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Extent of disease activity assessed by ^{18}F-FDG PET/CT in a Dutch sarcoidosis population

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Abstract. *Background:* Sarcoidosis is characterized by a wide range of disease manifestations. In the management and follow-up of sarcoidosis patients, knowledge of extent of disease, activity and severity is crucial. *Objectives*: The aim of this study was to assess the extent, distribution and consistency of inflammatory organ involvement using ^{18}F-FDG PET/CT (PET) in sarcoidosis patients with persistent disabling symptoms. *Methods:* Retrospectively, sarcoidosis patients who underwent a PET between 2005 and 2011 (n=158) were included. Clinical data were gathered from medical records and PET scans were evaluated. Positive findings were classified as thoracic and/or extrathoracic. *Results:* Of the studied PET positive sarcoidosis patients (n=118/158; 75%), 93% had intrathoracic activity (79% mediastinal and 64% pulmonary activity, respectively) and 75% displayed extrathoracic activity (mainly peripheral lymph nodes, bone/bone marrow, and spleen). Hepatic positivity was always accompanied by splenic activity, whereas the majority of patients with parotid gland, splenic or bone/bone marrow activity showed lymph node activity. A substantial number of patients with PET positive pulmonary findings (86%) had signs of respiratory functional impairment. No obvious association between hepatic, splenic or bone/bone marrow activity and their corresponding laboratory abnormalities suggestive of specific organ involvement, was found. *Conclusions:* The majority of studied patients appeared to have PET positive findings (75%), of which a high proportion (75%) displayed extrathoracic activity. Hence, PET can be especially useful in the assessment of extent, distribution and consistency of inflammatory activity in sarcoidosis to provide an explanation for persistent disabling symptoms and/or to provide a suitable location for biopsy. *(Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 37-45)*

Key words: Fluorine^{18}-fluorodeoxyglucose (^{18}F-FDG), Positron emission tomography/computed tomography (PET/CT), Inflammation, Extrathoracic, Sarcoidosis

Introduction

Sarcoidosis is a multisystemic disease characterized by inflammatory activity with formation of non-caseating granulomas in various organ systems (1, 2). Although the lungs are most commonly affected, no organ is immune to sarcoidosis (3). Sarcoidosis activity can lead to a wide range of disease severity, varying from minimal involvement to derangement of organ

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physiology with functional impairment, such as pulmonary fibrosis or devastating extrapulmonary complications (1, 2, 4-6). Since practically every organ can be involved, patients may present with a wide variety of clinical signs and symptoms (1, 2). Since the clinical course of sarcoidosis is extremely variable, careful assessment of disease extension, severity and activity by organ, with emphasis on vital target organs, is warranted (2, 7). The assessment of inflammatory disease activity is helpful to monitor the course of the disease and guide therapeutic strategies and also in defining endpoints of various disease manifestations for clinical trials (2, 4, 8).

An objective system for specific organ assessment to estimate sarcoidosis disease activity, cause and extent, is still lacking. In general, there is no single test or marker available to evaluate specific organ involvement. Each of the currently available markers has its shortcomings and assessment of specific organ involvement may be beyond the scope of the diagnostic tools used (9). A correct estimation of the incidence of organ involvement is therefore, hampered by the difficulty of a reliable confirmation of disease activity for each separate organ. In the ACCESS (A Case Control Etiologic Study of Sarcoidosis) research group study, organ involvement was determined by using an assessment system based on findings from history, physical examination, and laboratory testing (3, 10). In recent years, fluorine18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT or PET) has been shown to be a sensitive method to assess inflammatory activity and the extent of disease in sarcoidosis (11-21).

The aim of this retrospective study was to assess the extent, distribution and consistency of organ involvement detected by PET in sarcoidosis patients with persistent disabling symptoms.

