of 140 patients with IUO (67 men, 73 women; mean age 64, 2 years, age range 18-87 years) underwent a ^{18}F-FDG PET/CT scan. ^{18}F-FDG PET/CT was considered helpful when the imaging findings led to a diagnosis, either confirmed by histopathology, microbiological assays, clinical and imaging follow-up, or response to treatment.

Results: In 104 patients (73%) a final diagnosis could be established: infection in 35 patients, malignancy in 18 patients, non-infectious inflammatory disease in 44 patients and a variety of uncommon conditions in 7 patients. ^{18}F-FDG PET/CT was true positive in 95 patients, true negative in 30 patients (i.e. self-limiting conditions), false positive in 6 patients and false negative in 9 patients (predominantly systemic diseases). In this population the positive predictive value, negative predictive value and diagnostic accuracy of ^{18}F-FDG PET/CT was 94%, 77% and 89%, respectively. In a multivariate analysis CRP was the only independent predictor for the outcome of ^{18}F-FDG PET/CT.

Conclusion: ^{18}F-FDG PET/CT correctly identified or excluded a causal explanation in approximately 90% of patients with IUO. However, a negative ^{18}F-FDG PET/CT is indicative for a self-limiting condition only after systemic diseases are excluded by other diagnostic tests.

Introduction

Inflammation underlies a wide variety of physiological and pathological processes. The classic instigators of inflammation - infection and tissue injury - are at one end of a large range of adverse conditions that induce inflammation. Inflammation accompanied by fever and without an apparent explanation is a syndrome well-known as fever of unknown origin (FUO), and remains a major medical problem.[1] However, patients may also present with inflammation of unknown origin (IUO); without fever. The aetiology of IUO may vary from a self-limiting condition to occult malignancy.[2] IUO without fever and FUO may reflect differences in clinical presentation of the same disease entities.[3] In search for an explanation of IUO, patients may therefore undergo extensive and expensive investigations and medical treatment. Interventions that may not only be inappropriate but at the same time unnecessarily exposes patients to the risks of these investigations.[4] In addition unnecessary use of healthcare resources is perceived as unsatisfactory from the perspective of patient, physician and from a cost aspect.

The use of potential diagnostic clues (PDC) defined as all localizing signs, symptoms, and abnormalities potentially pointing toward a possible diagnosis, in the diagnostic work-up proved to be misleading in the majority of patients. In addition PDC alone did not directly lead to a diagnosis in any of the patients with FUO.[5]

^{18}F-FDG PET(CT) is a well established technique in the evaluation of patients with fever of unknown origin (FUO).[6-10] In contrast little is known on the role of ^{18}F-FDG PET(CT) in patients with inflammation of unknown origin (IUO). Therefore the use of ^{18}F-FDG PET may offer substantial benefit to patients in the diagnostic work-up of patients with IUO. In addition, PET imaging is helpful in early diagnosis as it is able to reveal functional alterations that precede the morphological changes. Moreover, the use of hybrid PET/CT adds important advantages to stand-alone ^{18}F-FDG PET. The synergy of integrating anatomical and morphological images allows improved interpretation of both abnormal ^{18}F-FDG uptake and suspicious morphological findings.[11] The relative lack of literature that covers the role of ^{18}F-FDG PET(CT) in IUO is remarkable and allows no guidance for a diagnostic strategy in these patients.[3,12-14]

In this multicenter retrospective study we aimed to evaluate the contribution of hybrid ^{18}F-FDG PET/CT in the diagnosis of patients with IUO. Secondly, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) - as markers of disease severity - were assessed as possible predictors for the outcome of ^{18}F-FDG PET/CT.

Patients and methods

IUO definition

In this study IUO was defined as prolonged and perplexing inflammation; with repeated CRP values more than 20 mg/l or ESR more than 20 mm/h, with clinical complaints and body temperature below 38.3 ºC (100.9 °F) and without a diagnosis after conventional diagnostic procedures, referred by the departments of internal medicine or rheumatology for ^{18}F-FDG PET/CT. Because of the lack of diagnostic accuracy complaints or PDC were not evaluated in this study.

Exclusion criteria:

Patients that had FUO according to the current generally used interpretation; 'fever higher than 38.3 °C (100.9 °F) on several occasions and no diagnosis after appropriate inpatient or outpatient evaluation', were excluded.[15] HIV-infected patients were excluded. In these patients infections represent the most common aetiology, and urgent evaluation is necessary as rapidly progressive infection may be life-threatening if untreated and may therefore require prompt empirical antimicrobial therapy.[16] Patients with recent surgical procedures were excluded. Patients that had a clinical suspicion or PDC for a certain diagnosis that was confirmed by ^{18}F-FDG PET/CT were excluded. Finally, patients in whom insufficient documentation or information concerning the follow-up could be obtained were excluded.

Patient selection

Patients were selected using the databases from the Academic Medical Center, University of Amsterdam (AMC) and the Medical Center Leeuwarden (MCL). The search for patients was limited to those referred by the departments of Internal Medicine and/or Rheumatology. The query in the databases was limited to the period between June 2005 and August 2012. Files of these patients were extracted from the digital hospital information systems.

The AMC is a tertiary academic hospital and the MCL is a large secondary community and teaching hospital. Both hospitals serve as referral sites for community hospitals without a PET/CT camera. Only sufficiently validated diagnoses were retained for analysis; the final diagnosis was not based on the ^{18}F-FDG PET/CT results. The definitive diagnosis was based on both invasive and non-invasive procedures, such as biopsy or surgery, serology or cultures (blood, urine, or tissues) and follow up to evaluate the response of therapy. For patients from the surrounding community hospitals the treating/referring physicians were asked both by phone and fax for information on how the final diagnosis was arrived at. Of the multiple CRP and ESR measurements only the value most close to the date of the ^{18}F-FDG PET/CT was used for further analysis.

Prior relevant medical history

Patients were stratified in two groups; with and without a prior relevant medical history. A prior relevant medical history was defined as a previous disease (e.g. malignancy) or current condition (e.g. prosthetic material) that could be a logical explanation for the IUO

Follow-up and final diagnosis

The final diagnosis made at discharge or during follow-up was classified into five categories: 1) infections, 2) malignancies, 3) non-infectious inflammatory disease (NIID) including connective tissue diseases, vasculitis syndromes, and granulomatous disorders, 4) miscellaneous causes and 5) no diagnosis during admission and follow up. This is a classification generally used for FUO.[17] The time point for requesting the ^{18}F-FDG PET/CT was chosen by the referring physician. Follow-up was obtained for all 140 patients, also for those with a negative ^{18}F-FDG PET/CT finding. The mean follow-up was 2 years and 8 months (range between 6 months and 7 years).

PET/CT Acquisition and Processing

In the AMC a Gemini time of flight PET combined with a Premium Brilliance 16 slice CT scanner was used as a hybrid PET-CT (Philips Healthcare, Eindhoven/Best, the Netherlands). In the MCL a Biograph 6 LSO HI-REZ hybrid PET/CT scanner was used (Siemens Medical Systems Inc, Hoffman Estates, IL, USA). In both centers an oral contrast agent was used in all examinations. Blood glucose levels were measured before administration of ^{18}F-FDG. As higher glucose levels (> 180 mg/dl [10 mmol/l]) might influence the sensitivity of the ^{18}F-FDG PET we also checked for glucose. All patients had glucose levels below 180 mg/dl (10 mmol/l), also in 6 patients with diabetes mellitus, at the time of ^{18}F-FDG administration. Patients were fasting for 6 h prior to the injection of ^{18}F-FDG (dosage corrected for BMI in both centers). Sixty minutes after the ^{18}F-FDG administration, the CT acquisition was started (depending on clinical indication either a “diagnostic” with i.v. contrast or “low-dose” CT). The CT acquisition was directly followed by a 3-dimensional PET acquisition, with the patient in the same supine position. The field of investigation ranged from sub-cranial to above the knees (length dependent) with 2-minute bed positions (with 50% overlap between two bed positions) in the AMC, and six to nine 3-minute bed positions in the MCL. Attenuation correction was based on CT.

PET images were reconstructed iteratively using ordered-subset expectation maximization software. PET, CT and fused PET/CT images were available for review and were displayed as non-corrected and attenuation-corrected images in combination with a rotating maximum-intensity projection (MIP) view.

Interpretation and analysis of PET/CT images

The initial PET/CT reading, at the department of Nuclear Medicine and/or in combination with the department of Radiology, was done the same day of the investigation. The reading resulted in a combined report where both readers had knowledge of the patient's clinical history and results of previous imaging studies.

A positive study showed ^{18}F-FDG uptake, with intensity higher than that of surrounding tissues, and in correlation to the corresponding CT slices, localized to an area that did not correspond to the physiologic bio-distribution of the radio-pharmaceutical.

A negative study was defined as a PET study showing only a physiologic ^{18}F-FDG distribution without any sites of abnormal ^{18}F-FDG uptake, and without any pathology on the corresponding CT images. Anatomical abnormalities without pathologic ^{18}F-FDG uptake (e.g. liver cysts, mucus in the maxillary sinus, a partial vertebral fracture, or lung atelectasis) were defined as a negative study.

Classification of outcome data

Outcome data were related to the results of the initial PET/CT images and the predictive value of the ^{18}F-FDG PET/CT was assessed according to the following criteria:

- True negative (TN); a normal ^{18}F-FDG PET/CT with further investigations or clinical follow-up excluding disease process(es).
- False negative (FN); was defined as a normal ^{18}F-FDG PET/CT in combination with a disease process subsequently detected by other diagnostic modalities, or when there was a tangible response to a medical treatment.
- True positive (TP);^{18}F-FDG PET/CT demonstrating a) disease process, confirmed by further investigations, as being the cause of IUO, or could be related to a tangible response to medical treatment.
- False positive (FP);^{18}F-FDG PET/CT demonstrating a disease process that could not be confirmed as being the cause of the IUO, or could not be related to the absence of response to treatment.

Statistical analysis

Data are presented as mean ± standard deviation, unless indicated other wise. Positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of ^{18}F-FDG PET/CT were calculated. PPV was defined as the proportion of patients with a positive ^{18}F-FDG PET/CT who were correctly diagnosed. NPV was defined as the proportion of patients with a negative ^{18}F-FDG PET/CT who were correctly diagnosed. Diagnostic accuracy was defined as the proportion of patients with a true positive and true negative ^{18}F-FDG PET/CT.

Differences between groups for continuous data were compared using ANOVA with a post hoc Bonferoni. Categorical data were compared using the Chi-square test. A forward stepwise logistic multivariable regression analysis was performed to determine

independent predictors of a true positive ^{18}F-FDG PET/CT. CRP, ESR, age and gender were used as explanatory variables. A $p<0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed with SPSS *(IBM SPSS Statistics 20 for windows, IBM Corporation Inc, New York, United States of America).*

Table 1. Diagnostic procedures prior the F18-FDG PET/CT

X-ray	Chest, 116; other radiographic investigations, 11
CT	Chest and/or abdominal, 37; brain, 7; sinuses, 4
MRI	Spine or brain, 9
Ultrasound	Abdomen, 79; artery temporalis, 7; thyroid 3
Transesophageal echocardiography	6
Leukocyte scintigraphy	1
Bone scintigraphy	4
Microbiologic cultures	Urine, 11; feces, 4; blood, 24
Viral serology	12; HIV test, 5
Autoimmune serology	11
Electromyography	1
Biopsies	Bone marrow, 6; artery temporalis, 4; skin, 1
	Kidney, 1; lymph node, 1
Punctures with biopsy	Lumbar, 4; synovial, 3; pleural, 1
Endoscopy with biopsy	Gastroduodenal, 11; colonic, 10
Tuberculin sensitivity test	2

Results

The query in the databases revealed 2794 patients referred for an ^{18}F-FDG PET/CT by the departments of Internal Medicine and Rheumatology. Of this cohort there were 235 patients that initially fulfilled our definition of IUO. After the exclusion criteria were applied, 140 (67 men, 73 women; age range, 18-87 y, mean age 64.2 years) eligible patients remained for analysis. Hundred-and-twelve (81%) patients were referred by the department of Internal Medicine and 28 (19%) patients were referred by the department of Rheumatology.

Prior to the ^{18}F-FDG PET/CT all 140 patients underwent a variety of diagnostic procedures to obtain a diagnosis. These procedures ranged from conventional radio-diagnostic tests to a variety of biopsies (Table 1), the choice which diagnostic procedure to opt for was based on PDC. However, in none of the 140 patients did these investigations result in an explanation for the clinical problem. Mean CRP value was 84 mg/l (range 3 - 550 mg/l) and mean value of the ESR was 60 mm/h (range 5 - 121 mm/h).

Follow-up and Final Diagnosis

In 104 patients (74%) a final diagnosis could be established at discharge or during follow-up These diagnoses were based on serology (n=5), microbiologic cultures (blood, urine, biopsy/surgery specimens) (n=18), histopathology (n=29) or response to treatment (n=52). In our study a final diagnosis could not be established in 36 patients.

The final diagnosis was related to infection in 35 patients, malignancy in 18 patients, non-infectious inflammatory disease (NIID) in 44 patients and a variety of uncommon conditions in 7 patients. Table 2 shows the individual diagnoses within the four diagnostic categories. NIID was the main category with polymyalgia rheumatica (PMR) (18 patients) as the first main diagnosis. Large-vessel vasculitis (LVV)/giant cell arteritis (GCA) (12 patients) was the second most established diagnosis.

Thirty-six patients (26%) remained without a diagnosis. During follow-up in most patients the inflammatory syndrome remained unexplained and resolved spontaneously.
In three overweight patients (body mass index [BMI] 25-29.9 kg/m^2) the CRP and ESR values remained marginally increased and in two obese patients (BMI > 30 kg/m^2) CRP and ESR values remained in the 20-40 (mg/l, mm/h) range without pathologic explanation during a 3-year and 2 year follow-up respectively.

Negative- and positive predictive value

Hybrid ^{18}F-FDG PET/CT contributed to the diagnosis in 95 patients of 140 patients (68%). Interpretation of the CT images alone would have contributed to the diagnosis in 15 patients; diffuse large-cell B-cell lymphoma, lung cancer, pancreatic carcinoma, renal cell carcinoma, recto-sigmoid carcinoma, peritonitis carcinomatosa, and also in the case of pericarditis, lung vasculitis, retroperitoneal fibrosis-like systemic disease and a large splenic abscess.

Table 2. Final diagnosis in patients with IUO and ^{18}F-FDG PET/CT outcome.

Category	Total Cases, %	No. Cases	TP	FN
Infection	35 (25%)			
Spondylodiscitis		3	3	
Focal *Bartonella henselae* infection (cat-scratch disease)		1	1	
Abscess (aneurysm iliac artery)		1	1	
Helicobacter Pylori gastritis and diverticulitis		2	2	
Abdominal aortic prosthesis infection with fistulation		1	1	
Complicated infected knee prosthesis		1	1	
Diverticulitis		3	3	
Pericarditis		2	1	1
Endocarditis		1		1
Lymphadenitis		1	1	
Pulmonary infection		5	5	
Infection liver cyst(s)		2	2	
Infection renal cyst(s)		3	3	
Abscess sternotomy		1	1	
Maxillary sinusitis		2	2	
Lingual tonsillitis		1	1	
Septic arthritis		1	1	
Axillary hydradenitis		1	1	
Splenic abscess		1	1	
Cholecystitis and liver abscesses		1	1	
Decubitus with bone involvement		1	1	
Malignancy	18 (13%)			
Diffuse large cell B-cell lymphoma		3	3	
Squamous cell vaginal carcinoma		1		1
Chronic eosinophilic leukemia		1		1
Lung cancer		4	4	
Skeletal metastasis with unknown primary		1	1	
Pancreatic carcinoma		2	2	
Multiple myeloma (stage I)		1		1
Renal cell carcinoma		1	1	
Rectosigmoid carcinoma		3	3	
Peritonitis carcinomatosa		1	1	
NIID	44 (31%)			
LVV		12	12	
PMR		18	18	
Cryptogenic organizing pleuritis		1	1	
Systemic lupus erythematosus		3	3	
Lupus-like disease		1		1
Peripheral spondylarthropathy		1	1	
Leukocytoclastic vasculitis		1		1
Rheumatoid arthritis with pulmonary noduli (exacerbation)		3	3	
Pleuritis (rheumatoid arthritis related)		1	1	
Small-vessel dermal vasculitis		1		1
Lung vasculitis		1	1	
Arthritis psoriatica (exacerbation)		1	1	
Miscellaneous	7 (5%)			
Necrosis uterus myomatosis		1	1	
Chronic pancreatitis		1	1	
Foreign body reaction lungs with lymphadenopathy		1	1	
Inflammation shoulder cuff rupture		1	1	
Gastritis (Morbus Crohn related)		1	1	
Acute demyelinating encephalomyopathy		1		1
Retroperitoneal fibrosis-like systemic disease		1	1	
No diagnosis	36 (26%)			
Total	140	104	95	9

Hybrid ^{18}F-FDG PET/CT was true positive in 95 patients, true negative in 30 patients, false positive in 6 patients and false negative in 9 patients.

The PPV of ^{18}F-FDG PET/CT was 93% with a NPV of 77% and a diagnostic accuracy of 89%. Due to the intrinsic relatively limited spatial resolution of PET systems, ^{18}F FDG PET can have problems in detecting systemic diseases with relatively limited changes in glucose metabolism. When in our population patients with such systemic diseases (n=9, e.g. leukemia, acute demyelinating encephalomyopathy, multiple myeloma (stage1), or lupus like disease) were categorized as true negative, the NPV increased to 100% with an increased diagnostic accuracy of 95% and an unchanged PPV of 93%.

IUO with or without prior relevant medical history

There were 69 patients (49%) with IUO and no prior relevant medical history. In 51 out of these 69 patients (74 %) a diagnosis was reached (15 infections, 8 malignancies, 25 cases of NIID, 3 miscellaneous) and 18 remained without a diagnosis.

Seventy-one patients (51%) had a prior relevant medical history (predominantly malignancies, vascular-, valvular- and orthopaedic prostheses) albeit none of which was diagnosed as the current aetiology of the IUO by any of the diagnostic procedures performed prior to the ^{18}F-FDG PET/CT. In 53 patients of 71 (75%) a final diagnosis was reached (20 infections, 10 malignancies, 19 cases of NIID, 4 miscellaneous) and 18 remained without a diagnosis. Although previous diagnostic tests found no diagnosis, in 16 of these 71 patients, the diagnosis was proven related to the medical history after ^{18}F-FDG PET/CT; mainly infections (of prostheses and liver/renal cysts) and NIID.

CRP and final diagnosis

Table 3 shows the percentage of patients with a final diagnosis related to the CRP values. Only in 2 patients the ESR was below 20 mm/h: in a patient with a lung infection (ESR 5 mm/h and CRP 115 mg/l), and in a patient with diverticulitis (ESR 12 mm/h and CRP 34 mg/l).

Stepwise multivariable regression analysis showed that of the variables CRP, ESR, age and gender, CRP was the only independent predictor of a true positive ^{18}F-FDG PET/CT (odds ratio 1.011; 95% confidence interval 1.003 - 1.019).

Table 3 Numbers of patients and percentage with diagnosis in patients stratified according CRP values

	No. of Patients and Percentage With Diagnosis
CRP >20 mg/L (n = 120)	96/120 (80%)
CRP 10–20 mg/L (n = 11)	6/11 (54%)
CRP <10 mg/L (n = 9)	2/9 (22%)

- CRP values <10 mg/l (in all 9 patients ESR value > 20 mm/h with a mean ESR value of 43 mm/h),
- CRP values between 10- 20 mg/l (in all 11 pts ESR value was > 20 mm/h with a mean ESR value of 49 mm/h),
- CRP values > 20 mg/l.

Discussion

A surprisingly small amount of literature describes unexplained prolonged inflammatory syndrome or inflammation of unknown origin. In 2002 Perrin et al. described a retrospective series of 46 patients gathered over a 7 years period, with an inflammatory syndrome without diagnosis during hospital admission (for a median of 20 days). Eighteen of the 46 patients were reported to have periods of fever. During a total of 67 hospitalizations of these 46 patients, a final diagnosis was established in 14 patients. However, without a PET or PET/CT camera at their disposal these diagnoses were made at the expense of: 115 bacterial cultures, 42 tuberculine tests, 217 serology tests, 305 immunological tests, 78 tumour marker tests, 112 standard radiographies, 99 ultrasound investigations, 39 CT scans, 52 endoscopies, 75 biopsies, 2 laparotomies and 63 inter-disciplinary consultancies.[4] Other recent studies report similar results and underline the lack of uniformity in the definition of IUO, and the large diversity of patient populations and diagnostic approaches.[14,18]

In an attempt to validate the proposition that IUO may be caused by the numerous diseases that are included in the spectrum of FUO related diseases, Vanderschueren et al. prospectively collected a series of 57 consecutive patients with IUO (defined as CRP values >30 mg/L and/ body temperatures not exceeding 38.3°C (100.9 °F) with diagnosis uncertain despite appropriate investigations, after at least 3 outpatient visits or at least 3 days in hospital). These patients were compared with a set of age- and sex-matched patients with classical FUO, according to the definition of Durack and Street; “a fever higher than 38.3 °C (100.9 °F) on several occasions during at least 3 days in hospital or at least three outpatient visits, with uncertain diagnosis after diagnostic tests”.[1] The authors concluded that the diagnostic-yield, case-mix, contribution of stand-alone ^{18}F-FDG-PET (without CT) and vital outcome were similar in both groups. In addition the authors came to the conclusion that the 38.3 °C boundary of FUO seems arbitrary. Therefore the diagnostic approaches used in unexplained prolonged febrile disorders can probably be applied to unexplained prolonged inflammatory disorders.[3] Our results support the notion by Vanderschueren et al that IUO and FUO are “Two of a kind” and that similar numbers of malignancies, infections an non-infectious inflammatory diseases were diagnosed.

In our population of 140 patients with prolonged and unexplained increased inflammatory parameters ‘or inflammation of unknown origin’, a final diagnosis could be established in 104 patients (74%). ^{18}F-FDG PET/CT contributed to the diagnosis in 95 patients of 140 patients (68%). This high percentage is almost double the 36% of patients in the IUO patient group of Vanderschueren et al. for which the stand-alone ^{18}F-FDG PET scans contributed to the diagnosis. The difference may have been due to selection-bias, their population could have consisted of more patients for which the ^{18}F-FDG PET study meant a ‘last-resort’ chance for an explanation of reaching a diagnosis. On the other hand, at least half of the patients in our population were included in recent years at a time when the referring physicians were already well aware of the merits of a ^{18}F-FDG PET/CT study, with

the probable consequence that the barrier for the request of a ^{18}F-FDG PET/CT was less high. Ongoing technological improvements in medical imaging equipment may have played an important role as well; the overall helpfulness of stand-alone ^{18}F-FDG PET (mostly without attenuation correction) in 8 publications describing a total of 386 patients with FUO was 39% in identifying the aetiology of the fever.[19-26] The overall helpful contribution of hybrid ^{18}F-FDG PET/CT was 57%, in 7 publications that included a total of 226 patients.[6-9,27-29]

The concept that PET imaging is helpful in early diagnosis as it is able to reveal functional alterations that precede the morphological changes is supported by the 71 patients with a prior relevant medical history that were without a diagnosis after previous diagnostic tests. After ^{18}F-FDG PET/CT the diagnosis was proven to be related to the medical history in 16 of these 71 patients (mainly infections of prosthetic material and renal/liver cysts and NIID). Also the relative high contribution of infection and (NIID) to the total number of diagnoses supports the notion that ^{18}F-FDG PET imaging is helpful in early diagnosis, which is illustrated by figure 1 and 2. Furthermore, the synergy of integrating anatomical and morphological images allows not only improved interpretation of abnormal ^{18}F-FDG uptake but also of morphological findings on CT otherwise interpreted as suspicious.

Our results support the substantial underestimation of the incidence of LVV, which is probably higher than 20-30/100.000 persons (0,03%) generally mentioned in literature reports. For that matter a retrospective study of arterial changes in 20,591 autopsy subjects showed that PMR with signs of aortic involvement is far more common than is diagnosed clinically, arteritis was found in 0,4% and only half of them had temporal arteritis.[30]

All 9 patients with a false negative^{18}F-FDG PET/CT were later diagnosed during follow up with a disease without a focal presentation (Table 2). An accurate calculation of the sensitivity and specificity of ^{18}F-FDG PET/CT in our population of patients with IUO is therefore cumbersome. Calculation of sensitivity and specificity is also difficult as a final diagnosis was not established in all patients.

Thirty-six patients (26%) remained without a diagnosis. During follow-up in most of these patients the inflammatory syndrome remained unexplained and resolved spontaneously. In these cases of self-limiting conditions there was apparently a beneficial and controlled inflammatory or immune response.[2] In the three overweight patients and the two obese patients with increased CRP and ESR values without pathologic explanation during a 3-year and 2 year follow-up respectively, the question remains open whether this reflects a state of low-grade systemic inflammation.[31] Adipose tissue is an active endocrine organ that releases a variety of hormones and cytokines, such as interleukin-6, that contribute to CRP elevation.[32]

^{18}F-FDG PET/CT may guide further diagnostic procedures, e.g. by more precisely targeted CT-guided biopsies, which minimizes the risk of a sample error. In addition as corticosteroid administration/immunosuppressive therapy may normalize ^{18}F-FDG uptake in inflammatory lesions, patients should undergo ^{18}F-FDG PET/CT, preferably before a trial with steroids.[33,34]

The design of this retrospective study has some disadvantages, most importantly the occurrence of selection bias; the search for patients with IUO was limited to those referred

for ^{18}F-FDG PET/CT by the departments of Internal Medicine and Rheumatology. In addition the lack of a non-structured diagnostic approach might have further attributed to this bias.

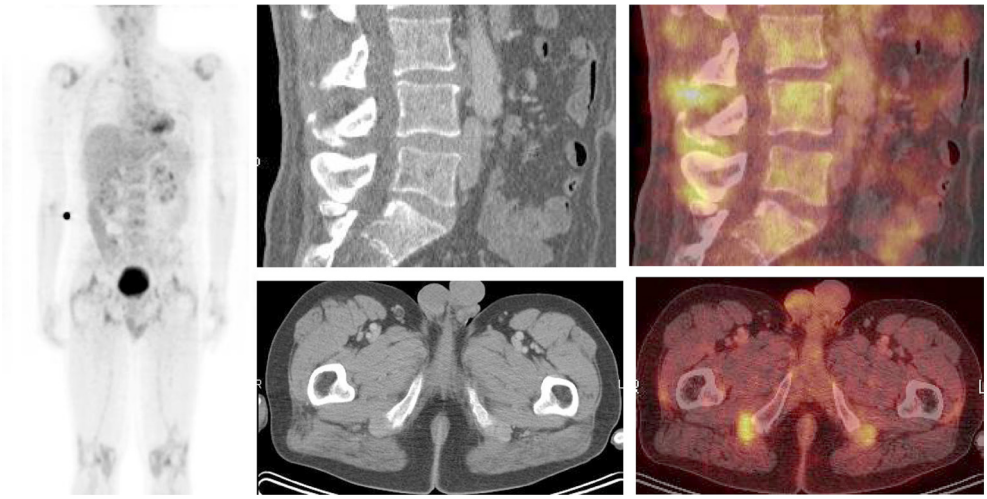

Figure 1. A 48-year-old man presented with initial painful calves followed by progressive painful arms and legs, shoulders, and knees. No hydrops or other clinical signs of arthritis. Normal body temperatures; CRP level, 84 mg/L; ESR, 41 mm/h; normal routine laboratory values; rheumatoid factor negative; cyclic citrullinated peptide antibody test negative; serum angiotensin-converting enzyme, 10.3 units/L; antinuclear antibody test negative; and anticytoplasmic autoantibodies negative. Urine sediment; albumin trace. Glomerular basal membrane antibody test negative. Viral serology negative. Chest x-ray and abdominal ultrasonography without abnormalities. X-ray of hands, feet, and knees revealed no erosive changes. Ultrasonography of the hips revealed no abnormalities either. ^{18}F-FDG PET/CT showed pathological perisynovial uptake at the major joints, as well as pathological lumbar interspinous uptake in the soft tissue (bursae) lateral to both of the greater trochanters and dorsal to both of the tuber ischii.[34] The diagnosis of PMR was made; after treatment with steroids, the patient became pain free, and the CRP values remained less than 10 mg/L.

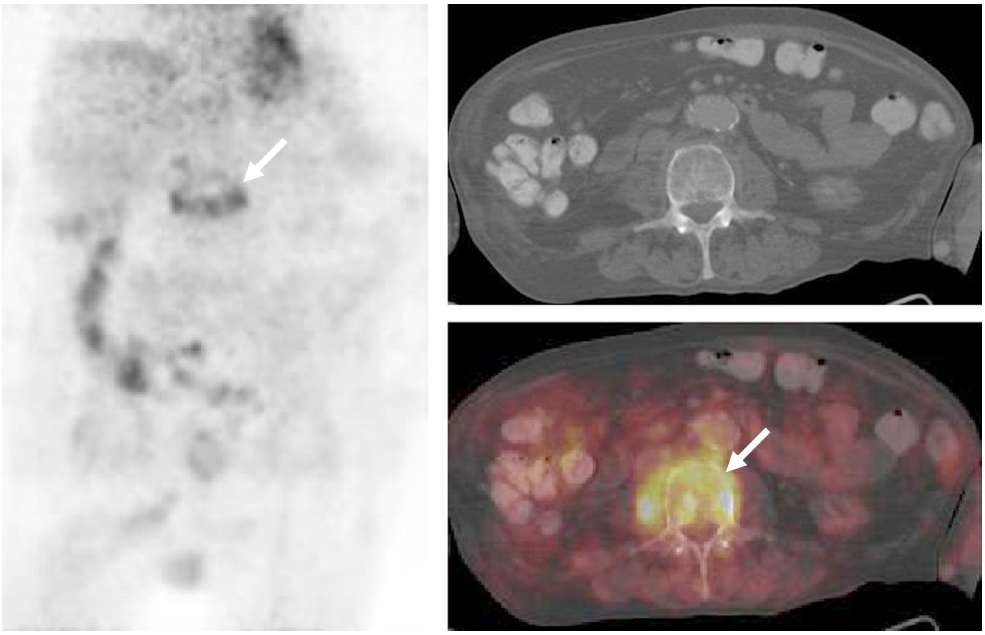

Figure 2. A 71-year-old man was known with chronic heart failure and a pacemaker. The highest CRP value is 48 mg/L. Subfebrile body temperatures. Ultrasonography of the abdomen showed steatosis hepatis. Chest radiograph was suspect for infiltration in the right upper lobe, CT chest revealed only bilateral pleural fluid. Blood cultures were positive for *Staphylococcus epidermidis*. In suspicion for an infected pacemaker, treatment with vancomycin and gentamicin was started. However, CRP values remained high. ^{18}F-FDG PET/CT showed pathologic findings in the vertebral body of L3 and in the adjacent soft tissue of the right musculus iliopsoas (white arrow). Antibiotic treatment of spondylodiscitis was continued for 2 months. (Note: the upper part of the maximum-intensity projection image is missing; because of claustrophobia, the patient refused further cooperation for the remaining bed positions.)

