The Value of Serum SIL-2R and $^{18}$F-FDG-PET/CT for the Diagnosis of Ocular Sarcoidosis in Patients with Uveitis

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Abstract

Background/Aim Sarcoidosis is a frequent cause of uveitis, but difficult to diagnose since uveitis is often the first sign. Currently $^{18}$Fluorodeoxyglucose Positron Emission Tomography with Computer Tomography ($^{18}$F-FDG-PET/CT) is used to make sarcoidosis more likely, but this method is expensive and may result in unnecessary biopsies. This set us out to compare various diagnostic screening strategies for sarcoidosis in patients with uveitis.

Methods In 64 patients with uveitis referred to our uveitis outpatient clinic, four strategies to screen for sarcoidosis were retrospectively simulated on collected data. Test-characteristics were calculated using IWOS-criteria (International Workshop on Ocular Sarcoidosis) as golden standard. Chest X-ray alone, serum soluble Interleukin-2 receptor (sIL-2R) alone, chest X-ray in combination with liver enzymes and Angiotensin-Converting Enzyme (ACE) and chest X-ray with serum SIL-2R were evaluated. Finally, we explored the value of finding extra-thoracic biopsy localizations or alternative diagnosis with $^{18}$F-FDG-PET/CT in patients with positive screening results.

Results Fourteen of sixty-four patients were diagnosed with sarcoidosis (22%). The combination of chest X-ray and serum sIL-2R resulted in the highest sensitivity (100%) compared to all screening strategies. Serum sIL-2R had a sensitivity and specificity of 92% and 60%. In 18 patients with an elevated serum sIL-2R an $^{18}$F-FDG-PET/CT was performed. In 5 patients (28%) the $^{18}$F-FDG-PET/CT resulted in better accessible biopsy localizations or alternative diagnosis as obtained by chest CT.

Conclusion The combination of chest X-ray and serum sIL-2R provided best test characteristics to screen for sarcoidosis in uveitis patients. $^{18}$F-FDG-PET/CT is recommended as the following step instead of chest CT.

Keywords

Soluble Interleukin-2 Receptor; $^{18}$F FDG-Positron Emission Tomography; Sarcoidosis; Uveitis; Diagnosis; Chest X-Ray

Abbreviations

ACE: Angiotensin-Converting Enzyme
AF: Alkaline Fosfatase
ALAT: Alanine-Amino Transferase
CT: Computer Tomography

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ELISA: Enzyme-Linked Immunosorbent Assay