Methods

Study population

The material and methods used in this study have been previously described by our group (18, 19, 22). Between June 2005 and September 2011 a PET was performed in 191/608 sarcoidosis patients referred to the former ild (interstitial lung disease) care team, a tertiary referral centre of the Department of Respiratory Medicine of the Maastricht University Medical Centre+ (MUMC+) in the Netherlands. 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) ≥22) (23), symptoms compatible with small fibre neuropathy (SFN; SFN Screenings List (SFNSL) score ≥11) (24), arthralgia and/or muscle pain, dyspnea (Medical Research Council (MRC) dyspnea scale ≥3), exercise intolerance or cough. Lung function testing and laboratory tests were performed within an interval of less than two weeks of the PET scanning. In the routine workup all patients completed the FAS (23) and the SFNSL (24). Sarcoidosis was proven by the presence of noncaseating 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 consisted of other diseases that are able to cause PET positive findings. Therefore, five patients with common variable immunodeficiency, five patients with malignancy and one patient with both rheumatoid arthritis and amyloidosis were excluded. Due to an inappropriate interval between PET scanning and obtaining blood samples another 22 patients were excluded. Finally, 158 patients were included. Inflammatory activity was considered to be present in case the PET demonstrated positive findings. Relevant clinical data were gathered retrospectively. This study was approved by the Medical Ethics Board of the MUMC+ (METC 11-4-116) and all patients signed an informed consent.

Laboratory tests

Serum levels of angiotensin-converting enzyme (ACE), soluble-interleukin2-receptor (sIL2R), C-reactive protein (CRP), alanine aminotransferase

(ALT), and alkaline phosphatase (ALP) were determined as described previously (22). Serum liver test abnormalities (LTA) were defined as being present, if the level of the upper limit of normal times 1.5 was exceeded by ALT (>60 U/L for men and >52.5 U/L for women) and/or ALP (>187.5 U/L for both men and women). Hemoglobin (Hb) level, white blood cell (WBC) count and thrombocyte count were determined on a Sysmex XE-5000 (Sysmex, Hamburg, Germany), according to the manufacturer's instructions. Lower reference values for Hb were 7.3 mmol/L for the female population and 8.2 mmol/L for the male population; $3.5x10^9$/L for WBC and $150x10^9$/L for thrombocyte count.

Pulmonary function tests

Forced expiratory volume in 1 s (FEV1) and the forced vital capacity (FVC) were measured with a pneumotachograph (Masterlab, Jaeger). The diffusing capacity for carbon monoxide (DLCO) was measured by the single-breath method (Masterlab, Jaeger, Würzburg, Germany) (25). Values were expressed as a percentage of predicted values (25). Respiratory functional impairment (RFI) was defined as present if FEV1 was <80%, FVC was <80%, or DLCO was <80% (25).

^{18}F-FDG PET/CT

A ^{18}F-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 of respectively 57.6 and 18 cm. The transverse spatial resolution is around 5 mm. Patients were fasting for at least 6 hours before the examination. In all patients blood glucose was measured to ensure that the blood glucose was below 10 mmol/L. ^{18}F-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 used for attenuation correction of the PET images. Typical values were 120 kVp; 30mAs; volume computed dose index, and 1.8 mGy. The PET images were acquired in 5-minute 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 evaluated blinded and independently by two experienced nuclear physicians (MvK and SV). The inter-observer agreement concerning the PET scores was excellent (weighted kappa varied from 0.912-1.000) (18). Findings were scored as either positive or negative. PET findings were described as positive if increased FDG-uptake was seen in the mediastinum, lung parenchyma or on extrathoracic sites including peripheral lymph nodes, spleen, liver, bone/bone marrow, parotid glands, nasopharynx, skin, muscle, and myelum. Positive findings were classified as thoracic and/or extrathoracic. Positive thoracic PET findings were subdivided as PET positive findings in the pulmonary parenchyma and/or mediastinal lymph nodes.

Statistical procedure

Statistical analyses were performed using SPSS, version 16.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Results are presented as means (±SD) for normally distributed continuous variables and as absolute numbers and percentages for nominal or ordinal variables. Differences between groups in demographic and clinical characteristics were tested for statistical significance using the Student's t-test iteratively for independent samples in case of continuous variables or Pearson's Chi-squared test in case of nominal or ordinal variables. A p-value of ≤0.05 was considered to indicate statistical significance.