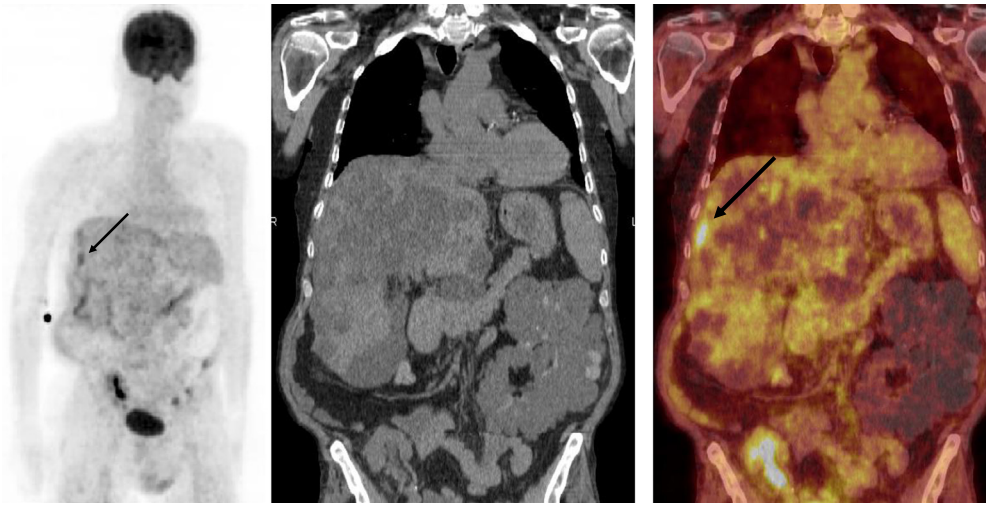

FIGURE 3. A 61-year-old man known with multiple liver cysts and renal cysts and a renal transplant in the right fossa iliaca. The CRP value is125 mg/L. Subfebrile body temperatures. Blood cultures were positive for *Escherichia coli* and *Enterococcus faecalis*. After initial Ciproxin, which was later followed by Augmentin without clinical improvement, ^{18}F-FDG PET/CT showed pathological uptake at the margin of a lateral localized liver cyst (black arrow). In consequence of the rising CRP levels with an infected liver cyst, IV application of cefotaxime was started for 4 weeks, after which the patient gradually recovered.

Conclusions

The diagnosis of IUO is problematic as it may be caused by rare presentations of common aetiologies or common presentations of rare aetiologies. However, this study supports the notion that the diagnostic approaches and the outcomes in patients with IUO show many similarities with FUO patients. Due to its relatively high PPV for focal aetiologies in IUO patients, ^{18}F-FDG PET/CT has a potential role in helping to establish a final diagnosis.

In addition, especially in patients without systemic/(non-focal) diseases ^{18}F-FDG PET/CT has a high NPV and is therefore helpful in identifying patients with benign and self-limiting conditions. A negative ^{18}F-FDG PET/CT may avoid further diagnostic tests and therapeutic trial with steroids or antibiotics.

Uncertainty remains in which (early) stage of the diagnostic approach ^{18}F-FDG PET/CT is to be used. It has the potential to become a routine imaging technique indicating the direction for further diagnostic decisions and thereby avoiding unnecessary, invasive and expensive diagnostic investigations. However, this should be confirmed in well designed prospective studies with a uniform selection of patients.

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Diagnosis of Abdominal Aortic Prosthesis Infection With ^{18}F-FDG-PET/CT

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Abstract

A 79-year-old man was referred with recurrent periods of fever and chills. Six years earlier an aortic bifurcation graft had been implanted. Blood examination showed elevated infection parameters. A regular computed tomographic (CT) scan in the previous hospital showed no signs of graft infection. When blood cultures revealed multiple enteric bacteria, a 2-deoxy-2- [^{18}F]fluoro- d-glucose-positron emission tomographic/CT (^{18}F-FDG PET/CT) scan was performed that demonstrated ring-shaped pathological uptake at the proximal anastomosis. The patient was operated on and an infected graft was found, with a 1-cm defect in the distal part of the duodenum. Bacterial cultures of the explanted graft were positive. The patient recovered well from surgery and is on a regimen of prolonged antibiotic and antimycotic treatment.

Introduction

Vascular prosthesis infection ranks among the most serious complications in surgery. Aortic prosthetic graft infection is associated with high morbidity and mortality in the absence of immediate, definitive antibiotic therapy and surgical intervention.[1] Infection of a vascular graft is usually diagnosed using computed tomography (CT) or magnetic resonance imaging. Ultrasound scanning, labeled white blood cell scintigraphy, and gallium scintigraphy have also been used as ancillary methods to establish vascular graft infection.[2] The high spatial resolution of CT provides exquisite detail of the vascular structure and perivascular spaces. CT affords visualization of the structural changes secondary to infection. However, in the duodenum, for example, hematomas and seromas in the vicinity of a vascular graft may appear anatomically similar to an abscess, making it difficult sometimes to distinguish between noninfected and infected prosthetic grafts.[2]

Positron emission tomography (PET) with 2-deoxy-2- [^{18}F]fluoro-d-glucose (^{18}F-FDG) is becoming increasingly important in diagnosis, staging, and therapy monitoring in clinical oncology, and has recently been used in the diagnosis of infectious diseases with elevated intracellular glucose metabolism.[3] The uptake mechanism in infectious and inflammatory diseases has not yet been fully elucidated, but it seems to be the case that glucose is the sole energy source of granulocytes during their metabolic burst.[4]

Investigators have recently shown that ^{18}F-FDG PET has a diagnostic performance superior to that of CT in the diagnostic assessment of patients with suspected aortic graft infection, when specific uptake patterns of ^{18}F-FDG are included in the diagnostic criteria.[5] The fusion of ^{18}F-FDG PET and CT, acquired in a single session, enables the precise localization of any abnormal ^{18}F-FDG uptake.[6]

Case Report

A 79-year-old man was investigated in another hospital for recurrent periods of fever, chills, and illness during 5 to 6 months. Medical history revealed the implantation of an aortic bifurcation graft for an aortic aneurysm 6 years earlier. Initial bacterial blood cultures were negative. Blood examination showed multiple times elevated erythrocyte sedimentation rate (ESR) (highest value 29 mm/1st h) and elevated C-reactive protein (CRP) concentrations (highest value 88 mg/L). Leukocyte counts were all within normal ranges. Because a vascular graft infection was also suspected in the previous hospital, a contrast-enhanced CT scan was performed that showed (also in retrospect) no perigraft gas graft or signs of infection.

Just before the patient's admission to our hospital, blood cultures had shown multiple enteric bacteria. A combined ^{18}F-FDG PET/CT examination was performed (3 weeks after the contrast-enhanced CT that was done in the previous hospital). Ninety minutes after intravenous administration of 333 MBq of ^{18}F-FDG, data acquisition of CT was started, with intravenous administration of 120 ml of Optiray 300. This was followed by a 3-dimensional PET, with the patient in the same position, performed with the Biograph 6 LSO hybrid PET/CT scanner (Siemens Medical Systems Inc, Hoffman Estates, IL). The field of investigation ranged from just subcranial to above the knees in seven 3-minute bed positions.

Initially, the CT images of this PET and CT investigation were not regarded as suspicious for an infected aortic prosthesis, as the perigraft gas was not recognized by the radiologist (Figure 1). The ^{18}F-FDG PET images clearly demonstrated ring-shaped intense pathological uptake at the site of the proximal anastomosis, suspicious for infection. It was only at the time of the reading session of the fused PET and CT images (by both the radiologist and the nuclear physician) that the presence of gas in the ventral wall of the proximal anastomosis was recognized.

The patient was operated on and an infected graft was found with a 1-cm defect in the distal part of the duodenum. The defect in the duodenum was sutured, and the graft was completely explanted and replaced by a silver-coated prosthesis soaked in rifampicin. The outcome in mortality and risk for reinfection of an extra-anatomical bypass is comparable to an in situ replacement, but the patency is better for in situ replacement.[7] The graft was covered completely with tissue from the omentum majus. Bacterial cultures of the explanted graft revealed the presence of *Enterobacter, Citrobacter, Klebsiella,* and *Candida species*. The patient recovered well from surgery and was on a regimen of augmentin en fluconazol for 6 months. Termination of antibiotic and antimycotic treatment was based on both laboratory values and clinical symptoms.

A CT scan of the aortic graft 6 months after surgery showed no perigraft gas or other signs of infection (Figure 2).

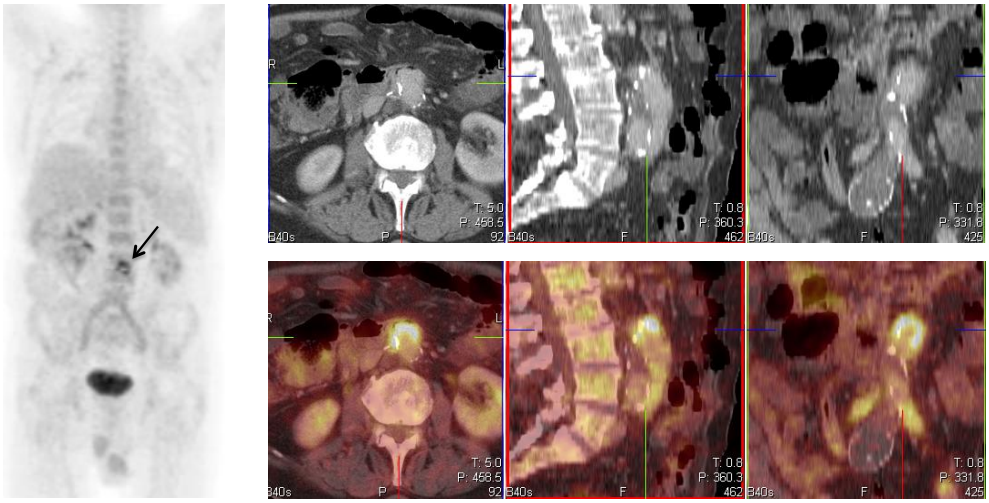

Figure 1. Left image is the maximum intensity projection (MIP). The transverse, sagittal, and coronal CT slices show the presence of gas, the 18F-FDG PET/CT slices the intense ring-shaped pathological uptake at the proximal anastomosis of the aortic bifurcation graft.

Discussion

Infection of the aortic graft after vascular surgery is a life-threatening complication with high morbidity and mortality. Accurate and rapid diagnosis of an aortic graft infection is crucial. A prompt diagnosis is essential when a life-threatening aortoenteric fistula exists at the site of the infected vascular graft.[8]

Compared with conventional nuclear medicine techniques such as single photon emission computed tomography (SPECT) of the gamma camera, PET provides higher quality images with superior contrast, resulting in more sensitive quantification of inflammatory activity.[3] Previous reports indicated that prosthetic vascular graft replacement was sometimes associated with a false-positive ^{18}F-FDG uptake in the graft or stent regions.[9] This false-positive accumulation might be explained as ^{18}F-FDG uptake during the process of normal foreign body reaction or inflammation during the normal postoperative course after reconstruction of the aorta.[5] Other scintigraphic studies confirm this hypothesis; white blood cell or leucocyte scintigraphy also showed a certain number of false-positive results for this specific indication.[10] The possibility of other reasons for false-positive findings must be kept in mind: venous thrombosis, sterile inflammation, vasculitis, or retroperitoneal fibrosis may all lead to pathological high uptake of ^{18}F-FDG.[11]

In a study by Fukuchi et al, 8 of 33 cases showed various degrees of false-positive ^{18}F-FDG uptake, but the pattern of uptake was diffuse along the prosthetic graft in all false-positive cases. Using focal pathological uptake as a diagnostic criterion resulted in a statistically significant increase in the specificity and PPV (positive predictive value) of ^{18}F-FDG PET in the diagnosis of graft infection.[5]

The case in hand emphasizes that the fusion of ^{18}F-FDG PET and CT images may have additional value compared with the value of CT images alone. The information about the combination of intensity and pattern of ^{18}F-FDG uptake, related to the anatomical localization of pathological tracer uptake, may allow a better differentiation between infected and noninfected aortic grafts.[12]

Hybrid ^{18}F-FDG PET/CT scanning may improve the potential use of ^{18}F-FDG PET in the diagnosis of infected vascular grafts. ^{18}F-FDG PET/CT is a useful noninvasive diagnostic modality for the evaluation of suspected infected aortic grafts, especially when the clinical suspicion remains after nonconclusive conventional CT scanning.

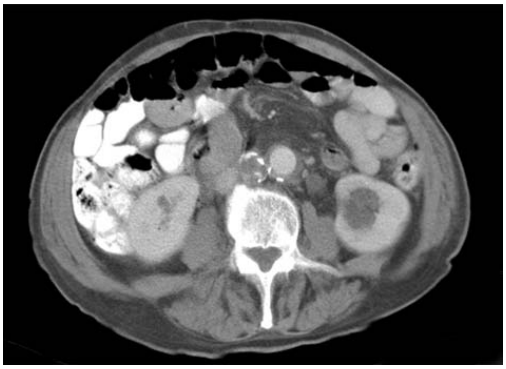

Figure 2. A transverse slice of the abdominal computed tomography made 6 months after surgery showing no signs of infection in the proximity of the proximal anastomosis.

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Occult Prolactinoma Diagnosed by FDG PET/CT

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Abstract

An elderly woman, with a fever of unknown origin was investigated for an underlying pathologic process. A whole-body FDG PET/CT study unmasked an occult pituitary macroadenoma, as confirmed by brain magnetic resonance imaging (MRI). Subsequently, results of functional endocrinological tests were compatible with a prolactinoma. This case report highlights the usefulness of including the brain in a whole-body PET/CT study, when fever of unknown origin is the dilemma.

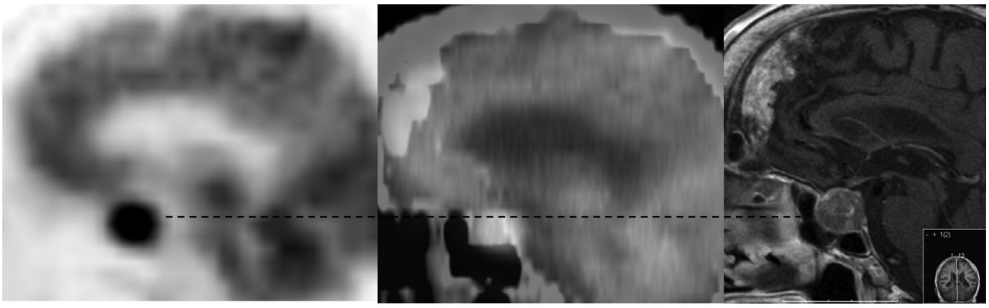

Figure 1. An 84-year-old woman, with known Alzheimer disease, was admitted to the hospital with general as well as mental deterioration, and fever of unknown origin. After various investigations in the work-up, whole body ^{18}F FDG-PET coregistered with a 6-multislice CT (HiRez Siemens, Biograph), including the brain, was performed. Surprisingly, the PET/CT examination revealed only marked FDG uptake (SUVmax of 10) in the pituitary gland (see selected (A) sagittal PET and (B) fused PET/CT images of the brain). On the selected sagittal MRI image after administration of gadolinium, diffuse enhancement is seen of a large (25 x 20 x 25 mm) macroadenoma localized in the pituitary gland. Moreover, there was extension into the left suprasellar region and cavernous sinus (see selected (C) sagittal MRI image).

Endocrinological functional tests showed a highly increased prolactin level of 30.130 mU/L (normal 70–500 mU/L) with a macroprolactin level of 65 mU/L, and a suppressed cortisol level, indicating a prolactin-secreting pituitary adenoma (or prolactinoma) and secondary Addisons disease. Subsequently, the patient was appropriately treated.

Pituitary adenomas are the most common cause of a mass in the sella turcica, accounting for up to 10% to 15% of intracranial neoplasms.[1] Normal pituitary glands do not accumulate FDG. There is limited and rather controversial data about the FDG avidity of pituitary nonfunctional and functional or hormonal secreting micro- and macroadenomas. While Francavilla et al reported the highest FDG uptake in a nonfunctional pituitary adenoma, to the contrary, more recently, there is some evidence that, among other intracranial tumors, the highest metabolic activity was found indeed in prolactinoma, which correlated well with the serum prolactin level.[2–9] Recently, in a small series of patients with Cushing disease, it was demonstrated that PET/CT and MRI can be complementary for the localization of an occult adrenocorticotropin-secreting pituitary adenoma.[10] Other etiologies must be considered in the differential diagnosis of sellar masses including meningiomas, metastastic tumors, systemic lymphomas, germ cell tumor, gliomas, and on the other hand, granulomatous, infectious, and inflammatory processes.[1] Finally, a very rarely reported neoplasm is the primary central nervous system lymphoma variant, with sole involvement of the pituitary gland.[1,11]

This is probably a rare report describing the usefulness of hybrid FDG PET/CT in unmasking an incidentally found prolactinoma. This case report emphasizes the fact that additional PET scanning covering the brain can be crucial in patients presenting with fever of unknown origin.

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The role of PET/CT in Cogan's syndrome

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Abstract

We report on the case of a 60-year-old woman with complaints of fatigue, coughing, anorexia, atypical chest pain, recurrent fever, and also ear pain and hearing loss. A test for anti-neutrophil cytoplasmic antibody (ANCA) was myeloperoxidase positive with p-ANCA specificity. Laboratory acute phase parameters were increased. A 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission tomography/computed tomography investigation showed pathological uptake in the aorta ascendens, with no other involvement of the large vessels. After therapy with methylprednisolon intravenously and later prednisolon orally with methothrexate, her general condition and hearing loss improved both subjectively and objectively. “Atypical” Cogan’s syndrome was diagnosed on the basis of sensorineural deafness with improvement on steroids and large-vessel vasculitis of the aortic arch.

Introduction

The association of nonsyphilitic interstitial keratitis and audiovestibular involvement was first reported in 1934 by Mogan and Baumgartner. Their description was extended several years later by Cogan.[1]

In "typical" Cogan's syndrome, the presence of interstitial keratitis is necessary, the term "atypical" Cogan's syndrome is used when other types of inflammatory eye disease, including conjunctivitis, uveitis, scleritis, and choroiditis are associated with the vestibuloauditory abnormalities.[2] In many cases, the symptomatology is not only restricted to the eyes and the ears but also other organs, thus resembling systemic vasculitis in one third of the patients. The most common symptoms are cardiovascular, musculoskeletal, neurological, gastrointestinal, and mucocutaneous.[3]

Positron emission tomography (PET) with 2-deoxy-2- [^{18}F]fluoro-D-glucose (FDG) is becoming increasingly important in diagnosis, staging, and therapy monitoring in clinical oncology and has recently been used in the diagnosis of infectious diseases with elevated intracellular glucose metabolism. Activated inflammatory cells have been shown to overexpress glucose transporters and to accumulate increased amounts of glucose and structurally related substances such as ^{18}F-FDG.[4,5]

Therefore FDG-PET is also introduced as a diagnostic means to assess involvement in large vessel vasculitis [6]. In this report, we report the use of FDG-PET/computed tomography (CT) scanning in the diagnosis of Cogan's syndrome.

Case report

A 60-year-old Caucasian woman was admitted to the hospital with a 4-month history of excessive fatigue, coughing, anorexia and weight loss, night sweats, and atypical chest pain. She also experienced short periods of fever. She experienced headaches and ear pain and hearing loss for over the last month, mainly on the left side, and felt sometimes dizzy. No blurred vision complaints or eye problems were noted. She was not known with any allergies.

For her hypothyroidism (multinodular goiter), she used Thyrax (L-thyroxine)150 mcg once a day. She did not smoke and consumed alcohol only moderately.

The family history revealed a daughter with systemic lupus erythematosus.

Physical examination revealed a pulse of 104, and bloodpressure was 125/85 mmHg and the temperature 37.1°C. Heart sounds were normal, and the lungs were clear. The outer ears were normal. No lymphadenopathy was detected and no scalp tenderness or decreased pulsation at the temporal arteries was noted.

Laboratory tests revealed an erythrocyte sedimentation rate (ESR) of 51 mm/h and C-reactive protein (CRP) of 53 mg/L. Test for rheumatoid factor was 42 kU/L (<10), and tests for antinuclear facor and double-stranded DNA antibodies were negative.

A test for anti-neutrophil cytoplasmic antibody (ANCA) appeared to be myeloperoxidase positive with p-ANCA specificity.

Serum electrolytes and creatinine were normal. Her differential blood count, alkaline phosphatase, and transaminases were normal. The urine gave a negative test for protein, and the sediment contained no white cells, red cells, or casts in the urine.

Initially arteritis temporalis was suspected, but Doppler ultrasonography of the temporal arteries showed no abnormalities. A chest X-ray revealed no interstitial or focal abnormalities. Subsequently, a PET/CT was performed, which showed pathological uptake in the wall of the aortic arch. More intens pathological uptake was seen at the beginning of the aorta descendens in the lateral wall, most likely a sign of perivascular inflammation. Maximum standard uptake value (SUV max) measured 11.9. No other involvement of large vessels was noted (Fig. 1). A magnetic resonance imaging (MRI) scan of the cerebrum showed abnormalities suspicious for bilateral mastoiditis, possibly as a consequence of bilateral otitis media.

After placing inner ear tubes, her hearing loss improved only little. Culture of the ear secretion was negative for pathogenic microorganisms. Audiograms confirmed sensorineural hearing loss, particularly in the left ear. Investigation of the eyes revealed no abnormalities, especially no keratitis.

Therapy was started with three cycles of 1,000 mg methylprednisolon intravenously and later 60 mg prednisolon daily orally. Her general condition and hearing loss improved subjectively. Audiograms 6 weeks later showed also objective improvement of hearing. A control CT scan showed improvement of the abnormalites in both mastoid regions.

As a consequence of the high doses of steroids, risedronate and calcium supplementation were started, and also methothrexate was added for the reason of its steroidsparing effect. “Atypical” Cogan’s syndrome was diagnosed on the basis of sensorineural deafness with improvement on steroids and large-vessel vasculitis of the aortic arch.

A follow-up PET/CT investigation 3 weeks later showed clearly decreased uptake in the aortic arch, especially a dramatic decrease at the location of the focal uptake in the lateral wall, compared to the first PET/CT. The SUV max was calculated 4.3. ESR and CRP after 2 weeks of therapy were, respectively, 11 mm/h and <2 mg/L. White cell count was still elevated (16.9.109 L).

Six months later, she was in a stable condition with methotrexate and low-dose prednisone, and her ESR, CRP, and white cell count were now, respectively, 24 mm/h, 14 mg/L, and 13.7.109 L.

A third PET/CT showed higher pathological activity, compared to the first PET/CT, in the wall of the aortic arch and in the perivascular space adjacent to the truncus pulmonalis (the SUV max was 12.9 compared to the SUV max of 11.9 of the first pretherapy PET/CT investigation). Consequently, the dose of methothrexate and prednisone were both increased to 20 mg/day.

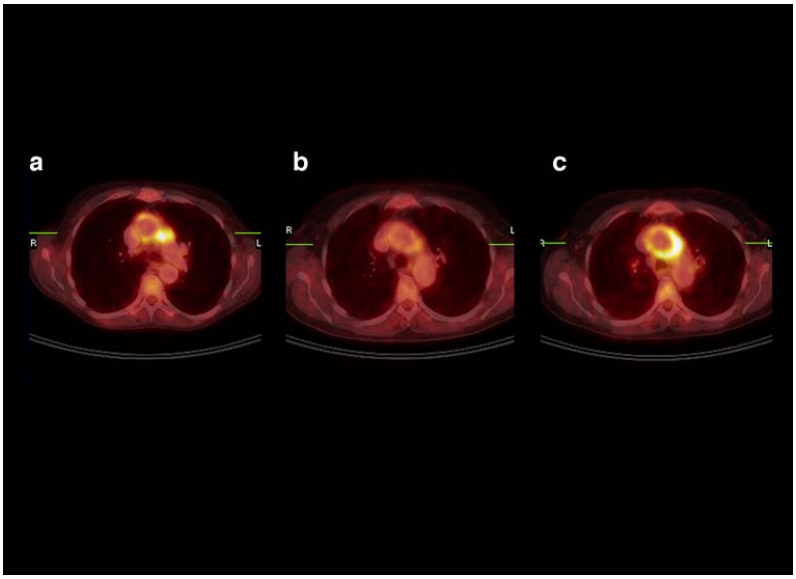

Figure 1a. Transverse fused PET/CT slice showing pathological uptake in the wall of the aortic arch and particularly in the lateral wall and perivascular space adjacent to the truncus pulmonalis (SUV max 11.9). **1b.** Follow-up PET/CT 3 weeks later, after treatment with methylprednisolon i.v. and prednisolon orally, showing clearly decreased uptake in the aortic arch (SUV max 4.3). **1c.** Second follow-up PET/CT 6 months later, while patient was in a stable condition with methotrexate and low-dose prednisone. Again, high pathological uptake in the aortic arch with higher intensity in the lateral wall and perivascular space adjacent to the truncus pulmonalis (SUV max 12.9)

Discussion

The etiology of Cogan's syndrome is unknown; a minority of patients have rheumatoid factor, antinuclear bodies, and diminished complement levels. Histology of biopsies shows often vasculitis and perivascular inflammation. Giant cells may be present.[7] Specific involvement of large arteries has been reported in Cogan's syndrome.[8] Aortitis in Cogan's syndrome is indistinguishable from Takayasu's arteritis. Cardiac involvement during the course of Cogan's syndrome is, above all, aortic insufficiency. It is a severe complication that may require valve replacement, without which left ventricle involvement insufficiency develops, which can be fatal.[9, 10]

Standard diagnostic modalities such as biopsy, angiography, ultrasound, and MRI are commonly unable to demonstrate the full extent of vascular involvement in large-vessel vasculitis. PET investigations might play an important role here as large-vessel ^{18}F-FDG uptake is positively correlated with the level of acute phase reactant markers in patients with large vessel vasculitis. In a study of 18 patients with Takayasu's arteritis, the ^{18}F-FDG PET examination showed a sensitivity of 92% and a specificity of 100%.[11]

This is, to the best of our knowledge, the first report of Cogan's syndrome diagnosed by the use of ^{18}F-FDG PET/CT scanning. This case report is also supportive in the hypothesis that with PET, the inflammatory activity of large-vessel vasculitis is more accurately assessed compared to laboratory acute phase parameters.[12] The CT component of PET/CT is useful in the precise anatomical localization of the PET abnormalities and may provide information about changes in the wall structure or luminal flow.[13]

The conclusion seems justified that ^{18}F-FDG PET/CT is helpful in risk assessment of large-vessel vasculitis, as it provides intrinsically fused morphologic and functional data in a single examination.

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Early recognition of syphylitic aortitis with ^{18}F-FDG PET/CT

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Abstract

We present the case of a 42-year-old woman known with a human leukocyte antigen B27 positive ankylosing spondylitis. Despite treatment with a tumor necrosis factor blocking agent, the patient was not pain free and inflammation markers remained elevated. An ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) was performed in an attempt to exclude possible other inflammatory processes. The ^{18}F-FDG PET/CT revealed increased metabolic activity in the ascending aortic wall, which appeared unexpectedly related to late syphilis. Based on this case and existing literature on this subject, we come to the conclusion that ^{18}F-FDG PET/CT can help in an early establishment of syphilitic aortitis before the possible life-threatening sequelae of syphilitic aortitis occur.

Background

Syphilis is an infectious disease transmitted mainly through sexual intercourse with a wide spectrum of clinical presentations depending on the disease stage. In the nineteenth century, syphilis used to be so common - estimated to affect 15 % of US adults during that period - that an entire specialty (syphilology) focused on it.[1] Although cardiovascular syphilis once accounted for 5–10 % of all cardiovascular deaths, the introduction of antibiotics has made, especially in developed countries, the prevalence of cardiovascular syphilis distinctly rare. Cardiovascular complications of syphilis are at least life-threatening, if not fatal, and occur after a latent period of usually 10–25 years.[2-4] Thoracic aortic aneurysm formation is a known complication; large aneurysms may cause symptoms via mass effect on neighboring mediastinal structures. Rupture of the ascending or descending aorta as the cause of death is described in postmortem studies of patients with syphilitic aortitis.

Despite the steady decline in the incidence in the developed countries, serious sequelae of syphilitic aortitis continue to be the basis of many case reports. Therefore, syphilitic aortitis should not be regarded as a medical curiosity.[5-10]

Case report

A 42-year-old woman, originally from the Czech Republic, is known with axial spondylarthtropathy; ankylosing spondylitis according to the New York criteria (human leukocyte antigen B27 positive and bilateral grade III radiographic sacroiliitis) since 3 years. Because of active disease (Bath Ankylosing Spondylitis Disease Activity (BASDAI) of 6.1 (scale 0–10)) and increasing functional impairment, she was treated with the tumor necrosis factor (TNF) blocking agent, etanercept 50 mg/week subcutaneously.[11] Despite this treatment, her complaints of neck pain and pain along the spine remained, and 18 out of the 18 tender points according the American College of Rheumatology (ACR) criteria for fibromyalgia were positive.[12] After a multidisciplinary rehabilitation program, BASDAI remained high (7.8). The erythrocyte sedimentation rate (ESR) remained high as well, 52 mm, with a slightly increased C-reactive protein (CRP) value of 10 mg/l. However, the MRI (STIR) did not show any signs of active sacroiliitis nor spondylitis.

To exclude inflammatory processes in or beyond the axial skeleton, an ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) was performed.

The ^{18}F-FDG PET/CT total-body images were in line with the MRI and showed no signs of active sacroiliitis or spondylitis and no signs of inflammation or malignancy elsewhere. The only abnormality was moderately increased ^{18}F-FDG uptake in the wall of the ascending aorta, suggestive of inflammation. The maximum diameter of the ascending aorta was slightly enlarged to 3.7 cm (Fig. 1). The absence of a cardiovascular medical history including hypertension as well as the lack of calcifications in the wall of the ascending aorta made inflammation due to atherosclerosis less likely. In the wall of the descending aorta and other large vessels, increased uptake was not noticed. In addition, a MRI of the thorax showed diffuse increased signal of the wall of the ascending aortic wall with a wall thickness of 4 mm further adding to the likelihood of aortitis.

On suspicion of aortitis as a complication of the axial ankylosing spondylitis, treatment with etanercept was switched to another TNF blocking agent, infliximab 5 mg/kg intravenously every 8 weeks. Although this switch in medication reduced the physical complaints of neck pain and pain along the spine (BASDAI 2.1), the ESR remained high (57 mm/h) and on MRI images the thickness of the aortic wall only slightly diminished from 4 to 3.5 mm.

