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Inflammatory activity assessment by F18 FDG-PET/CT in persistent symptomatic sarcoidosis

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Soluble interleukin-2 receptor

Summary
Background: Establishing inflammatory activity in sarcoidosis patients with persistent disabling symptoms is important. Whole body F^{18}-FDG PET/CT (PET) appeared to be a sensitive method to detect inflammatory activity in newly diagnosed symptomatic sarcoidosis. The aim was to assess the presence of inflammatory activity using PET in sarcoidosis patients with unexplained persistent disabling symptoms and the association between PET findings and serological inflammatory markers.
Methods: Sarcoidosis patients who underwent a PET between June 2005 and June 2010 ($n = 89$), were retrospectively included. All PET scans were examined and positive findings were classified as thoracic and/or extrathoracic. As serological markers of inflammatory activity angiotensine-converting enzyme (ACE), soluble interleukin-2 receptor (sIL-2R), and neopterine were considered.
Results: In 65/89 (73%) of the studied patients PET was positive, 52 of them (80%) had serological signs of inflammatory activity. In 14/15 patients with a Chest X-ray stage IV PET was positive. In 80% of the PET positive patients extrathoracic inflammatory activity was found. Sensitivity of combined serological inflammatory markers for the presence of inflammatory

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activity as detected by PET was 80%, specificity 100%, positive predictive value 100%, negative predictive value 65%.
Conclusions: The majority of sarcoidosis patients with persistent disabling symptoms, even those with radiological stage IV, had PET positive findings with remarkably 80% extrathoracic lesions. In 20% PET was positive without signs of serological inflammatory activity. PET appeared to be of additional value to assess inflammatory activity in patients with persistent symptoms in the absence of signs of serological inflammatory activity and to detect extrathoracic lesions.

Introduction

Sarcoidosis is a multisystemic disease characterised by activity of cellular immunity with formation of non-caseating granuloma in various organ systems.[1] Establishing the presence of inflammatory activity is helpful in monitoring the course of sarcoidosis and in the follow-up of the effect of treatment.[2–4] In contrast to acute sarcoidosis,[5,6] assessment of inflammatory activity in sarcoidosis patients with persistent disabling symptoms remains a challenge for the clinician.

The assessment of inflammatory activity by clinical and radiographic features can be complicated by the fact that other organs than evaluated might be involved. Symptoms like fatigue can be nonspecific and difficult to objectify.[7–9] Furthermore, symptoms like cough and dyspnoea might be related to ongoing inflammatory activity as well as to end-stage disease, i.e. pulmonary fibrosis. It is important to be informed about the presence or absence of inflammatory activity as fibrosis itself is irreversible. In general, patients with fibrosis without ongoing inflammatory activity are supposed not to benefit from immunosuppressive treatment.[7] A technique, able to evaluate the presence of inflammatory activity per organ system, is therefore desirable.

Inflammatory activity is characterised by ongoing T-cell and macrophage activity and granuloma formation, reflected by an increase of serological markers of inflammatory activity, i.e. angiotensine-converting enzyme (ACE), soluble interleukin-2 receptor (sIL-2R) and neopterine, or abnormality in glucose metabolism.[6,10,11] The reported sensitivity and specificity of ACE, produced in granuloma is moderate, even if corrected for genotype (ACE).[12,13] sIL-2R, mainly secreted by activated T-cells, is elevated in patients with active sarcoidosis.[5,14,15] Neopterin represents activation of the monocyte/macrophage system, and is found to be increased in active disease as well.[5,14,15] Although the value of these separate markers for assessing disease activity has been studied, the value of combining these serological markers is unknown.[5,14–18]

F^{18}-FDG PET/CT (PET) is used for detecting high glucose metabolism in malignancies, infectious diseases and fever of unknown origin.[10,11,19] High uptake of F^{18}-FDG has also been reported in patients with sarcoidosis.[6,20–22] Presumably inflammatory cells including activated macrophages, lymphocytes and neutrophils are responsible for the accumulation of FDG.[19,23–25] To date, an increase of the number of neutrophils in BAL-fluid was found to be associated with an unfavourable outcome.[5,26] According to these findings it is tempting to speculate that increased FDG uptake in the pulmonary parenchyma is associated not only with inflammatory activity but also with disease severity.

Recently, the value of PET in assessing inflammatory activity in newly diagnosed, symptomatic sarcoidosis patients was shown with a high (94%) sensitivity.[6] However, the potential of PET to depict inflammatory activity in patients with persistent disabling symptoms has to be established. The aim of this retrospective study was to assess the presence of inflammatory activity using PET in sarcoidosis patients with unexplained persistent disabling symptoms for at least one year and the association between PET findings and serological inflammatory markers.