Results

Demographic and clinical characteristics

In Figure 1 the enrolment and outcome of interpretation of the PET scans of the studied sarcoidosis sample are shown. A summary of the demographic and clinical characteristics of the 158 studied patients, subdivided in patients with PET negative (n=40: 25%) and PET positive (n=118: 75%)

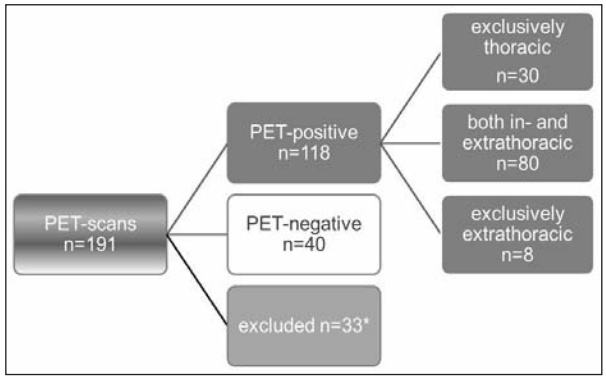

Fig. 1. Enrolment, exclusion and outcome of interpretation of the PET scans of the studied Dutch sarcoidosis sample. *A total of 33 PET scans, obtained from 33 patients, were excluded due to co-morbity (n=11) or an inappropriate interval between PET scanning and obtaining blood samples (n=22); PET, ^{18}F-FDG PET/CT.

findings, is shown in Table 1. The total group consisted of 146 Caucasians, eight were of African-American origin and four of Asian origin. Reported disabling symptoms consisted of fatigue (81%; FAS ≥22), symptoms compatible with SFN (72%; SFNSL score ≥11), arthralgia and/or muscle pain (58%), dyspnea (48%; MRC dyspnea scale ≥3), exercise intolerance (38%), and/or cough (20%). The FAS score of the total studied population was 30.4 ±7.8 and the SFNSL 24.9 ±14.8, without significant differences between PET positive and PET negative patients (data not shown). Mean sIL2R level in PET positive patients was significantly higher compared with PET negative patients ($p<0.001$), whereas ACE and CRP did not significantly differ between the two groups.

At inclusion 41 patient (25.9%) were on pharmacological treatment: 10 of these patients (24.4%) used prednisone alone (median dose 15 mg daily (range 10-40 mg)), 18 patients (43.9%) used methotrexate (MTX) alone (median dose 10 mg a week (range 7.5-12.5 mg)), and 13 patients (31.7%) used a prednisone and MTX combination (all patients 10 mg prednisone daily and median dose MTX 10 mg a week (range 10-12.5 mg)).

Table 1. Summary of demographic and clinical characteristics of the studied sarcoidosis patients divided according to the absence (n=40) and presence (n=118) of PET abnormalities and subdivided in a treatment and no treatment group.

	PET negative patients			PET positive patients		
	total PET negative population	treatment	no treatment	total PET positive population	treatment	no treatment
Number	40	12 (30.0%)	28 (70.0%)	118	29 (24.6%)	89 (75.4%)
Age (yrs)	48.7 ±12.3	51.0 ±14.0	57.7 ±11.7	47.1 ±11.5	48.7 ±11.4	46.6 ±11.5
Sex (female/male)	16/24	6/6	10/18	48/70	12/17	36/53
Time since diagnosis (yrs)	6.0 ±8.5	4.3 ±4.0	6.8 ±9.8	5.7 ±6.8	7.5 ±7.3	4.9 ±6.6
Chest X-ray stage 0/I/II/III/IV	26/3/4/5/2	7/0/3/1/1	19/3/1/4/1	22/31/27/7/31	3/6/7/0/13	19/25/20/7/18
Thoracic PET+	0	0	0	110 (93.2 %)	26/110 (23.6%)	84/110 (76.3%)
Extrathoracic PET+	0	0	0	88 (74.6%)	20/88 (22.7%)	68/88 (77.3%)
Solitary thoracic PET+	0	0	0	30 (25.4%)	8/30 (26.7%)	22/30 (73.3%)
Solitary extrathoracic PET+	0	0	0	8 (6.8%)	3/8 (37.5%)	5/8 (62.5%)
FVC (% of predicted)	100.0 ±21.5	96.5 ±23.9	101.7 ±20.6	91.2 ±22.7**	77.0 ±19.1	95.5 ±22.1
DLCO (% of predicted)	78.6 ±16.6	70.7 ±11.1	82.0 ±17.5	71.2 ±19.4**	60.8 ±19.6	74.3 ±18.3
ACE (9-25 U/L; n=144)	20.9.4 ±19.0	19.8 ±25.1	21.4 ±16.6	21.8 ±16.2	22.0 ±13.2	21.7 ±17.0
sIL2R (240-3154 pg/mL; n=139)	2525 ±2951	2490 ±3203	2541 ±2900	4541 ± 2877*	4627 ±3081	4510 ±2822
CRP (2-9 µg/mL; n=139)	6.4 ±8.2	8.5 ±12.7	5.4 ±4.9	15.0 ±41.3	9.3 ±9.7	16.9 ±47.7