As part of the workup for the differential diagnosis of aortitis, syphilis serology was performed and found to be positive in the screening test: Syfilis TP antibody test (CMIA, Abbot). This was confirmed by a positive Treponema pallidum particle agglutination test (TPPA) and a positive fluorescent treponemal antibody absorbent test. In addition, a positive Venereal Disease Research Laboratory test (VDRL) was reported. This serology made the diagnosis of late syphilis with syphilitic aortitis probable. A test for HIV was negative. Other laboratory tests are as follows: ANA slightly positive, p-ANCA titer 1:40. AENA, ACA, anti-ds DNA, RF, aCCP, anti-MPO, anti-PR3, and Lyme serology were all negative.

A repeated patient's sexual history revealed a period of internet dating 8 years prior to the current episode in the Czech Republic. Her current husband had negative syphilis serology.

In the absence of ankylosing spondylitis complaints, the TNF blocking treatment was interrupted for 1 month and antibiotic treatment with benzylpenicillin (2.4 million units) intramuscularly on days 1, 8, and 15 was given. After 2 months, the patient remained free of complaints and functional impairment. The ESR fell below 25 mm and the CRP values below 2 mg/l.

The ^{18}F-FDG PET/CT 24 weeks after treatment with benzylpenicillin showed evidently decreased ^{18}F-FDG uptake in the wall of the ascending aorta (Fig. 2).

Follow-up serology showed a slight but nonsignificant decline in antibody titers of TPPA as well as VDRL over the 2 years after treatment (Table 1). To rule out asymptomatic neurosyphilis, a lumbar puncture was performed. Syphilis serology of the liquor was negative.

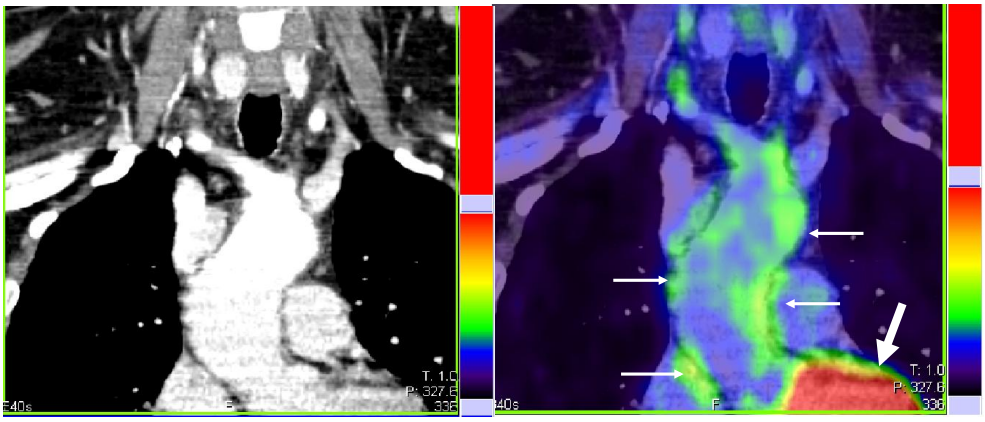

Figure 1. Hybrid F18-FDG PET/CT images of a patient initially on suspicion of inflammation of only the ascending aorta as a complication of her axial spondylarthropathy after treatment with etanercept later switched to the TNF blocking agent, infliximab, and before treatment with benzylpenicillin for syphilitic aortitis. The total body images revealed no pathological F18 FDG uptake in the wall of the descending aorta and other large vessels, and no signs of spondylarthropathy or other pathology.

-The coronal fused PET/CT slice (right image) shows moderately increased metabolic activity, suggesting inflammation, in the wall of the ascending aorta (thin arrows).

(Note:The high uptake in the myocardium of the left ventricle (thick arrow) is a consequence of a flaw in the patient preparation; due to language problems the patient did not follow the instructions for a Fat-Allowed and Carbohydrate-Restricted diet during 24 h before scanning).

-The same 'CT-only' slice, left image, reveals an enlarged transverse diameter of 3.7 cm.

Discussion

Syphilitic aortitis predominantly involves the proximal aorta and is only rarely reported to extend below the renal arteries, probably related to the more rich vascular and lymphatic circulation of the aortic arch. Syphilitic heart disease can be divided into syphilitic aortitis (eventually leading to syphilitic aortic aneurysm), syphilitic aortic valvulitis with aortic regurgitation, and syphilitic coronary ostial stenosis.[1]

A necropsy study of 100 cases of syphilitic aortitis mentioned that a combination of at least two of these complications may occur, and all four could coexist as well [13]. In general, aortitis - regardless of the etiology - frequently results in dilatation of the aortic root leading to aortic valve insufficiency, which often necessitates valve replacement with aortic root reconstruction. In line with this, the most common complications of syphilitic aortitis are aortic valve insufficiency and rupture of the aneurysmatic aorta.

Epidemiological data show that aortitis may occur in 70– 80 % of patients with untreated syphilis. Clinical complications usually develop 10 to 20 years after primary infection in 10–15 % of untreated patients, and cardiovascular syphilis is the main cause of death in patients who die as a direct result of syphilis.[14]

Aortitis caused by syphilis is difficult to proof because the spirochete T. pallidum has never been convincingly histologically demonstrated in the aortic wall. In addition T. pallidum cannot be cultured from tissue samples.

Aortitis can be generally classified as infectious or noninfectious. Noninfectious causes for aortitis are predominantly caused by large vessel vasculitis, Takayasu's arteritis (TA), and giant cell arteritis (GCA). Inflammation with aortic root aneurysm has been reported in patients with sarcoidosis, Behcet's disease, rheumatoid arthritis, ankylosing spondylitis, and other autoimmune diseases like lupus erythematosus and Wegener's granulomatosis.[15] Albeit in these patients, the link between the systemic disease and the aortic aneurysm was not always clear. Chronic (peri-)aortitis has been described in ankylosing spondylitis patients and usually occurs late in the course of (untreated) ankylosing spondylitis; it is characterized by inflammation evolving to fibrosis and it is localized in the periaortic and peri-iliac retroperitoneum.[16]

Because the morphological changes in the vessel wall are preceded by hypermetabolic changes due to inflammatory cell activity (when resting cells are activated to phagocytes), large vessel vasculitis can be diagnosed with hybrid ^{18}F-FDG PET/CT at an earlier stage as compared with the conventional imaging techniques. Hybrid ^{18}F-FDG PET/CT is also able to reduce the likelihood of atherosclerosis as the cause of the increased aortic wall ^{18}F-FDG uptake by identifying focal vascular inflammation and focal vascular calcification as different phases.[17] ^{18}F-FDG PET(/CT) may also help in the distinction of syphilitic aortitis from large vessel vasculitis:

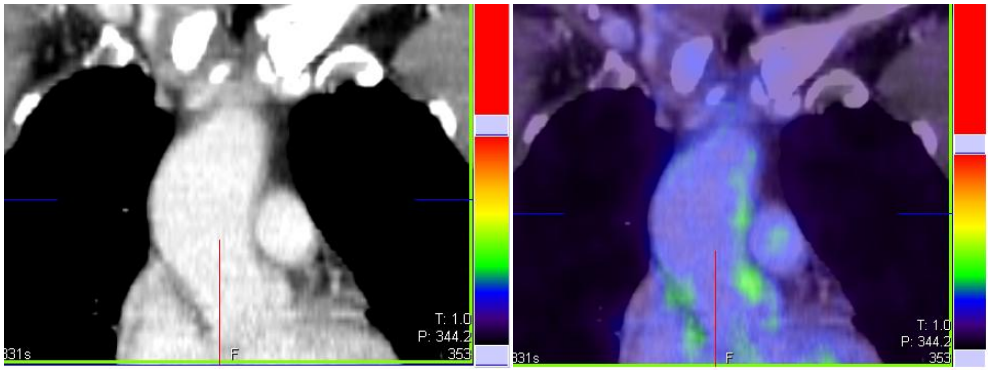

Figure 2. Hybrid F18-FDG PET/CT images of the same patient after treatment with benzylpenicillin for syphilitic aortitis. The F18-FDG uptake in the wall of the ascending aorta is decreased.
(The physiologic uptake in the myocardium of the left ventricle is now minimal, as the patient concisely followed the instructions for a Fat-Allowed and Carbohydrate-Restricted diet during 24 h before scanning.)

- GCA is reported to show homogeneous/smooth linear or long segmental pattern of ^{18}F-FDG uptake in the thoracic aorta and its main branches.[18]
- TA affects the aorta and its branches but may show a more focal and localized, inhomogeneous pattern of ^{18}F-FDG uptake and has usually a more aggressive clinical course.[19]

The complexity of this case lies in the differentiation of syphilitic aortitis from other causes of aortitis. We hypothesize that in this case the moderate increased metabolic activity in the ascending aorta is caused by latent syphilitic aortitis, supported by several observations:

1. The localization of the increased metabolic activity seems only present in the ascending aorta. This specific ^{18}F-FDG distribution pattern is in line with the abovementioned postmortem examinations in syphilis.
2. The patient had persistent elevated inflammation parameters in the absence of active ankylosing spondylitis confirmed with her total-body ^{18}F-FDG PET/CT.[20]
3. Positive non-treponemal test results can be associated with various medical conditions unrelated to syphilis, including autoimmune conditions.[21] However, this patient had positive syphilis serology in treponemal as well as non-treponemal tests, and no history of treatment, making late syphilis a likely diagnosis.
4. The total-body ^{18}F-FDG PET/CT images gave no support for another etiology of the aortitis, either infectious or noninfectious inflammatory diseases.

The titers of non-treponemal tests usually decline after treatment and might become nonreactive with time. However, especially in patients with late syphilis, like our patient,

treponemal as well as non-treponemal antibodies can persist for a long period of time - a response referred to as the "serofast reaction".[22] To the best of our knowledge, only one case report of a patient with syphilis and increased ^{18}F-FDG uptake in the ascending aorta has been published so far. This case describes a patient diagnosed with HIV-1 2 years earlier and who was treated soon after diagnosis and presented to the clinic with blurred vision and pain in his left eye.[23]

Syphilis may behave atypical in the immunocompromised patient, such as a HIV patient [22] or a patient treated with biologicals (in our case etanercept and infliximab). Probably, these patients are more prone to treatment failure and therefore needing a longer duration of antibiotic treatment as compared to patients without an immunocompromised state.

The plethora of recent case reports on syphilitic (ascending) aortic aneurysms support the view that aortic aneurysm has displaced aortic insufficiency as the major complication of syphilitic aortitis. The increased proportion of aneurysms may also be related to the greater longevity, with the synergistic effect of superimposed atherosclerosis playing an important pathogenetic role. Another consequence of a longer life expectancy is the risk of developing hypertension, possibly to be considered as a synergistic effect.

Hybrid ^{18}F-FDG PET/CT is a sensitive investigation to detect inflammation in the ascending aorta. The intensity of the ^{18}F-FDG uptake and its distribution pattern may improve the specificity in order to exclude syphilitic aortitis from other etiologies. However, without a larger number of studied cases with syphilitis aortitis, we do not know yet all possible presentations as could be visualized with ^{18}F-FDG PET/CT.

Table 1. Follow-up serology of TPPA and VDRL showed a slight but nonsignificant decline in antibody titers in both TPPA as well as VDRL over the 2 years after treatment

	TPPA (titer)	VDRL (titer)
June 2010 (6 months after treatment)	1:81,920	1:64
October 2010	1:40,960	1:32
March 2012	1:40,960	1:32
July 2012	1:40,960	1:32
October 2012	1:40,960	1:32

Conclusion

In the event of a patient with late syphilis, the synergy of anatomic–metabolic information of hybrid ^{18}F-FDG PET/CT may be of value in diagnosing asymptomatic syphilitic aortitis. Also, ^{18}F-FDG PET/CT may be of value in follow-up of these patients, especially when follow-up serology shows no significant decline in titers like in our patient. Early recognition of syphilitic aortitis is essential, as it is well known that anti-syphilitic therapy does not reverse already developed cicatricle lesions and their subsequent functional consequences. Further studies are needed to validate the use of ^{18}F-FDG PET/CT for the diagnosis and follow-up of syphilitic aortitis, as well as the addition of syphilitic aortitis to the list of possible opportunistic infections in patients treated with biologicals.

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Parameters related to positive FDG-PET(/CT) findings for large vessel vasculitis: a multicenter retrospective study

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Abstract

The purpose of this study was to identify clinical and laboratory parameters that may improve the effectiveness of the use of fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET)(/CT) for diagnosing large vessel vasculitis (LVV), and secondarily to assess the contribution of ^{18}F-FDG PET/CT in finding other diagnoses for patients without signs of LVV on the scan. A multicenter retrospective study of ^{18}F-FDG PET(/CT) scans performed between January 2000 and December 2009 for clinical suspicion of LVV was conducted. A total of 304 ^{18}F-FDG PET(/CT) scans were included, of which 62 (20%) were positive and 242 (80%) were negative for LVV. Univariate analysis showed that patients with a positive scan were older (65.9±13.4 versus 58.6±16.5 years, p=0.002), were more frequently female (76% versus 55%, p=0.002), more often had a history of temporal arteritis (10% versus 3%, p= 0.044), less frequently had artralgia (31% versus 67%, p=0.000), and had higher thrombocyte counts (434±161 versus 373±168×109/l, p=0.049) and a higher erythrocyte sedimentation rate (ESR) (72.6±31.0 versus 51.4± 30.5 mm/h, p=0.001) than patients with a negative scan. In the multivariate analysis, only artralgia (OR 0.091; 95% CI 0.023–0.366) and ESR (OR 1.024; 95% CI 1.002–1.046) remained statistically significant predictors. The presence of artralgia is a statistically significant negative predictor and an elevated ESR a statistically significant positive predictor of LVV showing up on ^{18}F-FDG PET(/CT). A reliable prediction of the outcome of the scan, based on these two parameters, is not possible however. ^{18}F-FDG PET(/CT) allows early diagnosis of LVV and may discover occult inflammatory or neoplastic disorders.

Introduction

During the chapel Hill Consensus Conference in 1994 two forms of large vessel vasculitis were distinguished: giant cell arteritis (GCA) and Takayasu arteritis (TA). [1] GCA is the most common form and has an incidence of 20 per 100,000 in the population aged over 50 years. Women are affected twice as often as men. [2-5] Characteristically it affects the temporal artery, resulting in temporal arteritis as a synonym for GCA. Temporal arteritis does not cover the whole clinical spectrum however, since the whole aorta and al its branches can be affected. [6] The clinical presentation is variable and includes several non-specific symptoms, such as fever, malaise, fatigue, myalgia and headache. [2-4, 7] GCA is also associated with polymyalgia rheumatica in about 40% of the cases. [8] The diagnostic reference method for diagnosing GCA is a temporal artery biopsy, but the test results can be false negative. A false-negative rate of 15-70% is reported; therefore, the incidence of GCA might be underestimated. [9-14]

TA is the second form of large vessel vasculitis and primarily affects the aorta and its main branches as well as the coronary and pulmonary arteries. It has an incidence of only 2 per 1,000,000. The mean age of onset is 35 years and the prevalence in women approximately 10 times higher than in men. [2, 4] The clinical picture is fairly similar to that of giant cell arteritis. [15, 16]

Imaging studies play an important role in diagnosing and monitoring large vessel vasculitis. Angiography, ultrasonography, CT and MRI used to be the most utilized imaging techniques. The differential diagnosis with accompanying atherosclerotic changes can be very difficult however. Even if vasculitis can be diagnosed by angiography, differentiation between active vasculitic lesions and plaque formation is difficult.

In more recent years ^{18}F-FDG PET(/CT) has become an increasingly important diagnostic tool for diagnosing large vessel vasculitis. [17-22] Because the morphological changes in the vessel wall are preceded by metabolic changes, large vessel vasculitis can be diagnosed at an earlier stage than with the conventional imaging techniques. [18] ^{18}F-FDG PET(/CT) also identifies more regions of the aorta and its branches involved in the inflammatory process than MRI. [17, 19] Hybrid ^{18}F-FDG PET/CT seems to be superior to ^{18}F-FDG PET alone in this; by fusing the functional images of the ^{18}F-FDG PET with the anatomical images of the CT, it is easier to localize regional ^{18}F-FDG uptake. [23, 24] Hybrid ^{18}F-FDG PET/CT is able to identify focal vascular inflammation and focal vascular calcification as different phases of atherosclerosis in order to exclude this as the cause for the increased ^{18}F-FDG uptake. [25] Although both ^{18}F-FDG uptake and calcification often occur in the same vessel, they rarely occur at the same site within the vessel. [26] As a result, the number of false positive test results will be reduced, thereby increasing the specificity of the technique.

Because of the aforementioned considerations, ^{18}F-FDG PET(/CT) is increasingly used in patients with a vague pattern of clinical findings and increased inflammatory parameters. In a certain number of these cases ^{18}F-FDG PET(/CT) will directly point to large vessel vasculitis,

thereby avoiding several time-consuming and sometimes unpleasant tests. On the other hand, due to the low incidence, a high proportion of negative test results of ^{18}F-FDG PET(/CT) for large vessel vasculitis can be expected. This is unfavorable from a cost-effectiveness point of view, although a negative test result for large vessel vasculitis can still be of use, by giving clues to other diagnoses (e.g. lymphoma, infection). The aim of this study is to identify clinical and laboratory parameters that may improve the efficient use of ^{18}F-FDG PET(/CT) scans in patients who are suspected of large vessel vasculitis.

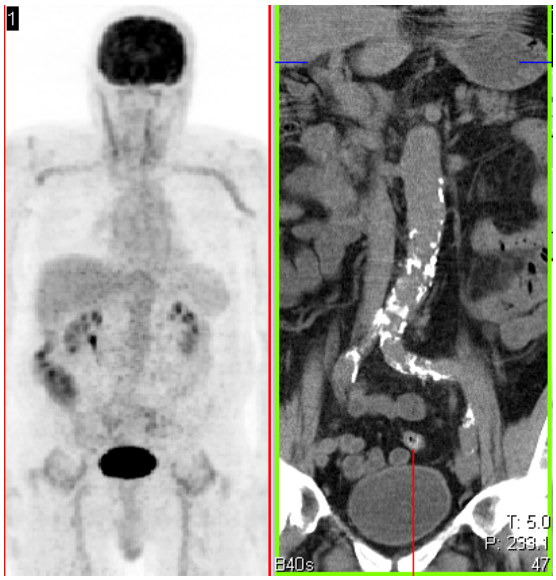

Figure 1. Left image is a maximum intensity projection (MIP) of the PET investigation. Right image is a coronal CT slice. Left image is a maximum intensity projection (MIP) of the PET investigation. Two years earlier patient was on prednisolon for arteritis temporalis. Prednisolon was stopped for only a few weeks, since then development of pain in shoulders and neck, tiredness and headache. CRP 62 , ESR 62. PET images show pathological uptake in the carotids and subclavia bilateral. SUV max 2.4. Discete increased uptake in thoracal aorta. The patchy uptake, with low intensity, in the abdominal aorta is mainly due to atherosclerosis seen on the coronal CT slice.

Materials and methods

2.1 Patients

This multicenter retrospective study was performed at the Medical Center Leeuwarden, University Medical Center Groningen, VU University Medical Center and the Isala Klinieken with its affiliated hospitals,in the Netherlands. Patients who had undergone a ^{18}F-FDG PET(/CT) scan between January 2000 and December 2010 with large vessel vasculitis as the query, were included. Patients who had undergone a ^{18}F-FDG PET(/CT) scan for e.g. oncological reasons, but were diagnosed with large vessel vasculitis as an incidental finding, were also included. Patients had to be 18 years or older at the time of the performance of the scan. In case a patient had undergone multiple ^{18}F-FDG PET(/CT) scans for large vessel vasculitis, only the first scan was included. Patients whose files explicitly stated that they used immunosuppressive drugs at the time of the scan, were excluded. The time point for requesting a ^{18}F-FDG PET(/CT) in the diagnostic work-up was chosen by the referring physician.

2.2 Data

The clinical and laboratory data were recorded from the electronic medical records. Besides sex and age at the time of the performance of the ^{18}F-FDG PET(/CT) scan, the following data were recorded, based on findings in the literature [2]:

- Systemic: malaise, weight loss, nausea, fatigue, fever, night sweats.
- Temporal arteritis: jaw claudication, hyperesthesia of the scalp, thickening of the temporal artery or pain on palpation, temporal arteritis in the past, visual disorders.
- Musculoskeletal: myalgia, arthralgia, polymyalgia rheumatica in the past.
- Cardiovascular: claudication of the arms, claudication of the legs, weak peripheral pulse, Raynaud phenomenon, orthostatic hypotension, aortic regurgitation.
- Pulmonary: pulmonary infiltrate.
- Neurological: dizziness, headache, cerebrovascular accident or transient ischemic attack in the past, symptoms of polyneuropathy (weakness, numbness, tingling, pain), electromyographically proven polyneuropathy.
- Laboratory tests: hemoglobin, lymphocytes, thrombocytes, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin, creatinine, alkaline phosphatase.

The symptoms ought not to be explainable by another medical condition the patient had already been diagnosed with. For some parameters there were additional criteria:

- Aortic regurgitation: echocardiographically confirmed.
- Pulmonary infiltrate: less than a year prior to the scan radiographically confirmed.

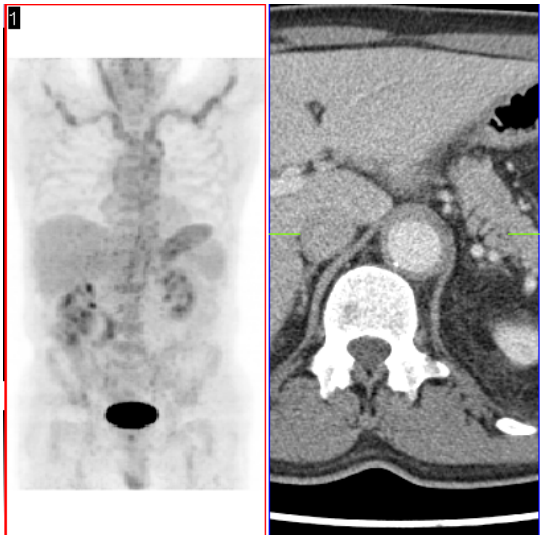

Figure 2. Left image is a maximum intensity projection (MIP) of the PET investigation. Right image is a transverse CT slice. Patient had since 4-5 weeks feelings of discomfort and triredness, and reported pain in both arms. CRP 147, ESR 70. The PET images show pathological activity in aortic arch and abdominal aorta until the bifurcation, and in both subclavian arteries and art. brachialis on both sides. SUV max 4,3. The transverse CT slice shows wall thickening of the aorta at the level of the crus of the diaphragm.

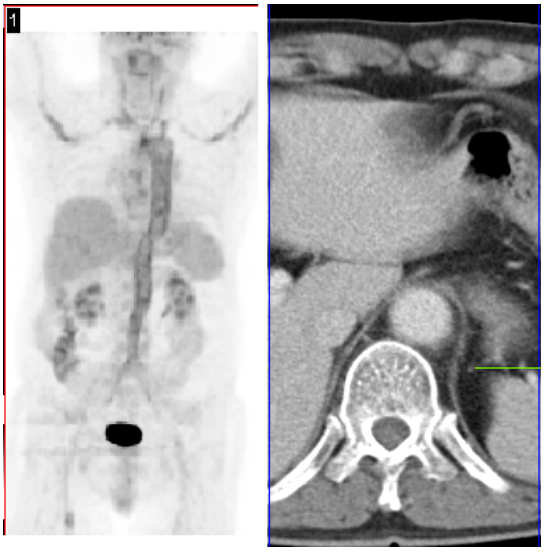

Figure 3. Left image is a maximum intensity projection (MIP) of the PET investigation. Right image is a transverse CT slice. Fever since 3 months, mainly in the evening and early morning. Complaints of . headache. CRP 88, ESR 33. The PET images show pathological activity in aortic arch and abdominal aorta until the bifurcation, and in the subclavian, brachial and carotic arteries. SUV max 5.4. The CT transverse slices showed no wall thickening in thorocal and abdominal aorta.

- Cerebrovascular accident or transient ischemic attack in the past: less than a year prior to the scan occurred.
- Laboratory tests: the most recent results that were also less than two weeks old at the time of the performance of the scan.

The symptoms ought not to be explained by another medical condition the patient had already been diagnosed with. The clinical parameters were considered positive or negative only when the results were explicitly stated in the patient's history and as missing data when no data were recorded. Temporal arteritis in the past, PMR in the past, and cerebrovascular accident or transient ischemic attack in the past were considered negative when no data were recorded. The ^{18}F-FDG PET(/CT) scans were considered positive if a smooth linear pattern of 18F-FDG uptake was found in the aorta or its main branches with an intensity higher than the liver[34].

2.3 ^{18}F-FDG PET(/CT) scanners

Each participating medical center used varying equipment and protocol:

- Medical Center Leeuwarden:

  Siemens Biograph 6 LSO HI-REZ (hybrid PET/CT); 4 MBq/kg; 90 minutes between injection and start acquisition; 3 minutes per bed position.

- University Medical Center Groningen:

  Siemens ECAT HR+ (stand-alone PET); 5 MBq/kg; 60 minutes between injection and start acquisition; 7 minutes per bed position.

- VU University Medical Center:

  Siemens HR+ (stand-alone PET); 3,8 MBq/kg; 60 minutes between injection and start acquisition; 5 minuten per bed position. Philips Gemini TF (hybrid PET/CT); 3,8 MBq/kg; 60 minutes between injection and start acquisition; 2 minutes per bed position.

- Isala Klinieken:

  GE (hybrid PET/CT); 3,8 MBq/kg; 60 minutes between injection and start acquisition; 4 minutes per bed position.

2.4 Statistical analysis

The statistical analysis was performed with SPSS (version 17.0) for Windows. For the analysis of the categorical parameters, the chi-square test was used. Where applicable the Fisher's exact test was used. The continuous parameters were analyzed using the independent t test or, in case of a non-normal distribution, the Mann–Whitney U test. The multivariate analysis was performed using logistic regression; for the inclusion a p value of 0.05 was chosen, for the exclusion a p value of 0.10. All tests were two sided, and results with a p value of ≤0.05 were considered statistically significant.

Results

3.1 Patient characteristics

Between January 2000 and December 2009, a total of 304 ^{18}F-FDG PET(/CT) scans were performed for large vessel vasculitis in the participating centres. The total number of scans consisted of 162 ^{18}F-FDG PET scans and 142 ^{18}F-FDG PET/CT scans. The patients from the different hospitals were equally distributed between the group with a positive test result for large vessel vasculitis and the group with a negative test result.

A total of 62 scans (20%) had a positive test result for large vessel vasculitis. In 12 patients (19%) the diagnosis had been confirmed with a temporal artery biopsy. In another 12 patients (19%) the test results of the biopsy were negative. In the remaining cases no temporal artery biopsy was performed. These and other baseline characteristics are shown in Table 1.

Of the 242 patients with a negative test result of the ^{18}F-FDG PET(/CT) scan for large vessel vasculitis, 17 patients (7%) were subsequently treated for large vessel vasculitis. In these cases the diagnosis was based on the clinical picture, and usually involved patients with typical signs of temporal arteritis. Other frequent diagnoses in this group were polymyalgia rheumatica, inflammatory disorders of the joints, other systemic diseases and malignancies. These diagnoses were based on the results of the ^{18}F-FDG PET(/CT) scan in about 50% of the cases. In 86 patients (36%) no diagnosis could eventually be made. The most frequent diagnoses and their respective numbers are shown in Table 2.

3.2 Comparing both groups

The clinical parameters in both groups are shown in Table 3. Because of a large amount of missing data, the number of recorded patients varied widely between parameters. In the group with a positive test result of the ^{18}F-FDG PET(/CT) scan, the most frequent symptoms were fatigue, headache and weight loss. In the group with a negative test result, arthralgia, fatigue and myalgia were the most frequent symptoms. Both groups differed significantly regarding age (65.9±13.4 years versus 58.6±16.5 years, p=0.002), female sex (76% versus 55%, p=0.002), temporal arteritis in the past (10% versus 3%, p=0.044) and arthralgia (31% versus 67%, p=0.000). In the group with a positive test result only 1 patient (1.6%) was below the age of 30, compared to 13 patients (5.4%) in the group with a negative test result. This difference was non-significant however.

The results of the laboratory tests in both groups are shown in Table 4. Both groups differed significantly regarding thrombocytes (434±161 x10^9/l versus 373±168 x10^9/l, p=0.049) and ESR (72.6±31.0 mm/hour versus 51.4±30.5 mm/hour, p=0.001). When for the CRP a cut-off point of 10 mg/l was chosen, none of the patients in the group with a positive test result had a normal

value. In the group with a negative test result 42 patients (26.1%) had a normal value for the CRP. This difference was significant with a p-value of 0.001.
On the parameters that differed significantly between both groups in the univariate analysis, univariate and multivariate logistic regression were performed. Temporal arteritis in the past was not included, as there were only 2 patients with enough data to be included. Of the total number of patients, 69 patients remained with enough data to be included.
The results of the analysis with logistic regression are shown in Table 5. In the multivariate analysis only arthralgia (OR 0.091; 95%-CI 0.023-0.366) and ESR (OR 1.024; 95%-CI 1.002-1.046) remained as statistically significant predictors of a positive test result. An odds ratio of 1.024 (95%-CI 1.002-1.046) for 1 unit of the ESR, is equal to an odds ratio of 1.268 (95%-CI 1.020-1.568) for 10 units of the ESR.