FAG: Fluorescent Angiography

**18F-FDG-PET/CT:** 18Fluorodeoxyglucose Positron Emission Tomography with Computer Tomography

ICG: Indocyanine Green Angiography

IWOS: International Workshop on Ocular Sarcoidosis

KP: Keratic Precipitate

OCT: Optical Coherence Tomography

PAS: Peripheral Anterior Synechiae

SIL-2R: Soluble Interleukin-2 Receptor

SUN: Standardization of Uveitis Nomenclature

TM: Trabecular Meshwork

**Introduction**

Uveitis is the umbrella term used for all intraocular inflammations, except scleritis and episcleritis. It is an important cause of morbidity and can eventually cause blindness. The incidence in the western world is 52/100,000 person-years with a period prevalence of 115/100,000 persons per year [1]. Uveitis can exist as a primary, ophthalmic entity (such as Birdshot chorioretinopathy), or more frequently as a co-manifestation of an established underlying disease [2]. The underlying diseases can be infectious or non-infectious [3], which differ per race, area and socio-economic status [1]. In the western world 30% of the patients with uveitis has an underlying systemic disease (such as ankylosing spondylitis, sarcoidosis and Bechter disease) and 30% has an infection (for example tuberculosis, toxoplasmosis, syphilis and Lyme’s disease) [4-6]. The diagnosis of the underlying disease in uveitis patients is essential to determine prognosis and to provide personalized treatment and follow-up. Sarcoidosis is increasingly recognized as underlying systemic disease in patients with uveitis in some studies [7-10]. Improved detection by the widespread use of chest computer tomography (chest CT) and 18Fluor-deoxy-glucose positron emission tomography combined with computer tomography (18F-FDG-PET/CT) in patients with uveitis may explain this increase. Sarcoidosis is a systemic auto-inflammatory granulomatous disease that can affect almost all organs in the body [11]. However, uveitis can be the single and first manifestation of this disease while extra-ocular sites of inflammation remain undetected unless extensive imaging techniques are used such as 18F-FDG-PET/CT. 18F-FDG-PET/CT may identify accessible locations for tissue diagnostics. However, inherent to its high sensitivity, it may also result in false-positive observations with the risk of subsequent unnecessary biopsies. Thus, there is a need for an easily accessible and validated screening procedure to select those patients with a uveitis that will gain from the application of these expensive imaging modalities. Serum concentration of soluble interleukin-2 receptor (sIL-2R) has recently been recognized as a sensitive serum marker (sensitivity: 64-98% [12-14]) of inflammatory processes with T-cell activation such as sarcoidosis. In our multidisciplinary outpatient tertiary referral center for patients with uveitis, we use this serum marker, routine laboratory tests (including liver enzymes) and chest X-ray to select patients for additional imaging with 18F-FDG-PET/CT and subsequent histological confirmation of extra-ocular diseases including sarcoidosis. However, this approach has never been evaluated for its accuracy to detect sarcoidosis. Furthermore, the added value of whole body 18F-FDG-PET/CT above a limited chest CT is not known for patients with uveitis. A few studies and case reports have described the value of 18F-FDG-PET/CT in patients with uveitis [15-17]. These results are favorable, but still inconclusive.

Therefore, this study was performed to evaluate our diagnostic approach for its efficacy to detect sarcoidosis in patients with uveitis. We aimed to answer two questions: 1. What is the diagnostic value of serum sIL-2R in the screening for sarcoidosis and 2. What is the added value of whole body 18F-FDG-PET/CT to a regular chest CT as subsequent imaging modality. In addition, we explored sIL-2R for its potential to predict optimal therapy modality and course of the uveitis.

**Patients and Methods**

**Patients**

This retrospective study included adult patients who were seen by the ophthalmologist and internist at the multidisciplinary outpatient clinic of our tertiary referral center for inflammatory eye diseases (Radboudumc, Nijmegen, the Netherlands) between September 2014 and August 2016. Uveitis patients with a pure ophthalmological...
entity (diagnosed after first ophthalmic screening) were not referred to this outpatient clinic. We included all patients with a proven uveitis and who were seen at our clinic for complete or additive screening for an underlying extraocular disease. As this was a retrospective study collecting data that were obtained during routine clinical work-up, ethics board approval for this study was not required in accordance with the policy of our institution.

Ocular Evaluation

We retrospectively collected the following data from the Electronic Medical Record: unilateral or bilateral uveitis, classification according to Standardization of Uveitis Nomenclature (SUN) [18] and presence of the signs for intraocular sarcoidosis according to International Workshop on Ocular Sarcoidosis (IWOS) during ocular exams, Fluorescein Angiography (FAG), Optical Coherence Tomography (OCT) or Indocyanine Green Angiography (ICG): mutton-fat keratic precipitates (KPs), small granulomatous KPs, iris nodules (Koeppe/Busacca), trabecular meshwork (TM) nodules, tent-shaped Peripheral Anterior Synechiae (PAS), vitreous opacities displaying snowballs/strings of pearls, multiple chorioretinal peripheral lesions (active and/or atrophic), nodular and/or segmental peripheral angiitis (+/- candlewax drippings) and/or retinal macroaneurism in an inflamed eye, optic disc nodule(s)/granuloma(s) and solitary choroidal nodule(s) [19].

Additional Diagnostic Evaluation

We also collected the levels of alanine aminotransferase (ALAT), alkaline phosphatase (AF), Angiotensin-Converting enzyme (ACE), serum sIL-2R, and results of chest X-ray, chest CT, 18F-FDG-PET/CT, tuberculin or quantiferon-TB tests and histological results. Test results performed under systemic immunosuppressive therapy were not collected.

