Ocular Diseases in Patients with Rheumatic Diseases

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Abstract
To study the distribution of ocular involvement among persons with rheumatic disease, a cross-sectional survey was performed in 224 patients attending the Division of Rheumatology, Department of Medicine, Maharaj Nakorn Chiang Mai Hospital. Of these patients, 102 presented with rheumatoid arthritis, 74 systemic lupus erythematosus, 39 systemic sclerosis, 6 mixed connective tissue disease, 2 polymyositis and 1 juvenile rheumatoid arthritis. It was found that the ocular involvement probably related to diseases including dry eye (19.9%) and uveitis (0.4%). The ocular involvement was presumably related to treatment including retinopathy (7.6%), cataract (6.3%), and glaucoma (0.9%). Rapid recognition of these complications would lead to early and appropriate management, which would prevent their sequelae.

Key word: Rheumatic Disease, Dry Eye, Uveitis, Cataract, Glaucoma, Retinopathy

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Patients with rheumatic disease may have various ocular complications(1). Many ocular complications are an indicator of the active process of diseases and some of them are the marker for severe and potentially lethal systemic involvement(2). Drugs that are an effective treatment for these disorders may also cause ocular side effects, which sometimes lead to permanent visual damage(3,4).

The objective of this study was to determine the distribution of ocular involvement among

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rheumatic disease patients. Early detection, timely and appropriate management of these ocular complications would save the patient’s sight and also improve their quality of life.

**PATIENTS AND METHOD**

**Study population**

A cross-sectional study was performed in patients consulting at the Division of Rheumatology, Department of Medicine, Maharaj Nakorn Chiang Mai Hospital. A total of 224 patients were recruited into this study. There were 102 who presented with rheumatoid arthritis (RA), 74 systemic lupus erythematosus (SLE), 39 systemic sclerosis (SS), 6 mixed connective tissue disease (MCTD), 2 polymyositis and 1 juvenile rheumatoid arthritis (JRA).

**Examination**

The patients were questioned and their current medication recorded for both systemic and topical drugs.

The order of ocular examinations was visual acuity assessment, Ishihara color-vision testing and Amsler grid testing in patients who received chloroquine, slit-lamp examination, fluorescein staining, tear film break-up time (TBUT), lissamine green staining, Schirmer’s test, Goldman’s applanation tonometry, pupil dilatation, and lens and fundus examination. Visual field assessment by a Humphrey Field Analyzer or Goldman perimetry was performed on other days in some cases.

After visual acuity assessment, the patients who received chloroquine were asked to read the Ishihara color-vision plates with one eye covered. The test was considered abnormal when less than 8 of 12 correct plates were identified. The patients were then examined by Amsler grids. Any irregularities in the design, i.e. wavy lines, differences in box sizes, or fuzzy areas, were considered abnormal.

Slit-lamp examination was used to determined the presence of conjunctival injection, dryness of the bulbar conjunctiva, and cornea verticillata. Cornea verticillata was graded from 0 to 3 as follows: grade 0, no keratopathy; grade 1/2+, mild changes; grade 2+, changes greater than 1+ with more lines; and grade 3+, changes with a whorl-like pattern seen without the slit-lamp.

Fluorescein staining with a slit-lamp examination was used to determine the presence of mucous debris, scanty tear meniscus (height <0.1 mm), superficial punctate keratopathy, punctate epithelial erosion, and filamentous keratopathy.

The tear film break-up time (TBUT) was recorded after fluorescein staining. The patient was asked to blink and then keep the eyes open. The cornea was scanned with a slit lamp using a cobalt-blue filter. A dry area was indicated by the appearance of a black spot. The time in seconds between the last blink and the appearance of a random dry spot was recorded as the TBUT. The test was repeated three times in each eye, and the average was recorded.

Lissamine green staining was performed by instilling one drop of 1 per cent lissamine green (Dakryon, Texas, USA) in the inferior fornix of each eye and examining the eye under a slit lamp for any staining of the conjunctiva and cornea.

Grading of lissamine green staining was modified from rose bengal staining in keratoconjunctivitis sicca according to Bijsterveld, from grade 0 to 3, as follows: grade 0, normal; grade 1, mild (staining scattered interpalpebral conjunctiva); grade 2, moderate (staining diffuse interpalpebral conjunctiva); and grade 3, severe (definite corneal staining).

The Schirmer’s test was performed, without an anesthetic eye drop, by placing a pre-calibrated filter strip (Sno strip, Akorn Inc., LA, USA) temporarily in each lower fornix and leaving it in place for 5 minutes before the strips were removed and the millimeters of wetting recorded.