Table 1. Baseline characteristics

	Positive PET(/CT) (*N*=62)	Negative PET(/CT) (*N*=242)
Age	65.9±13.4	58.6±16.5
Female sex	47 (76%)	132 (55%)
Stand-alone FDG-PET	33 (53%)	129 (53%)
Hybrid FDG-PET/CT	29 (47%)	113 (47%)
Positive result temporal artery biopsy	12 (19%)	
Negative result temporal artery biopsy	12 (19%)	

Table 2. Most frequent diagnoses in the group with a negative test result for large vessel vasculitis

	Frequency (*N*=242)
Large vessel vasculitis	17 (7%)
Polymyalgia rheumatica	22 (9%)
Inflammatory disorders of the joints[a]	25 (10%)
Other systemic disorders[b]	31 (13%)
Malignancies	13 (5%)
Other diagnoses[c]	48 (20%)
No classifying diagnosis[d]	86 (36%)

[a] Among others: rheumatoid arthritis and spondylarthropathies

[b] Among others: small vessel vasculitis and M. Sjögren

[c] Among others: vascular disease and infections

[d] No classifying diagnosis made or no diagnosis recorded in medical record

Table 3. Clinical variables in both groups

	Positive PET(/CT) (*N*=62)	Negative PET(/CT) (*N*=242)	*p*
Age	65.9±13.4	58.6±16.5	0.002
Female	47/62 (76%)	132/242 (55%)	0.002
General			
Malaise	17/19 (89%)	60/69 (87%)	NS
Weight loss	27/36 (75%)	62/106 (58%)	NS
Nausea	6/11 (55%)	13/29 (45%)	NS
Fatigue	29/31 (94%)	77/81 (95%)	NS
Fever	18/35 (51%)	61/137 (45%)	NS
Night sweats	9/14 (64%)	22/47 (47%)	NS
Temporal arteritis			
Jaw claudication	5/18 (28%)	7/34 (21%)	NS
Hyperesthesia of the scalp	7/16 (44%)	6/24 (25%)	NS
Thickening temporal artery or pain on palpation	1/23 (4%)	5/28 (18%)	NS
Temporal arteritis in the past	6/62 (10%)	8/242 (3%)	0.044
Visual disorders	10/25 (40%)	16/52 (31%)	NS
Musculoskeletal			
Myalgia	18/24 (75%)	69/81 (85%)	NS
Arthralgia	9/29 (31%)	78/116 (67%)	0.000
Polymyalgia rheumatica in the past	8/62 (13%)	14/242 (6%)	NS
Cardiovascular			
Claudication of the arms	6/10 (60%)	5/9 (56%)	NS
Claudication of the legs	3/4 (75%)	6/14 (43%)	NS
Weak peripheral pulse	7/23 (30%)	11/56 (20%)	NS
Raynaud phenomenon	2/9 (20%)	19/40 (48%)	NS
Orthostatic hypotension	2/2 (100%)	2/3 (67%)	NS
Aortic regurgitation	2/5 (40%)	5/9 (56%)	NS
Pulmonary			
Pulmonary infiltrate	4/39 (10%)	21/175 (12%)	NS
Neurological			
Dizziness	5/9 (56%)	15/20 (75%)	NS
Headache	28/40 (70%)	43/78 (55%)	NS
CVA or TIA in the past	3/62 (5%)	11/242 (5%)	NS
Polyneuropathy (symptoms)	6/12 (50%)	30/45 (67%)	NS
Polyneuropathy (EMG)	0/1 (0%)	9/16 (56%)	NS

NS non-significant ($p<0.05$)

Table 4. Results of the laboratory tests in both groups

	Positive PET(/CT) (*N*=62)	Negative PET(/CT) (*N*=242)	*p*
Hemoglobin (mmol/l)	6.94±1.14	7.33±1.21	NS
Thrombocytes ($\times 10^9$/l)	434±161	373±168	0.049
Leukocytes ($\times 10^9$/l)	9.79±3.93	9.68±4.38	NS
CRP (mg/l)	85.8±64.7	63.0±68.5	NS
ESR (mm/h)	72.6±31.0	51.4±30.5	0.001
Albumin (g/l)	33.2±9.28	33.7±6.91	NS
Creatinin (μmol/l)	84.2±31.2	79.8±34.8	NS
Alkaline phosphatase (U/l)	112±65.7	98.9±73.6	NS

NS non-significant ($p<0.05$)

Discussion

To the best of our knowledge, no studies have previously been published with the intention to identify clinical and analytical parameters that may improve the effectiveness of the use of ^{18}F-FDG PET(/CT) scans for diagnosing LVV. A few studies have been published with a similar goal concerning biopsies of the temporal artery for diagnosing GCA. Mari et al. found headache, jaw claudication, and palpable abnormalities of the temporal artery as predictors of a positive test result, whereas anemia appeared to be a predictor of a negative test result [11]. In the study of Hayreh et al., neck pain, an elevated ESR, an elevated CRP, and an age above 75 were predictors of a positive test result [14]. Regarding the fact that the temporal artery is not always involved in GCA, these symptoms and abnormalities do not necessarily have to be predictive of a positive test result of the ^{18}F-FDG PET(/CT) scan [9–14, 38]. This is reflected by the low number of reported symptoms of temporal arteritis in our study.

Temporal artery biopsy is considered the cornerstone of the diagnosis of GCA; however, it is invasive and can be false negative in 15–70% of the cases, which may delay the diagnosis [9–14, 38]. This could explain why visual loss in one eye was reported to be prevalent in only 16–18% of patients at initial diagnosis [39, 40]. LVV may often remain undiagnosed when using conventional diagnostic methods. The American College of Rheumatologists (ACR) defined specific criteria for LVV, both for GCA and TA. However these criteria are based on the diagnosis of advanced cases, resulting in a possible delayed diagnosis [31, 41.]

The results of the ^{18}F-FDG PET scans were compared to biochemical markers of inflammation; the intensity of ^{18}F-FDG uptake appeared to be significantly correlated with CRP, ESR, and thrombocytes [42]. On the contrary, it has also been reported that the levels of biochemical markers of inflammation do not always correlate with the results of the ^{18}F-FDG PET scan [26, 43]. In our study, something similar is seen -all patients with a positive test result for LVV had an elevated CRP, only one of the patients had a normal ESR.

Table 5. Logistic regression

	Univariate analysis OR (95% CI)	*p*	Multivariate analysis OR (95% CI)
Age	1.032 (1.012–1.053)	0.002	–[a]
Female	2.611 (1.385–4.922)	0.003	–[a]
Arthralgia	0.219 (0.091–0.527)	0.001	0.091 (0.023–0.366)
Thrombocytes	1.002 (1.000–1.004)	0.053	–[a]
ESR	1.022 (1.009–1.035)	0.001	1.024 (1.002–1.046)

[a] Not in the equation

The aorta and its main branches are not suitable for routine histological examination; direct proof of vascular inflammation is therefore not possible. However, the hypothesis that a homogeneous/smooth linear pattern of ^{18}FFDG
uptake in the aorta and its main branches, with an intensity higher than the liver uptake, is highly suggestive for GCA has considerable indirect evidence:

- There is an established close association between PMR and GCA; cytokine mRNA levels (mainly IL-2) are almost identical in specimens [44, 45]. Interestingly; moderately increased ^{18}F-FDG uptake in the large vessel walls as a sign of vasculitis in patients with active PMR is reported [42, 46, 47].
- A study from 1968 of six autopsy cases revealed involvement of the aorta and other arteries in patients with coexisting giant cell arteritis, as well in patients with PMR in whom a temporal artery biopsy was negative or clinical signs of vasculitis were absent [48].
- In patients with GCA, with or without symptoms of PMR, late sequelae of vasculitis such as stenosis, aneurysm, or dissection predominantly occur in the thoracic aorta and its main branches [49].

In our study the mean age of the patients with a positive test result for LVV was 65.9 years. In this group 76% of the patients were female. Both are comparable to patient populations of other studies on LVV [2–5]. The percentage of negative test results of the temporal artery biopsy on the total amount of biopsies performed varies widely between different studies and lies between 15.3% and 71.6% [9–14]. In our study this percentage was 50%. It should be noted, however, that in our study only 39% of the patients with a positive ^{18}F-FDG PET(/CT) scan had undergone a biopsy of the temporal artery. In the cases that no temporal artery biopsy was performed, the clinical picture and the test results of the ^{18}F-FDG PET(/CT) scan provided the clinician with enough certainty to diagnose the patient with LVV, supported by the clinical response to immunosuppressive drugs.

In the univariate analysis, both groups differed significantly regarding age (65.9±13.4 versus 58.6±16.5 years, p=0.002), female sex (76% versus 55%, p=0.002), temporal arteritis in the past (10% versus 3%, p=0.044) and artralgia (31% versus 67%, p=0.000), thrombocytes (434±161 versus 373±168×109/l, p=0.049), and ESR (72.6±31.0 versus 51.4±30.5 mm/h, p=0.001). In the multivariate analysis, only artralgia (OR 0.091; 95% CI 0.023–0.366) and ESR (OR 1.024; 95% CI 1.002–1.046) remained as statistically significant predictors. However, the clinical relevance of both parameters is small. For one, even the odds ratio of 10 units of ESR is only 1.268 and still close to 1. Consequently, although the relationship between the ESR and a positive test result is statistically significant, the clinician cannot base the decision whether or not to perform a ^{18}F-FDG PET(/CT) scan on the ESR. Artralgia, on the other hand, has a negative instead of a positive association with a positive test result. The explanation of this could be the fact that most patients in the group with a negative test result do not have LVV, but that they do have another disorder. Some of these disorders, for example PMR and

inflammatory joint disorders, have artralgia as a main complaint. Since only two parameters ended up as statistically significant predictors, the results were not corrected for the multiple comparisons performed, so the results should be considered exploratory.

In the group with a positive test result, significantly more patients were aged over 50 (90% versus 69%, p=0.001); this is in line with the first ACR criterion of GCA of age at onset of disease over 50 years. For the CRP, when a cutoff point of 10 mg/l was chosen, none of the patients in the group with a positive test result had a normal value, resulting in a sensitivity of 100% and a specificity of 26%. Although the mean CRP did not differ significantly between both groups, the sensitivity of 100% for a cutoff point of 10 mg/l indicates that it is not helpful to perform a ^{18}F-FDG PET(/CT) scan for LVVin patients with a normal CRP. For the ESR, when a cutoff point of 20 mm/h was chosen, a sensitivity of 94% and a specificity of 16% were found, indicating that it is not helpful to perform a ^{18}F-FDG PET(/CT) scan for LVV in patients with a normal ESR either.

In the group with a negative test result, 17 patients had ^{18}F-FDG uptake in the wall of the aorta and its main branches that was less intense than that of the liver. Despite the results of the ^{18}F-FDG PET(/CT) scan, these 17 patients were diagnosed and treated for LVV. In 64% of the cases without large vessel ^{18}F-FDG uptake on the ^{18}F-FDG PET(/CT) scan, another diagnosis could eventually be made. In about half of these cases, this was done based on the results of the ^{18}F-FDG PET(/CT) scan. In 22 of these 242 cases (9%), the diagnosis PMR was made. The images of the ^{18}F-FDG PET(/CT) scan in these patients revealed a characteristic pattern of pathological ^{18}F-FDG uptake in the soft tissues and ligaments (perisynovitis or enthesitis) around the shoulders, lumbar spinous processes, and ischial tuberosities[50, 51]. As GCA and PMR may occur together, ^{18}F-FDG PET/(CT) may diagnose patients with PMR or GCA as an isolated condition, which is clinically relevant as GCA patients are more prone to develop thoracic aortic dilatation and therefore need more monitoring [52].

Moreover, even a normal ^{18}F-FDG PET(/CT) scan can be helpful in the diagnostic process by ruling out LVVand other disorders. This is supported by different studies on fever of unknown origin and inflammation of unknown origin. In a study of Vanderschueren et al., ^{18}F-FDG PET contributed to the diagnosis in about a third of the patients in both groups [53]. This is comparable to the contribution of ^{18}F-FDG PET found in other studies on fever of unknown origin [54–56]. An even higher contribution of 56% was found for hybrid ^{18}F-FDG PET/CT [57]. It is therefore suggested that ^{18}F-FDG PET(/CT) may be incorporated in the diagnostic algorithm of fever of unknown origin or inflammation of unknown origin, of which a relatively high number is caused by LVV [58].

There are some limitations to this study. The first problem is the large amount of missing data, especially regarding the clinical parameters, caused by the retrospective design of this study. Because of this, the results of the study can be somewhat biased. When a clinical parameter was not mentioned in the medical record, this could have meant that the clinician did not ask about this, but also that the clinician thought mentioning the absence of the parameter was not worthwhile. Besides, a lot of the parameters would have been mentioned

by the patient spontaneously if they had been present. This means that a relative large part of the missing data actually consists of parameters that are negative. To consider all missing data as negative parameters would probably have biased the results too.

The second problem with the retrospective design of the study is that there are no clear criteria for considering the ^{18}F-FDG PET(/CT) scan to have a positive or negative test result. Because of the number of participating hospitals and the duration of the period of which the scans were included, different nuclear medicine physicians have reviewed the scans. However, in all participating centers, a smooth linear or long segmental pattern of ^{18}F-FDG uptake in the aorta and its main branches with an intensity higher than the liver uptake was regarded as positive for GCA [34]. Because the patients in this study were gathered from different hospitals, the results of the laboratory tests should be considered with some caution. The used equipment and the tuning of the equipment differ between hospitals, so each hospital uses its own reference values. In addition, the reference values have probably changed in the course of years. Regarding the fact that these differences and changes will be small, the influence on the results will be small too. Even if such a small change would have influenced the statistical significance of the results, this would still not be clinical relevant.

A future prospective study is needed, to study possible predictive parameters without the above-mentioned limitations of a retrospective study. A second study scope could be the use of ^{18}F-FDG PET(/CT) during the follow-up of LVV.

Conclusions

The presence of artralgia is a statistically significant predictor of a negative test result of the ^{18}F-FDG PET(/CT) scan and an elevated ESR of a positive test result in patients suspected for LVV who are not on steroid treatment. However, the clinical relevance of both parameters is small. Artralgia as a predictor is too strongly correlated with one or more of the other parameters, and the odds ratio of the ESR is too close to 1 to help the clinician with the decision whether or not to perform a ^{18}F-FDG PET(/CT) scan. Furthermore, ^{18}F-FDG PET(/CT) is not helpful in patients with a CRP of <10 mg/l.

Our finding that the temporal artery is not always involved in GCA is in line with other studies; ^{18}F-FDG PET/(CT) may be the next diagnostic procedure when temporal artery biopsy and ultrasonography findings are equivocal. ^{18}F-FDG PET(/CT) enables diagnosis of LVV in the early phase before the development of sequelae like stenosis or aneurysm.

In addition, in the group with a negative test result for LVV, the ^{18}F-FDG PET(/CT) scan led to an alternative diagnosis in approximately half of the cases, such as occult inflammatory or neoplastic disorders. As GCA and PMR are closely associated, ^{18}F-FDG PET/(CT) may diagnose patients with PMR or GCA as an isolated condition, which is clinically relevant as GCA patients are more prone to develop thoracic aortic dilatation and therefore need a more intensive treatment and monitoring as compared to PMR patients.

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The role of ^{18}F-FDG PET/CT in Large Vessel Vasculitis: Appropriateness of current classification criteria?

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Abstract

Patients with clinical suspicion of large vessel vasculitis (LVV) may present with non-specific signs and symptoms like fatigue, malaise, weight loss, anorexia, (sub-)febrile temperatures or night sweats, and increased C-reactive protein (CRP) levels or erythrocyte sedimentation rate (ESR). This patient population may remain without a diagnosis after routine diagnostic procedures. Both the non-specificity of the radiofarmaceutical ^{18}F-FDG and the synergy of integrating functional and anatomical images with hybrid PET/CT offer substantial benefit in the diagnostic work-up of patients with clinical suspicion for LVV. An important feature of ^{18}F-FDG PET imaging is the ability to reveal increased metabolism and functional alterations that precede the morphological changes. A negative temporal artery biopsy, an ultrasonography without an arterial halo, or a MRI without aortic wall thickening or oedema does not exclude the presence of LVV, and should therefore not exclude the use of ^{18}F-FDG PET/CT when LLV is clinically suspected.

This overview further discusses the notion that there is substantial underdiagnosis of LVV, supported by autopsy observations. A late diagnosis of LVV may lead to surgery or angioplasty in occlusive forms and is often accompanied by serious aortic complications and a fatal outcome.

In contrast to the American College of Rheumatology 1990 criteria for vasculitis, based on late LVV effects like arterial stenosis and/or occlusion, ^{18}F-FDG PET/CT sheds new light on the classification of giant cell arteritis (GCA) and Takayasu arteritis (TA) and strengthens the idea that GCA and TA are more likely to be different expressions of a common histopathological entity.

The combination of these observations makes the role of ^{18}F-FDG PET/CT in the assessment of patients suspected for having LVV promising.

Introduction

This paper focuses on the role of ^{18}F-FDG PET/CT in patients with symptoms possibly related with large vessel vasculitis (LVV), and the pathophysiologically associated polymyalgia rheumatica (PMR). Patients with clinical suspicion of LVV may present with non-specific signs and symptoms like fatigue, malaise, weight loss, anorexia, (sub-)febrile temperatures or night sweats, and increased C-reactive protein (CRP) levels or erythrocyte sedimentation rate (ESR). This patient population may remain without a diagnosis after routine diagnostic procedures. Both the non-specificity of the radiofarmaceutical ^{18}F-FDG and the synergy of integrating functional and anatomical images with hybrid PET/CT may offer substantial benefit in the diagnostic work-up of patients with clinical suspicion for LVV. An important feature of ^{18}F-FDG PET imaging is the ability to reveal increased metabolism and functional alterations that precede the morphological changes. In addition this paper discusses whether the specific characteristics of ^{18}F-FDG PET/CT may shed new light on the American College of Rheumatology (ACR) classification of LVV in giant cell arteritis (GCA) and Takayasu arteritis (TA).

Background

Vasculitides are a heterogeneous group of syndromes; the 1990 American College of Rheumatology (ACR) established criteria designed to differentiate among patients with 7 types of vasculitis.[1] Historically, TA and GCA have been considered distinct diseases based on differences in age at onset, ethnic distribution, and clinical features, including predilection for involvement of certain arterial territories.[2,3]

The goals of the first International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides (CHCC1994) were to reach consensus on names for the most common forms of vasculitis and furthermore to construct a specific definition for each form.[4] The CHCC1994 classification organized vasculitis according to vessel size:

- Large vessels: Giant cell arteritis (GCA), Takayasu arteritis (TA).
- Medium vessels: Peri-arteritis nodosa, Kawasaki's arteritis, Primary CNS vasculitis, Buerger's disease (thromboangiitis obliterans).
- Small vessels: Wegener's disease, Churg-Strauss syndrome, microscopic polyangiitis, Henoch-Schonlein purpura, essential cryoglobulinaemic vasculitis.

Because of advances in understanding the pathophysiology of vasculitis another International Chapel Hill Consensus Conference (CHCC2012) was convened. With respect to LVV, changes in definition were made. Criteria for TA based on late effects of arterial lumen narrowing or occlusion were removed; "claudication of an extremity, decreased brachial artery pulse, difference in systolic blood pressure between arms, a bruit over the subclavian arteries or the aorta, arteriographic evidence of narrowing or occlusion of the entire aorta". Furthermore, the previous existing gap in age between the onset of < 40 years for TA of age and ≥ 50 years of age for GCA was closed. The following definitions were formulated:

- Giant cell arteritis: Arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries. Often involving the temporal artery. Onset usually in patients older than 50 years and often associated with polymyalgia rheumatica.
- Takayasu arteritis: Arteritis, often granulomatous, predominantly affecting the aorta and/or its major branches. Onset usually in patients younger than 50 years.

The term "temporal arteritis" was not regarded as a suitable alternative for GCA because not all patients have temporal artery involvement, and other categories of vasculitis can affect the temporal arteries. The CHCC2012 made notation that in patients with LVV large arteries may not be the predominant type of vessel affected, because especially medium size arteries may be affected as well, or even smaller arteries e.g. ciliary and retinal arteries.[5, 6] It was recognized that the histopathological features of TA and GCA are indistinguishable, but the CHCC2012 participants did not seek to resolve the important question whether or not CGA and TA are the same disease.[5]

Giant cell arteritis and Takayasu arteritis

The idea that GCA and TA are part of a spectrum of conditions of a single disease was first proposed by Hall in 1973, who suggested that polymyalgia rheumatica (PMR), GCA, and TA constitute an "unholy trinity" of a single disease.[7]

GCA is characterised by arterial injuries affecting the smooth muscle cells located in the media with fragmentation of the internal elastic lamina, and also lymphocyte-monocyte transmural infiltration with the presence of macrophages.[8] GCA is associated with polymyalgia rheumatica (PMR) in approximately 40% of patients.[9, 10] GCA involvement of the aorta and/or its major branches may be asymptomatic or induce non-specific clinical complaints, which explains why it is often overlooked. This is underlined by the fact that late effects/complications of extracranial GCA may only be discovered after life-threatening events such as stroke, myocardial infarction, ruptured aortic aneurysm, or aortic dissections.[11-14]

TA is a pan-arteritis with mononuclear infiltrates and giant cells, mostly located in the adventitia and the media.[15] TA has an estimated incidence of only 2 cases per 1 million persons. The mean age at onset is 35 years, and prevalence of the disease in women is 2–25 times higher than that in men. During the course of the disease, stenoses, occlusions, and aneurysms may occur.[16] TA is reported to be potentially life-threating, reflected in mortality rates as high as 35% at 5 years after diagnosis, similar to that seen in malignancies.[17]

The pathogenesis of both GCA and TA is unknown. Both are thought to be antigen-driven cell mediated autoimmune processes, although the specific antigenic stimulus and or stimuli have not been identified.[18] Interleukin-6 (IL-6) may be a key mediator in GCA, TA, and PMR. Patients with GCA, TA, and PMR have elevated concentrations of IL-6 in both their peripheral circulation and their inflamed tissues, and serum levels of IL-6 correlate with disease activity. IL-6 receptor blockade with tocilizumab led to clinical and serologic improvement in patients with refractory or relapsing GCA, TA, and PMR.[19]

Recent observations have shown that the histopathology of arterial lesions in GCA and TA is difficult to distinguish. [18,20] On angiography strong similarities and subtle differences in these lesions were observed between GCA and TA.[21]

Temporal artery biopsy

Temporal artery biopsy is considered the cornerstone of the diagnosis of GCA, which explains why review articles were published under the title 'Large-Vessel Vasculitis" but dealt almost entirely on the problems of interpreting laboratory results and the results of ultrasonography and temporal artery biopsy.[22] Temporal artery biopsy is invasive and can be false negative, due to e.g. skip lesions, in 15–70% of the cases, which may considerably delay the diagnosis.[23] Large-vessel arteritis may occur in isolation, without classical features such as headache and scalp tenderness, making a clinical diagnosis difficult. In a recent study of 74 patients with subclavian/axillary GCA diagnosed by angiography and 74 control patients with temporal artery biopsy-proven GCA and without large vessel involvement at angiography, were

matched for the date of first diagnosis. PMR occurred with similar frequency in both patient groups and temporal artery biopsy findings were negative in 42% of patients with large-vessel GCA. Large-vessel GCA was associated with higher concentrations of interleukin-2 gene transcripts in arterial tissue and overrepresentation of the HLA-DRB1*0404 allele, indicating differences in pathogenetic mechanisms. GCA is apparently not a single entity but may comprise of several variants of the same disease. In the spectrum of clinical manifestations it often occurs without involvement of the cranial arteries.[24]

This interpretation is supported by the variable phenotypes in patients at different ages that are reported in analyses of other autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, and dermatomyositis.[20]

Underestimation of the prevalence/incidence of LVV

The incidence of LVV generally mentioned in the literature is 20-30/100,000 persons (0,02%).[25] Based on the largest retrospective series, the prevalence of involvement of extracranial vessels in GCA is around 15%.[26] The notion that there is substantial underdiagnosis of LVV is supported by several autopsy observations.

A small study from 1968 of six autopsy cases revealed involvement of the aorta and other arteries in patients with co-existing giant cell arteritis, as well in patients with PMR in whom a temporal artery biopsy was negative or clinical signs of vasculitis were absent.[27] Most convincing is a retrospective study (from 1973!) of arterial changes in 20,591 autopsy subjects in Sweden, which revealed that PMR with signs of aortic involvement is far more common than is diagnosed clinically, arteritis was found in 0,4% and only half of them had temporal arteritis.[28] The often asymptomatic course of LVV was demonstrated by a retrospective review of 1,204 aortic surgical specimens that were gathered over a period of 20 years, 52 (4.3%) were clinically and pathologically classified as idiopathic aortitis. In 31%, aortitis was associated with a remote patient history of vasculitis and a variety of other systemic disorders.[29]

The heterogeneity of LVV was substantiated in a report on 72 cases of, during life, documented GCA with aortic and extracranial large vessel involvement. The disease process affected the entire aorta in 35/72 cases, the head and neck or upper limb arteries in 24/72 cases and the lower limb arteries in 13/72 cases.[30]

Importance of early diagnosis of LVV

Additionally, a late diagnosis of LVV leading to surgery or angioplasty in occlusive forms (with higher frequency in patients classified as TA) is often accompanied by serious aortic complications and a fatal outcome.[31] Manifestations are very polymorphous, with presentations that range from asymptomatic to neurologic complications. LVV has also been reported to manifest as isolated involvement of renal arteries (for which renal revascularization was required), or pulmonary arteries resulting in occlusion, and of coronary arteries, requiring bypass surgery.[32 - 36] Especially in older patients visual loss in one eye was

reported to be prevalent in 16–18% of patients at initial diagnosis.[37, 38] In Great Britain visual loss in patients diagnosed with temporal arteritis occurs in as much as 20% of patients.[39]

Abdominal aortic aneurysms (AAA) are a substantial burden on health care. Recent studies may bridge a gap between the clinical signs and diagnosis of AAA and immune-mediated large vessel vasculitis. Serum levels of IL-1β, TNF-α and IL-6 were proven elevated in AAA patients. In AAA tissue samples, levels of TNF-α were found to be higher in small-sized AAA's than in large-sized AAA's, and may be related to infiltration of macrophages.[40,41] In a follow up of 96 GCA patients that all fulfilled the ACR criteria, and of which 88 had artery biopsy specimens showing GCA (87 temporal, 1 occipital) it was found that these patients were 17 times more likely to develop a thoracic aneurysm and 2.4 times more likely to develop an AAA compared with the general population.[26] In the same cohort of 96 patients (diagnosed between January 1950 and December 1999) the median time from diagnosis of GCA to detection for AAA was 6.3 years and for thoracic aortic aneurysms 10.9 years.[42]

Utility of ^{18}F-FDG PET/CT in the diagnosis of LVV, PMR and temporal arteritis

LVV

In a review from 2003 and later in 2009 it was stated that in patients presenting with a prolonged inflammatory syndrome with non-conclusive signs and symptoms, the presence of diffuse increased ^{18}F-FDG uptake in the wall of the aorta and its main branches may efficiently guide to the diagnosis of LVV.[43,44]

To further substantiate this statement, ^{18}F-FDG PET/CT was recently performed in a series of 140 patients with inflammation of unknown origin (IUO). IUO was defined as; repeated CRP values more than 20 mg/l or ESR more than 20 mm/h, with non-specific signs and complaints, body temperature below 38.3 ºC (100.9 °F) and without a diagnosis after conventional diagnostic procedures. The final diagnosis was related to infection in 35 patients, malignancy in 18 patients, non-infectious inflammatory disease (NIID) in 44 patients and a variety of uncommon conditions in 7 patients. NIID was the main category with PMR in 18 patients as the first main diagnosis, and LVV in 12 patients as the second most established diagnosis. Signs of PMR were seen in 3 patients with LVV, and vice versa LVV signs on the PET images in 4 patients with PMR. None of the 12 patients with LVV had clinical signs or symptoms of temporal arteritis, nevertheless biopsy was positive for GCA in 1 patient and another patient with LVV had wall thickening with ultrasonography of the temporal artery.[45] Another recent study on IUO included 88 patients aged 50 years or older with non-specific complaints and an ESR of more than 50 mm/h for which routine evaluation revealed no diagnosis. Of the 88 included patients 18 were diagnosed with LVV and 6 with PMR, with only one of these patients eventually diagnosed with temporal arteritis.[46] In both IUO studies parameters like the proportion of patients with disease, the contribution of ^{18}F-FDG PET/CT to the diagnosis and the distribution of diseases in infection, NIID and malignancy were similar to 'fever of unknown origin' (FUO) patient populations.[47-52]

In the literature reports on LVV -with the presence of diffuse and mildly intense ^{18}F-FDG uptake in the wall of the aorta and its main branches- are numerous and mostly comprise large patient numbers (Figure 1). The reported initial response to immunosuppressive therapy is better in LVV patients with non-specific symptoms at the time of diagnosis, compared to patients that comply to the ACR 1990 criteria with measurable effects of arterial stenosis. [49, 53 - 61]

Reports on patients with LLV limited to the aortic arch or only in isolated arteries e.g. the carotic or vertebral arteries are scarce (only case reports) and the images display a more intense ^{18}F-FDG in the aortic or arterial wall, compared to patients with LVV in the entire wall of the aorta and its main branches. A relatively high number of patients have symptoms at the time of diagnosis due to arterial occlusion and both relapse and progression (metabolic and angiographic) despite immunosuppressive therapy is reported. [33 - 36, 62- 64]

Polymyalgia rheumatica

^{18}F-FDG PET/CT images of patients with PMR reveal a characteristic pattern of pathologic ^{18}F-FDG uptake in the soft tissue and ligaments (perisynovitis or enthesitis) around the shoulders and hips, lumbar (and in many cases cervical) spinous processes, and ischial tuberosities (Figure 2). [65,106] ^{18}F-FDG PET/CT may show 2 different patterns of interspinous uptake: focal and diffuse. Diffuse uptake may reflect interspinous ligament inflammation, focal interspinous uptake may represent interspinous bursitis.[106] After chronic ligamentous interspinous inflammation, interspinous bursae may develop, leading to interspinous bursitis.[107] MRI is widely used to detect bone marrow edema and enthesitis in patients with spondyloarthritides (SpA). ^{18}F-FDG PET/CT may provide an alternative diagnostic method and will likely contribute to the early diagnosis of SpA in PMR.[108] Both LVV and PMR may be detected, in the early onset of the disease, by ^{18}F-FDG PET/CT. In some patients LVV is associated with PMR and vice versa. [66, 67]

Temporal arteritis

The first introduced stand-alone PET cameras provided a spatial resolution of 10 mm; a study from 2004 concluded, as a consequence, that stand-alone ^{18}F-FDG PET was not yet suitable for the diagnosis of temporal arteritis and therefore could not replace invasive biopsy.[68] Ongoing improvements in technology created an evolution in spatial resolution from 6 mm to 4 mm. In recent years increased ^{18}F-FDG uptake is visualized in patients with arteritis temporalis.[69] The most recently introduced PET/CT cameras claim a 2.5 mm spatial resolution for the PET component under optimal conditions. It is therefore to be expected that pathologic ^{18}F-FDG uptake in temporal arteritis will be reported more frequently. However, in patient populations with prolonged inflammatory parameters and non-specific complaints and a positive ^{18}F-FDG PET/CT result for the diagnosis of LVV, temporal artery biopsy was negative in 50%.[49, 70]

Specificity and differential diagnosis of pathologic ^{18}F-FDG uptake in the arterial wall.

Many patients assessed for malignant disease but without a history of vasculitis, may show some uptake of ^{18}F-FDG in e.g. the walls of the aorta, the subclavian arteries and with highest incidence in the iliofemoral arteries.[109, 110] Therefore, nuclear medicine physicians and other PET/CT practitioners have to be aware of the clinical significance of the different vascular patterns. As ^{18}F-FDG accumulates in macrophage-rich areas, it cannot distinguish between sterile inflammation -such as large vessel vasculitis- and infectious inflammation. In the differential diagnosis, the pattern and the localisation of the vascular involvement as well as the intensity of ^{18}F-FDG vascular uptake in the arterial wall should be taken into account for interpretation and especially differentiated from blood pool activity.