For the entire follow-up period of the included patients, the course of treatments was extracted from the patient charts. For each patient the drugs used until last follow-up was also categorized into: 1. Only topical noninvasive therapy/ no therapy, 2. Local invasive therapy (intravitreal or parabulbar injections or implants with/without topical therapy) or 3. Systemic immunosuppressive (with/without topical or local invasive) therapy. Finally, data on ocular disease activity at the last available follow-up visit was collected. Remission or no remission of uveitis was determined. Data was anonymously registered in an electronic data collection program (Castor, Castor EDC, Amsterdam, the Netherlands).

Laboratory Procedures

Determination of ALAT and AF were performed by a routine random access analyzer according to manufactures instruction (Cobas 6000, ROCHE). ACE was determined on a Pentra 400 clinical analyzer (Horiba ABX Diagnostics). Collected test results were categorized as abnormal according to the following cut-off values: ALAT > 70 U/l, AF >200 U/l, ACE >20,0 U/l.

Soluble interleukin-2 receptor (sIL-2R) levels were analyzed with two different methods. Part of the samples were analyzed with a commercially available Diaclone enzyme-linked immunosorbent assay (ELISA) kit (Sanquin, Amsterdam, Netherlands). Serum samples were diluted 5-fold and analyzed in duplicate. Concentrations were calculated from a 6-point standard curve ranging from 69 to 2200 pg/ml, taking into account the dilution factor.

Concentrated samples (>2200 pg/ml) were diluted further as required. Results above 3154 pg/ml were considered elevated. After March 2016 sIL-2R was measured with the IMMULITE 2000 Xpi Automated Analyser, by means of a two-site chemiluminescent enzyme immunometric assay, with a detection limit of 50 U/ml and a measuring range 50–7500 U/ml (Siemens Healthcare, Erlangen, Germany). IL2R reagent (LIP2) consists of alkaline phosphatase conjugated to rabbit polyclonal anti-IL2R antibody. Results above 600 U/ml were considered elevated.

Imaging

The chest X-ray, chest CT and 18F-FDG-PET/CT were registered as abnormal according to the radiology report, describing the images as possibly caused by sarcoidosis. In addition, for all 18F-FDG-PET/CTs which were performed, we (retrospectively) registered if the scan resulted in alternative (easier to access) extra thoracic biopsy localizations or signs of a more likely alternative diagnosis.

Diagnostic Algorithms and Statistical Analyses

The IWOS-criteria designed by the International Workshop on Ocular Sarcoidosis14 for the diagnosis of ocular sarcoidosis were used as golden standard to calculate sensitivity, specificity, positive and negative predictive value of four different screening approaches;
1. chest X-ray alone, 2. serum sIL-2R alone, 3. chest X-ray plus ALAT, AF and ACE and 4. chest X-ray plus sIL-2R. A screening was positive when (one of) these test(s) was abnormal. These 4 screening procedures were simulated based on the data available. To compare the value of either 18F-FDG-PET/CT or chest CT on top of these four screening modalities, we evaluated detection of extra-thoracic biopsy localization and clues for alternative diagnoses.

To explore the potential role of serum sIL-2R as a predictor of response to therapy, patients were classified according to disease activity (remission or persistent uveitis) at the last recorded follow-up visit, by clinical judgment of the ophthalmologist, based on a combination of cells and flare in the anterior chamber and corpus vitreum, findings on FAG and/or OCT, medication adjustment in the last 3 months and the need for ocular controls. Patients with normal sIL-2R and elevated sIL-2R (according to predefined cut-off values) were compared with respect to various patient characteristics, used therapy and achievement of remission at last available follow-up visit. Comparisons were analyzed statistically with the Fisher exact’s test, t-tests and Mann-Whitney-U tests as appropriate. All statistical analyses were performed with SPSS statistics 22. P-value < 0.05 (two-sided) was considered to indicate statistical significance.

Results

Patients

We registered 120 patients with inflammatory eye diseases, from whom 53 patients were not eligible because they did not have a uveitis or were not referred for screening purposes (Figure 1). Patient characteristics of the remaining 67 patients are summarized in table 1. Three of these patients were excluded from comparison of four diagnostic strategies because available laboratory data did not allow appropriate application of IWOS criteria.

