EXTENDED REPORT

Correlation between 18-fluorodeoxyglucose accumulation in large vessels and serological markers of inflammation in polymyalgia rheumatica: a quantitative PET study

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Objective: To quantify 18-fluorodeoxyglucose (FDG) accumulation in large vessels in patients with polymyalgia rheumatica by positron emission tomography (PET), and to compare these data with serological markers of inflammation.

Methods: 13 untreated patients with active polymyalgia rheumatica underwent FDG positron emission tomography; eight were analysed in a second PET when in clinical remission. Six patients with other highly inflammatory conditions served as controls. For quantitative analysis, FDG uptake over nine defined vascular regions, divided by an individual background value, was expressed as a region of interest (ROI) index. These data were compared with the clinical status of the patient and with erythrocyte sedimentation rate (ESR), C reactive protein, haemoglobin, and platelet and leucocyte counts.

Results: By visual evaluation, 12 of the 13 patients showed an increased tracer uptake of the aorta or its major branches. By quantitative analysis, FDG uptake was significantly increased in polymyalgia rheumatica. In patients with active disease, the mean ROI index for all vascular regions exceeded that of controls by 70% (mean (SD): 1.58 (0.37) *v* 0.93 (0.12); $p<0.001$). In the eight patients who underwent follow up PET, the index declined substantially. In active polymyalgia rheumatica, FDG uptake was significantly correlated with C reactive protein ($r=0.8$), ESR ($r=0.79$), and platelet counts ($r=0.68$).

Conclusions: The observed FDG accumulation in the aorta and its branches and a strong correlation between tracer uptake and markers of inflammation is suggestive of large vessel arteritis. Quantitative ROI analysis appears to be a sensitive tool for detecting such inflammation.

Polymyalgia rheumatica is an inflammatory disorder clinically characterised by proximal muscle pain and stiffness (for review see Salvarani *et al*[1]). Despite intensive research, the primary site of inflammation has not yet been defined but there is clear evidence that vasculitis of medium sized and large arteries plays an important role.[2] However, the true extent of vascular involvement in polymyalgia rheumatica may be underestimated for various reasons. In patients with coexisting giant cell arteritis, stenosis and other complications usually occur several years after the onset of the disease[3]. Among the imaging techniques, duplex ultrasound—which has been shown to be of value for examining the temporal arteries[4 5]—is difficult to apply to the aortic arch and its proximal branches. Magnetic resonance imaging, which could be of some value in polymyalgia rheumatica,[6] has not been used in large series.

Recently, positron emission tomography (PET) studies by Blockmans and colleagues showed increased uptake of radiolabelled 18-fluorodeoxyglucose (FDG) by the aortic arch and other large vessels in more than 50% of patients who had been diagnosed as having either polymyalgia rheumatica or giant cell arteritis[7 8]. Although these data are highly suggestive of a hitherto unexpected prevalence of vascular inflammation in polymyalgia rheumatica, the clinical significance of PET is not well defined (for review and discussion see Salvarani *et al*[1 9]).

Our hypothesis was that PET might help in identifying a subgroup of patients with polymyalgia rheumatica who have subclinical large vessel vasculitis. Quantitative measures of tracer uptake and correlation with laboratory markers of disease activity might be useful to define the clinical significance of PET in polymyalgia rheumatica. Therefore, in addition to the work by Blockmans *et al*,[7 8] quantification of the tracer uptake and re-evaluation after steroid treatment in patients with a definitive diagnosis of polymyalgia rheumatica was included in our study.

METHODS

Patients and controls

Between July 2000 and June 2002, 13 consecutive patients with a diagnosis of polymyalgia rheumatica (11 women and two men), median age 65.5 years, were included in the study. The diagnosis was based on exclusion of other causes of inflammation and on the criteria suggested by Chuang *et al*. The criteria of Healy were also fulfilled retrospectively. The criteria of Chuang and Healy are cited in Salvarani's review.[1] Three of the patients had biopsy proven giant cell arteritis. In nine patients without clinical evidence of temporal arteritis and normal findings on duplex ultrasound, no biopsies were taken owing to very low pre-test probability. In one patient without clinical signs but with an inconclusive duplex ultrasound examination, biopsy was negative. The patient characteristics are given in table 1.

All patients underwent standardised FDG-PET before initiation of steroid treatment at an initial daily dose of 1 mg/kg. In eight of these patients, a second PET was done after they had achieved remission according to clinical and laboratory findings. The median time between the first and second investigation was three months.