A definite diagnosis of dry eye was established if two or more signs in these findings were observed:

1. Slit-lamp examination with fluorescein staining had three or more of the following abnormalities: mucous debris, scanty tear meniscus, superficial punctate keratopathy, punctate epithelial erosion, and filamentous keratopathy.
2. TBUT was less than 5 seconds.
3. Lissamine green staining was grade 3.
4. Schirmer’s test without anesthesia was less than 5 millimeters.

Applanation tonometry was performed after the instillation of anesthetic eye drops. Then the eyes were dilated, with 1 per cent tropicamide, for lens and fundus examination.

Visual field measurement with a Humphrey Field Analyzer or Goldman perimetry was carried out later in cases with an abnormal color-vision test, abnormal Amsler grid test, high intraocular pressure (>21 mmHg), or abnormal fundus.
Data analysis
All analyses were performed with SPSS for Windows Version 9.01 (SPSS Inc., Chicago, USA). Chi-square tests were used to evaluate significant differences in proportion among groups. A p-value <0.05 was considered to be statistically significant.

RESULTS
Two hundred and twenty-four patients were recruited. Of these, 206 were women and 18 were men. The age range was from 14 to 78 years with a mean age $\pm$ SD of 44.3 $\pm$ 13.7 years. Table 1 lists the sex and age group distribution of these patients. The overall ocular involvement in these patients is shown in Table 2. Table 3 lists the distribution of dry eye among various types of rheumatic disease.

Seventy one eyes of these patients presented with cataract, which comprised posterior subcapsular cataract (PSC) in 33 eyes (7.4%), nuclear sclerosis (NS) in 23 (5.1%), cortical cataract (CC) in 10 (2.2%), and mixed types in 5 (1.1%). Table 4 shows the distribution of various types of cataract by the age groups of the patients.

Systemic corticosteroid administration was considered to be a risk factor for cataract. Table 5 demonstrates the relationship between various types of cataract and corticosteroid administration.

Intraocular pressure (IOP) of more than 21 mmHg, which was suspected glaucoma, presented in 4 eyes (0.9%) of these patients. IOP distribution among patients in various age groups is shown in Table 6. Table 7 demonstrates the relationship between IOP and corticosteroid administration in these patients.

One hundred and eighty-eight patients received chloroquine therapy. Ocular abnormalities from chloroquine, which included cornea verticillata, an abnormal color vision test, abnormal fundus and abnormal visual field, are shown in Table 8.

DISCUSSION
Dry eye is the most common ocular finding in many rheumatic diseases. Coll et al.\(^\text{11}\) found that 35 per cent of patients with a variety of autoimmune disorders, suffered from dry eye compared to 6 per cent of a normal control group. Dry eye was the most common ophthalmic manifestation in 4,500 patients examined with RA. This was the largest series reported, and it disclosed that 11 per cent of these patients suffered from dry eye\(^\text{1}\), while most authors cited a prevalence of 15 per cent to 25 per cent\(^\text{12-14}\). In a study from Greece, only 18 per cent of patients with RA had subjective complaints of dry eye, but 52.3 per cent had positive rose bengal staining and 45 per cent had abnormal Schirmer I test results\(^\text{15}\).

Dry eye is also the most common ocular finding that occurs in 7 per cent to 54 per cent of SLE patients\(^\text{16-18}\). Spaeth found that 87 per cent of the SLE patients in his study had fluorescein corneal staining\(^\text{19}\).

As many as 37 per cent to 48 per cent of the SS patients had dry eye\(^\text{20,21}\), whereas, dry eye was found in 36 per cent of MCTD patients\(^\text{22}\).

In the present study, the authors found dry eye in 23 per cent of RA patients, 14.2 per cent of SLE patients, 20.5 per cent of SS patients, and 25 per cent of MCTD patients (Table 3).

Cataract is another common ocular abnormality that was found in 71 eyes (15.8%) of the patients in this study (Table 4). Some types of cataract are age-related, but PSC, which was found in 28 eyes (6.3%) is statistically significant in relation to corticosteroid administration (Table 5).

The association between corticosteroid use and PSC has been noted consistently since 1960\(^\text{23-25}\). Fournier et al found that a daily dosage, cumula-

Table 1. Distribution of sex and age groups.