Materials and methods

Study population

Between June 2005 and June 2010 a PET was performed in 122/512 sarcoidosis patients referred to the interstitial lung disease service (ild care team) of the department of Respiratory Medicine at the Maastricht University Medical Centre (Maastricht, The Netherlands), a tertiary referral centre. The indication for the PET was the presence of unexplained disease related disabling symptoms that persisted for at least one year. Persistent disabling symptoms were defined as the presence of more than one symptom that had substantial influence on quality of life, and that could not be explained with the results of routine investigations including lung function tests or Chest X-rays (CXR). These symptoms included fatigue (Fatigue Assessment Scale (FAS) $\geq$22),[27] symptoms compatible with small fibre neuropathy (SFN; SFN Screenings List (SFNSL) score $\geq$11),[28] arthralgia and/or muscle pain, dyspnoea (MRC dyspnoea scale $\geq$3), exercise intolerance or cough. Laboratory testing, lung function testing and a CXR were performed within an interval of less than two weeks of the PET scanning. Blood samples were simultaneously obtained. In the routine workup all patients completed the FAS[27] and the SFNSL.[28] Sarcoidosis was proven by the presence of non-caseating granulomas on biopsy according with a compatible clinical picture. Moreover, other causes of granulomatous disease were excluded, according with the consensus statement on sarcoidosis of the American Thoracic Society (ATS)/European Respiratory Society (ERS)/World Association of Sarcoidosis and Other Granulomatous

Disorders (WASOG).[1] Exclusion criteria were the coexistence of other diseases that are able to cause PET positive findings. Therefore, five patients with common variable immunodeficiency (CVID), five patients with malignancy and one patient with both rheumatoid arthritis and amyloidosis were excluded. After exclusion for these criteria, 111 patients were selected. Due to an inappropriate interval between PET scanning and obtaining blood samples another 22 patients were excluded. Finally, 89 patients were included. Inflammatory activity was considered to be present in case the PET demonstrated positive findings. Relevant clinical data were gathered retrospectively. All patients signed an informed consent.

Laboratory tests

Serum ACE was measured by colorimetric method (cat. no. FU 116; Fujirebio Inc.). The imprecision of the ACE assay was $<5.6\%$ and the reference interval 9–25 $U \cdot L^{-1}$.

Serum levels of sIL-2R were analysed in commercially available Diaclone ELISA kits (Sanquin, Amsterdam, The Netherlands). Normal values were assessed in 40 healthy controls mean $\pm$ 2SD: 240–3154 pg mL^{-1}. Serum levels of neopterin were evaluated by the principle of a competitive ELISA, using a kit produced by IBL (Hamburg, Germany). Serum levels were considered elevated if >2.5 ng mL^{-1}.

Results for combined serological inflammatory marker testing (ACE, sIL-2R and neopterin) were considered positive if at least one of the serological markers was elevated.

CRP was measured using a turbidimetric method performed using the Beckman synchron CX-7 system (kit 465231; Mijdrecht, The Netherlands. The detection limit for CRP was 2 μg mL^{-1}, with a normal range of 2–9 μg mL^{-1}.

Radiology

According to the Scadding radiographic staging system, five stages of radiographical abnormality were recognised: stage 0 (normal Chest X-ray (CXR)), stage I (bilateral hilar lymphadenopathy (BHL)), stage II (BHL and parenchymal abnormalities), stage III (parenchymal abnormalities without BHL) and stage IV (end-stage lung fibrosis).[1]

Lung function tests

Forced vital capacity (FVC) was measured with a pneumotachograph (Masterlab, Jaeger, Würzburg, Germany). The diffusing capacity for carbon monoxide (DLCO) was measured by the single-breath method (Masterlab, Jaeger, Würzburg, Germany). Values were expressed as a percentage of predicted values.[29]

F^{18}-FDG -PET/CT

A Fluorine^{18}-Fluorodeoxyglucose-Positron emission tomography/Computed tomography (F^{18}-FDG-PET/CT) scan was performed. Patients were scanned using a Gemini® PET-CT (Philips Medical Systems) scanner with time-of-flight (TOF) capability, together with a 64-slice Brilliance CT scanner. This scanner has a transverse and axial Field of View (FOV) of, respectively 57.6 and 18 cm. The spatial resolution is around 5 mm.

Patients were fasting for at least 6 h before the examination. In all patients blood glucose was measured to ensure that the blood glucose was below 10 mmol L^{-1}. F^{18}-FDG (GE Health, Eindhoven, The Netherlands) was injected intravenously and followed by physiologic saline (10 mL). The injected total activity of FDG depended on the weight of the patient. Mean injected dose was: 200 MBq. After a resting period of 45 min (time needed for uptake of FDG) PET and CT images were acquired from the head to the feet. A low dose CT-scan was performed without intravenous contrast and was used for attenuation correction of the PET images. The PET images were acquired in 5-min bed positions. The complete PET data set was reconstructed iteratively with a reconstruction increment of 5 mm to provide isotropic voxel.