Six patients (four women and two men, median age 37.5 years) with highly inflammatory diseases other than polymyalgia rheumatica served as controls. There were no

Table 1 Characteristics of patients with polymyalgia rheumatica and controls

Patient No	Sex	Age (years)	ESR (mm)	CRP (mg/dl)	Leucocytes (/nl)	Platelets (/nl)	Haemoglobin (g/dl)	Control diagnosis
1	M	62	88	129	10.4	452	12.2	
2	F	77	105	135	8.6	626	10.5	
3	F	50	81	46	12.8	665	11.5	
4	F	77	44	65	9.5	370	12.4	
5	F	62	65	69	8.4	449	13.9	
6	F	65	96	170	12	520	10	
7	F	67	112	72	17.5	872	10.5	
8	F	63	46	48	6.7	465	11.9	
9	M	71	61	64	7	307	13.7	
10	F	54	99	20	14.7	772	11.2	
11	F	48	81	169	9.6	549	11.6	
12	F	64	116	198	10.4	598	9.7	
13	F	61	96	197	6.7	554	10.6	
Patients with second PET								
1			12	16	9.1	247	16	
4			5	2	10.6	333	13.1	
5			8	5	8.2	370	15.4	
6			6	3	22.3	209	11.1	
7			39	18	10.7	389	12.7	
8			5	1	11	302	14.4	
10			25	3	14.6	434	13.2	
11			7	17	12.5	322	13.2	
Controls								
1	F	29	91	138	18.6	647	10.5	Adult Still's disease
2	F	59	73	107	8.9	484	11.9	Abscess
3	M	35	39	57	7.9	272	13.1	Rheumatic fever
4	F	34	77	90	15.5	351	12	Behçet's disease
5	M	64	98	121	14.4	146	10.9	Pneumonia
6	F	40	18	116	12	270	13.6	Adult Still's disease

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; F, female; M, male.

significant differences between patients with active polymyalgia rheumatica and the controls with regard to C reactive protein levels, erythrocyte sedimentation rate (ESR), or platelet counts. Their characteristics are also given in table 1. All patients gave their informed consent to the studies.

FDG imaging

After at least six hours of fasting, 450 MBq of FDG were injected intravenously; 90 minutes after the injection, images of the torso including the carotid arteries and in some cases the iliac arteries were obtained with a field of view of 54 cm using a PET scanner (CTI, 951–31).

The PET scans were analysed visually in a descriptive manner, as well as by a quantitative computed method. For quantitative evaluation, regions of interest (ROI) were placed over nine defined vascular areas (ascending thoracic aorta, descending thoracic aorta, abdominal aorta, right and left subclavian arteries, right and left external carotid arteries, right and left common iliac arteries). A peripheral region of the lung served as the background region and an ROI index was calculated by dividing the respective vascular ROI scores by the individual background values.

Statistics

We used the GraphPad™ software package for the statistical analyses. Where applicable the Wilcoxon matched pairs test was used. Other analysis were done using the Mann–Whitney test. For the calculation of correlations we used the Spearman rank order test.

RESULTS

Visual examination

In 12 of the 13 patients, visual examination of the PET scans showed an increased tracer uptake of the aorta or its major branches compared with the controls. In one patient (patient 3) the PET could not be evaluated because of technical problems.

Quantitative PET analysis

Patients with active disease had significantly greater FDG uptake than control patients, the mean (SD) ROI index for all nine regions evaluated being 1.58 (0.37), *v* 0.93 (0.12) in controls ($p<0.001$). Among the various vascular areas evaluated, the regions best discriminating between active polymyalgia rheumatica and controls were the subclavian and external carotid arteries.

PET re-evaluation after clinical remission

Eight patients underwent re-PET after achieving a complete or partial remission with corticosteroid treatment, as judged by the clinical and laboratory findings. The laboratory data are given in table 1. In this group of patients, tracer uptake was reduced from a mean index of 1.50 (0.16) in the initial PET to 1.09 (0.08) in the follow up PET ($p<0.001$). In three patients, re-PET was completely normalised according to visual analysis. An example is given in fig 1.

When comparing these patients with the controls, the mean ROI index for all regions and the values obtained for the subclavian region were higher in patients who were in clinical remission than in the controls (0.74 (0.15) *v* 0.47 (0.11) for the right subclavian artery; 0.72 (0.17) *v* 0.51 (0.10) for the left; $p<0.001$ for both comparisons). There where no significant differences in other vascular regions. The results for the subclavian region are shown in fig 2.

Correlations between quantitative PET measures and laboratory data

In the patients with polymyalgia rheumatica the ESR was strongly correlated with PET values obtained for all

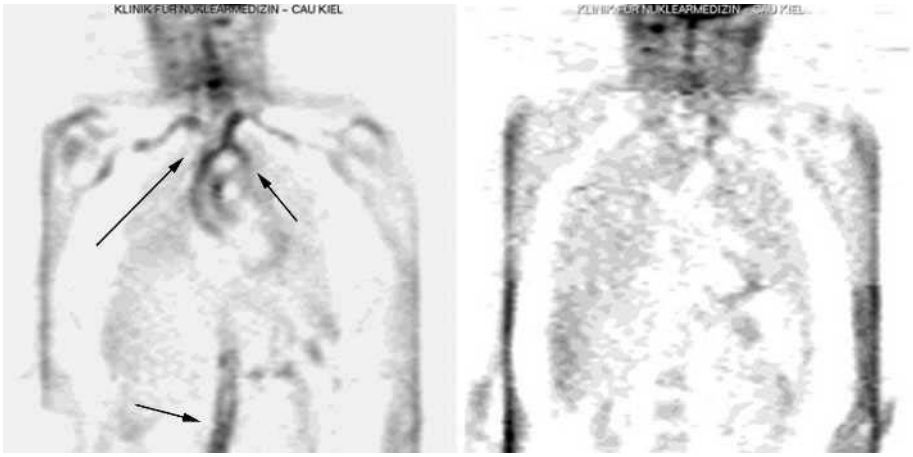

Figure 1 Normalisation of tracer uptake in a patient with polymyalgia rheumatica (PMR) on steroid treatment.