The differentiation of atherosclerosis from large vessel vasculitis is considered less problematic with PET/CT compared to a stand-alone PET.[71] Atherosclerosis usually displays a patchwork of partially normal vessel wall, focal inflammation and calcifications. In terms of patient age, arterial inflammation precedes calcification; a study from 2005 with ^{18}F-FDG PET/CT showed that inflammation and calcification only had overlap in <2% of cases, suggesting that calcification and focal arterial inflammation represent different stages in the evolution of atheroma (Figure 4).[43, 72] Future studies will tell if this simple interpretation of the images holds true; the possible link between vasculitis, inflammation and atherosclerosis was already suggested more than a decade ago.[73-75] Subsequent studies showed that waist circumference and atherogenic risk factors were the strongest determinants of a patchy ^{18}F-FDG arterial uptake pattern, and for that reason 'metabolic syndrome' associated.[76, 77]

In addition to GCA and Takayasu arteritis, other rheumatologic disorders, including rheumatoid arthritis, systemic lupus erythematosus, Wegener granulomatosis, Behçet disease, polyarteritis nodosum, and microscopic polyangiitis, may lead to aortitis. In the case of rheumatoid associated aortitis, rheumatoid nodules are reported in the aortic wall in up to 50% of pathological specimens.[78] Furthermore, aortitis was reported in the HLA-B27–associated sero-negative spondyloarthropathies, Reiter syndrome and ankylosing spondylitis.[79] Case reports exist of aortitis associated with sarcoidosis.[80] Cogan's syndrome is an unusual disorder characterized by episodes of interstitial keratitis and vestibuloauditory dysfunction (i.e., eye and ear symptoms); aortitis occurs in up to 10% of cases of Cogan syndrome. [62, 81] Syphilitic aortitis, localized in only the wall of the ascending aorta, is reported in several recent case reports.[82-84] Aortitis also occurs in association with idiopathic retroperitoneal fibrosis (Ormond disease), inflammatory abdominal aortic aneurysm, and perianeurysmal retroperitoneal fibrosis, a group of clinical disorders now categorized as chronic periaortitis.[85]

However, the above mentioned disease entities are different from LVV in that the inflammation is limited to the aorta and periaortic tissues rather than a manifestation of a widespread vasculitis of the aorta and its main branches.

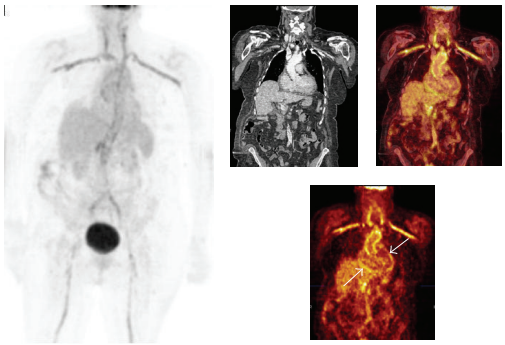


Figure 1. Patient history: lack of appetite and pain between the shoulder blades. Cardiologic evaluation and gastroscopy negative. CRP 224 mg/L. Increased ^{18}F-FDG uptake in the aorta and its main branches and less intense FDG uptake in the distal abdominal aortic wall; corresponding CT slices show calcifications here. The mild increased perisynovial ^{18}F-FDG uptake at both shoulders, which might be indicative of associated PMR. The increased ^{18}F-FDG uptake at the pericardium is suggestive of pericarditis (white arrows). Note: patient had a carbohydrate restricted diet for 2 days before the ^{18}F-FDG PET/CT investigation to decrease the ^{18}F-FDG uptake in the myocardium. Patient had a TIA one year earlier and subsequent carotid artery desobstruction. LVV was not suspected at that time; no immunosuppressive therapy was given. After the diagnosis of LVV patient was in remission during 4 years with Prednisolon orally tapered from10 to 7.5 and later 5 mg daily. Due to relapse Prednisolon was increased to 15 mg daily. Patient died 5 years after the diagnosis of LVV after a severe CVA.

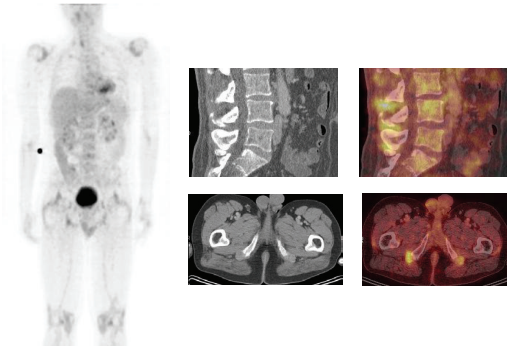


Figure 2. A 48-year-old man presented with initial painful calves followed by progressive painful arms and legs, shoulders, and knees. No hydrops or other clinical signs of arthritis. Normal body temperatures; CRP level, 84 mg/L; ESR, 41 mm/h; normal routine laboratory values; rheumatoid factor negative; cyclic citrullinated peptide antibody test negative; serum angiotensin-converting enzyme, 10.3 units/L; antinuclear antibody test negative; and anticytoplasmic autoantibodies negative. Urine sediment: albumin trace. Glomerular basal membrane antibody test negative. Viral serology negative. Chest X-ray and abdominal ultrasonography without abnormalities. X-ray of hands, feet, and knees revealed no erosive changes. Ultrasonography of the hips revealed no abnormalities. Also ^{18}F-FDG PET/CT showed pathological perisynovial uptake at the major joints, as well as pathological lumbar interspinous uptake in the soft tissue (bursae) lateral to both of the greater trochanters and dorsal to both of the tuber ischii.The diagnosis of PMR was made; after treatment with steroids, the patient became pain free, and the CRP values remained less than 10 mg/L [25].

As ^{18}F-FDG PET/CT will be more frequently used as a screening tool in more complex diagnostic settings like fever and inflammation of unknown origin, a routine investigator-independent strategy for establishing the diagnosis of LVV is needed. In this respect semi-quantification might be helpful: a ratio of the ^{18}F-FDG maximal standardized uptake values (SUVmax) of the aorta-to-liver appeared more reliable compared to the SUVmax of the aorta-mediastinum ratios for the diagnosis of LVV, and was not affected by minor inflammation-associated changes in hepatic metabolism. [56]

Sensitivity and specificity of ^{18}F-FDG-PET/CT in comparison to other imaging modalities

In the knowledge that ultrasonography, MRI, arteriography and PET/(CT) have proven useful image techniques in the diagnostic approach of LVV or suspicion of LVV, it remains difficult to compare the different imaging modalities. Results have to be interpreted with caution as metabolic changes in the arterial wall usually precede the anatomic changes. [86-90] Furthermore, the instigating inflammatory process may have subsided in arterial stenosis or aortic aneurysm. Problems rise therefore in the interpretation ^{18}F-FDG PET/CT results in the many reports that describe patient populations that met the ACR 1990 classification criteria for GCA (i.e. with temporal artery abnormalities and /or a positive biopsy for arteritis) and TA (i.e. with clinical and measurable effects of arterial stenosis). (Table 1). Furthermore, in the majority of studies patients were already receiving steroids, which negatively influences the sensitivity of ^{18}F-FDG PET for inflammatory processes, while sequelae like oedema and aortic/arterial wall thickening (CT or MRI) need more time to respond to therapy.
Reported discrepancies in ^{18}F-FDG PET/CT results, disease activity measured by inflammatory parameters, and radiologic evaluation with MRI may very well be caused by interpreting monitoring immunosuppressive therapy response with ^{18}F-FDG PET/CT as an initial staging procedure.[54,58,64]

The active phase of recruitment, activation, migration and infiltration of T cells, macrophages and leucocytes usually precedes the appearance of inflammatory oedema, ^{18}F-FDG PET/CT may therefore be positive at an earlier stage than an MRI scan.[91] Also angiography is suboptimal for the diagnosis of LVV because it detects only the late anatomical changes such as arterial wall abnormalities, arterial stenosis or aortic aneurysm.[92] However, the chronic inflammation in asymptomatic AAA's was not sufficiently metabolically active to result in detection with ^{18}F-FDG PET/CT. Despite that histologic examination of large asymptomatic AAA's (range 52-66 mm) and small AAA's (range 34-40 mm) showed residual inflammatory cell infiltration with T-cells and macrophages.[93]

In addition the lack of a gold standard creates problems in the calculation of sensitivity and specificity, in some reports LVV diagnosed by ^{18}F-FDG PET/CT was confirmed by histology (of the temporal artery while patients with LVV have involvement of the temporal artery in only approximately 50% of the cases!) or MRI angiography. [61]

Table 1. Definitions for large vessel vasculitis according to the American College of Rheumatology (ACR) 1990 criteria for the classification of giant cell arteritis and Takayasu's arteritis and the definitions revised by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides (CHCC2012).

	ACR 1990 criteria	CHCC2012 definition
Large-vessel vasculitis (LVV)		Vasculitis affecting large arteries more often than other vasculitides Large arteries are the aorta and its major branches
Giant cell arteritis (GCA)	Age at onset of disease ≥ 50 yr New headache Temporal artery abnormality Elevated erythrocyte sedimentation rate Abnormal findings on biopsy of temporal artery Diagnosis: at least 3/5 criteria	Arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries Often involves the temporal artery Onset usually in patients older than 50 years and often associated with polymyalgia rheumatica Arteritis, often granulomatous, predominantly affecting the aorta and/or its major branches
Takayasu arteritis (TA)	Age at onset of disease ≤ 40 yr Onset usually in patients younger than 50 years Claudication of an extremity Arteritis, often granulomatous, Decreased brachial artery pulse predominantly affecting the aorta and/or its major Difference in systolic blood pressure between arms branches A bruit over the subclavian arteries or the aorta Arteriographic evidence of narrowing or occlusion of the entire aorta Diagnosis: at least 3/6 criteria	Onset usually in patients younger than 50 years Arteritis, often granulomatous, predominantly affecting the aorta and/or its major branches

Table 2. Sensitivity and specificity of different imaging modalities for LVV with their pathognomonic/typical imaging findings. (data on US and MRI from [111]).

	Pathognomonic/typical findings	Sensitivity/specificity
(Color-doppler) ultrasonography	(i) Edema, halo around the (temporal) artery (ii) Stenosis, increased blood flow velocities (iii) Occlusion, absent colour signal	Sens. 87%, Spec. 96% (for late effects of arteritis temporalis)
MRI	(i) Wall thickening (ii) Increased mural gadolinium contrast enhancement	Sens. 81%, Spec. 97% (for late effects of LVV)
^{18}F-FDG PET/CT	Increased ^{18}F-FDG uptake in walls of aorta and main cervical and thoracic branches	(i) Able to detect early inflammation without (late) effects like oedema, wall thickening, or arterial stenosis or aortic dilatation (ii) How to calculate sensitivity and specificity in lack of a gold standard?

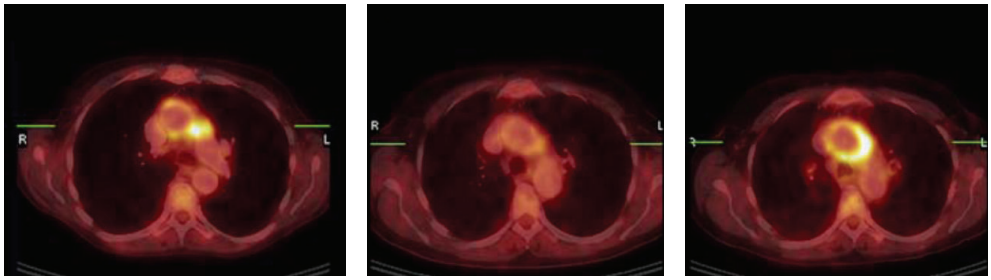
Or the diagnostic accuracy and sensitivity/specificity of an international expert panel was calculated and compared to computer calculated logistic regression models as a reference to assess the impact on clinical management with and without ^{18}F-FDG PET results.[55]
Because GCA and TA were considered as two independent distinct diseases, patients with Takayasu arteritis (i.e. patients younger than 50 years) were excluded in reports and reviews.[101]
In conclusion; a negative temporal artery biopsy, an ultrasonography without an arterial halo, or a MRI without aortic wall thickening or oedema does not exclude the presence of LVV, and should therefore not exclude the use of ^{18}F-FDG PET/CT when LLV is clinically suspected.

Cost-efficacy

In the 'new' era of health care technology assessment (HTA), the costs of a diagnostic procedure should be weighed against its effectiveness in daily clinical practice. ^{18}F-FDG PET/CT has the ability to visualize the early onset of inflammatory processes within a whole body scan, positive findings correlate well with clinical and laboratory markers of inflammation, in particular C-reactive protein. The level of ^{18}F-FDG uptake may also provide prognostic information in LVV.[92] The intensity of thoracic aortic wall ^{18}F-FDG uptake at the time of diagnosis correlated with later increased aortic diameter (as measured by CT) after a mean of 46.7 months follow-up (adjusted for age, sex, hypertension, diabetes, cholesterol levels, erythrocyte sedimentation rate, and CRP). On multivariate analysis, only ^{18}F-FDG uptake at baseline remained significantly associated with increased thoracic aortic diameter ($p = 0.039$).[59]

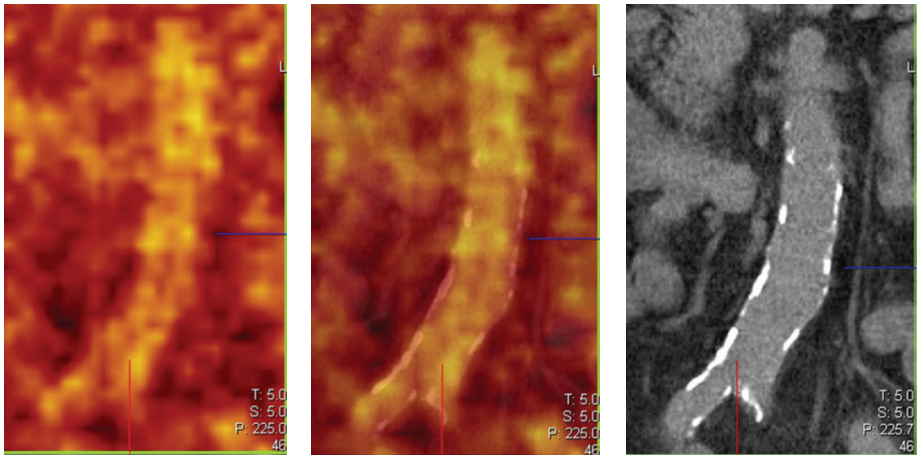
Repeated ^{18}F-FDG PET/CT procedures involve expenses and radiation exposure to patients with vasculitis.[94] On the other hand, patients diagnosed with PMR and without signs of LVV, an additional ^{18}F-FDG PET/CT will probably offer no advantage over the traditional follow-up of PMR patients, based on clinical evaluation and periodic determination of inflammatory laboratory parameters.[95] However, in patients diagnosed with LVV and treated with steroids, both normalization of laboratory data and symptomatic improvement of the patient correlated well with normalization of ^{18}F-FDG uptake in the large vessel walls. CT and MRI frequently show residual abnormal findings even after symptoms have completely resolved and with discrepancies concerning ESR and CRP laboratory data. [105,111]
Patients diagnosed with LVV probably need to be classified in different risk groups, as already suggested in 1999.[24] ^{18}F-FDG PET/CT is able to diagnose patients with LVV without cranial or cervical artery involvement, which is clinically relevant as patients with arteritis temporalis are probably more prone to develop thoracic aortic dilatation or arterial occlusion, and therefore need a more intensive treatment and close monitoring as compared to patients with isolated LVV or PMR. [95,96] Those patients with localized and more intense ^{18}F-FDG uptake limited to only one artery or e.g. in the cervical arteries need even more close monitoring due to a higher risk of relapse and vascular complications e.g. aortitis in Cogan's syndrome is indistinguishable from TA. During the course of Cogan's syndrome aortic insufficiency may

develop that may require valve replacement. Reports describe relapse and progression (both metabolic and angiographic) despite immunosuppressive therapy(Figure 3).[62,97-99.]



(a) (b) (c)

Figure 3. Aortitis in Cogan's syndrome. (a) Transverse hybrid PET/CT slice; pathological uptake in the wall of the aortic arch,more intense in the lateral wall and perivascular space adjacent to the truncus pulmonalis. (SUVmax 12, ESR 52 mm/h, CRP 53 mg/L). (b) Follow-up PET/CT showed clearly decreased uptake in the aortic arch after 3 weeks treatment with methyl-Prednisolon i.v. and Prednisolon orally. (SUVmax 4, ESR 11 mm/h, and CRP < 2 mg/L). (c) Second follow-up PET/CT 6 months later (patient was in a stable condition with methotrexate and low-dose prednisone) with again high uptake in the wall of the aortic arch, with higher intensity in the lateral wall and perivascular space adjacent to the truncus pulmonalis. Methotrexate and prednisone were both increased to 20mg/day (SUVmax 13, ESR 24 mm/h, and CRP 14 mg/L).



(a) (b) (c)

Figure 4. From left to right: PET, PET/CT, and CT coronal slices of atherosclerosis of the lower abdominal aorta. The focal and patchy increased FDG uptake representing inflammation and calcifications on CT do not show overlap.

ACR classification criteria of LVV in clinical practices using ^{18}F-FDG-PET/CT

The ACR vasculitis classification criteria were never intended for diagnostic purposes, as pointed out by Hunder and colleagues.[1] Nevertheless, clinicians often use these criteria to diagnose LVV. The ACR 1990 criteria for GCA and TA were based on the diagnosis of advanced cases. The criteria for GCA were developed at a time when involvement of the aorta and its main branches was not a well-recognized feature of GCA, and instead there was a focus on the involvement of cranial arteries of the disease. Already in 1998 it was concluded that the ACR 1990 classification criteria function poorly in the diagnosis of the specific vasculitides. Patients who do not have a vasculitis syndrome may meet very well the ACR criteria, and on the other hand patients who have a specific type of vasculitis may meet criteria for more than one of the vasculitides as specified by the ACR criteria.[100]

A retrospective review of 75 patients with TA and 69 patients with GCA (as defined by the ACR 1990 criteria) compared the signs and symptoms of disease. Patients with GCA had a greater prevalence of jaw claudication (GCA 33%, TA 5%), blurred vision (GCA 29%, TA 8%), diplopia (GCA 9%, TA 0%), and blindness (GCA 14%, TA 0%). The perception of clinicians that the widely recognized classic manifestations are distinct for GCA and TA may have led to bias in history taking, physical examination, and selection of diagnostic studies. This bias might have impaired the recognition of similarities between GCA and TA.[20]

The strict implementation of the ACR criteria in combination with ^{18}F-FDG PET/CT may create a significant source of confusion in the statistics and a significant bias in how the data are gathered in the classification of LVV. This is e.g. illustrated as patients with isolated and intense pathologic ^{18}F-FDG uptake in the vertebral arteries and with neurologic symptoms were diagnosed TA in one case report and as GCA in another, given an age of more or less than 50 years at the onset of disease.[33, 34] It is also puzzling that patients with a homogeneous pattern of increased ^{18}F-FDG uptake in the aorta and its main branches and no arterial wall abnormalities on the corresponding CT slices, are diagnosed as either TA or GCA, with only their age (≤ or ≥ 50 years) as the discriminating parameter.[54, 55, 58, 60, 101-103] TA is reported to be potentially life-threating, reflected in high mortality rates related to arterial stenoses, occlusions, and aortic aneurysms. Notwithstanding, complicated courses of GCA (mean age 66 years) were reported, with persistent inflammatory markers, arterial stenoses and aortic aneurysms despite immunosuppressive therapy, and ^{18}F-FDG PET showing signs of active vasculitis.[88]

To further describe the confusion that ^{18}F-FDG PET/CT results may create in LVV classification; patients older than 50 years with a homogeneous pattern of increased ^{18}F-FDG uptake in the wall of the aorta and its main branches were erroneously reported as having TA instead of GCA.[54,58,104,105]

Conclusions and Future Perspectives

This review illustrates the usefulness of ^{18}F-FDG PET/CT in the heterogeneity of the large vessel vasculitides. In patients with a clinical suspicion for LVV, ^{18}F-FDG PET/CT is able to diagnose LVV especially at the early onset of disease. In contrast to the ACR 1990 criteria for vasculitis, based on late LVV effects like arterial stenosis and/or occlusion, ^{18}F-FDG-PET/CT sheds new light on the classification of GCA and TA, and strenghtens the notion that GCA and TA are more likely to be different expressions of a common histopathological entity. ^{18}F-FDG PET/CT is a powerful metabolic imaging tool that may help to improve the current classification system, based on the intensity of the ^{18}F-FDG uptake and its distribution pattern:

- Isolated polymyalgia rheumatica (PMR) with pathologic ^{18}F-FDG uptake in the soft tissue and ligaments (perisynovitis or enthesitis) around the shoulders/hips and other major joints, lumbar/cervical spinous processes, and ischial tuberosities.
- Diffuse and mildly intense ^{18}F-FDG uptake in the wall of the aorta and its main branches and without arteritis temporalis, PMR, or anatomic arterial wall abnormalities
- Diffuse and mildly intense ^{18}F-FDG uptake in the wall of the aorta and its main branches with arteritis temporalis, PMR, or anatomic arterial wall abnormalities
- Intense and focal ^{18}F-FDG uptake in the aortic arch or intense ^{18}F-FDG uptake in isolated arteries.

In our opinion it is redundant to classify patients with a positive ^{18}F-FDG PET/CT for LVV in ≤ 50 years or ≥ 50 years of age.

An unintended problem that arises from the diagnosis of the early onset of LVV with ^{18}F-FDG PET/CT is the longer time period patients will be exposed to the adverse effects of glucocorticoids. Resulting in more pressure on the major need for more specific drugs to induce and maintain remission and to reduce the cumulative adverse effects of long-term glucocorticoid exposure. However, ^{18}F-FDG PET/CT may be useful in the increasing need for therapy monitoring resulting in better treatment planning and possibly reducing long term adverse treatment effects.

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The predictive value of C-reactive protein and erythtrocyte sedimentation rate for ^{18}F-FDG PET/CT outcome in patients with fever and inflammation of unknown origin

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Abstract

Objectives: The objective of this study was to determine the predictive value of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) to a positive ^{18}F-FDG PET/CT result in patients with unexplained prolonged inflammatory parameters and non-specific signs and symptoms like fatigue, malaise, weight loss, anorexia, night sweats or (sub)-febrile body temperatures; i.e. Inflammation of unknown origin (IUO) and fever of unknown origin (FUO)

Methods: Individual data of 498 patients were retrieved from 3 retrospective studies. Receiver-operating-characteristic (ROC) areas-under-the-curve (AUC) were used to assess ^{18}F-FDG PET/CT versus age, CRP and ESR. The discriminative value of age, CRP and ESR related to ^{18}F-FDG PET/CT was examined using the net reclassification improvement (NRI).

Results: A diagnosis was established in 331 patients; ^{18}F-FDG PET/CT had a diagnostic accuracy of 89%. ^{18}F-FDG PET/CT had the highest AUC (0.89, $p < 0.001$). The addition of ^{18}F-FDG PET/CT to a diagnosis prediction model including age, CRP and ESR resulted in a NRI of 42% ($p < 0.001$). In the same model with CRP values below 20 mg/l or ESR values below 20 mm/h the NRI was 64% ($p < 0.001$) and 29% ($p = 0.059$), respectively.
In 30 of 91 patients with CRP < 10 mg/l a diagnosis could be established, only in patients with CRP levels < 5mg/l ^{18}F-FDG PET/CT was 100% true negative.

Conclusion: In patients with FUO or IUO, ^{18}F-FDG PET/CT improved discrimination of patients with possible disabilitating disease. Elevated CRP predicts more reliable a positive ^{18}F-FDG PET/CT than ESR.

Introduction

Patients with unexplained prolonged inflammatory parameters and non-specific signs and symptoms like fatigue, malaise, weight loss, anorexia, night sweats or (sub)-febrile body temperatures after routine diagnostic evaluation, are a common diagnostic dilemma and a worrying condition in daily clinical practice. Inflammation of unknown origin -without fever- (IUO) and fever of unknown origin (FUO) may represent different clinical presentations of the same underlying disease.[1]

This concept was supported in three recent studies.[2, 3, 4]

These studies showed that the diagnostic yield, the distribution in categories of the underlying aetiologies (i.e. infection, non-infectious inflammatory diseases (NIID) and malignancy) and the diagnostic contribution of hybrid ^{18}F-FDG PET(/CT) were quite similar in patients with IUO and FUO. Furthermore, ^{18}F-FDG PET(/CT) had a relatively high negative predictive value for focal diseases and a causal explanation could be correctly identified or excluded in approximately 90% of patients. In addition, ^{18}F-FDG PET(/CT) may speed up the diagnostic process and may avoid further unnecessary, invasive and expensive diagnostic tests or therapeutic trials with steroids or antibiotics.[4, 5]

Nevertheless, concern may be raised about the safety, the radiation burden for the patients and the costs associated with a more widespread use of ^{18}F-FDG PET/CT for diagnosing potential non-oncologic diseases. Assessment of the acute phase reponse by C-reactive protein (CRP) levels is cheap and has been helpful for decades in both indicating and monitoring a large range of diseases, making CRP a relatively sensitive but a non-specific test.[6]

Using CRP levels as a marker of disease severity in combination with the decision to refer for ^{18}F-FDG PET(/CT) may overcome the limitations of both tests. For example in patients with IUO ^{18}F-FDG PET/CT had a high positive predictive value in patients with either a CRP higher than 20 mg/l or an erythrocyte sedimentation rate (ESR) more than 20 mm/h. In addition in these patients with IUO, CRP was the only independent predictor for the outcome of ^{18}F-FDG PET/CT.[3]

However, there is no consensus on the cut-off value for CRP in relation to the diagnostic yield and accuracy of ^{18}F-FDG PET/CT in patients with IUO or FUO.

Therefore, the objective of the study was to refine the limits of CRP/ESR to predict usefulness of ^{18}F-FDG-PET/CT in patients with FUO/IUO and to quantify the additional value of PET/CT to CRP/ESR levels.

Patients and methods

Patients

For this pooled analysis the individual data of 498 patients were derived from the queries of the medical records used for three (multicenter) retrospective studies performed in the Netherlands. The specific in- and exclusion criteria for these studies are described in detail in previous published reports.[2, 3, 7]

In short, 68 patients referred for ^{18}F-FDG PET/CT for the evaluation of FUO were included from Medical Center Leeuwarden; FUO was defined as prolonged fever higher than 38.3 °C (100.9 °F) with no diagnosis after appropriate inpatient or outpatient evaluation.[7]

The second cohort consisted of 290 patients referred for ^{18}F-FDG PET(/CT) with large vessel vasculitis mentioned in the differential diagnosis, with either IUO or FUO characteristics and without a diagnosis after a variety of conventional diagnostic procedures, (Isala Klinieken Zwolle, Medical Center Leeuwarden, University Medical Center Groningen and VU University Medical Center Amsterdam).[2]

The final cohort consisted of 140 patients with IUO referred for ^{18}F-FDG PET/CT (Academic Medical Center, University of Amsterdam and Medical Center Leeuwarden). IUO was defined as prolonged and perplexing inflammation; i.e. either a CRP higher than 20 mg/L or an ESR more than 20 mm/h, body temperatures < 38.3 ºC (100.9 °F) on multiple occasions and without a diagnosis after a variety of conventional diagnostic procedures.[3]

Double inclusion of the same patient was prevented, each patient was included in only one of the three populations.

Ethics statement: According to the Dutch legislation, written informed patient consent and institutional review board (IRB) agreement is not a prerequisite for retrospective data collection. All procedures were performed as part of clinical care.

^{18}F-FDG PET/CT

The imaging protocols used in the above mentioned hospitals were previously described in detail. [2, 3, 7]

Interpretation and analysis of hybrid PET/CT images

The assessment of the PET/CT images at the department of the local nuclear medicine and/or the radiology department resulted in a combined report where both nuclear medicine physician and radiologist had knowledge of the patient's clinical history and results of previous imaging studies.

A positive study was defined as ^{18}F-FDG uptake with an intensity higher than the physiologic bio distribution of the radio pharmaceutical in any anatomical structure, identified by the corresponding CT-slices. A negative study was defined as a PET study with only physiologic ^{18}F-FDG distribution and no pathology on any of the CT images. Indifferent

anatomical abnormalities or suspected for sequelae and without increased ^{18}F-FDG uptake (e.g. liver cysts, a partial vertebral fracture, or lung atelectasis) were included as a negative study. Criteria for true/false positive/negative results are described in Table 2.

Follow-up and final diagnosis

The time point for ^{18}F-FDG PET/CT referral was chosen by the referring physician. The final diagnosis was not based on the ^{18}F-FDG PET/CT results alone and only otherwise confirmed diagnoses were used. Information concerning the final diagnosis and methodology was derived from the hospital information system. This included both invasive and non-invasive procedures, such as biopsy or surgery, serology or cultures (blood, urine, or tissues) or a tangible response to therapy.

Of the multiple CRP and ESR measurements only the value with the shortest interval to the ^{18}F-FDG PET/CT was used for further analysis. Follow-up was obtained for all patients, especially for those with a negative ^{18}F-FDG PET/CT. Only diagnoses obtained within 6 months after the ^{18}F-FDG PET/CT were considered to be related to the PET/CT outcome.

Analysis and Statistics

Data are presented as mean ± standard deviation, unless indicated otherwise. Positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of ^{18}F-FDG PET/CT were calculated. PPV was defined as the proportion of patients with a positive ^{18}F-FDG PET/CT in whom a final diagnosis was made. NPV was defined as the proportion of patients with a negative ^{18}F-FDG PET/CT who had no final diagnosis at 6 month follow-up. Diagnostic accuracy was defined as the proportion of patients with a true positive and true negative ^{18}F-FDG PET/CT.

Differences between groups for continuous data were compared using a t test (two-tailed). Categorical data of Table 1 were compared using the Chi-square test.

Receiver-operating-characteristic (ROC) derived area under the curve (AUC) was used to assess the diagnostic most optimal single method (^{18}F-FDG PET/CT, age, CRP and ESR) for correctly predicting disease: i.e. the highest AUC corresponding with the highest diagnostic potential.

The discriminative value of CRP and ESR in relation to ^{18}F-FDG PET/CT was further examined with the net reclassification improvement (NRI).[8]

In general this index measures the proportion of individuals who are reclassified from one risk stratum (based on estimated risk provided from a first model) to a different risk stratum (based on estimated risk from a different model, or a model that has additional variables compared with the first model). Some of these risk reclassifications would be appropriate (based on subsequent observed events), meaning that some individuals who have events (confirmed diagnosis) are reclassified to higher predicted-risk strata, and some who do not have events (resolving FUO or IUO without treatment) would be reclassified to lower

predicted-risk strata. However, some reclassifications would be incorrect or inappropriate (e.g. by moving cases to lower predicted-risk strata). In general, the net reclassification index indicates how much more frequently appropriate reclassification occurs than inappropriate reclassification with use of the new model.