In the remaining 64 patients, sarcoidosis was diagnosed in 14 patients (22%) according to the IWOS criteria. In 12 patients (19%) the diagnosis sarcoidosis was histologically confirmed. In the two patients without histological confirmation, sarcoidosis was based on the presence of bilateral hilar lymphadenopathy with a compatible uveitis and a negative quantiferon-TB test.
In 50 of the 67 patients (78%) there was no suspicion for sarcoidosis.

The median follow-up time of all 67 patients was 9 months (8-41 months)(25th-75th percentiles)). Seven of the 67 patients (10%) were treated with only topical therapy during the entire follow-up, 18 patients (27%) received local invasive therapy and in 42 patients (63%) therapy included systemic immunosuppressive treatment. Data on the uveitis activity at the end of follow-up was available in 63 patients (94%). Reasons for drop-out during follow-up were: referral to another hospital for follow-up (n=1) and recent ocular surgery prior to the last follow-up visit (n=3, 1x cataract, 1x retinal detachment and 1x pucker).

**Test Characteristics of the 4 Screening Strategies**

The first screening strategy, consisting of the chest X-ray, liver enzymes and ACE, led to 16 patients with suspected sarcoidosis and 26 patients without. Respectively 9 and 2 patients of these had sarcoidosis (figure 1). The sensitivity and specificity of this screening method was 82% and 77% (Table 2).

The second strategy, chest X-ray alone, had a sensitivity of 50% and a specificity of 90%. The third strategy, serum sIL-2R alone, was performed in 50 patients. In 1 of the 14 sarcoidosis patients, based on IWOS-criteria, no serum sIL-2R was performed. Of the other 13 patients, 12 had an abnormal serum sIL-2R (sensitivity 92%). In 22 of the 37 patients without sarcoidosis in whom serum sIL-2R was available, serum sIL-2R was elevated (specificity 59%). Lastly, the combination of the chest X-ray and the serum sIL-2R resulted in a sensitivity of 100% and a specificity of 54%.

**Table 1: Patients Characteristics**

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<thead>
<tr>
<th>Characteristics</th>
<th>42/25</th>
<th>56 ± 15</th>
<th>55 (82)</th>
<th>5 (8)</th>
<th>19 (28)</th>
<th>36 (54)</th>
<th>19 (28)</th>
<th>27/51* (53)</th>
<th>13/66* (20)</th>
<th>6/15* (40)</th>
<th>11/21* (52)</th>
<th>12/17* (71)</th>
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<td>Gender (female/male)</td>
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<td>Bilateral uveitis (%)</td>
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<td>Classification of uveitis (SUN-classification)[18]</td>
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<td>Evaluations Elevated ALAT/AF (%)</td>
<td>2/59* (3)</td>
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<td>Elevated ACE (%)</td>
<td>4/47* (9)</td>
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<td>Elevated serum sIL-2R (%)</td>
<td>27/51* (53)</td>
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<td>Abnormal Chest X-ray (%)</td>
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<td>Abnormal Chest CT (%)</td>
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<td>Abnormal 18F-FDG-PET/CT (%)</td>
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<td>Biopsy positive for sarcoidosis (%)</td>
<td>12/17* (71)</td>
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<td>Local eye disease (%)</td>
<td>4 (6)</td>
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<td>Systemic disease including sarcoidosis (%)</td>
<td>22 (33)</td>
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<td>Uveitis eci (%)</td>
<td>41(61)</td>
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<td>Sarcoidosis according to IWOS 19 (%)</td>
<td>14/64** (22)</td>
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<td>Follow-up time in months (median, 25-75th percentiles)</td>
<td>9 (4-28)</td>
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<td>Therapy Topical therapy (%)</td>
<td>7 (10)</td>
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<td>Local invasive therapy (%)</td>
<td>18 (27)</td>
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<td>Systemic immunosuppressive therapy (%)</td>
<td>42 (63)</td>
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<td>In remission at last follow-up visit (%)</td>
<td>13/63*** (21)</td>
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Eighteen 18F-FDG-PET/CT scans were performed in the 32 patients with an abnormal chest X-ray or elevated serum sIL-2R (see Figure 2). In the remaining 14 patients, chest CT scans were performed to investigate whether other underlying diseases (for example infectious diseases) were more likely or whether additional imaging was not necessary.