All PET scans were examined independently and blindly by two experienced nuclear physicians (MvK and SV) to assess the inter-observer variability. Findings were scored as either positive or negative. PET findings were described as positive if increased FDG-uptake was seen in the mediastinum and/or lung parenchyma or on extrathoracic sites like lymph nodes, visceral organs (like parotis, liver, spleen), nasopharynx, skin, muscle, and bone. Positive findings were classified as thoracic and/or extrathoracic. Thoracic PET positive findings were subdivided as PET positive findings in the pulmonary parenchyma and/or mediastinal lymph nodes. The maximal Standard Uptake Value (SUVmax) was measured at the various PET positive localisations.

Statistical procedure

Statistical analyses were performed using SPSS, version 15.0 for Windows. Differences between groups in demographic characteristics and clinical characteristics (such as duration of disease and pulmonary function tests) were tested for statistical significance using the Student's *t*-test for independent samples in case of continuous variables or chi-square test in case of categorical variables. A *p*-value of <0.05 (two sided) was considered to indicate statistical significance. ROC analysis was performed for assessing the association between PET positive results and the results of the separate serological markers. As a measure of internal consistency and reliability to assess the inter-observer agreement, kappa statistics were used. A κ-value less than 0.20 indicates poor, between 0.21 and 0.40 moderate, between 0.41 and 0.60 fair, between 0.61 and 0.80 good and between 0.81 and 1.00 excellent agreement, respectively.

Results

General clinical characteristics

Disabling symptoms of the 89 studied patients (81 Caucasians, 6 Negroids and 2 Asians) included fatigue (80%; FAS $\geq$22), symptoms compatible with small fibre neuropathy (SFN; 70%; SFNSL score $\geq$11), arthralgia and/or muscle pain

(59%), dyspnoea (45%; MRC dyspnoea scale ≥3), exercise intolerance (38%) or cough (21%).

Treatment at admission (20 cases: 22.5%) consisted of prednisone alone (median dose 15 mg daily (range 10—40 mg) in nine patients (10%), methotrexate (MTX) alone (median dose 10 mg a week (range 7.5—12.5 mg)) in four patients (4%), prednisone combined with MTX (all patients 10 mg prednisone daily and median dose MTX 10 mg a week (range 10—12.5 mg)) in seven patients (8%).

PET scan results

A summary of the demographic and clinical characteristics of the 89 studied sarcoidosis patients subdivided in PET negative ($n = 24$: 27%) and PET positive ($n = 65$: 73%) cases is shown in Table 1. Ninety-two % of these latter patients demonstrated PET positive thoracic findings, 80% one or more extrathoracic localisation(s), whereas 8% only extrathoracic localisations, respectively. The involved extrathoracic organs included peripheral lymph nodes ($n = 48$), bone ($n = 14$), spleen ($n = 11$), muscle ($n = 10$) liver ($n = 6$), skin ($n = 2$), and central nervous system ($n = 2$), respectively. No correlation between serologic inflammatory markers and the various involved extrathoracic organs was found. Analysis of the group with extrathoracic localisation compared with the group with exclusively thoracic PET positive findings showed no significant differences regarding serological markers or other patient characteristics.

Eight of the patients with CXR stage 0 (33%) were PET positive of whom only four had exclusively extrathoracic localisations and only three had serological signs of inflammation.

Only one of the included patients with CXR stage IV ($n = 15$) was PET negative, of the PET positive patients 13 were positive in the pulmonary parenchyma and 10 extrathoracic. Of the PET positive patients with CXR stage IV, the majority (85%) had serological signs of inflammation. An example of a sarcoidosis patient with Chest X-ray stage IV and signs of inflammatory activity on PET/CT is shown in Fig. 2.

The inter-observer agreement concerning the PET scores is shown in Table 2.

Median SUV of the PET positive localisations was 7.0 (2.5—33.3).

Serological inflammatory markers and PET results

Mean ACE levels were calculated after exclusion of ACE values <9U/L ($n = 9$), because these values were under the lower limit of the reference value and due to the use of ACE-inhibitors. Neopterin values were only available in 62 patients (70%). Levels of sIL-2R and neopterin differed

Table 1 Summary of relevant clinical characteristics of the studied sarcoidosis patients divided according to the absence ($n = 24$) and presence ($n = 65$) of PET abnormalities and subdivided in a treatment and no treatment group.