individual vascular regions except for those over the iliac arteries, for which only eight sets of data were available. The mean FDG uptake for all regions showed the best correlation ($r = 0.79$; $p<0.0001$).

The C reactive protein concentration correlated significantly with the PET values obtained for each vascular region as well as with the mean value ($r = 0.80$; $p<0.001$).

There was also a significant correlation between tracer uptake for all vascular regions and the platelet count, the strongest correlation being for the mean values of all vascular regions ($r = 0.68$; $p = 0.001$).

The haemoglobin concentration was inversely correlated with the FDG uptake detected in the abdominal aorta and with the mean value of all regions ($r = -0.47$; $p = 0.037$), but not with values obtained for other regions.

DISCUSSION

Our study shows increased FDG accumulation in the aorta and its proximal branches in all except one of 13 patients with polymyalgia rheumatica. Furthermore, the tracer uptake quantified by computer based evaluation showed a strong correlation with laboratory markers of disease activity. Hence the data presented here confirm and extend the studies undertaken by Blockmans *et al*.[7 8]

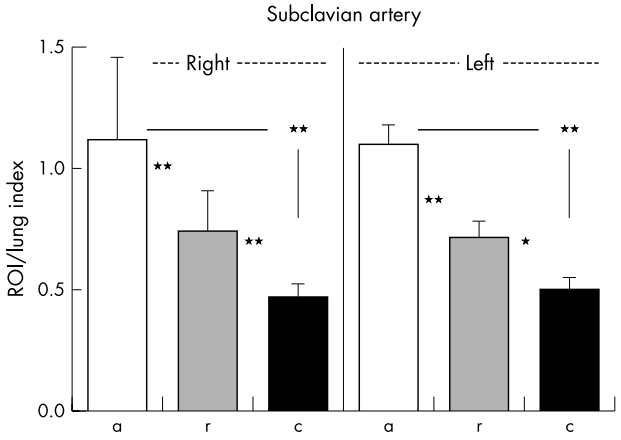

Figure 2 Mean region of interest (ROI) index for the subclavian arteries in patients with polymyalgia rheumatica and controls; a, active disease; c, control; r, remission. *p<0.01; **p<0.001.

According to our hypothesis it might be concluded that PET evidence of large vessel vasculitis may be found in many patients with polymyalgia rheumatica without direct clinical signs of vasculitis such as stenosis or aneurysm. However, as these blood vessels are not suitable for routine histological examination, direct proof of vascular inflammation is not possible. Nonetheless, there is considerable indirect evidence:

First, there is an established close association between polymyalgia rheumatica and giant cell arteritis.[2] In the patients with giant cell arteritis—about 50% of whom also present with the symptoms of polymyalgia rheumatica—late sequelae of vasculitis such as stenosis, aneurysm, or dissection predominantly occur in the vessels showing pathological changes in our PET series.[3] Second, earlier necropsy studies showed involvement of the aorta and other arteries not only in patients with coexisting giant cell arteritis, but also in those with polymyalgia rheumatica in whom a temporal biopsy was negative or clinical signs of vasculitis were absent.[10] Turkalow *et al* recently reported a patient with the typical manifestations of polymyalgia rheumatica in whom PET was done because of a mediastinal mass suspicious of malignancy. The PET images were very similar to the ones we have obtained in active polymyalgia rheumatica, and a biopsy taken from the mediastinal mass proved the vasculitic nature of the process and excluded malignancy.[11]

Third, there are striking similarities in the pathobiology of giant cell arteritis and polymyalgia rheumatica. As demonstrated by Weyand *et al*, cytokine mRNA levels (mainly IL-2) are almost identical in temporal artery specimens.[12 13]

There are some limitations to our study: The control group was relatively small and the average age of the controls was significantly lower than in the patients. Thus age related conditions such as atherosclerosis cannot completely be ruled out as confounding factors. For that reason we analysed a further eight patients (two women and six men, median age 64 years) with different types of neoplasia without serological signs of inflammation. In these patients no increased tracer uptake into vessel walls was observed (data not shown).

Overall, our data support the assumption that polymyalgia rheumatica is often accompanied by subclinical vasculitis of the aorta and its branches. Quantitative ROI analysis appears to be a sensitive tool for detecting vascular inflammation.

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