In these 18 18F-FDG-PET/CT scans that were performed, 5 scans had an additional value (28%). In three patients extra-thoracic biopsy localizations were detected (nasal septum, esophagus and popliteal fossa) and in three patients clues for other systemic diseases were found (cancer associated uveitis, Granulomatosis with polyangiitis and M. Sjögren). One patient who had a new probable diagnosis (Granulomatosis with polyangiitis), had also a new biopsy localization (nasal septum).

Table 2: Test Characteristics of the Four Screening Strategies for Sarcoidosis in Patients with Uveitis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest Xray, ALAT/AF and ACE</td>
<td>82%</td>
<td>77%</td>
<td>56%</td>
<td>92%</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>50%</td>
<td>90%</td>
<td>58%</td>
<td>86%</td>
</tr>
<tr>
<td>Serum sIL-2R</td>
<td>92%</td>
<td>59%</td>
<td>44%</td>
<td>96%</td>
</tr>
<tr>
<td>Chest X-ray and serum sIL-2R</td>
<td>100%</td>
<td>54%</td>
<td>42%</td>
<td>100%</td>
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</table>

Added Value of the 18F FDG-PET-CT

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Follow-Up

In 51 of the 64 patients serum sIL-2R was measured. The median follow-up time for these patients was 9 months (4-27 months (25th-75th percentiles)). Twenty-four patients had normal serum sIL-2R levels and 27 had elevated serum sIL-2R levels. These groups with a normal and high serum sIL-2R did not differ in gender, age, unilateral or bilateral uveitis (Table 3).

Table 3: Patient Characteristics According to Presence of Elevated Serum Sil-2R

<table>
<thead>
<tr>
<th></th>
<th>Normal serum sIL-2R N=24</th>
<th>Elevated serum sIL-2R N=27</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (man)</td>
<td>7 (29%)</td>
<td>14 (52%)</td>
<td>P= 0.154</td>
</tr>
<tr>
<td>Age (years; mean ± SD)</td>
<td>57 ± 15</td>
<td>59 ± 15</td>
<td>P= 0.638</td>
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<tr>
<td>Uni-Bilateral (bilateral)</td>
<td>16 (67%)</td>
<td>23 (85%)</td>
<td>P=0.187</td>
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<tr>
<td>Classification of uveitis</td>
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<tr>
<td>Anterior</td>
<td>2 (8%)</td>
<td>3 (11%)</td>
<td>P= 1.00</td>
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<tr>
<td>Intermediair</td>
<td>6 (25%)</td>
<td>11 (41%)</td>
<td>P= 0.372</td>
</tr>
<tr>
<td>Posterior</td>
<td>16 (67%)</td>
<td>10 (37%)</td>
<td>P= 0.050</td>
</tr>
<tr>
<td>Panuveitis</td>
<td>4 (17%)</td>
<td>8 (30%)</td>
<td>P= 0.335</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical treatment</td>
<td>2 (8%)</td>
<td>4 (15%)</td>
<td>P= 0.671</td>
</tr>
<tr>
<td>Local invasive treatment</td>
<td>10 (42%)</td>
<td>7 (26%)</td>
<td>P= 0.254</td>
</tr>
<tr>
<td>Systemic immunosuppressive</td>
<td>12 (50%)</td>
<td>16 (59%)</td>
<td>P= 0.580</td>
</tr>
<tr>
<td>treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up time (months; median, 25th-75th quartiles)</td>
<td>8(3-20)</td>
<td>8 (4-19)</td>
<td>P= 0.940</td>
</tr>
<tr>
<td>Remission at last follow-up</td>
<td>2/22* (9%)</td>
<td>7/26* (27%)</td>
<td>P=0.151</td>
</tr>
</tbody>
</table>

There was a significant difference in serum sIL-2R levels in patients with a uveitis posterior (p=0.050). Patient with a uveitis posterior, had less frequently elevated serum sIL-2R levels. There was no significant difference in type of treatment (no treatment/topical treatment, local invasive treatment, or systemic immunosuppressive treatment) between patients with a normal or an elevated serum sIL-2R (table 3). Patients with an elevated serum sIL-2R were more often in remission compared to patients with a normal serum sIL-2R (27% vs 9%), however this difference was not statistically significant.