All statistical analyses were performed with SAS version 9.2 (SAS Institute Inc., NC 27513-2414, USA).

Table 1. Variables related to diagnosis and ^{18}F-FDG PET/CT results.

	No diagnosis (n = 167)	Diagnosis (n = 331)	p-value
Gender (F/M)	82/85	179/152	0.30
Age (range yrs)	55.5 ± 17.4 (17.0 – 92.0)	64.1 ± 13.7 (18.0 – 92.0)	<0.001
CRP (mg/l)	49.1 ± 65.7 (1.0 – 439.0)	85.8 ± 73.5 (1.0 – 550.0)	<0.001
ESR (mm/hr)	43.2 ± 29.9 (1.0 – 140.0)	60.0 ± 27.8 (3.0 – 140.0)	<0.001

Data are presented as mean ± standard deviation (range). Data on ESR were missing in 137 patients (i.e. in 47 patients without a diagnosis and in 90 patients with a diagnosis). F/M: female to male ratio; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate

Results

Patient characteristics

A diagnosis could be established in 331 out of 498 patients. ESR values were not determined for all patients in the three included studies, in 361 patients (72%) ESR values were available. All other parameters were available for all 498 patients. Patients with a diagnosis were older and had higher CRP and ESR values compared with patients without a diagnosis ($p < 0.001$). In 30 of 91 patients with CRP < 10 mg/L a diagnosis could be established. Only in patients with CRP levels < 5mg/L ^{18}F-FDG PET/CT was 100% true negative.

There was no difference in gender between patients with a diagnosis and those without a diagnosis (Table 1). Infection was found in 97 patients, malignancy in 32 patients and non-infectious inflammatory diseases (NIID) in 202 patients.

^{18}F-FDG PET/CT diagnostic characteristics

Using the information obtained at follow-up as reference for the presence of disease, ^{18}F-FDG PET/CT had a PPV of 94% (293/312) and a NPV of 80% (148/186), with a diagnostic accuracy of 89% with corresponding 89% (293/331) sensitivity and 89% (148/167) specificity (Table 2).

ROC analysis

The ROC analysis showed that the AUC for the establishment of disease for ^{18}F-FDG PET/CT (0.89) was significantly higher compared to the AUC for age (0.65), ESR (0.67) and CRP (0.70) (Figure 1). No statistically significant differences in AUC were found between age, ESR and CRP.

NRI for ^{18}F-FDG PET/CT to CRP or ESR

The NRI requires an a priori event risk category and was for the analysis set at a cut-off value of 0.66: 331 out of our case mix of 498 patients (i.e. 66%) eventually had a disease.

The addition of ^{18}F-FDG PET/CT to a model with only ESR caused the AUC of the model to increase from 0.67to 0.91($p < 0.001$). The NRI was approximately 55% ($p < 0.001$).

The addition of ^{18}F-FDG PET/CT to a model with only CRP caused the AUC of the model to increase from 0.70 to 0.92($p < 0.001$). The NRI was approximately 52% ($p < 0.001$).

NRI for ^{18}F-FDG PET/CT to age, CRP and ESR

When ^{18}F-FDG PET/CT was added to a prediction model for disease with age, CRP and ESR the AUC of the model increased from 0.75 to 0.94($p < 0.001$). Table 3 shows that the patient

reclassification after the addition of ^{18}F-FDG PET/CT to the model (that included age, CRP and ESR) had a NRI of 42% ($p < 0.001$).

NRI for ^{18}F-FDG PET/CT in sub-cohorts

To determine the role of ^{18}F-FDG PET/CT in specific sub-populations first patients with CRP values above 20 mg/L and ESR values above 20 mm/h were selected. In 201 out of 258 patients of this sub-cohort a diagnosis could be established (78%). The addition of ^{18}F-FDG PET/CT to this model (i.e. age, CRP and ESR) significantly increased the AUC from 0.63 to 0.93 ($p<0.001$). The NRI in these patients was 67%, with the improvement predominantly related to substantial down-reclassification (i.e. 42 patients) by a negative ^{18}F-FDG PET/CT in the group of patients without a diagnosis.

Using the same model (age, CRP and ESR) but limited to only CRP values below 20 mg/L (n = 103) the addition of ^{18}F-FDG PET/CT resulted in a NRI of 64% ($p < 0.001$). The improvement was mainly based on 28 correct up-reclassifications. However, the addition of ^{18}F-FDG PET/CT to the same model (age, CRP and ESR) in patients with ESR values below 20 mm/h (n = 49), just failed to reach a statistically significant NRI of 29% ($p = 0.059$).

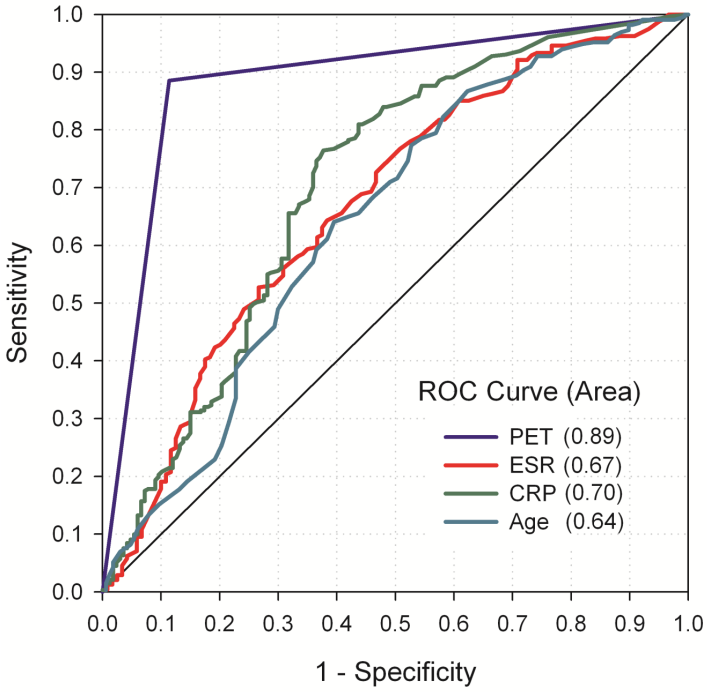

Figure1. The receiver operating characteristic curve (ROC) area under the curve for 18F-FDG PET/CT, ESR, CRP and age for the prediction of disease based on the entire cohort of 498 patients (based on 361 patients for the ESR, due to missing data).

Table 2. ^{18}F-FDG PET/CT in relation to final diagnosis.

		Diagnosis		
		+	-	
^{18}F-FDG PET/CT	+	293	19	312
	-	38	148	186
		331	167	498

Follow-up and final diagnoses were related to the results of the PET/CT images and the predictive value of the ^{18}F-FDG PET/CT was assessed according to the following criteria:

- True negative (TN); a normal ^{18}F-FDG PET/CT with further investigations or clinical follow-up excluding (focal) disease process(es).
- False negative (FN); was defined as a normal ^{18}F-FDG PET/CT in combination with a (focal)disease process subsequently detected by other diagnostic modalities, or when there was a tangible response to a medical treatment.
- True positive (TP); ^{18}F-FDG PET/CT demonstrating a (focal) disease process, confirmed by further investigations, as being the cause of IUO or FUO, or could be related to a tangible response to medical treatment.
- False positive (FP); ^{18}F-FDG PET/CT demonstrating a (focal) disease process that could not be confirmed as being the cause of the IUO or FUO, or could not be related to the absence of response to treatment

Table 3. NRI of ^{18}F-FDG PET/CT added to a model with age, CRP and ESR.

			No diagnosis (n = 120)	Diagnosis (n = 241)
^{18}F-FDG PET/CT	+	Up-classification	7	62
		No change of class	80	166
	-	Down-classification	33	13
NRI		0.42	-0.2167	0.2033

Discussion

In this retrospective multicenter individual patient data meta-analysis of patients with FUO and IUO, ^{18}F-FDG PET/CT had a relatively high diagnostic accuracy (89%), which is mainly a result of 3 factors. An important feature of ^{18}F-FDG is its non-specificity: ^{18}F-FDG shows increased uptake not only in malignant cells, but also in cells involved in infectious and inflammatory processes.[9] Secondly, ^{18}F-FDG PET/CT imaging is able to reveal functional alterations that precede the morphological changes.[10] Thirdly, the integration of anatomical and functional images allows improved interpretation of both abnormal ^{18}F-FDG uptake and suspicious morphological findings.[11]

The 498 patients in this analysis are representative for a diagnostic dilemma in clinical daily practice. Related to the costs of ^{18}F-FDG PET/CT, they represent a highly selected population to refer for a ^{18}F-FDG PET/CT by the departments of rheumatology and internal medicine. The patients comprised of 3 previously described patient populations, i.e. FUO, IUO and patients with large vessel vasculitis (LVV) mentioned in the differential diagnosis, with either IUO or FUO characteristics. At first impression these 3 groups appear to represent different patient populations. However, patient populations defined as either IUO or FUO already have an inherent lack of uniformity due to the large heterogeneity of reported populations and diagnostic approaches. Differences in clinical reasoning and judgement will remain to exist in the decision after which preceding -and negative- diagnostic procedures a patient is referred for ^{18}F-FDG PET/CT. Furthermore, for the 290 patients with LVV mentioned in their differential diagnosis, the diagnostic yield, the distribution in categories of the underlying aetiologies (i.e. infection, NIID and malignancy) and the diagnostic contribution of hybrid ^{18}F-FDG PET(/CT) were quite similar to IUO and FUO. Therefore, the common denominator of these 3 populations was a persisting clinical suspicion of disease based on non-specific non-localizing signs and symptoms, increased inflammatory parameters and a variety of conventional diagnostic procedures that did not lead to a diagnosis. Inclusion of the seemingly 'different' patient populations appears justified by the absence of heterogeneity of the diagnostic contribution of ^{18}F-FDG PET/CT across the 3 included studies. In addition, the non-specific clinical signs and symptoms in the 3 included patient populations, were not helpful in identifying the underlying cause.[7]

This is in line with the observation that in the majority of patients with FUO, clinical signs and symptoms or potential diagnostic cues (PDC) do not lead to the proper diagnosis.[12]

In humans, plasma levels of CRP may rise rapidly (within 6-10 hours) and markedly (as much as 1000-fold or more) after an acute inflammatory stimulus, largely reflecting increased synthesis by hepatocytes.[6] CRP plasma levels reduce rapidly towards normal values as the inflammatory response subsides.[13]

On the other hand, ESR results may be spuriously elevated by e.g. anemia, age, female gender, erythrocyte morphology, renal dysfunction, obesity, a variety of medications or technical

factors like tilting of the test tube. In addition, various intrinsic factors like polycytemia, microcytosis or fibrinogen consumption lead to a decreased ESR.[14]

Our results seem to confirm that CRP serum concentrations are not affected by any other factor than the presence and the degree of inflammation. Although the percentage of established diagnoses increased with higher CRP levels, a clinical relevant cut-off value for CRP that more accurately established a diagnosis with ^{18}F-FDG PET/CT in patients with IUO or FUO could not be defined. This is reflected by the NRI that remained high, as much as 64%, in patients with CRP levels below 20 mg/l. In contrast, the NRI in patients with ESR levels below 20 mm/h was statistically not significant.

Notwithstanding, using higher cut-off levels for CRP or ESR did not decrease the number of true negative ^{18}F-FDG PET/CT results. This observation is corroborated by a recent study by Lensen et al. that included 88 patients aged 50 years or older with non-specific symptoms and an ESR of more than 50 mm/h for which routine evaluation revealed no diagnosis. The percentage true negative ^{18}F-FDG PET/CT studies of 33% was quite congruent to the 30% true negative ^{18}F-FDG PET/CT studies in our patient population. And not surprisingly, parameters like the proportion of patients with disease, the contribution of ^{18}F-FDG PET/CT to the diagnosis and the distribution of diseases in categories (infection, NIID and malignancy) were similar to FUO and IUO patient populations.[4]

The relatively high rate of patients (n=148) with increased inflammatory parameters and a true negative ^{18}F-FDG PET/CT in this analysis and the study by Lensen et al. may be partially explained by a state of low-grade systemic inflammation.[15] Or possibly by self-limiting conditions, with apparently a beneficial and controlled inflammatory or immune response.[16]

The ^{18}F-FDG PET/CT results were obtained using pattern recognition, without quantification (i.e. standardized uptake value (SUV)). This might be regarded as a limitation hampering extrapolation of the obtained results. Albeit, ^{18}F-FDG PET/CT was considered helpful through pattern recognition of more common diseases e.g. large vessel vasculitis or polymyalgia rheumatica.[17, 18]

Also in rare aetiologies like Cogan's syndrome or syphilitic aortitis of the ascending aorta, pattern recognition without quantification contributed to the diagnosis.[19, 20]

The limited negative predictive value of ^{18}F-FDG PET(/CT) in systemic/(non-focal) diseases (e.g. leukaemia or early stage multiple myeloma) makes it important to realize that systemic diseases need to be excluded with high accuracy.[2, 3, 7]

The inclusion of the 140 patients with IUO referred for ^{18}F-FDG-PET/CT with either a CRP higher than 20 mg/L or an ESR more than 20 mm/h, may have caused selection bias.[3]

Consequently the results found in the subgroup analyses may have been driven by this selection. Indeed in this cohort 86% (120/140) of patients had a CRP higher than 20 mg/L compared to 67% (239/358) in the remainder of the study population ($p < 0.001$).

All ^{18}F-FDG-PET/CT scans in this analysis were performed as daily clinical routine in the local setting of each participating hospital, which indicates a certain validity.

Although the subgroup analyses indicate a role for ^{18}F-FDG-PET/CT, the extrapolation of the outcome of the subgroup analyses should be primarily seen in the context of our selected population. Our results need to be confirmed in well designed prospective studies.

Conclusions

In patients with non-localizing or non-specific signs and symptoms like (sub-)febrile body temperature, weight loss, malaise and prolonged increased inflammatory parameters and without a diagnosis after routine diagnostic evaluation, i.e. with IUO or FUO, ^{18}F-FDG PET/CT was helpful in recognizing or excluding disease in almost 90% of patients. ^{18}F-FDG PET/CT is therefore of significant additional value in this population with a diagnostic dilemma. Elevated CRP levels more truly reflected the presence and the degree of inflammation and CRP levels < 20 mg/L were a more reliable predictor of a positive ^{18}F-FDG PET/CT than ESR levels < 20 mm/h. In 30 of 91 patients with CRP < 10 mg/L a diagnosis could be established, only in patients with CRP levels < 5 mg/L ^{18}F-FDG PET/CT was 100% true negative.

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^{18}F-FDG PET/CT in inflammation of unknown origin: a cost-effectiveness pilot-study

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Abstract

Objectives: Patients with increased inflammatory parameters, non-specific signs and symptoms without fever and without a diagnosis after a variety of diagnostic procedures are a diagnostic dilemma and is referred to as inflammation of unknown origin (IUO). The objective of this pilot study was to compare the cost-effectiveness of a diagnostic work-up/strategy with and without ^{18}F-FDG PET/CT in patients with IUO using a published data set as a reference.

Methods: 46 IUO patients without ^{18}F-FDG PET/CT (Group A) and 46 IUO patients referred for ^{18}F-FDG PET/CT (Group B) were selected. IUO was defined as the combination of non-specific signs and symptoms and a prolonged erythrocyte sedimentation rate (ESR): ESR ≥ age/2 for males or ESR ≥ (age + 10)/2 in mm/h for female patients, and/or C-reactive protein (CRP) ≥ 15 mg/l. The costs for all tests and procedures, the number of hospitalization days, in each patient to reach a diagnosis, were calculated with current Dutch tariffs.

Results: In Group A a diagnosis was reached in 14/46 patients. The mean costs for all the diagnostic procedures were €2,051 per patient. Adding the costs of hospitalization increased the mean amount to €12,614 per patient. In Group B a diagnosis could be made in 32/46 patients. The mean costs for all diagnostic procedures were €1,821 per patient, significantly lower compared to Group A ($p<0.0002$). Adding the costs of hospitalization increased the mean amount to €5,298 per patient.

Conclusion: In IUO ^{18}F-FDG PET/CT has the potential to become a cost-effective routine imaging technique indicating the direction for further diagnostic decisions and thereby avoiding unnecessary, invasive, and expensive diagnostic investigations and possibly reducing the duration of hospitalization. However a prospective multi-centre “bottom-up micro-costing” cost-effectiveness study is warranted before these preliminary data can be extrapolated to clinical practice.

Introduction

Inflammation of unknown origin (IUO) is defined by an increased C-reactive protein (CRP) level or erythrocyte sedimentation rate (ESR) in patients presenting with non-specific signs and symptoms like fatigue, malaise, weight loss, anorexia, sub-febrile temperatures or night sweats and without a diagnosis after conventional diagnostic procedures. Just as in fever of unknown origin (FUO), the aetiology of IUO may vary from a self-limiting condition to occult malignancy.[1,2]

The literature on IUO is scarce and does not yet allow a uniform diagnostic strategy. In search for the origin of IUO, patients may undergo extensive and expensive investigations that may not only be inappropriate but also expose patients to the risks of these investigational procedures, e.g. lumbar or bone marrow biopsy and gastroduodenal or colonic endoscopy. The non-specificity of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and the synergy of integrating functional and anatomical images with hybrid PET/CT may offer substantial benefit in the diagnostic work-up of patients with IUO. Furthermore, metabolic PET imaging with ^{18}F-FDG is able to reveal functional alterations that precede morphological changes.[3]

Four recent studies showed that the diagnostic yield, the character of the underlying aetiologies (i.e. infection, non-infectious inflammatory diseases (NIID) and malignancy) and the diagnostic contribution of hybrid ^{18}F-FDG PET/CT were quite similar in patients with IUO and FUO.[4,5,6,7] ^{18}F-FDG PET/CT showed a high negative predictive value for focal diseases and based on ^{18}F-FDG PET/CT a causal explanation could be correctly identified or excluded in approximately 90% of patients. ^{18}F-FDG PET/CT has the potential to speed up the diagnostic process and may avoid further unnecessary, invasive and expensive diagnostic tests or inappropriate therapeutic trials with steroids or antibiotics.[5,8]

Despite the Dutch tariff of €1,148, the inclusion of ^{18}F-FDG PET/CT could therefore be cost-effective. However no data on cost-effectiveness of ^{18}F-FDG PET/CT in this population is available.

To assess whether there is an incentive for a prospective multi-centre study, the objective of this pilot study was to compare the cost-effectiveness of a diagnostic work-up/strategy with and without ^{18}F-FDG PET/CT in patients with IUO using a published data set as a reference.[9] In addition an estimation could be made to what extent the introduction of ^{18}F-FDG PET/CT changed the diagnostic work-up of patients with IUO.

Patients and methods

Patient selection

Group A: To reflect a semi-recent clinical situation without the use ^{18}F-FDG PET/CT, the data set from a retrospective study from Perrin et al. was used.[9]
In this study 46 patients were retrieved from the medical files of the Strasbourg University Hospital (France) in the period between April 1992 and June 1999. Inclusion criteria were prolonged ESR ≥ age/2 for males or ESR ≥ (age + 10)/2 in mm/h for female patients, and/or CRP ≥ 15 mg/L, and with non-specific signs and symptoms. The exclusion criteria were; (sub-)febrile temperature without increased inflammatory parameters, regression of the inflammatory syndrome during evaluation, incomplete medical files, and patients that after initial diagnostic workup refused complementary investigations.[9]

Group B: This group consisted of IUO patients referred for ^{18}F-FDG PET/CT. To ensure adequate comparability between the two patient groups (Group A and Group B) the same inclusion and exclusion criteria of Perrin et al were used. Data of age and gender matched 46 patients with IUO and who were referred for ^{18}F-FDG PET/CT, were extracted from the digital hospital information system of the Medical Center Leeuwarden (MCL). The query in the databases was limited to the period between January 2013 and November 2013.

Methodology of cost analysis

In this retrospective analysis the cost effectiveness of ^{18}F-FDG PET/CT in patients with IUO was estimated from a 'hospital perspective', in the setting of a relatively large teaching hospital. Indirect costs components from a 'healthcare providers perspective' that concerned overheads (e.g. general expenses, administration, energy, maintenance, personnel costs) were not included in the analysis. Use of medications were explicitly excluded from this study, because they are considered to be highly dependent on the disease and treatment strategy under consideration and often explain total cost differences between alternative treatments in economic evaluations.
Direct cost components were all the diagnostic tests and procedures, and the number of hospitalization days, performed in each patient in order to reach a diagnosis. For Group A the data set of diagnostic procedures, without the use of ^{18}F-FDG PET/CT, and the number of hospitalization days were used as described by Perrin et al. To the best of our knowledge, the only study that describes all diagnostic procedures and hospitalization days needed for the evaluation of patients with IUO, without the use of either ^{18}F-FDG PET or ^{18}F-FDG PET/CT.
To prevent a potential bias of different costing methodologies, the theoretical costs were not calculated using the unit costs of diagnostic procedures of both hospitals. Instead, the 2014 tariffs of the Dutch Healthcare authority were used (Nederlandse Zorgauthoriteit (NZa)). (http://www.nza.nl/regelgeving/tarieven/ TB/CU-7078-01 of 1 January 2014), together with

the reference prices of the most recent update of the Dutch Manual for costing in economic evaluations.[10]
Costs were based on 2014 cost data and when necessary costs were adjusted to 2014 using the general price index from the Dutch Central Bureau of Statistics (http://www.statline.nl). Total directs costs of the two diagnostic strategies (with and without 18F-FDG PET/CT) were determined by multiplying the total number of each diagnostic procedure by the corresponding current Dutch tariff.
Concerning laboratory analyses for both groups the current tariff of €56 for a total blood examination (hematology, chemistry) and urinalysis was appointed to both groups. As for Group A no specification was given for standard radiographies, CT, US and MRI investigations (e.g. thoracic or abdominal) the mean current tariff was used. Also for endoscopies (bronchial, gastroduodenal or colonic) the mean current tariff was used.
Additional costs in Group B due to diagnostic procedures instigated by false positive 18F-FDG PET/CT results were included in the analysis.
Statistical analyses were conducted with SAS version 9.2 (SAS Institute Inc., NC 27513-2414, USA).

^{18}F-FDG PET/CT

The time point for requesting the ^{18}F-FDG PET/CT was chosen by the referring physician. The imaging protocol, interpretation and analysis of hybrid PET/CT images were previously described in detail.[6, 11]

Follow-up and final diagnosis

The final diagnosis was not based on the ^{18}F-FDG PET/CT results alone, only sufficiently validated diagnoses were used. Information concerning the final diagnosis and methodology was derived from the hospital information system. This included both invasive and non-invasive procedures, such as biopsy or surgery, serology or cultures (blood, urine, or tissues) or a tangible response to therapy. Follow-up was obtained for all patients. Only diagnoses obtained within 4 months after the ^{18}F-FDG-PET/CT were considered to be related to the PET/CT-result.
According to Dutch legislation, retrospective data collection does not require approval of an ethical committee. All procedures were performed as part of clinical care, nonetheless for the current analysis the data were anonymized.

Results

Patient characteristics

Group A: Initially 376 files could be extracted from the hospital information system in Strasbourg, 46 patients were considered eligible.
Group B: From the 1880 ^{18}F-FDG PET/CT scans performed in Leeuwarden between January 2013 and November 2013, 385 were performed for non-oncologic reasons and were considered potentially eligible. The hospital information system was searched backwards in time. After 46 eligible patients (using the same inclusion and exclusion criteria described by Perrin et al.) the search could be stopped. Patient characteristics are listed in table 1.

^{18}F-FDG PET/CT effectiveness

Group A: Without ^{18}F-FDG PET/CT a diagnosis was reached in 14/46 patients (infection in 2 patients, and non-infectious inflammatory disease (NIID) in 12 patients). In 13 patients the inflammatory syndrome resolved spontaneously, in 12 patients the inflammatory syndrome persisted. Seven patients were lost to follow up. No patients died during 12 months follow up.
Group B: In IUO patients with ^{18}F-FDG PET/CT available a diagnosis could be made in 32/46 patients (infection in 6 patients, NIID 23 patients and malignancy in 3 patients). In 14 patients a diagnosis was not reached during follow up; the inflammatory syndrome subsided in 11 patients and persisted in three (obese) patients. Of the patients with a diagnosis, two died during six months follow up.

Number of diagnostic procedures and costs

The results are summarized in table 2. In the patient group without ^{18}F-FDG PET/CT an overall higher number of imaging procedures, invasive and non-invasive diagnostic procedure was performed.
Group A: Using current tariffs the estimated mean costs for all the diagnostic procedures were €2,051 per patient without ^{18}F-FDG PET/CT. Adding the costs of the mean number of 21 hospitalization days per patient, increased the mean costs to €12,614 per patient.
Group B: With the use of ^{18}F-FDG PET/CT the estimated mean costs for all diagnostic procedures were €1,821 per patient. The mean number of hospitalization days was 6.9 (median 1,5 days, range 0 - 32 days). Adding the costs of 6.9 hospitalization days per patient increased the mean costs to €5,298 per patient.
The costs per patient spent in Group B, excluding the costs of ^{18}F-FDG PET/CT, (mean €673; range €90 - €1,856) were significantly lower compared to the mean costs spent per patient in Group A. Although the addition of ^{18}F-FDG PET/CT to the diagnostic process in Group B

increased the mean costs per patient to €1,821 (range €1,238 - €3,004) the costs remained significantly lower compared to the mean costs spent per patient in Group A.
The total costs for patients in Group B included €1,120 due to diagnostic procedures that followed 5 false positive ^{18}F-FDG PET/CT results. In 4 patients with a positive ^{18}F-FDG PET/CT guided diagnosis, collateral false-positive ^{18}F-FDG PET/CT results led to negative diagnostic procedures (1 colonoscopy, 1 gastroscopy, 1 thyroid biopsy and 1 ultrasonography of the breast). In one patient without a diagnosis, a sigmoidoscopy guided by ^{18}F-FDG PET/CT was without result.

Table 1 Patient characteristics

	Group A	Group B
Male/Female	15/31	17/29
Age (years)	Range 21-90 (mean 67)	Range 19-83 (mean 64)
CRP (mg/l)	Range 10-277 (mean 73)	Range 12-268 (mean 78)
ESR (mm/h)	Range 28-140 (mean 85)	Range 25 - >100 (mean 78) Not available in 21 pts
Hospitalization days	Range 5-47 (mean 21)	Range 0-32 (mean 7)

Table 2. The number of diagnostic procedures and costs for both group A and B.

		Group A without ^{18}F-FDG PET/CT		Group B with ^{18}F-FDG PET/CT	
Procedures	**costs per procedure**	**number of procedures**	**euro**	**number of procedures**	**euro**
laboratory (complete blood count, routine blood chemistry, urinalysis)	56	46	€2.576	46	€2.576
bacterial cultures	34	115	€3.910	36	€1.224
tuberculine tests	25	42	€1.050	3	€75
viral serology tests	93	46	€4.278	14	€1.302
immunological tests	258	46	€11.868	25	€6.450
tumour marker tests	30	78	€2.340	0	€0
standard radiographies	42	112	€4.704	52	€2.340
ultrasound investigations	101	99	€9.999	36	€3.636
CT scans	187	39	€7.293	13	€2.431
MRI	272	0	€0	4	€1.088
endoscopies	275	52	€14.300	17	€4.675
biopsies (& histology)	195	75	€14.625	16	€3.120
laparotomies	7000	2	€14.000	0	€0
inter-disciplinary consultancies	54	63	€3.402	38	€2.052
^{18}F-FDG PET/CT	1148	0	€0	46	€52.808
hospitalization days	457	966	€441.462	318	€145.326
Total		**1781**	**€535.807**	**664**	**€229.103**

Discussion

The use of ^{18}F-FDG PET/CT in the diagnostic work-up of IUO in our hospital appears not to increase costs. Despite the tariff of €1,148 the inclusion of ^{18}F-FDG PET/CT seems to be cost-effective due to the decreased number of both invasive and non-invasive procedures.

Since the introduction of the PET/CT camera in 2005 in our hospital the referring physicians apparently went through 'a learning curve'. This is e.g. expressed in the absence of tumour marker determination in Group B. Referring physicians are well aware that in case of abnormal ^{18}F-FDG PET/CT results, the results not only guide the best biopsy localization but provide an optimal staging procedure as well. This is not only reflected in the relatively low number of biopsies and endoscopies in Group B, but as well in the observation that 6/15 biopsies were performed after the ^{18}F-FDG PET/CT. In Group B all tests with low costs and high accessibility were done before ^{18}F-FDG PET/CT, the larger proportion (55%) of the more expensive and/or invasive procedures (e.g. endoscopies and biopsies) were performed after the ^{18}F-FDG PET/CT investigation.

The role of 'blind' biopsies in IUO or FUO is a matter of discussion. This is illustrated in a study from 2009 which showed that the diagnostic yield of a 'blind' bone marrow biopsy (BMB) in FUO was modest, even after careful patient preselection. Of 280 patients with FUO, the yield of BMB in 130/280 patients after a routine diagnostic work up was 23%.[12]

The concept that ^{18}F-FDG PET imaging is able to reveal functional alterations that precede morphological changes, is supported by the observation that a major part of the NIID diagnoses constituted 19 patients diagnosed and treated as large vessel vasculitis and/or polymyalgia rheumatica. Therefore, the question is raised what the ^{18}F-FDG PET/CT results would have been in the 12 patients in Group A with an unexplained persisting inflammatory syndrome. In Group B the inflammatory syndrome subsided in 11 patients, in these cases of self-limiting conditions there was apparently a beneficial and controlled inflammatory or immune response.[2]

In 3 (obese) patients with a persisting inflammatory syndrome the question remains open whether this reflects a state of low-grade systemic inflammation.[13] Adipose tissue is an active endocrine organ that releases a variety of hormones and cytokines, such as interleukin-6, that contribute to CRP elevation.[14]

Literature on IUO and the role of ^{18}F-FDG PET/CT in IUO is scarce compared to FUO. A PubMed literature search for ^{18}F-FDG, PET, PET/CT, IUO, unexplained, inflammatory, inflammation,elevated CRP or ESR delivered 4 studies.[1, 5, 6, 7]

A PubMed literature search for "^{18}F-FDG PET/CT, FUO and febris eci" yielded 76 results, of which more than 30 were reviews or meta-analyses. Only 1 publication dedicated to cost-effectivenes could be found; a Spanish study that included 20 patients with FUO. The mean costs per patient of the diagnostic procedures preceding ^{18}F-FDG PET/CT were €11,167, including an average of 11 days of hospitalization and outpatient controls.[15] These costs are in line with our retrospectively calculated costs using the data of Perrin et al. In addition

the authors calculated that if ^{18}F-FDG PET/CT had been performed earlier in the diagnostic process (before endoscopies and other invasive procedures), €5,471 per patient would have been saved on diagnostic tests and hospitalization days.