*Data are presented as means ± SD; absolute numbers or percentages if appropriate; +, positive; % of predicted, percentage of predicted values; ACE, serum angiotensin-converting enzyme; CRP, C-reactive protein; DLCO, diffusion capacity for carbon monoxide; FVC, forced vital capacity; PET, ^{18}F-FDG PET/CT; sIL2R, soluble-IL2-receptor; yrs, years; *p<0.001 PET positive versus PET negative; **p<0.05 PET positive versus PET negative.*

Distribution of organ involvement in PET positive patients

Of the PET positive patients (n=118, 69% female and mean age 47.1 ±11.5 years), 93% demonstrated thoracic involvement, whereas 75% showed one or more positive extrathoracic localisations (Table 1). In 30 patients (25%) the PET activity was limited to the thorax, and in eight patients (7%) this activity was limited to extrathoracic localisations. In almost one fifth of patients (21; 18%) one single organ was positive, whereas in 38 (32%) two organs, in 22 (19%) three organs, in 14 (12%) four organs, and in 23 (20%) five or more organs, respectively, with PET activity were found. One of these patients had eight organs involved, as depicted in Figure 2.

The distribution of specific organ involvement is shown in Table 2. Thoracic lesions were seen most frequently (PET positive mediastinal lymph nodes in 79% and pulmonary PET positive findings in 64% of the patients, respectively), followed by extrathoracic lesions consisting of peripheral lymph nodes (51%), bone/bone marrow (35%), spleen (22%), and parotid gland (19%). Nasopharyngeal, muscle, liver, skin, and neurological activity were seen in a small number of the PET positive scans.

In Table 2 the distribution of organ involvement assessed by PET is compared with the data reported by the ACCESS study (3, 10). Ocular inflammation is not detectable using a PET scan. Due to normal renal uptake and excretion of ^{18}F-FDG, detection of renal involvement is less reliable and therefore not mentioned in our results. Furthermore, for the evaluation of cardiac PET activity, the use of a cardiac protocol, consisting of among others dietary preparation of the patient, is necessary. Hence this was not performed routinely, establishment of the incidence of cardiac PET activity was not possible.

Associations of PET positivity between various organs

In Table 3 the distribution of PET positivity between various organs is shown. All patients with hepatic PET positive findings demonstrated splenic and pulmonary PET positivity, and PET positive findings in the mediastinal lymph nodes were present in the majority of these patients (80%). Every organ (system) assessed, demonstrated in majority of cases the concurrent presence of peripheral and/or mediastinal lymph node activity, with especially high percentages for the parotid gland (100%), spleen (85%) and bone/bone marrow (81%). In these cases, pulmonary PET positivity was less often concurrently present (60-80%). Furthermore, pulmonary PET positivity and mediastinal lymph node PET positivity appeared to be concurrently present in 78% of cases.

Respiratory functional impairment, laboratory abnormalities and PET results

Patients with PET positive lung parenchyma (n=76, 64% of PET positive patients) demonstrated a