Discussion

This retrospective observational study has two main findings: 1. The combined use of chest X-ray and serum sIL-2R appeared most effective as screening instrument for sarcoidosis in patients presenting with uveitis. 2. After positive screening, $^{18}$F-FDG-PET/CT is superior to chest CT to confirm or exclude sarcoidosis as PET/CT (but not chest CT) identified alternative diagnoses and more easily accessible extra-thoracic sites for biopsy. Ocular sarcoidosis is often difficult to detect, even with extensive testing. Previous studies show that 1.5-12.4% of all sarcoidosis patients have eye lesions at first presentation [20, 21], and a portion of these patients have only ocular sarcoidosis without evidence of extra-ocular disease [21]. Diagnosing sarcoidosis has therapeutic consequences and a different prognosis compared to other (acute) diseases. Early diagnosis, adequate treatment and screening organ involvement (such as lungs and heart) are beneficial and can prevent worsening of eyesight and extension of the disease.

The amount of patients with sarcoidosis in a uveitis population varies and depends on the patients’ characteristics and the definition/diagnosis of sarcoidosis [7]. The amount of sarcoidosis in uveitis patients varies from 2.2% up to 30.1% [5, 6, 8, 10, 14, 22-27]. According to the IWOS criteria, sarcoidosis was present in 22% of
the uveitis patients included in our study, which is a higher incidence of sarcoidosis than most of the studies, but still in the range. This high variation in identification of underlying sarcoidosis between various centers probably reflects referral bias as well as detection bias.

Currently, a wide range of diagnostic strategies are being used for the first-step screening. We evaluated the most used combinations with or without chest X-ray, liver enzymes and ACE. In literature, positive liver enzymes are found in 10-25% [28, 29] of sarcoidosis patients, positive ACE in 22-41,4% [14, 30, 31] and positive chest X-ray in 50% [14], comparable to our results, and thereby not sufficiently sensitive to use as a screening test. Previous studies have shown the value of serum sIL-2R in sarcoidosis [12, 13], and also in patients with specific ocular sarcoidosis [14, 32] similar to our study. The high sensitivity of serum sIL-2R, with even a higher sensitivity in combination with the chest X-ray, makes this method optimal for screening and includes most of the patients with ocular sarcoidosis. Whole body ¹⁸F-FDG-PET/CT scan on a regular basis.

Based on the results of this study, we propose following 2-step diagnostic approach to detect sarcoidosis in uveitis patients. In the screening phase, chest X-ray and serum sIL-2R should be used to select patients for additional imaging. Subsequently, whole body ¹⁸F-FDG-PET/CT may show biopsy (extra)thoracic localizations when diagnostic confirmation is requested and can give clues for other underlying systemic diseases.

To prove if serum sIL-2R could be used as a marker for prognosis, disease activity or optimal selection of therapy, prospective studies should be performed. In our patient population, limited data of follow-up suggest that elevated serum sIL-2R predicts a more favorable course of the uveitis.

Strengths and Limitations of this Study

The strengths of this study is that it includes a population of well-defined patients which were initially seen by both an ophthalmologist and internist in a multidisciplinary setting. Furthermore, a well-controlled follow-up during additional diagnostic steps and therapy was secured. However, this research is based on retrospective data and therefore, in a selected uveitis population since test results, including the serum sIL-2R and ¹⁸F-FDG-PET/CT were not available in all patients, and may selectively being ordered during the diagnostic process by the consulting internist. Clinical signs that were used to determine the IWOS-criteria may be underdiagnosed because of the retrospective character of this study. Other factors that may have influenced the results are that serum sIL-2R was measured with 2 different methods (because of a change in technique of the serum sIL-2R measurement during inclusion time).

Conclusion

The combination of a non-invasive chest X-ray and serum sIL-2R is an adequate selecting first-step in the diagnosis of sarcoidosis in patients presenting with uveitis, which can be further assessed by imaging and/or tissue investigation on the basis of whole body ¹⁸F-FDG-PET/CT.

References