Defining the cost-effectiveness of ^{18}F-FDG PET/CT in the diagnosis of IUO and FUO is a relevant issue. The major problem for cost-effectiveness calculations is the variety in number and the heterogenity of the diagnostic procedures needed prior to the moment that the patient fulfills the criteria of either IUO or FUO. After the investment of the considerable extra costs of ^{18}F-FDG PET/CT, in many cases further invasive or non-invasive diagnostic procedures with high specificity are needed to confirm or establish a diagnosis. Consequently, the costs of ^{18}F-FDG PET/CT may be further increased by the risk of false positive results, related to the high sensitivity and the non-specificity of the tracer, and the subsequent unnecessary diagnostic procedures. The extra costs of €1,120 were 13% of the total costs of all diagnostic procedures in Group B.

In the context of the heterogeneity of IUO and FUO patient populations, a distinction can be made between the very detailed "micro-costing" and the less precise "gross-costing" method.[16] Depending on their relevance for the cost-benefit evaluation, the diagnostic procedures may be measured either for individual patients ("bottom up approach") or for average patients ("top down approach").[17]

Furthermore, the evaluation of the diagnostic procedures may be based on existing unit costs (e.g., reference prices) or the local unit cost calculations.

"Bottom-up micro-costing" with the application of a standardized costing methodology may enable the most meaningful comparison of actual cost differences between health care services, and allows for the best identification of costs directly used for a patient and for insight in patient subgroups. However, this methodology is lengthy and expensive and has not been widely used in economic health care evaluations.[18] Furthermore the question is raised whether the heterogeneity of the patients and the broad range in possible diagnostic procedures will not undermine the accuracy of "bottom-up micro-costing".

This comparative costs analysis has some limitations. The study by Perrin had no intention to define or calculate the cost-efficacy of the diagnostic procedures used. The main goal was to describe the long-term follow-up and the prognosis of patients that were hospitalized (many of which on multiple occasions) for an inflammatory syndrome without a causal diagnosis. One may assume that the longer duration of hospitalization was needed to perform all the necessary diagnostic procedures. Evaluation on an outpatient basis was apparently limited and most likely a reflection of clinical practice of that era. Current clinical practise shows an ongoing trend in the decrease of hospitalization days. This is illustrated for the Netherlands by the fact that the mean number of hospitalization days per patient was 6.3 in 2005 and decreased to a mean of 4.8 days per patient in 2012. (http://www.nvz-ziekenhuizen.nl/_library/11481). In the study by Perrin patients were selected and recruited by internal medicine physicians. In our study the same in- and exclusion criteria were used, but applied to only those patients who were referred for ^{18}F-FDG PET/CT. This difference

may have caused a bias in patient selection. Both patient populations were selected in different time periods. Since the last patient of Group A was included in 1999, health care has incorporated ongoing progression and innovations in medical technology, e.g. laparotomies were more expensive primarily driven by a larger amount of hospitalization days compared to the nowadays used minimal invasive laparascopic procedures.[19] The fact that indirect cost components as well as medication were excluded represents a further limitation of this analysis.

In our opinion the results of this pilot study warrant a prospective multi-centre "bottom-up micro-costing" cost-effectiveness study for ^{18}F-FDG PET/CT in patients with IUO. A standardized protocol will have some difficulties to develop. The initial diagnostic procedures will continue to be based on the cues presented by a full physical examination, and a thorough interview - including family history, intoxication clues and travel history - with particular attention for exposure to animals, work environment and recent contact with persons exhibiting similar symptoms. Inevitably, invasive procedures will be performed directed by localizing complaints or cues.[20]

Patients should be included for ^{18}F-FDG PET/CT based on a uniform definition of an appropriate minimal diagnostic workup. This workup should contain at least the following routine diagnostic procedures: extensive blood and urine investigation, including ANA/ANCA, bacterial cultures, a HIV, EBV and CMV test, plus extra serology based on local epidemiology, a tuberculin skin test, ECG, chest radiography and abdominal ultrasound. In addition patients should be included before invasive diagnostic procedures such as lymph node, liver, bone marrow or temporal artery biopsy, endoscopies (of stomach, colon, bronchial with their respective biopsies) and trans-oesophageal ultrasonography.

Conclusions

In patients with IUO ^{18}F-FDG PET/CT has the potential to become a cost-effective routine imaging technique indicating the direction for further diagnostic decisions and thereby avoiding unnecessary, invasive, and expensive diagnostic investigations. In addition these advantages could therefore possibly reduce the duration of hospitalization.

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Summary, general discussion, future perspective and conclusions

Summary

Patients with fever of unknown origin (FUO) and inflammation of unknown origin (IUO) are a diagnostic dilemma. In **chapter 1**, diagnostic approaches in investigations, both invasive or non-invasive, and imaging techniques are reviewed. The advantages and disadvantages of fundoscopy, Doppler imaging of the lower extremities, and invasive investigations such as bone marrow aspiration, percutaneous liver biopsy, skin and muscle biopsy, temporal artery biopsy, bronchoalveolar lavage and exploratory laparotomy are discussed. The relatively high specificity but limited sensitivity of these investigations hampers the generalization of these diagnostic approaches in FUO and IUO. The role of radiological techniques i.e. radiography, ultrasonography (US), including echocardiography, computed tomography (CT), magnetic resonance imaging (MRI) is reviewed. In general radiological techniques show anatomical changes. Consequently, malignant, infectious, and inflammatory foci cannot be detected at an early phase because substantial anatomical changes appear relatively late. After surgery or other therapeutic interventions like radiotherapy, discrimination of active malignant, infectious or inflammatory lesions from residual anatomical changes is often difficult. Compared to radiological techniques, scintigraphic imaging, by nature, is able to detect these processes in an earlier phase. The planar images of scintigraphic methods had the lack of providing anatomic detail and contrast between pathology and surrounding tissue. With the introduction of three dimensional single photon computerized tomography (SPECT) and more recently with the introduction of hybrid SPECT/CT, these shortcomings were alleviated. However, the main disadvantage of conventional radiopharmaceuticals remains; each (apart from ^{67}Ga), covers only a part of the spectrum of possible diagnoses in the broad setting of FUO and IUO. The clinical application of ^{67}Ga is limited though, due to unfavourable imaging characteristics, delayed imaging, and high radiation burden to the patient.

The generally accepted patient preparation protocols for ^{18}F-FDG PET/(CT) involve fasting for approximately 6 hours, with the purpose to produce lower levels of serum glucose and insulin, enabling optimal uptake of ^{18}F-FDG in pathology characterized by increased glycolysis. However, patients show variable myocardial ^{18}F-FDG uptake, which may result in difficult interpretation of ^{18}F-FDG uptake in the left ventricle and potentially masks myocardial pathology or focal lung disease adjacent to the left ventricle.
In **chapter 2** a retrospective study is described looking at the effect of a fat-allowed, carbohydrate-restricted diet (starting the day before the ^{18}F-FDG administration) on myocardial ^{18}F-FDG uptake comparing daily clinical routine between two hospitals, i.e. 100 patients with and 100 patients without such a diet preparation. The results justify the conclusion that a fat-allowed, carbohydrate-restricted diet suppressed myocardial ^{18}F-FDG uptake satisfactorily.

Chapter 3 describes a retrospective study assessing the utility of ^{18}F-FDG PET/CT in identifying the aetiology of FUO in 68 patients. ^{18}F-FDG PET/CT was considered helpful when abnormal results allowed for an accurate diagnosis, based on histopathology, micro biologic assays, or follow-up (clinical and/or by imaging).
Overall 56% of the ^{18}F-FDG PET/CT studies contributed in the identification of the aetiology in patients with FUO. In 6 of 27 patients with negative ^{18}F FDG PET/CT results, a systemic disease (without focal manifestation) was the cause for FUO. In the remaining 21 patients, fever and other signs subsided during follow-up. ^{18}F-FDG PET/CT had a high positive predictive value (93%) and high negative predictive value (100%) for focal aetiologies. ^{18}F-FDG PET/CT was not helpful in patients with fever and normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). In conclusion, when systemic diseases are excluded by other diagnostic tests, a negative ^{18}F-FDG PET/CT (after negative first-level diagnostic tests, such as routine laboratory tests, serology, urine and blood cultures) may avoid the need for further invasive and expensive investigations or therapeutic trials with steroids or antibiotics.

In **chapter 4** the results of a multicentre retrospective study are described. The goal of this study was to evaluate the contribution of ^{18}F-FDG PET/CT in the diagnosis of 140 patients with inflammation of unknown origin (IUO). IUO was defined as prolonged and perplexing inflammation with repeated CRP values more than 20 mg/L or ESR more than 20 mm/h, with clinical complaints and body temperature not exceeding 38.3˚C (100.9˚F), and without a diagnosis after conventional diagnostic procedures. In 104 patients (73%), a final diagnosis could be established. ^{18}F-FDG PET/CT was true positive in 95 patients, true negative in 30 patients (i.e. self-limiting conditions), false positive in 6 patients, and false negative in 9 patients (predominantly systemic diseases). The diagnostic yield, the distribution in categories of the underlying aetiologies (i.e. infection, non-infectious inflammatory diseases (NIID) and malignancy) and the diagnostic contribution of hybrid ^{18}F-FDG PET/CT was quite similar to the use of this technique in patients with FUO.
^{18}F-FDG PET/CT correctly identified or excluded a cause for the syndrome in approximately 90% of patients with IUO. A negative ^{18}F-FDG PET/CT was indicative for a self-limiting condition only after systemic diseases were excluded by other diagnostic tests.

Chapter 5 consists of four clinical cases illustrating the role of ^{18}F-FDG PET/CT in IUO or FUO.

Case 1 reports of a 79-year-old man referred for recurrent episodes of fever and chills. Six years earlier an aortic bifurcation graft had been implanted. Blood examination showed elevated ESR and CRP levels. A CT scan showed no signs of graft infection. When blood cultures revealed multiple enteric bacteria, ^{18}F-FDG PET/CT was performed demonstrating ring-shaped pathological uptake only at the proximal anastomosis. Surgical intervention revealed an infected graft combined with a 1-cm defect/ulcer in the distal part of the duodenum.

Case 2 reports the case of an 84-year-old woman with FUO, admitted to the hospital with a variety of nonspecific complaints as well as mental deterioration. The latter was initially attributed to her known Alzheimer disease. After various investigations a whole-body ^{18}F-FDG PET/CT study revealed a metabolically active pituitary mass, confirmed by brain magnetic resonance imaging (MRI). Subsequent results of functional endocrinological tests were compatible with a prolactinoma. This case report highlights the usefulness of including the brain in whole-body ^{18}F-FDG PET/CT acquisitions in case of FUO.

Case 3 is a report of a 60-year-old woman admitted to the hospital with a 4-month history of excessive fatigue, coughing, anorexia and weight loss, night sweats, and atypical chest pain. She also experienced short periods of fever, head-aches and ear pain and hearing loss for over the last month, mainly on the left side, and felt sometimes dizzy. No complaints of blurred vision or other eye problems were noted. CRP and ESR levels were increased. A test for anti-neutrophil cytoplasmic antibody (ANCA) was myeloperoxidase positive with p-ANCA specificity. Ultrasonography of the temporal arteries showed no abnormalities. ^{18}F-FDG PET/CT showed focal pathological uptake in the ascending aorta and particularly in the lateral wall and perivascular space adjacent to the truncus pulmonalis, with no other involvement of the large vessels. After therapy with methyl-prednisolon intravenously and later prednisolon orally combined with methothrexate, her general condition and hearing loss improved both subjectively and objectively. “Atypical” Cogan’s syndrome was diagnosed on the basis of sensorineural deafness and focal large-vessel vasculitis of the aortic arch, both with improvement on steroids. While patient was in a stable condition with methotrexate and low-dose prednisone, a second follow-up ^{18}F-FDG PET/CT, 6 months later, showed focal relapse in the lateral wall of the ascending aorta with metablic progression compared to the first ^{18}F-FDG PET/CT.

Case 4 presents the case of a 42-year-old woman known with a human leukocyte antigen (HLA)B27 positive ankylosing spondylitis. Despite treatment with a tumour necrosis factor blocking agent, the patient was not pain free and CRP and ESR levels remained elevated. MRI (STIR) did not show any signs of active sacroiliitis nor spondylitis. ^{18}F-FDG PET/CT was performed to exclude other inflammatory processes, beyond the skeleton. Only increased metabolic activity in the wall of the ascending aorta was noted. A positive Treponema pallidum serology made the diagnosis of late syphilis with syphilitic aortitis probable. The ^{18}F-FDG PET/CT 24 weeks after treatment with benzylpenicillin showed markedly decrease of ^{18}F-FDG uptake in the wall of the ascending aorta.

Patients with large vessel vasculitis (LVV) may present clinically as either FUO or IUO. **Chapter 6** describes a multicentre retrospective study with the purpose to identify clinical and laboratory parameters that may improve the effectiveness of the use ^{18}F-FDG PET/CT for diagnosing LVV. The secondary aim was to assess the contribution of ^{18}F-FDG PET/(CT) in finding alternative diagnoses for patients without signs of LVV on the scan. In the analysis were included; laboratory tests, age, sex, general and non-specific complaints, signs and

complaints related to temporal arteritis, and a variety of musculoskeletal, cardiovascular, pulmonary and neurological related signs and symptoms.
A total of 304 patients with LVV in the differential diagnosis were included, of which 62 (20%) were positive and 242 (80%) were negative for LVV. The contribution of ^{18}F-FDG PET/(CT) to the diagnoses and the distribution of all diagnoses in polymyalgia rheumatica, inflammatory (joint) disorders, systemic diseases, malignancies and infections were comparable to the FUO and IUO populations described in **chapter 3 and 4**. In 86 of 242 patients no classifying diagnosis could be made, i.e. in 28% of the 304 included patients.
Of all parameters included in the analysis only the presence of artralgia was an independent predictor of a negative ^{18}F-FDG PET/(CT) and an elevated ESR of a positive ^{18}F-FDG PET/(CT).

Chapter 7 discusses the observation that there is substantial underdiagnosis of LVV. Late diagnosis of LVV may lead to surgery or angioplasty in occlusive forms and is often accompanied by serious aortic complications and a fatal outcome.
The American College of Rheumatology (ACR) 1990 criteria for vasculitis, were based on late LVV effects such as arterial stenosis and/or occlusion. Also age was used for classification; age at onset of disease ≥ 50 years for giant cell arteritis (GCA) and age at onset of disease ≤ 40 years for Takayasu arteritis (TA). In 2012 the ACR formulated the following definitions:

- GCA: arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries. Often involving the temporal artery. Onset usually in patients older than 50 years and often associated with polymyalgia rheumatica.

- TA: arteritis, often granulomatous, predominantly affecting the aorta and/or its major branches. Onset usually in patients younger than 50 years.

A review of the literature revealed that ^{18}F-FDG PET/CT is a powerful metabolic imaging tool as it is able to diagnose LVV especially at the early onset of disease. Therefore ^{18}F-FDG PET/(CT) may help to improve the current classification system, based on the intensity of the ^{18}F-FDG uptake and its distribution pattern:

- Isolated polymyalgia rheumatica (PMR) with pathologic ^{18}F-FDG uptake in the soft tissue and ligaments (perisynovitis or enthesitis) around the shoulders/hips and other major joints, lumbar/cervical spinous processes, and ischial tuberosities;
- Diffuse and mildly intense ^{18}F-FDG uptake in the wall of the aorta and its main branches and without arteritis temporalis, PMR, or anatomic arterial wall abnormalities;
- Diffuse and mildly intense ^{18}F-FDG uptake in the wall of the aorta and its main branches with arteritis temporalis, PMR, or anatomic arterial wall abnormalities;
- Focal and intense ^{18}F-FDG uptake in the aortic arch or intense ^{18}F-FDG uptake in isolated arteries, with or without stenosis or occlusion. Reports of these cases describe relapse and progression (both metabolic and angiographic) despite immunosuppressive therapy, irrespective of age. It is therefore redundant to classify patients with a positive ^{18}F-FDG PET/CT for LVV in ≤50 years or ≥50 years of age.

^{18}F-FDG PET/ CT sheds new light on the classification of GCA and TA and strengthens the notion that GCA and TA are more likely to be different expressions of a common histopathological entity.

The objective of the study described in **chapter 8** was to determine the predictive value of CRP and ESR to a positive ^{18}F-FDG PET/CT result in patients with FUO or IUO. Individual data of 498 patients were retrieved from three retrospective studies. Receiver-operating-characteristic (ROC) derived areas-under-the-curve (AUC) were used to assess ^{18}F-FDG PET/CT versus age, CRP and ESR. The discriminative value of age, CRP and ESR related to ^{18}F-FDG PET/CT was examined using the net reclassification improvement (NRI). A diagnosis was established in 331 patients; ^{18}F-FDG PET/CT had a diagnostic accuracy of 89%. ^{18}F-FDG PET/CT had the highest AUC (0.89, $p < 0.001$).
The addition of ^{18}F-FDG PET/CT to a diagnosis prediction model including age, CRP and ESR resulted in a NRI of 42% ($p < 0.001$). In the same model with CRP values below 20 mg/L or ESR values below 20 mm/h the NRI was 64% ($p < 0.001$) and 29% ($p = 0.059$), respectively. In 30 of 91 patients with CRP < 10 mg/L a diagnosis could be established. Only in patients with CRP levels < 5mg/L ^{18}F-FDG PET/CT was 100% true negative. Elevated CRP predicts a positive ^{18}F-FDG PET/CT more reliably than ESR.

The objective of the pilot study described in **chapter 9** was to compare the cost-efficacy of a diagnostic work-up/strategy with and without ^{18}F-FDG PET/CT in patients with IUO using a published data set as a reference.
46 IUO patients without ^{18}F-FDG PET/CT (Group A) and 46 IUO patients referred for ^{18}F-FDG PET/CT (Group B) were selected. IUO was defined as the combination of non-specific signs and symptoms and a prolonged ESR ≥ age/2 for males or ESR ≥ (age + 10)/2 in mm/h for female patients, and/or CRP ≥ 15 mg/L. The costs for all tests and procedures, the number of hospitalization days, in each patient to reach a diagnosis, were calculated with current Dutch tariffs.
In Group A a diagnosis was reached in 14/46 patients. The mean costs for all the diagnostic procedures were €2,051 per patient. Adding the costs of hospitalization increased the mean amount to €12,614 per patient. In Group B a diagnosis could be made in 32/46 patients. The mean costs for all diagnostic procedures were €1,821 per patient, significantly lower compared to Group A ($p<0.0002$). Adding the costs of hospitalization increased the mean amount to €5,298 per patient.
In IUO ^{18}F-FDG PET/CT has the potential to become a cost-effective routine imaging technique indicating the direction for further diagnostic decisions and thereby avoiding unnecessary, invasive, and expensive diagnostic investigations and possibly reducing the duration of hospitalization.

General Discussion

Evolution of definitions of FUO and IUO.

Fever of unknown origin (FUO) was first used in 1955 by Kiefer and Leard in their book "prolonged and perplexing fevers".[1] In a seminal article from 1961 Petersdorf and Beeson defined (FUO) as: (1) an illness of at least 3 weeks' duration, (2) with fever; body temperature higher than 38.3°C (101°F) on several occasions, and (3) no established diagnosis after 1 week of hospital investigation.[2] The period of 3 weeks was chosen to eliminate self-limiting viral illnesses and other benign transient causes of fever, and also to allow sufficient time to complete the appropriate diagnostic procedures.

Since 1961 health care has shifted from inpatient oriented healthcare to a more outpatient setting.In addition sophistication of medical technology has increased. In 1991 these developments led Durack and Street to propose a change with regard to the required duration of investigation before qualifying a fever as FUO; at least 3 days in hospital or at least three outpatient visits.[3] In the same article they proposed a new system for the classification of FUO: classic FUO in nonimmunocompromised patients, nosocomial FUO, neutropenic FUO, and FUO associated with HIV infection.[3] Immunocompromised patients with fever require urgent evaluation and prompt empirical antimicrobial therapy as rapidly progressive infection may be life-threatening if untreated.[4]

The FUO criteria 'duration of illness' and 'no diagnosis after 1 week of hospital investigation' have undergone further modification and the general interpretation is nowadays; 'no diagnosis after appropriate inpatient or outpatient evaluation'.[5]

The second criterion of FUO (body temperature higher than 38.3°C (101°F) on several occasions) became also a matter of discussion. As pointed out in **chapter 1** of this thesis, low-grade fever (body temperature between 37.5 and 38.3°C) required the same diagnostic approach as 'classic' FUO because there was no relationship between body temperature values and the severity of the underlying diseases. In addition the aetiological spectrum was also in line with the causes related to FUO.[6] The results of ^{18}F-FDG PET/CT in IUO, described in **chapter 4**, support these observations. Also the results are in line with the findings of Vanderschueren et al [7]: the diagnostic yield, the distribution in categories of the underlying aetiologies (i.e. infection, non-infectious inflammatory diseases (NIID) and malignancy) and the diagnostic contribution of hybrid ^{18}F-FDG PET/CT were quite similar to patients with FUO.

^{18}F-FDG PET/CT results

Stand-alone ^{18}F-FDG PET was reported helpful in 36% of included IUO patients, in 61% of patients a diagnosis could be established.[7] Hybrid ^{18}F-FDG PET/CT contributed to the diagnosis 68% of patients with IUO, while in 74% a diagnosis could be made (**chapter 3**).

A similar difference is noticed between the contribution to the diagnosis of stand-alone ^{18}F-FDG PET and hybrid ^{18}F-FDG PET/CT results in FUO.

In 8 studies on FUO (total number of patients 386), stand-alone ^{18}F-FDG PET had a mean overall helpful contribution to the diagnostic approach in 39 % of the cases, with the mean overall percentage of finding a final diagnosis calculated at 67%.[8-15]

In contrast, the outcome from 7 studies (total number of patients 226) resulted in a mean helpful contribution of hybrid ^{18}F-FDG PET/CT in FUO of 57%. The mean percentage of patients for whom a final diagnosis could be established with hybrid ^{18}F-FDG PET/CT was 73%. [16-22]

It should be pointed out that most of these seven studies also stress the high negative predictive value of the hybrid technique in the assessment of FUO. A negative ^{18}F-FDG PET/CT performed after the initial workup, with the exclusion of (non^{18}F-FDG avid) focal systemic diseases, allowed a wait-and-see strategy and obviated the need for further investigations.

These results should be interpreted cautiously as there is heterogeneity between the outcome of the individual studies. For a meta-analysis 9 studies were considered to have good methodological quality (including **chapter 3** of this thesis) that collectively evaluated 388 patients in whom conventional diagnostic methods failed to localize the focal origin of fever. According this meta-analysis, 32% of the stand-alone ^{18}F-FDG PET scans and 62 % of the hybrid ^{18}F-FDG PET/CT findings contributed to obtaining a final diagnosis. [23]

Of note, this meta-analysis found a lower overall specificity for stand-alone ^{18}F-FDG PET; approximately 25% of all the PET scans analysed were classified as false positive. An important advantage of hybrid ^{18}F-FDG PET/CT compared to stand-alone ^{18}F-FDG PET may be due to the precise anatomic localization of small lesions, the additional diagnostic information provided by the CT, and better differentiation between physiological and pathological metabolic foci. The integration of anatomical and morphological images allows improved interpretation of both abnormal ^{18}F-FDG uptake and suspicious morphological findings.

Nonetheless, there are probably more reasons why ^{18}F-FDG PET/CT is reported with higher diagnostic accuracy compared to stand-alone ^{18}F-FDG PET. The last decade the spatial resolution and the sensitivity of the PET systems has improved. The first introduced stand-alone PET cameras provided a spatial resolution of 10 mm (under optimal conditions). Ongoing improvements in technology created an evolution in spatial resolution from 6 mm to 4 mm. The most recently introduced PET/CT cameras claim a 2.5 mm spatial resolution for the PET component under optimal conditions.

The difference in diagnostic accuracy between stand-alone ^{18}F-FDG PET and hybrid ^{18}F-FDG PET/CT may be related to a certain selection bias. In the early PET days an ^{18}F-FDG PET study was probably more a 'last resort' chance to reach a diagnosis. In recent years referring physicians are more aware of the merits of ^{18}F-FDG PET/CT, with the probable consequence that patients are referred for a ^{18}F-FDG PET/CT earlier on in the diagnostic process.

Over the years, the interpretation of the fused images has improved (and still does) through feedback with referring clinicians. Not only from a semiological point of view, the pattern and the level of ^{18}F-FDG uptake should be taken into account for accurate interpretation. Also

the knowledge of clinicians of the histopathology of diseases that may fit in the differential diagnosis of a specific ^{18}F-FDG PET/CT scan, is of invaluable importance in the interpretation of the images. E.g. it took some time after the introduction of ^{18}F-FDG PET before the majority of the nuclear medicine community, appreciated the characteristic pattern of pathologic ^{18}F-FDG uptake in the soft tissue and ligaments (perisynovitis or enthesitis) around the shoulders and hips, lumbar (and in many cases cervical) spinous processes, and ischial tuberosities, as pathognomonic for polymyalgia rheumatica. Other examples of the importance of a good collaboration with (and feedback from) the referring physician are given in detail in case 3 and 4 of **chapter 5** of this thesis.

The case reports described in **chapter 5** illustrate the heterogeneity that patients with IUO and FUO present to a clinician. Which strikes at first glance is the heterogeneity of diagnoses, IUO or FUO may very well be a rare presentation of a common aetiology or a common presentation of a rare aetiology. In addition, the heterogeneity in diagnostic approaches before patient is referred to PET/CT and finally, the heterogeneity in the diagnostic procedures that are needed for positive ^{18}F-FDG PET/CT results, to allow an accurate diagnosis, i.e. clinical and imaging follow-up, biopsy or surgery with histopathology, micro-biologic assays or monitoring therapy response.

Comparison of ^{18}F-FDG PET/CT with other techniques.

Based on published literature there are several reasons that make a diagnostic performance comparison between ^{18}F-FDG PET/CT and various other imaging techniques in FUO and IUO difficult:

- Definition of FUO or IUO may vary among individual patient cohorts, the diagnostic workup may differ at different medical facilities, and diagnostic protocols are not standardized worldwide.
- Heterogeneity of the different patient populations.
- Non-uniformity in PET and CT techniques (including the specific preparation of the patient), and use of contrast media.

Consequently, the percentage of patients for whom no cause for the symptoms can be established using these modalities can range from 10% to 50%. For patients with a negative ^{18}F-FDG PET, a limited variety of systemic (non-focal) diseases may still be found through other diagnostic testing. This makes an accurate calculation of sensitivity and specificity of ^{18}F-FDG PET for patients with FUO or IUO difficult.

Furthermore, in patients that already received steroids or antibiotics, the sensitivity of ^{18}F-FDG PET for inflammatory processes and infections is most likely negatively influenced.

The instigating inflammatory process may have subsided while sequelae like oedema and aortic/arterial wall thickening (on CT or MRI) need more time to respond to therapy. Reported discrepancies in ^{18}F-FDG PET(/CT) results, disease activity measured by inflammatory parameters, and radiologic evaluation with MRI may very well be caused by interpreting monitoring immunosuppressive/antibiotic therapy response with ^{18}F-FDG PET/CT as an initial staging procedure.

The active phases of recruitment, activation, migration, and infiltration of T cells, macrophages, and leucocytes usually precede the appearance of inflammatory oedema; ^{18}F-FDG PET/CT may therefore be positive at an earlier stage than an MRI scan or ultrasonography.

Socioeconomic Considerations.

Patients with non-specific signs and symptoms like fever, weight loss, malaise and prolonged increased inflammatory parameters, and without a diagnosis after routine diagnostic evaluation may undergo extensive investigation and medical treatment, which may not only be inappropriate but also hazardous.

Often patients with FUO or IUO have a long history before a diagnosis is reached at: a diagnostic process that starts at the general practitioner, to multiple diagnostic procedures in a community hospital, and further investigations in an academic hospital. The subsequent uncertainty for a patient is sometimes difficult to cope with; a psychologist or psychiatrist was reported necessary in a few cases.

Hybrid ^{18}F-FDG PET/CT may very well become a cost-effective modality, the high diagnostic yield allows adequate early diagnosis and limits the number of other non-contributing (invasive) tests required and the time to diagnosis, and thereby the duration of hospitalization for diagnostic purposes.

Although the nonspecificity of both CRP and ESR is acknowledged, ESR measurement is affected by numerous factors that can spuriously elevate and also decrease the ESR. The number of influencing factors is to a point that the clinical usefulness of ESR is severely compromised. Especially considering the costs of ^{18}F-FDG PET/CT in patients with unexplained prolonged inflammatory parameters and non-specific signs and complaints, it may be appropriate to quote Jurado here; “those health care professionals who still use the ESR determination in clinical practice adhere more to the traditions of medicine than to its scientific basis and simple logic”.[24]

Future perspectives

Future prospective studies

The value of hybrid ^{18}F-FDG PET/CT imaging in the assessment of patients with FUO is reported in multiple predominantly European publications. In 2012 a joint task force of the European Association of Nuclear Medicine (EANM) and the USA based Society of Nuclear Medicine and Molecular Imaging (SNMMI) published guidelines for the use of ^{18}F-FDG PET/CT in infection and inflammation. Based on cumulated reported accuracies >85%, these guidelines state that the major indications for the use of ^{18}F-FDG PET/CT in infection and inflammation are: sarcoidosis, peripheral bone osteomyelitis, spondylodiscitis, FUO and the primary evaluation of vasculitis. [25] Despite these efforts reimbursement for the use of ^{18}F-FDG PET/CT in FUO is not accomplished in the USA.

Moreover, the contribution and efficacy of ^{18}F-FDG PET/CT in the diagnosis of patients with IUO needs to be confirmed by well-designed prospective studies. Although the preliminary data of **chapter 4 and 9** of this thesis give some direction, these results cannot be extrapolated to clinical practice. Therefore these future trials should also study the cost-effectiveness of ^{18}F-FDG PET/CT in FUO/IUO and preferably designed based on the "bottom-up micro-costing" cost-efficacy principle.

A standardized protocol will have some difficulties to develop. The initial diagnostic procedures will continue to be based on the cues presented by a full physical examination, and a thorough interview. Ideally, patient inclusion for ^{18}F-FDG PET/CT should be based on a uniform definition of an appropriate minimal diagnostic workup. Which routine diagnostic procedures this workup should contain will most likely initiate discussion between the participating centres, (e.g. extensive blood and urine investigation, including bacterial cultures, and tests for antinuclear antibodies and antineutrophil cytoplasmic antibodies (ANA/ANCA), human immunodeficiency virus (HIV), Epstein–Barr virus (EBV) and cytomegalovirus (CMV), plus extra serology based on local epidemiology, a tuberculin skin test, electrocardiography (ECG), chest radiography and abdominal ultrasound).