	PET negative patients			PET positive patients		
	total PET - population	treatment	no treatment	total PET + population	treatment	no treatment
Number	24	6	18	65	14	51
Age, yrs	49 (24—73)	44 (33—55)	50 (24—73)	45 (26—76)	48 (28—66)	44 (26—76)
Sex (male)	15 (63%)	2 (33%)	13 (72%)	35 (54%)	9 (64%)	26 (51%)
Time since diagnosis, yrs	4 (1—14)	1 (1—13)	7 (1—14)	2 (1—27)	3 (1—19)	1 (1—27)
BMI	27.7 ± 4.9	26.7 ± 3.9	28.0 ± 5.2	28.1 ± 5.6	28.0 ± 3.8	28.5 ± 6.1
Chest X-ray stage 0/I/II/III/IV	16/2/3/2/1	3/0/2/1/0	13/2/1/1/1	8/17/24/2/14	1/3/3/0/7	7/14/21/2/7
Thoracic PET +	0	0	0	60 (92%)	14 (100%)	46 (90%)
Mediastinal lymph nodes PET +	0	0	0	54 (83%)	12 (86%)	42 (82%)
Pulmonary parenchyma PET +	0	0	0	43 (66%)	10 (71%)	33 (65%)
Extrathoracic PET+	0	0	0	52/65 (80.0%)	10 (71%)	42 (82%)
FVC (% pred)	101 ± 19	90 ± 21	105 ± 18	91 ± 26	74 ± 20	96 ± 25
DLCO (% pred)	80 ± 15	75 ± 8	82 ± 16	71 ± 19	58 ± 19	76 ± 17
ACE (9—25 $U \cdot L^{-1}$)	17 ± 4	13 ± 3.0	18 ± 4	21 ± 6	21 ± 5	21 ± 7
sIL-2R (240—3154 pg mL^{-1})	1599 ± 671	1275 ± 633	1706 ± 666	4526 ± 2577[a]	4340 ± 2438[a]	4577 ± 2634[a]
Neopterin (<2.5 ng mL^{-1}; $n = 62$)	1.7 ± 0.4	1.5 ± 0.7	1.7 ± 0.3	3.2 ± 1.6[a]	2.8 ± 1.0[a]	3.3 ± 1.7[a]
CRP (2—9 μg mL^{-1}; $n = 85$)	4.3 ± 4.2	4.7 ± 4.6	4.1 ± 4.2	11.9 ± 16.1[b]	9.6 ± 11.2	12.5 ± 17.3

Data are presented as median with range in parentheses; mean ± SD; absolute numbers or percentages if appropriate. PET: Positron Emission Tomography; -: negative; +: positive; yrs: years; BMI: Body Mass Index; FVC: forced vital capacity; % pred: percentage of predicted values; DLCO: diffusion capacity for carbon monoxide; ACE: serum angiotensine converting enzyme; sIL-2R: soluble interleukin-2 Receptor; CRP: C-reactive protein.

[a] $p<0.001$ PET + versus PET-.

[b] $p<0.05$ PET + versus PET-.

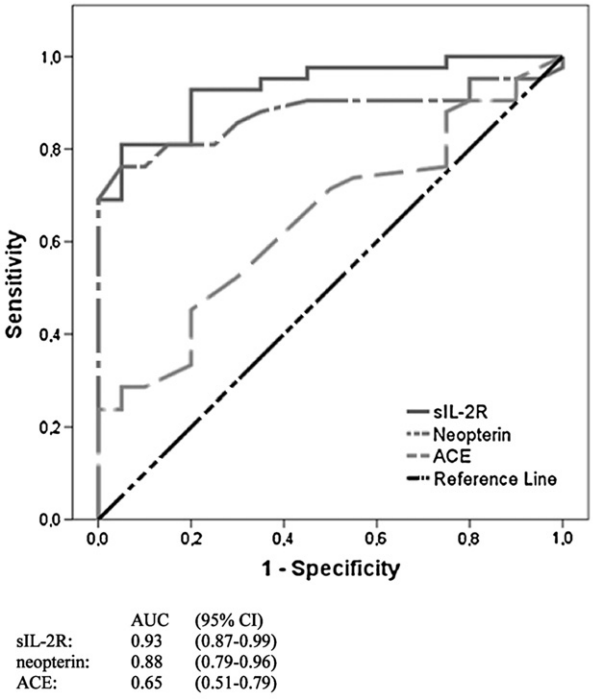
Table 2 Inter-observer agreement concerning PET scores.

	Weighted kappa
PET positivity	1.000
Thoracic PET positivity	0.975
Mediastinal lymph nodes PET positivity	0.931
Pulmonary parenchyma PET positivity	0.912
Extrathoracic PET positivity	1.000

PET: Positron Emission Tomography.

significantly between the PET positive and PET negative group ($p < 0.001$; Table 1). In the PET negative group, in none of the patients serological signs of inflammation were found, whereas in the PET positive group 13 patients (20%) had no serological signs of inflammation (Table 3).