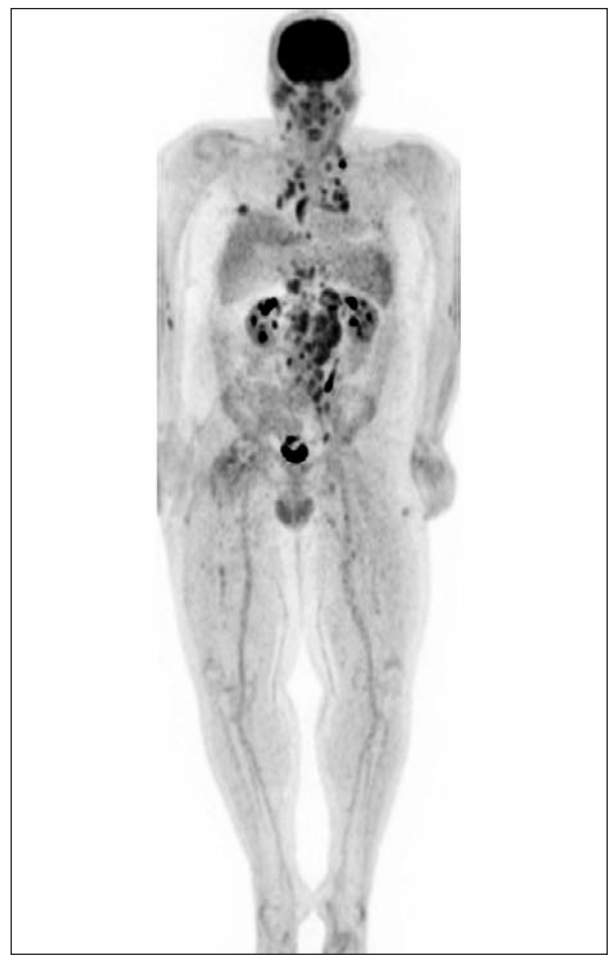

Fig. 2. Example of a 45-year-old male patient with a history of 8 years of sarcoidosis. Multiple signs of inflammatory activity were seen on ^{18}F-FDG PET/CT in the parotid glands, nasopharynx, and in cervical, mediastinal and hilar lymph nodes. Extensive lymphadenopathy was observed in the abdominal and inguinal region. Lung, liver and spleen showed locations with increased ^{18}F-FDG uptake, which could also be seen in the muscles and bone/bone marrow.

Table 2. Number and percentage of sarcoidosis patients with specified organ involvement according to PET findings (n=118) and comparison with results from the ACCESS research group, in which organ involvement was determined using an assessment system based on findings from history, physical examination, and laboratory testing (n=736) (3, 10).

	PET positive population (n=118)		ACCESS study 2001 (3, 10) (n=736)	
Organ involvement	Number	Percent	Number	Percent
Mediastinal lymph node(s)	93	78.8	n.a.	n.a.
Lung	76	64.4	699	95.0
Extrathoracic lymph node(s)*	60	50.8	112	15.2
Bone/Bone marrow†	41	34.7	33	4.4
Splenic	26	22.0	49	6.7
Parotid gland‡	22	18.6	29	3.9
ENT§	15	12.7	22	3.0
Muscle	14	11.9	3	0.4
Liver	10	8.5	85	11.5
Skin	4	3.4	117	15.9
Neurologic||	3	2.5	34	4.6
Eye	n.a	n.a.	87	11.8
Renal	n.a.	n.a.	5	0.7
Cardiac	n.a.	n.a.	17	2.3

**Involvement of aortal, liver, abdominal, iliacal, inguinal, cervical, axillary or popliteal lymph nodes; †Involvement of bone and bone marrow in present study, involvement of bone, joints and/or bone marrow in ACCESS study (10); ‡Involvement of parotid gland in present study, involvement of parotid and/or salivary glands in ACCESS study (10); §Nasopharyngeal involvement in the present study, nasopharyngeal and/or ear involvement in ACCESS study (10); ||Involvement of myelum in the present study, involvement of cranial nerve, brain, leptomeningeal and/or peripheral nerve in ACCESS study (10); ACCESS, Case Control Etiologic Study of Sarcoidosis; n.a., not applicable; PET, ^{18}F-FDG PET/CT.*

substantial higher percentage of RFI compared with patients without PET activity in the lungs: 86% versus 58%, respectively (p=0.003; Table 4). Furthermore, impaired lung function (FVC and DLCO) was associated with PET positivity (p<0.05; Table 1).

Hepatic PET activity was established in 10 of the 118 PET positive patients (9%; Table 2). However, in none of these patients serological LTA could be observed. Furthermore, the serological albumin levels were normal in all patients with liver PET activity. However, in 13.4% of the PET positive patients without hepatic PET activity LTA were found (elevated ALP in 5.3% and ALT in 13.0% of patients). Signs of decreased haematopoiesis were present in two of 41 patients with bone/bone marrow PET activity (4.9%). One young female had a slight anemia (Hb 6.8 mmol/L) and a minor leucopenia (WBC count 3.2x10^9/L). Another young female had a Hb level of 5.9 mmol/L. Two PET positive patients without bone/bone marrow activity (2.6%) demonstrated signs of decreased haematopoiesis. No patients with splenic PET activity demonstrated thrombocytopenia.