In addition, patients should be included before invasive diagnostic procedures such as lymph node, liver, bone marrow or temporal artery biopsy, endoscopies (of stomach, colon, bronchial with their respective biopsies) and trans-oesophageal ultrasonography.

Paediatric setting

In children the diagnostic workup of FUO and unexplained signs of inflammation may be traumatic, including biopsies and bone marrow examinations. Without a diagnosis, there is frequently a need for a treatment with either antibiotic or steroid therapy. In addition, when the workup is not contributory, these diagnostic tests prolong the time to diagnosis. The consequent delay in treatment may cause prolonged illness resulting in retardation of growth and development, and possibly increased morbidity and higher mortality rates. Therefore, a short and adequate diagnostic protocol is important in finding the cause of FUO in children.

Reports of ^{18}F-FDG PET/CT in paediatric setting are scarce, although the results suggest ^{18}F-FDG PET/CT appears a promising diagnostic tool in the evaluation of children with FUO and unexplained signs of inflammation.[26, 27] In addition, the combination of the usually low-dose CT setting for the CT part of PET/CT and the reduced ^{18}F-FDG activity (to bodyweight) result in a radiation exposure less than 4 mSv for a total body ^{18}F-FDG PET/CT, which is approximately half of a standard-dose CT.[28, 29]

Other (PET) radiopharmaceuticals

^{18}F-FDG merely detects increased glucose metabolism with the advantage of a relatively high sensitivity and low specificity irrespective the possible aetiology, i.e. infection, inflammation or malignancy. It is this characteristic that makes ^{18}F-FDG PET/CT a powerful diagnostic tool as it gives accurate localization of metabolic abnormalities and direction for further diagnostic procedures in search for a diagnosis in FUO and IUO.

As mentioned in the Introduction (**chapter 1**) of this thesis, many other radiopharmaceuticals were developed and tested, however designed to be more specific tracers for targeting specific cells and molecules involved in a specific disease.[30] The main disadvantage of conventional radiopharmaceuticals is therefore that each (apart from ^{67}Ga), covers only a part of the spectrum of possible diagnoses in the broad setting of FUO and IUO. This is also a disadvantage for the use ^{18}F-FDG labelled leucocyte imaging in FUO and IUO.
Only a few radiopharmaceuticals have comparable characteristics to ^{18}F-FDG making them potentially suitable for the search for a diagnosis in FUO and IUO.
To resolve the disadvantages of ^{67}Ga, a method of synthesis for the PET equivalent ^{68}Ga-citrate was developed. Besides the better imaging characteristics (higher spatial resolution and the possibility for quantification) of PET, the optimal time for infection imaging was within a few hours after injection and the target-to-background ratio was clearly much higher than using the SPECT-tracer ^{67}Ga-citrate. High background activity of ^{68}Ga-Citrate in the thorax and upper abdomen at 60 min post-injection may interfere with detecting lesions in these regions; therefore, ^{68}Ga-PET is more suitable for imaging lesions in the lower abdomen and the extremities. The available literature clearly indicates that ^{68}Ga-citrate is useful for the detection of malignancy and infection and to a more limited extent for non-infectious inflammation.[31]

Radiolabelled interleukin-2 (IL2) allows visualization of both lymphocytic infiltration and T-cell lymphocyte activation. Both ^{99m}Tc- and ^{123}I-labelled IL2 had promising results in the detection of chronic inflammation related to autoimmune and inflammatory diseases and malignancies like cutaneous melanoma. Routine application of this radiopharmaceutical was limited because of complex labelling procedures and the low spatial resolution of single photon emission computed tomography (SPECT). Recently, IL2 was labelled with ^{18}F and proven stable. In animal studies ^{18}F-labelled IL2 was able to detect in vivo activated lymphocytes. However, the radio-ligand is under clinical evaluation and not commercially available.[32]

PET/MRI

The use of PET/MRI may have some advantages in the assessment of patients with IUO or FUO:

- Absolute match between the tissue information of both modalities under the same physiological conditions.
- Identical position of the patient during simultaneous image acquisition of both modalities leading to a substantial reduction in motion artefacts due to heart beating, intestinal motion and breathing.
- Better localization of the PET signal within the soft tissues.
- No radiation burden from the MRI, which is of interest in paediatric FUO/IUO setting.[33]

Nevertheless, MRI cannot image all body parts at once (different body parts may require different MR acquisition sequences). Furthermore, the long examination time of a total body investigation hampers routine clinical application. In addition it seems likely that the intensity of the noise during such a long investigation time will not be appreciated by all patients. It is probably of both economical and clinical importance to identify those body parts of possible relevance for further PET/MRI examination with a preceding PET/CT.[33]

Conclusions

This thesis describes the role and the interpretation of imaging results with hybrid ^{18}F-FDG PET/CT in patients with non-localizing or non-specific signs and symptoms like fever, weight loss, malaise and prolonged increased inflammatory parameters, without a diagnosis after routine diagnostic evaluation. Patients with either FUO or IUO are a diagnostic dilemma, as the aetiology may vary from a self-limiting condition to occult malignancy.
An important feature of ^{18}F-FDG is its non-specificity: ^{18}F-FDG shows increased uptake not only in malignant cells, but also in cells involved in infectious and inflammatory processes. Furthermore ^{18}F-FDG PET/CT imaging is able to reveal functional alterations that precede the morphological changes and the integration of anatomical and functional images allows improved interpretation of both abnormal ^{18}F-FDG uptake and suspicious morphological findings.
The heterogeneity of FUO and IUO aetiologies and the abundance of diagnostic possibilities have blurred an unambiguous diagnostic strategy in FUO and IUO. ^{18}F-FDG PET/CT, however, shows a high diagnostic yield despite the heterogeneity of underlying aetiologies of the syndromes. After exclusion of systemic (non-focal) diseases ^{18}F-FDG PET/CT has a high negative predictive value and is helpful in identifying patients with benign self-limiting conditions. Notwithstanding the relatively high costs ^{18}F-FDG PET/CT has the potential to become a cost-effective routine imaging technique indicating the direction for further diagnostic decisions and thereby avoiding unnecessary, invasive, and expensive diagnostic investigations.

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Nederlandse Samenvatting

Samenvatting

Patienten met koorts van onbegrepen origine (FUO) en ontsteking/inflammatie van onbegrepen origine (IUO) vormen een diagnostisch probleem. In **hoofdstuk 1** wordt een samenvatting gegeven van de diagnostische mogelijkheden, zowel invasieve als niet-invasieve, en ook van de diverse beeldvormende technieken. De voordelen en nadelen van fundoscopie, echo Doppler van de (onder)benen, en invasieve procedures zoals beenmerg punktie, percutane leverbiopsie, huid en spier biopsie, arterie temporalis biopsie, broncho alveolaire (long) spoeling en explorerende laparotomie worden kort weergegeven. De relatief hoge specificiteit maar beperkte sensitviteit van deze onderzoeken beperkt een meer algemene toepassing in geval van FUO en IUO. De rol van radiologisch onderzoek; röntgenonderzoek, echografie, CT, MRI is kort samengevat. In het algemeen kan gesteld worden dat radiologisch onderzoek anatomische afwijkingen weergeeft. Als gevolg daarvan kunnen maligne, infektieuze en inflammatoire haarden in de vroege fase gemist worden (door het ontbreken van herkenbare anatomische veranderingen in de vroege fase).
Een ander probleem is dat na chirurgie en andere therapeutische interventies zoals radiotherapie, het maken van onderscheid tussen blijvende post-therapeutische anatomische veranderingen(zoals bindweefselvorming) en aktieve maligne, infektieuze of inflammatoire lesies vaak moeilijk is of zelfs onmogelijk. In vergelijking met radiologisch onderzoek kan scintigrafische beeldvorming deze lesies in een vroeg stadium juist wel detecteren.
De planaire (twee-dimensionale) beelden misten echter anatomische details en contrast tussen pathologie en omliggende normale weefsels. Met de introductie van drie-dimensionale 'single photon computed tomography' (SPECT) en meer recent hybride SPECT/CT werden deze tekortkomingen grotendeels teniet gedaan.
Het grote nadeel van de routinematig toegepaste radiofarmaca blijft echter bestaan; ze bestrijken alle (op ^{67}Gallium na) slechts een beperkt deel van het uitgebreide spectrum aan ziekten dat FUO of IUO kan veroorzaken. De klinische toepassing van ^{67}Gallium is echter beperkt, door de zeer matige beeldkwaliteit, het enkele dagen wachten tussen het toedienen en de mogelijkheid tot beeldvorming, en de hoge stralings belasting voor de patient.

Een algemeen toegepast patienten voorbereidings protocol voor ^{18}F-FDG PET/(CT) onderzoek is het voorafgaand 6 uur vasten. De bedoeling hiervan is het teweegbrengen van een lager suiker en insuline gehalte in het bloed. Dit maakt namelijk een betere herkenning mogelijk van ^{18}F-FDG opnemende pathologie in het lichaam, gekenmerkt door een lokaal verhoogde stofwisseling ofwel een lokaal verhoogde glycolyse. Patienten hebben evenwel een zeer variabele opname van het ^{18}F-FDG in de linker ventrikel van het hart. Dit maakt in geval van hoge opname de interpretatie van de beelden van het hart moeilijk; eventuele pathologie in het hart zelf kan gemaskeerd worden of bv. een long haard dicht bij het hart gelegen.
In **hoofdstuk 2** wordt een retrospectieve studie beschreven over het effekt van een 'vet-toegestaan en koolhydraat-beperkt' dieet, dat patienten starten op de dag voor het ^{18}F-FDG

PET/CT onderzoek. In het ene ziekenhuis kregen 100 patienten een normaal dieet (en de gebruikelijke 6 uur vasten) en in het andere ziekenhuis 100 patienten het 'vet-toegestaan en koolhydraat-beperkt' dieet. De resultaten lieten zien dat een 'vet-toegestaan en koolhydraat-beperkt' dieet de ^{18}F-FDG opname in het hart adequaat onderdrukt.

Hoofdstuk 3 is een retrospectieve studie naar de bruikbaarheid van ^{18}F-FDG PET/CT om de oorzaak van onbegrepen koorts te achterhalen bij 68 patienten. Een ^{18}F-FDG PET/CT scan werd als 'nuttig' gekenmerkt of richtinggevend voor de diagnose als een positieve scan tot een accurate diagnose leidde. De diagnose was daarbij gebaseerd op histo-pathologie, micro-biologisch onderzoek of bevindingen gedurende de vervolgperiode (klinisch, of respons op de ingestelde therapie of door andere beeldvorming).
Bij 56% van de patienten was de ^{18}F-FDG PET/CT behulpzaam bij het stellen van de diagnose; het achterhalen van de oorzaak van de koorts. Van 6 van de 27 patienten met een negatieve ^{18}F-FDG PET/CT bleek een systemische ziekte (dus zonder een duidelijk focus of pathologische haard, bv. leukemie) de oorzaak voor de koorts. Bij de andere 21 patienten verdween de koorts uiteindelijk spontaan gedurende de follow up. ^{18}F-FDG PET/CT heeft derhalve een hoge positief voorspellende waarde(93%) en ook een hoge negatief voorspellende waarde (100%) voor ziekten met pathologische haarden. ^{18}F-FDG PET/CT was niet zinvol bij patienten met koorts en een normaal C-reactive proteine (CRP) en een normale bloedbezinkingssnelheid (BSE). Als conclusies werden gesteld:
- systemische ziekten dienen uitgesloten te worden door ander anderzoek,
- een negatieve ^{18}F-FDG PET/CT kan verdere invasieve en dure diagnostiek of een 'probeer'-therapie met corticosteroiden of antiobiotica voorkomen.

In **hoofdstuk 4** wordt een multicenter retrospectieve studie beschreven die de bijdrage aan de diagnose van ^{18}F-FDG PET/CT onderzocht bij 140 patienten met inflammatie van onbekende origine (IUO). IUO was gedefinieerd als;
- een langer bestaande ontsteking met CRP waarden hoger dan 20 mg/L en/of een BSE van meer dan 20 mm/h,
- met daarbij klinische klachten en symptomen en een lichaamstemperatuur niet hoger dan 38.3˚C,
- en zonder een diagnose na eerdere diagnostische verrichtingen.

Bij 104 patienten (73%) kon uiteindelijk een diagnose gesteld worden. ^{18}F-FDG PET/CT was terecht positief bij 95 patienten, terecht negatief bij 30 patienten (blijkbaar was hier sprake van zichzelf herstellende condities), fout positief bij 6 patienten en fout negatief bij 9 patienten (voornamelijk systemische ziekten). De diagnostische opbrengst, de verdeling in categorieen van de onderliggende ziektes (in infekties, niet-infectieuze inflammatoire ziektes en maligniteiten) en de bijdrage van ^{18}F-FDG PET/CT aan de diagnoses bij IUO was min of meer overeenkomstig aan het gebruik van deze techniek bij patienten met FUO.

Hoofdstuk 5 bestaat uit beschrijvingen van 4 verschillende patient geschiedenissen die de rol illustrateren van ^{18}F-FDG PET/CT in IUO or FUO.

Casus 1 betreft een 79-jarige man met terugkerende episodes van koorts en koude rillingen. Zes jaar eerder werd een vaatprothese in de grote buikslagader geplaatst. Bij laboratorium onderzoek van het bloed was sprake van verhoogde BSE en CRP waarden. Een eerdere CT scan toonde geen tekenen van een infektie van de vaat prothese. Bloedkweken bleken uiteindelijk positief voor meerdere darm bacteriën. Het hieropvolgende ^{18}F-FDG PET/CT onderzoek toonde ringvormig verhoogde ^{18}F-FDG opname alleen ter plaatse van de bovenste inhechting van de vaatprothese in de buikslagader. Bij chirurgie bleek naast een duidelijke infektie ook een 1-cm grote zweer in de 12-vingerige darm die tegen de prothese lag.

Casus 2 vertelt het verhaal van een 84-jarige vrouw met FUO, naar het ziekenhuis verwezen met verschillende niet-specifieke klachten en ook geestelijke achteruitgang. Dit laatste werd toegeschreven aan haar voortschrijdende ziekte van Alzheimer. Na verschillende eerdere onderzoeken toonde ^{18}F-FDG PET/CT een metabool hyperactieve massa ter plaatse van de hypofyse, bevestigd door 'magnetic resonance imaging' (MRI) van het brein. Het hieropvolgende endocrinologische onderzoek paste bij een prolactinoom, waarvoor patiente ook succesvol behandeld werd. Deze casus ondersteept ook het nut van het mee-scannen van het brein bij ^{18}F-FDG PET/CT in geval van FUO.

Casus 3 betreft een 60-jarige vrouw met sinds 4 maanden toenemende vermoeidheid, hoesten, verminderde eetlust en gewichtsverlies, nachtzweten, en
onduidelijke pijn op de borst klachten. Ze had ook kortdurende perioden van koorts doorgemaakt. Tevens hoofdpijn en oorpijn, met de laatste maand gehoorsverlies links meer dan rechts, en soms wat duizeligheid. Geen gezichtverlies of andere oogproblemen.

De CRP and BSE waarden waren verhoogd. Een test op anti-neutrofiele cytoplasmatische antilichamen (ANCA) was myeloperoxidase positief met p-ANCA specificiteit. Echo onderzoek van de temporaal arterieen was niet afwijkend. ^{18}F-FDG PET/CT toonde focaal pathologische opname in een deel van het stijgende deel van de thoracale aorta and particularly in the laterale wand en in het weefsel tussen de long arterie en de aorta. Er was geen sprake van betrokkenheid in de wanden van de andere grote arterieen. Na behandeling met methyl-prednisolon intra-veneus en later met prednisolon oraal gecombineeerd met methothrexate, verbeterde haar algemene toestand en ook haar gehoorsverlies zowel vanuit oogpunt patient als behandelend arts. De diagnose "atypisch Cogan's syndroom" werd gesteld op basis van de doofheid en de focale ontsteking in de wand van de aortaboog, en met verbetering door steroiden. Zes maanden later was patiente in een stabiele conditie met onderhoudsdosering methotrexaat en prednison. Bij gering gestegen CRP en BSE toonde een tweede controle ^{18}F-FDG PET/CT evenwel een recidief in de wand van de aortaboog en naast gelegen weefsels met nu hogere aktiviteit (duidend op voortschrijdende ziekte ondanks therapie) in vergelijking met de eerste ^{18}F-FDG PET/CT.

Casus 4 betreft een 42-jarige vrouw bekend met een humaan leukocyten antigeen(HLA)B27 positieve ziekte van Bechterew. Ondanks behandeling met tumor necrose factor blokkerende

middelen (alfaTNF), werd patiente niet pijnvrij en bleven de CRP en BSE waarden verhoogd. Een MRI toonde geen tekenen van aktieve onsteking rond de wervels of het staartbeen. Een ^{18}F-FDG PET/CT werd verricht om ontstekingen anders dan rond skeletdelen uit te sluiten. De beelden toonden alleen verhoogde metabole aktiviteit in grootste deel van de wand van het stijgende deel van de thoracale aorta. Door positieve Treponema pallidum serologie werd de diagnose 'late' syphilitische aortitis zeer waarschijnlijk. Een controle ^{18}F-FDG PET/CT 24 weken later, na behandeling met benzylpenicilline, toonde sterk afgenomen ^{18}F-FDG uptake in de wand van het stijgende deel van de thoracale aorta.

Patienten met een onsteking van de grote vaten (LVV) kunnen zich klinisch presenteren met IUO en ook wel met FUO. **Hoofdstuk 6** beschrijft een retrospectieve studie van de gegevens van meerdere ziekenhuizen, met het doel om mogelijke klinische en laboratorium parameters te achterhalen die de effectiviteit kunnen verbeteren van het aantonen van LVV met ^{18}F-FDG PET/CT. Het tweede doel was het bepalen van de bijdrage van ^{18}F-FDG PET/(CT) aan andere diagnoses bij die patienten die geen tekenen van LVV op de PET beelden hadden.
In de analyse werden opgenomen; laboratorium onderzoek, leeftijd, geslacht, algemene en niet-specifieke klachten, tekenen en klachten gerelateerd aan ontsteking van de temporaal arterie, en een variatie aan musculoskeletaal, cardiovasculair, pulmonaal en neurologisch gerelateerde klachten en signalen.
In totaal werden er 304 patienten geincludeerd die een ^{18}F-FDG PET/(CT hadden ondergaan en waarbij LVV in de differentiaal diagnose genoemd werd. 62 patienten (20%) hadden een positieve scan voor LVV en 242 (80%) was negatief voor LVV. De bijdrage van ^{18}F-FDG PET/(CT) aan de diagnoses anders dan LVV en de verdeling daarvan in polymyalgia rheumatica, inflammatoire (gewrichts) aandoeningen, systemische ziekten, maligniteiten en infecties was overeenkomstig die van FUO en IUO beschreven in **hoofdstuk 3** and **4**. In 86 van de 242 patienten kon geen diagnose gesteld worden, dus in 28% van de in totaal 304 geincludeerde patienten.
Van alle parameters opgenomen in de analyse was alleen de aanwezigheid van gewrichtsklachten van onafhankelijk voorspellende waarde voor een negatieve ^{18}F-FDG PET/(CT) voor LVV, en een verhoogde BSE voor een positieve ^{18}F-FDG PET/(CT) voor LVV.

Hoofdstuk 7 is een literatuur overzicht die de onderdiagnostiek van LVV bespreekt. Een late diagnose stelling van LVV kan leiden tot chirurgie of een angioplastiek (vaatwandcorrectie) in geval van arteriele verstopping en kan gevolgd worden door serieuze complicaties en mogelijk fatale afloop.
De 1990 criteria van 'the American College of Rheumatology (ACR)' voor LVV, waren gebaseerd op de late effecten van LVV zoals arteriele vernauwingen en/of verstoppingen. Ook leeftijd werd (en wordt) gebruikt voor classificatie; een leeftijd ≥ 50 jaar bij ontstaan van ziekte voor 'giant cell arteritis' (GCA) en een leeftijd bij het ontstaan van ziekte ≤ 40 years voor 'Takayasu arteritis' (TA). In 2012 werden door de ACR de volgende definities geformuleerd:

- GCA: arteritis, meestal granulomateuze ontsteking, gewoonlijk de aorta en de grote aftakkende arterieen betreffend, met een voorkeurs lokalistaie in carotiden en de vertebrale arterieen. Vaak ziekte betrokkenheid van de temporaal arterie. Ontstaat meestal bij patienten ouder dan 50 jaar en vaak met gelijktijdige polymyalgia rheumatica (PMR).
- TA: arteritis, meestal granulomateus, gewoonlijk de aorta en de grote aftakkende arterieen betreffend. Ontstaat meestal bij patienten jonger dan 50 jaar.

Uit de literatuur blijkt dat ^{18}F-FDG PET/CT een krachtig metabool beeldvormend onderzoek is dat het mogelijk maakt om LVV in een vroeg stadium van de ziekte aan te tonen. Derhalve maakt ^{18}F-FDG PET/CT het mogelijk om de huidige klassificatie te verbeteren, en dan gebaseerd op de intensiteit van de ^{18}F-FDG opname en het distributie patroon:

- Geisoleerde (PMR) with pathologische ^{18}F-FDG opname in de weke delen en ligamenten (duidend op perisynovitis of enthesitis) rond de schouders/heupen en andere grote gewrichten, lumbale/cervicale processus spinosi, en de tuber ischii.
- Diffuus en matig intens verhoogde ^{18}F-FDG uptake in wand van de aorta en de grote aftakkingen en zonder arteritis temporalis, PMR, of anatomische afwijkingen in de wanden van de betrokken arterieen.
- Diffuus en matig intens verhoogde ^{18}F-FDG uptake in wand van de aorta en de grote aftakkingen met arteritis temporalis, en/of PMR, en/of anatomische afwijkingen in de wanden van de betrokken arterieen.
- Focaal and intens verhoogde ^{18}F-FDG uptake in de aortaboog of intens verhoogde ^{18}F-FDG uptake in geisoleerde arterieen, met of zonder vernauwing of verstopping. Publicaties van zulke gevallen beschrijven vaak recidief en verergering van ziekte (zowel metabool als anatomisch/ angiografisch) ondanks behandeling met immunosuppressa en ongeacht de leeftijd.

Recente ^{18}F-FDG PET/ CT resultaten tonen dat het overbodig is om patienten met een positieve ^{18}F-FDG PET/CT voor LVV te klassificeren in leeftijd in ≤50 jaar of ≥50 jaar, en versterken het idee dat GCA and TA meer dan waarschijnlijk verschillende expressies zijn van een en dezelfde histopathologische ziekte entiteit.

Het doel van de studie beschreven in **hoofdstuk 8** was het bepalen van de voorspellende waarde van CRP en BSE voor een positief ^{18}F-FDG PET/CT resultaat voor ziekte bij patienten met FUO of IUO. De individuele gegevens van 498 patients werden gebruikt van drie eerdere retrospective studies (beschreven in hoofdstukken 3, 4 en 6).

De 'receiver-operating-characteristic (ROC) derived areas-under-the-curve (AUC)' werden toegepast om ^{18}F-FDG PET/CT te vergelijken met leeftijd, CRP en BSE.

De onderscheidende waarde voor het hebben van ziekte van leeftijd, CRP en BSE gerelateerd aan de ^{18}F-FDG PET/CT resultaten werd onderzocht door middel van het gebruik van de 'net reclassification improvement' (NRI). Bij 331 van de 498 patienten kon uiteindelijk een diagnose gesteld worden. Het ^{18}F-FDG PET/CT onderzoek had voor de totale patienten groep

een diagnostische accuratesse van 89%, voor het wel of niet hebben van ziekte. Zoals daarbij verwacht kon worden had ^{18}F-FDG PET/CT de hoogste AUC (0.89, $p < 0.001$).
Het toevoegen van de ^{18}F-FDG PET/CT resultaten aan een voorspellend model (voor wel of geen diagnose) met daarin de variabelen leeftijd, CRP en BSE resulteerde in een NRI van 42% ($p < 0.001$). In een zelfde voorspellend model maar dan naast leeftijd en BSE, CRP waarden van minder dan 20 mg/l was de NRI 64% ($p < 0.001$). In een voorspellend model met BSE waarden onder de 20 mm/h (naast leeftijd en CRP) was de NRI door toevoegen van ^{18}F-FDG PET/CT resultaten 29% ($p = 0.059$), de laatste NRI is derhalve niet statistisch signifikant. In 30 van de 91 patienten die een CRP < 10 mg/l hadden kon een diagnose worden gesteld. Alleen bij patienten met CRP waarden < 5mg/l bleken de ^{18}F-FDG PET/CT resultaten 100% terecht negatief. Verhoogde CRP waarden hebben een betere voorspellende waarde voor een positieve ^{18}F-FDG PET/CT dan de BSE.

In **hoofdstuk 9** wordt een kleine vergelijkende studie beschreven om de toepasbaarheid van een grotere kosten-effektiviteit studie in te schatten voor het toepassen van ^{18}F-FDG PET/CT bij patienten met IUO.
Daartoe werden 46 patienten met IUO zonder het toepassen van ^{18}F-FDG PET/CT (*Group A*) , zoals beschreven in een eerdere publicatie, vergeleken met 46 patienten met IUO die wel verwezen werden voor een ^{18}F-FDG PET/CT (*Group B*). IUO was gedefinieerd als een combinatie van niet-specifieke signalen en symptomen en langer bestaande BSE ≥ leeftijd/2 voor mannelijke patienten of BSE ≥ (leeftijd + 10)/2 in mm/h voor vrouwelijke patienten, en/of CRP ≥ 15 mg/l. De kosten voor alle verrichte diagnostische testen en procedures, het aantal opnamedagen in het ziekenhuis, voor iedere afzonderlijke patient om tot de diagnose te komen, werden berekend volgens de huidige Nederlandse tarieven.
In *Group A* kwam men tot een diagnose bij 14 van de 46 patienten. Het gemiddelde van de kosten voor alle diagnostische procedures was €2,051 per patient. Het optellen van de kosten van het aantal ligdagen leidde tot een gemiddelde van €12,614 per patient. In *Group B* kon een diagnose gesteld worden bij 32 van de 46 patienten. Het gemiddelde van de kosten voor alle diagnostische procedures was €1,821 per patient. Het optellen van de kosten van het aantal ligdagen leidde tot een gemiddelde van €5,298 per patient.
In IUO heeft ^{18}F-FDG PET/CT de potentie om een kosten-effectieve beeldvormende techniek te worden, die richting geeft in de keuze voor verdere diagnostiek en derhalve onnodige, invasieve, en dure diagnostische onderzoeken kan voorkomen en mogelijk het aantal ligdagen kan beperken.

Conclusies

Dit proefschrift beschrijft de rol en de interpretatie van de beelden van hybride ^{18}F-FDG PET/CT bij patienten met niet-specifieke en niet-lokalizerende klachten en symptomen zoals

vermoeidheid, koorts, nachtzweten, verminderde eetlust, gewichtverlies, malaise klachten en langer bestaande verhoogde inflammatie parameters in het bloed, en daarbij nog zonder een diagnose na een routinematige diagnostische evaluatie.
Patienten met FUO of IUO vormen een diagnostisch probleem, de onderliggende oorzaak kan variëren van een tijdelijke zichzelf herstellende inflammatie of conditie, tot een (nog niet ontdekte) maligniteit.
Een belangrijk kenmerk van het ^{18}F-FDG is het gebrek aan specificiteit. ^{18}F-FDG toont niet alleen verhoogde opname in het lichaam in maligniteiten, maar ook in ontstekings-processen en infekties. Beeldvorming met ^{18}F-FDG PET/CT maakt het mogelijk om de funktionele veranderingen (door de verhoogde stofwisseling) in beeld te brengen nog voor er anatomische veranderingen zijn opgetreden. Daarnaast leidt het samenvoegen van de beelden van de anatomie en de beelden van de stofwisseling, tot een betere interpretatie van eventueel afwijkende ^{18}F-FDG opname als in geval van mogelijk verdachte anatomische veranderingen of afwijkingen.
Het grote scala aan ziektes en oorzaken voor FUO en IUO enerzijds, en de uitgebreidheid van de verschillende mogelijke diagnostische onderzoeken anderzijds, bemoeilijken een eenduidige diagnostische strategie. Desondanks laat ^{18}F-FDG PET/CT een hoge diagnostische opbrengst zien in deze moeilijke patienten groep. Als systemische ziekten (zonder een pathologische haard of haarden) zijn uitgesloten door ander onderzoek heeft ^{18}F-FDG PET/CT een hoge negatief voorspellende waarde en helpt het die patienten te onderkennen met een zich zelf herstellende conditie. Niettegenstaande de relatief hoge kosten van ^{18}F-FDG PET/CT heeft het de potentie om een routine kosten-effectieve beeldvormende techniek te worden die richting geeft aan verdere diagnostische besluitvorming en daarbij onnodige, invasieve en dure diagnostiek kan vermijden.

Dankwoord

Dankwoord

Ook dit proefschrift kwam tot stand dankzij de hulp van velen.

Nadrukkelijk wil ik hierbij mijn dank betuigen aan mede-auteurs, co-promotores en promotor. (op het moment dat de AMC telefonist Henk uit zich zelf vroeg; “ah, zal ik u doorverbinden met collega Verberne?”, werd het tijd om te gaan afronden).

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Curriculum Vitae

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Johannes (Hans) Jozefus Maria Balink werd geboren in Bussum op 21 februari 1960. Het atheneum-B diploma haalde hij in 1979 aan het Petrus Canisius College in Alkmaar.
Een goed alternatief, na uitgeloot te zijn voor de studie geneeskunde, leek de studie sociale geografie aan de Vrije Universiteit te Amsterdam. Hierop volgde militaire dienst en werd hij alsnog ingeloot voor de studie geneeskunde aan de Universiteit van Amsterdam en behaalde in 1989 het arts-examen.

Vervolgens werkte hij een jaar als Clinical Research Associate voor Ciba-Geigy (het huidige Novartis) en werd hij arts-assistent nucleaire geneeskunde in het Spaarne ziekenhuis te Haarlem. Van begin 1993 tot eind 1998 werkzaam bij Mallinckrodt Medical, een producent van radiofarmaca, eerst als ondersteuning van de marketing afdeling en later als 'Associate Director Medical'. Na deze periode waarin vele internationale congressen nucleaire geneeskunde werden bezocht, starte hij de opleiding nucleaire geneeskunde in het Universitair Medisch Centrum Utrecht (bij Prof.dr. P.P. van Rijk).

Sinds zijn registratie in 2003 als nucleair geneeskundige is hij werkzaam op de afdeling nucleaire geneeskunde van het Medisch Centrum Leeuwarden.
Hij woont samen met Suzy Tan en heeft twee kinderen, Eline en Lukas.