ROC analysis results for the association between PET positive results and the results of the separate serological markers are presented in Fig. 1. Overall, the area under the curve (AUC) of sIL-2R and neopterin is significantly different from the null-hypothesis, true area = 0.5 (meaning no discrimination). Sensitivity and specificity of both the separate and the combined results of the serological



sIL-2R: soluble interleukin-2 Receptor; ACE: serum angiotensine converting enzyme; CI: confidence interval

Fig. 1 ROC curve of the association between PET positive results and serological inflammatory activity marker separately.

Table 3 The association between PET results and serological inflammatory activity markers.

Marker	PET -	PET +
serum angiotensine converting enzyme (ACE) number	24	65
ACE − ($n = 75$)	100% ($n = 24$)	78% ($n = 51$)
ACE + ($n = 14$)	0% ($n = 0$)	22% ($n = 14$)
soluble interleukin-2 receptor (sIL-2R) number	24	65
sIL-2R − ($n = 45$)	100% ($n = 24$)	32% ($n = 21$)
sIL-2R + ($n = 44$)	0% ($n = 0$)	68% ($n = 44$)
neopterin number	20	42
neopterin − ($n = 35$)	100% ($n = 20$)	36% ($n = 15$)
neopterin + ($n = 27$)	0% ($n = 0$)	64% ($n = 27$)
Combined serological inflammatory markers (CIM) number	24	65
CIM − ($n = 37$)	100% ($n = 24$)	20% ($n = 13$)
CIM + ($n = 52$)	0% ($n = 0$)	80% ($n = 52$)
C-reactive protein (CRP) number	23	62
CRP − ($n = 61$)	83% ($n = 19$)	68% ($n = 42$)
CRP + ($n = 24$)	17% ($n = 4$)	32% ($n = 20$)

PET: Positron Emission Tomography; -: negative; +: positive; Combined serological inflammatory markers: defined as positive if at least one serological marker (ACE, sIL-2R or neopterin) was elevated.

inflammatory markers for detecting inflammatory activity as shown by PET is demonstrated in Table 3. The sensitivity of combined results of the serological markers was 80%. Specificity was 100% for all serological markers. Positive predictive value (PPV) was 100% in all cases. Negative predictive value of combined results of the serological markers was 65%. As shown in Table 3, adding CRP to the serological inflammatory classification would increase the sensitivity, but decrease the excellent specificity and PPV of the combined serological markers.

Analysis of the relation between levels of the studied serological markers and the Chest X-ray (CXR) stages in the patients with PET positive findings in the pulmonary parenchyma showed no significant differences. In the group with PET positive findings in the pulmonary parenchyma, TLCO and FVC were significantly lower in the patients with CXR stage IV compared with the other CXR stages. Comparison of clinical or laboratory parameters between PET positive CXR stage IV patients ($n = 14$) and PET negative CXR stage IV patients ($n = 1$) was not possible due to the low number in the latter group.

Discussion

This study demonstrated that the majority of sarcoidosis patients with unexplained persistent disabling symptoms had signs of inflammatory activity detected by PET positive findings. PET positive findings were associated with increased levels of serological inflammatory parameters in sarcoidosis, especially with sIL-2R and neopterin levels.