Discussion

The extent, distribution and consistency of inflammatory organ involvement assessed by PET in the studied sarcoidosis patients with persistent disabling symptoms appeared to be remarkably high. The majority of patients displayed PET positive findings (75%), of which, besides intrathoracic positivity (93%), a high proportion (75%) had extrathoracic activity (mainly peripheral lymph nodes, bone marrow and spleen). Hence, PET can be especially useful in assessment of extent and distribution of inflammatory activity in sarcoidosis.

Distribution of organ involvement

In accordance with earlier results of our group in a smaller population (89 PET positive patients), in the present study in 75% extrathoracic positivity was found. (18). Comparing the number of PET positive lesions with the reported organ involvement in the ACCESS study (3, 10), demonstrated that assessment by PET established a higher rate of involvement of the

Table 3. Number and percentage of sarcoidosis patients with specified organ involvement according to positive PET findings (n=118).

Organ involvement	Lung+	Mediastinal LN+	Skin+	Extrathoracic LN+*	Liver+	Splenic+	Neurologic+†	Muscle+	Parotid gland+	Bone/Bone marrow+	ENT+‡	Mediastinal and/or extrathoracic LN+	Lungs+/mediastinal LN–	Lungs+/mediastinal LN+
Lung+ (n=76)	76/76 (100%)	59/76 (77.6%)	1/76 (1.3%)	39/76 (51.3%)	10/76 (13.2%)	22/76 (28.9%)	2/76 (2.6%)	5/76 (6.6%)	15/76 (19.7%)	27/76 (35.5%)	9/76 (11.8%)	65/76 (85.5%)	17/76 (22.4%)	59/76 (77.6%)
Mediastinal LN+ (n=93)	59/93 (63.4%)	93/93 (100%)	4/93 (4.3%)	51/93 (54.8%)	8/93 (8.6%)	20/93 (21.5%)	1/93 (1.1%)	9/93 (9.7%)	22/93 (23.7%)	30/93 (32.3%)	15/93 (16.1%)	93/93 (100%)	0/93 (0%)	59/93 (63.4%)
Skin+ (n=4)	1/4 (25.0%)	4/4 (100%)	4/4 (100%)	4/4 (100%)	0/4 (0%)	0/4 (0%)	0/4 (0%)	2/4 (50.0%)	0/4 (0%)	1/4 (25.0%)	3/4 (75.0%)	4/4 (100%)	0/4 (0%)	1/4 (25.0%)
Extrathoracic LN+* (n=60)	39/60 (65.0%)	51/60 (85.0%)	4/60 (6.7%)	60/60 (100%)	7/60 (11.7%)	20/60 (33.3%)	1/60 (1.7%)	9/60 (15.0%)	14/60 (23.3%)	25/60 (41.7%)	11/60 (18.3%)	60/60 (100%)	6/60 (10.0%)	33/60 (55.0%)
Liver+ (n=10)	10/10 (100%)	8/10 (80.0%)	0/10 (0%)	7/10 (70.0%)	10/10 (100%)	10/10 (100%)	0/10 (0%)	1/10 (10.0%)	4/10 (40.0%)	5/10 (50.0%)	4/10 (40.0%)	8/10 (80.0%)	2/10 (20.0%)	8/10 (80.0%)
Splenic+ (n=26)	22/26 (84.6%)	20/26 (76.9%)	0/26 (0%)	20/26 (76.9%)	10/26 (38.5%)	26/26 (100%)	1/26 (3.8%)	2/26 (7.7%)	7/26 (26.9%)	17/26 (65.4)	5/26 (19.2%)	22/26 (84.6%)	6/26 (23.1%)	16/26 (61.5%)
Neurologic+† (n=3)	2/3 (66.7%)	1/3 (33.3%)	0/3 (0%)	1/3 (33.3%)	0/3 (0%)	1/3 (33.3%)	3/3 (100%)	1/3 (33.3%)	0/3 (0%)	2/3 (66.7%)	0/3 (0%)	2/3 (66.7%)	2/3 (66.7%)	0/3 (0.%)
Muscle+ (n=14)	5/14 (35.7%)	9/14 (64.3%)	2/14 (14.3%)	9/14 (64.3%)	1/14 (7.1%)	2/14 (14.3%)	1/14 (7.1%)	14/14 (100%)	3/14 (21.4%)	6/14 (42.9%)	3/14 (21.4%)	11/14 (78.6%)	2/14 (14.3%)	3/14 (21.4%)
Parotid gland+ (n=22)	15/22 (68.2%)	22/22 (100%)	0/22 (0%)	14/22 (63.3%)	4/22 (18.2%)	7/22 (31.8%)	0/22 (0%)	3/22 (13.6%)	22/22 (100%)	11/22 (50.0%)	5/22 (22.7%)	22/22 (100%)	0/22 (0%)	15/22 (68.2%)
Bone/Bone marrow+ (n=41)	27/41 (65.9%)	30/41 (73.2%)	1/41 (2.4%)	25/41 (61.0%)	5/41 (12.2%)	17/41 (41.5%)	2/41 (4.9%)	6/41 (14.6%)	11/41 (26.8%)	41/41 (100%)	4/41 (9.8%)	33/41 (80.5%)	5/41 (12.2%)	23/41 (56.1%)
ENT+‡ (n=15)	9/15 (60.0%)	15/15 (100%)	3/15 (20.0%)	11/15 (73.3%)	4/15 (26.7%)	5/15 (33.3%)	0/15 (0%)	3/15 (20.0%)	5/15 (33.3%)	4/15 (26.7%)	15/15 (100%)	15/15 (100%)	0/15 (0%)	9/15 (60.0%)
Mediastinal and/or extrathoracic LN+ (n=102)	65/102 (63.7%)	93/102 (91.2%)	4/102 (3.9%)	60/102 (58.8%)	8/102 (7.8%)	22/102 (21.6%)	2/102 (2.0%)	11/102 (10.8%)	22/102 (21.6%)	33/102 (32.4%)	15/102 (14.7%)	102/102 (100%)	6/102 (5.9%)	59/102 (57.8%)
Lungs+/mediastinal LN– (n=17)	17/17 (100%)	0/17 (0%)	0/17 (0%)	6/17 (35.3%)	2/17 (11.8%)	6/17 (35.3%)	2/17 (11.8%)	2/17 (11.8%)	0/17 (0%)	5/17 (29.4%)	0/17 (0%)	6/17 (35.3%)	17/17 (100%)	0/17 (0%)
Lungs+/mediastinal LN+ (n=59)	59/59 (100%)	59/59 (100%)	1/59 (1.7%)	33/59 (55.9%)	8/59 (13.6%)	16/59 (27.1)	0/59 (0%)	3/59 (5.1%)	15/59 (35.4%)	23/59 (39.0%)	9/59 (15.3%)	59/59 (100%)	0/59 (0%)	59/59 (100%)