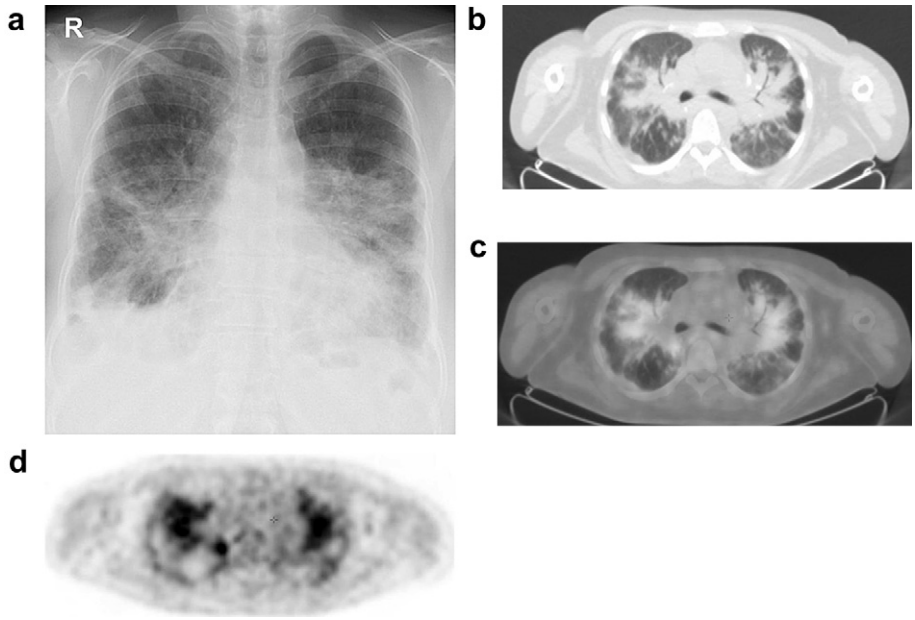


Fig. 2 Example of a sarcoidosis patient with Chest X-ray stage IV and signs of inflammatory activity on PET/CT. (a) Chest X-ray showing bilateral irregular opacities and some surrounding lung deformation. (b) CT-scan image at thoracic level showing bilateral perihilar opacities, bilateral hilar and mediastinal lymphadenopathy with calcifications and deformation of the surrounding lung architecture. (c) PET/CT fusion image at thoracic level showing diffuse increased FDG-uptake in the bilateral perihilar opacities. (d) PET image at thoracic level showing diffuse bilateral increased FDG-uptake in the pulmonary parenchyma.

Positive predictive value of serological inflammatory marker testing for the presence of inflammatory activity on PET was excellent (100% in this study). However, negative predictive value of serological inflammatory marker testing, even if the results were combined, was moderate.

Assessing inflammatory activity in sarcoidosis patients without lung functional or radiological deterioration but with unexplained persistent disabling symptoms often is problematic. In this study, the value of PET for assessment of inflammation in this difficult category of patients is demonstrated since almost 75% of the patients with persistent disease related symptoms had signs of inflammatory activity as detected by PET. Although the study design and population was not completely comparable this was in line with the results of Teirstein et al.[20] It is important to stress that either normal CXR findings (stage 0) or CXR stage IV (and thus signs of fibrosis) do not exclude inflammatory activity in the pulmonary parenchyma. The latter still harbours significant inflammatory lesions that might be target, together with respiratory functional impairment, for appropriate treatment. Because of the radiation dose and expense of performing PET, measurement of serological inflammatory markers should be, after excluding lung functional or radiological deterioration, first performed for assessing inflammatory activity in sarcoidosis patients with unexplained persistent disabling symptoms. Using the strategy of combining serological marker testing provided enough information to determine the presence of inflammatory activity in 58% of the studied patients (52/89). However, since the negative predictive value of serological marker testing is moderate (65%), negative serological test results do not exclude the presence of inflammatory activity and therefore the surplus value of PET for assessment of inflammatory activity is situated in the group of symptomatic sarcoidosis patients without serological signs of inflammatory activity.

In contrast with Grutters et al., no association between sIL-2R levels and extrathoracic localisations was found in our population.[15] A possible explanation would be that the prevalence of extrathoracic localisations in our study was higher, which could be due to a better sensitivity of PET for detecting extrathoracic localisation than the sensitivity of the used diagnostic techniques (no use of PET or Gallium scanning) in the latter study to detect extrathoracic localisation. The prevalence of extrathoracic localisation in the PET positive patients in our study is comparable to the prevalence found in other studies using PET in active sarcoidosis.[6,22] Although determination of the frequency of extrathoracic sarcoidosis localisations was not the aim of this study, the established high frequency of these findings shows that this is another merit of performing PET (assessing extent of the disease).

The disabling symptoms in the 24 PET negative patients can be caused by multiple factors.[9,30,31] Sleeping disorders may interact with fatigue in sarcoidosis.[32] Twenty four of the studied patients were evaluated for the presence or absence of OSAS. Five of these latter patients appeared to have an OSAS. However, these patients also suffered from other disabling symptoms despite adequate treatment for their OSAS. PET appeared to be positive in all these patients, showing that inflammatory activity was still present (data not shown).

In the Sarcoidosis Investigators study, results of the post hoc analysis suggested a greater benefit of infliximab therapy in patients with more severe disease.[33] This indicates the importance of establishing inflammatory activity in patients with CXR stage IV disease since it may have therapeutic implications and thus this underlines the value

of PET especially in this group of chronic sarcoidosis patients. However, the exact value of the presence of inflammatory activity for treatment decisions needs to be established in future studies. A study in a small cohort of sarcoidosis patients treated with infliximab showed that changes in PET-imaging correlated with clinical signs of improvement to a considerable extent.[4] Apart from the value of PET-imaging in treatment decisions or follow-up, simply validating that there is an organic cause for the symptoms can be extremely reassuring to many patients.[34]

Since this was a retrospective study and bronchoalveolar lavage (BAL) was infrequently performed close to the date of the PET, we only have gathered data on BAL fluid analysis of 20 PET-positive patients of whom 6 appeared to have stage IV disease on chest X-ray. All 20 cases showed signs of inflammation in the BAL (increased number of lymphocytes as well as polymorphonuclear neutrophils, indicating disease severity).[5,26] These signs were even more prominent in the 6 cases with chest X-ray stage IV (data not shown). This is in line with Keijsers R et al. who found that increased FDG uptake in the pulmonary parenchyma correlated with the number of neutrophils in BAL-fluid of sarcoidosis patients.[23]