** Involvement of aortal, liver, abdominal, iliacal, inguinal, cervical, axillary or popliteal lymph nodes; †Involvement of myelum; ‡Nasopharyngeal involvement; +, PET positive; –, PET negative; LN, lymph node; PET, ^{18}F-FDG PET/CT.*

Table 4. Respiratory functional impairment in the studied sarcoidosis patients subdivided according to the presence and absence of pulmonary involvement determined by PET (total PET positive group n=118, total PET negative group n=40).

	PET positive patients		
	PET positive lungs	PET negative lungs	PET negative patients
Total number of patients (%)	76/118 (64.4%)	42/118 (35.6%)	40/158 (25.3%)
RFI (n/n measured)			
• Impairment	57/66 (86.4%)	18/31 (58.1%)	18/35 (51.4%)
• No impairment	57/66 (86.4%)	13/31 (41.9%)	17/35 (48.6%)
p-value between groups		p1=0.003	p2=0.005
RFI not measured	10/76 (13.2%)	11/42 (26.2%)	5/40 (12.5%)

PET, ^{18}F-FDG PET/CT; RFI, Respiratory functional impairment; RFI was defined as DLCO <80%, FVC <80%, or FEV1 <80% (percentage of predicted) (25); p1=PET positive lungs versus PET negative lungs; p2=PET positive patients versus PET negative patients.