Several attempts to define disease activity in sarcoidosis have been undertaken. However, no single marker available can accurately predict the likelihood of activity or progression.[3,16] Comparing PET results with pulmonary function and CXR only addresses pulmonary involvement and does not provide any information about the presence or absence of systemic inflammatory activity. Since PET can be considered as a useful additional tool in the evaluation of systemic sarcoidosis, comparison with the already existing markers of systemic inflammatory activity is needed. Although we are aware of the limitations of serological markers, these were in the present clinical study the most appropriate.

Our centre is a referral centre for sarcoidosis, and, therefore the refractory character may be more severe than in a general sarcoidosis population. Moreover, PET was not performed in every referred patient. This might cause a selection bias. However, a PET scan was really not necessary in every patient. The questions and reasons for referring the patients to our interstitial lung disease service were very divers. It varied from a therapeutic advice in refractory sarcoidosis like hypercalcaemia, uveitis or severe respiratory impairment not responding to corticosteroids to questions about genetic issues or occupational exposures. In these patients a PET was not indicated to answer the questions appropriately. That does not mean the patients had less severe sarcoidosis, however. The subpopulation that did not have a PET scan did not differ from the population who underwent a PET regarding clinical data (data not shown). Although no other diseases that are able to cause PET positive findings were diagnosed during the follow-up, other causes of PET positive findings cannot be excluded completely.

In conclusion, in the absence of serological signs of inflammation, PET appeared to be of additional value to assess inflammatory activity in sarcoidosis patients with unexplained persistent disabling symptoms. In almost 75% of these sarcoidosis patients PET was positive, with the presence of extrathoracic lesions in 80% of them. Remarkably, the majority of patients with radiological stage IV disease had PET positive findings. Combining results of serological inflammatory markers increased sensitivity for detecting inflammatory activity in sarcoidosis without false positive results. Future studies are needed to evaluate the additional value of PET in the follow-up and management of the disease.

Conflicts of interests

No conflicts of interests.

References

1. Hunninghake GW, Costabel U, Ando M, et al. ATS/ERS/WASOG statement on sarcoidosis. American thoracic Society/European respiratory Society/World association of sarcoidosis and other granulomatous disorders. *Sarcoidosis Vasc Diffuse Lung Dis* 1999;**16**:149—73.
2. Baughman RP, Lower EE, Drent M. Inhibitors of tumor necrosis factor (TNF) in sarcoidosis: who, what, and how to use them. *Sarcoidosis Vasc Diffuse Lung Dis* 2008;**25**:76—89.
3. Consensus conference: Activity of sarcoidosis. Third WASOG meeting, Los Angeles, USA, September 8—11, 1993. Eur Respir J 1994;7:624—627.
4. Keijsers RG, Verzijlbergen JF, van Diepen DM, van den Bosch JM, Grutters JC. 18F-FDG PET in sarcoidosis: an observational study in 12 patients treated with infliximab. *Sarcoidosis Vasc Diffuse Lung Dis* 2008;**25**:143—9.
5. Ziegenhagen MW, Rothe ME, Schlaak M, Muller-Quernheim J. Bronchoalveolar and serological parameters reflecting the severity of sarcoidosis. *Eur Respir J* 2003;**21**:407—13.
6. Keijsers RG, Verzijlbergen FJ, Oyen WJ, et al. 18F-FDG PET, genotype-corrected ACE and sIL-2R in newly diagnosed sarcoidosis. *Eur J Nucl Med Mol Imaging* 2009;**36**:1131—7.
7. Lazar CA, Culver DA. Treatment of sarcoidosis. *Semin Respir Crit Care Med* 2010;**31**:501—18.
8. De Vries J, Rothkrantz-Kos S, van Dieijen-Visser MP, Drent M. The relationship between fatigue and clinical parameters in pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2004; **21**:127—36.
9. Marcellis RG, Lenssen AF, Elfferich MD, et al.: Exercise capacity, muscle strength and fatigue in sarcoidosis. Eur Respir J 2011;In press.
10. Love C, Tomas MB, Tronco GG, Palestro CJ. FDG PET of infection and inflammation. *Radiographics* 2005;**25**:1357—68.
11. El-Haddad G, Zhuang H, Gupta N, Alavi A. Evolving role of positron emission tomography in the management of patients with inflammatory and other benign disorders. *Semin Nucl Med* 2004;**34**:313—29.
12. Biller H, Zissel G, Ruprecht B, et al. Genotype-corrected reference values for serum angiotensin-converting enzyme. *Eur Respir J* 2006;**28**:1085—90.
13. Tomita H, Ina Y, Sugiura Y, et al. Polymorphism in the angiotensin-converting enzyme (ACE) gene and sarcoidosis. *Am J Respir Crit Care Med* 1997;**156**:255—9.
14. Ziegenhagen MW, Benner UK, Zissel G, et al. Sarcoidosis: TNF-alpha release from alveolar macrophages and serum level of sIL-2R are prognostic markers. *Am J Respir Crit Care Med* 1997; **156**:1586—92.
15. Grutters JC, Fellrath JM, Mulder L, et al. Serum soluble interleukin-2 receptor measurement in patients with sarcoidosis: a clinical evaluation. *Chest* 2003;**124**:186—95.
16. Prasse A, Katic C, Germann M, et al. Phenotyping sarcoidosis from a pulmonary perspective. *Am J Respir Crit Care Med* 2008;**177**:330—6.

17. Muller-Quernheim J. Serum markers for the staging of disease activity of sarcoidosis and other interstitial lung diseases of unknown etiology. *Sarcoidosis Vasc Diffuse Lung Dis* 1998;**15**: 22—37.
18. Rothkrantz-Kos S, van Dieijen-Visser MP, Mulder PG, Drent M. Potential usefulness of inflammatory markers to monitor respiratory functional impairment in sarcoidosis. *Clin Chem* 2003;**49**:1510—7.
19. Bomanji J, Almuhaideb A, Zumla A. Combined PET and X-ray computed tomography imaging in pulmonary infections and inflammation. *Curr Opin Pulm Med* 2011;**17**:197—205.
20. Teirstein AS, Machac J, Almeida O, et al. Results of 188 whole-body fluorodeoxyglucose positron emission tomography scans in 137 patients with sarcoidosis. *Chest* 2007;**132**:1949—53.
21. Braun JJ, Kessler R, Constantinesco A, Imperiale A. 18F-FDG PET/CT in sarcoidosis management: review and report of 20 cases. *Eur J Nucl Med Mol Imaging* 2008;**35**:1537—43.
22. Nishiyama Y, Yamamoto Y, Fukunaga K, et al. Comparative evaluation of 18F-FDG PET and 67Ga scintigraphy in patients with sarcoidosis. *J Nucl Med* 2006;**47**:1571—6.
23. Keijsers RG, Grutters JC, van Velzen-Blad H, et al. (18)F-FDG PET patterns and BAL cell profiles in pulmonary sarcoidosis. *Eur J Nucl Med Mol Imaging* 2010;**37**:1181—8.
24. Basu S, Saboury B, Werner T, Alavi A. Clinical Utility of FDG-PET and PET/CT in Non-malignant thoracic disorders. *Mol Imaging Biol*; 2010.
25. Ishimori T, Saga T, Mamede M, et al. Increased (18)F-FDG uptake in a model of inflammation: concanavalin A-mediated lymphocyte activation. *J Nucl Med* 2002;**43**:658—63.
26. Drent M, Jacobs JA, de Vries J, et al. Does the cellular bronchoalveolar lavage fluid profile reflect the severity of sarcoidosis? *Eur Respir J* 1999;**13**:1338—44.
27. de Kleijn WP, Elfferich MD, De Vries J, et al. Fatigue in sarcoidosis: american versus Dutch patients. *Sarcoidosis Vasc Diffuse Lung Dis* 2009;**26**:92—7.
28. Hoitsma E, De Vries J, Drent M. The small fiber neuropathy screening list: Construction and cross-validation in sarcoidosis. *Respir Med* 2011;**105**:95—100.
29. Quanjer PH, Tammeling GJ, Cotes JE, et al. Lung volumes and forced ventilatory flows. Report working Party Standardization of lung function tests, European Community for Steel and Coal. Official statement of the European respiratory Society. *Eur Respir J Suppl* 1993;**16**:5—40.
30. James DG. Complications of sarcoidosis. Chronic fatigue syndrome. *Sarcoidosis* 1993;**10**:1—3.
31. Korenromp IH, Heijnen CJ, Vogels OJ, van den Bosch JM, Grutters JC. Characterization of chronic fatigue in sarcoidosis in clinical remission. *Chest* 2011;**140**:441—7.
32. Verbraecken J, Hoitsma E, van der Grinten CP, et al. Sleep disturbances associated with periodic leg movements in chronic sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2004;**21**:137—46.
33. Baughman RP, Drent M, Kavuru M, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. *Am J Respir Crit Care Med* 2006;**174**:795—802.
34. Hoitsma E, Faber CG, van Santen-Hoeufft M, et al. Improvement of small fiber neuropathy in a sarcoidosis patient after treatment with infliximab. *Sarcoidosis Vasc Diffuse Lung Dis* 2006;**23**:73—7.