various organs: peripheral lymph nodes (51% and 15%, respectively), bone/bone marrow (35% and 4%, respectively), spleen (22% and 7%, respectively), and parotid gland (19% and 4%, respectively) (Table 2). These findings confirm that PET is a sensitive method to assess sarcoidosis activity and organ involvement, especially when compared to anamnestic findings, physical examination and laboratory testing. This is in accordance with recent publications (11-21). Nevertheless, hepatic and cutaneous involvement were less frequently detected by PET compared to the ACCESS study. A possible explanation could be the higher percentage of black subjects in the ACCESS study population (44%) compared with the present study (5%). Black subjects more likely display hepatic and cutaneous involvement due to sarcoidosis (3). Furthermore, PET is not a suitable technique to detect cutaneous activity, since FDG-uptake in small cutaneous or subcutaneous sarcoid infiltrations can be below the detection limit, especially when anatomic structures with physiologic or pathologic tracer accumulation are superimposed (12). Moreover, cutaneous lesions are usually visible during physical examination and, therefore, PET is usually not performed to assess disease activity in patients with obvious cutaneous manifestations.

Respiratory functional impairment, laboratory abnormalities and PET results

PET positivity of the lung parenchyma was associated with RFI, which is in accordance with findings of previous studies (19). Previously, it was shown that the severity of LTA appeared to be related to the degree of fibrosis and extensiveness of granulomatous inflammation detected by liver biopsy in hepatic sarcoidosis (26). In contrast, PET positivity of the liver parenchyma was not associated with LTA. This means that LTA are not necessarily present in case of hepatic PET positivity. Signs of decreased haematopoiesis were present in only two patients with bone/bone marrow PET activity (4.9%) and thrombocytopenia was found in none of the patients with splenic PET activity. The study of Mostard et al., using partly the same population, also showed that bone/bone marrow PET activity is not obviously related to decreased haematopoiesis (22). These findings demonstrate that in only a small minority of the patients with extrathoracic PET activity, associated laboratory abnormalities suggestive of specific organ involvement, were present. Hence, PET may be of additional value when assessing the extent of disease to provide an explanation for disabling extrathoracic symptoms.

Value of PET in sarcoidosis

PET has been shown to be a sensitive method to assess inflammatory activity and the extent of disease in sarcoidosis (11-21). However, due to costs and radiation exposure, PET scan should not routinely be performed in the diagnostic work-up of sarcoidosis patients (4, 27). Recent findings have shown that in specific situations or patient populations PET can be very helpful in disease management and monitoring, even when signs of objective functional organ impairment are absent (14, 18, 28).

First of all, PET appears especially helpful in patients with unexplained persistent disabling symptoms in the absence of serological signs of inflammatory activity (16, 18). Mostard et al. showed that 20% of patients with persistent disabling symptoms and PET positivity did not have signs of serological inflammatory activity (18).

In accordance with previous studies, in most of the studied patients pulmonary PET activity was found (11, 16, 18). The severity of pulmonary involvement, assessed by HRCT and pulmonary function tests, was found to be associated with PET activity in sarcoidosis (19). In patients with radiological signs of fibrosis on CXR or HRCT, PET can be of additional value to detect the presence of ongoing inflammatory activity between the fibrotic elements (19).

Furthermore, the value of PET to detect cardiac sarcoidosis disease activity is a major subject of recent studies. Detection of cardiac sarcoidosis is important, since it is a major cause of serious morbidity and mortality in sarcoidosis (29). PET with cardiac protocol is considered to be a sensitive test for detecting active sarcoid lesions and their response to treatment (20, 28, 30).

In addition, PET can have an important role in assessing the extent of organ involvement in an individual patient. Besides the assessment of sarcoidosis activity, depicting disease extent and severity is of great clinical relevance. Evaluation of the extent of disease can be helpful to explain persistent disabling (mainly extrathoracic) symptoms (20). Moreover, PET can uncover a suitable location for biopsy to obtain histological evidence for the diagnosis (11, 20).

In conclusion, the majority of studied patients appeared to have PET positive findings (75%), of which, besides intrathoracic positivity (93%), a high proportion (75%) displayed extrathoracic activity. Hence, PET can be especially useful in the assessment of extent, distribution and consistency of inflammatory activity in sarcoidosis to provide an explanation for persistent disabling symptoms and/or to provide a suitable location for biopsy.

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