<table>
<thead>
<tr>
<th>Age Group (year)</th>
<th>Sex</th>
<th>No. of female</th>
<th>%</th>
<th>No. of male</th>
<th>%</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤19</td>
<td></td>
<td>1</td>
<td>0.4</td>
<td>2</td>
<td>0.9</td>
<td>3</td>
<td>1.3</td>
</tr>
<tr>
<td>20-39</td>
<td></td>
<td>79</td>
<td>35.3</td>
<td>4</td>
<td>1.8</td>
<td>83</td>
<td>37.1</td>
</tr>
<tr>
<td>40-59</td>
<td></td>
<td>90</td>
<td>40.2</td>
<td>8</td>
<td>3.6</td>
<td>98</td>
<td>43.8</td>
</tr>
<tr>
<td>≥60</td>
<td></td>
<td>36</td>
<td>16.1</td>
<td>4</td>
<td>1.8</td>
<td>40</td>
<td>17.9</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>206</td>
<td>92.0</td>
<td>18</td>
<td>8.0</td>
<td>224</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Table 2. Distribution of ocular involvement.

<table>
<thead>
<tr>
<th>Ocular involvement *</th>
<th>No. of eyes</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry eye</td>
<td>89</td>
<td>19.9</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>34</td>
<td>7.6</td>
</tr>
<tr>
<td>PSC</td>
<td>28</td>
<td>6.3</td>
</tr>
<tr>
<td>IOP &gt;21 mm Hg</td>
<td>4</td>
<td>0.9</td>
</tr>
<tr>
<td>Uveitis</td>
<td>2</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* Some eyes had more than one involvement.

PSC = posterior subcapsular cataract, IOP = intra-ocular pressure, mm Hg = millimeters of mercury

tive dose and duration of corticosteroid therapy were not associated with cataract formation, but there was a significant difference in the distribution of HLA-CW3 antigen between patients with cataract and those without(26). The reason for the link between corticosteroid therapy and the formation of PSC remained unclear.

Another complication of corticosteroids is the elevation of IOP, which may lead to glaucoma. The authors found an IOP of greater than 21 mmHg in 4 eyes (0.9%) of the patients, all of whom had received corticosteroid therapy (Table 6 and Table 7).

It is necessary to monitor IOP in all patients who receive corticosteroids. In susceptible patients, a corticosteroid-induced elevation of IOP, as a result of reduced outflow, is possible from topical, local or systemic administration of corticosteroid preparations(27), although the frequency and severity of the IOP rise is greater with topical application than with systemic administration(28). Several mechanisms may be involved sequentially or in parallel, and may be different for each individual(27).

Chloroquine is a common drug for the treatment of various rheumatic diseases. One hundred and eighty-eight of our patients received chloroquine therapy. Ocular abnormalities that were found in these patients included cornea verticillata grade 1+ in 94 eyes (25%), grade ≥2+ in 20 (5.3%), abnormal visual field in 71 (18.9%), abnormal Amsler grid test in 44 (11.7%), abnormal color vision test in 36 (9.8%), and abnormal fundus in 34 (9%), as shown in Table 8.

Table 3. Distribution of dry eye by types of rheumatic disease.

<table>
<thead>
<tr>
<th>Type of rheumatic disease</th>
<th>No. of patients</th>
<th>No. of dry eyes</th>
<th>%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>102</td>
<td>47</td>
<td>23.0</td>
</tr>
<tr>
<td>SLE</td>
<td>74</td>
<td>21</td>
<td>14.2</td>
</tr>
<tr>
<td>SS</td>
<td>39</td>
<td>16</td>
<td>20.5</td>
</tr>
<tr>
<td>MCTD</td>
<td>6</td>
<td>3</td>
<td>25.0</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>2</td>
<td>2</td>
<td>50.0</td>
</tr>
<tr>
<td>JRA</td>
<td>1</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>224</strong></td>
<td><strong>89</strong></td>
<td><strong>19.9</strong></td>
</tr>
</tbody>
</table>

* The per cent of dry eye in the specific type of rheumatic disease.

RA = rheumatoid arthritis, SLE = systemic lupus erythematosus, SS = systemic sclerosis, MCTD = mixed connective tissue disorders, JRA = juvenile rheumatoid arthritis

Table 4. Distribution of types of cataract by age group.

<table>
<thead>
<tr>
<th>Type of cataract</th>
<th>Age Group (year)</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤19</td>
<td>20-39</td>
<td>40-59</td>
</tr>
<tr>
<td>PSC</td>
<td>0</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>NS</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>CC</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Mixed</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1</strong></td>
<td><strong>13</strong></td>
<td><strong>28</strong></td>
</tr>
</tbody>
</table>

PSC = posterior subcapsular cataract, NS = nuclear sclerosis, CC = cortical cataract
Table 5. Relationship between types of cataract and corticosteroid administration.

<table>
<thead>
<tr>
<th>Type of cataract</th>
<th>No. of eyes with steroid</th>
<th>No. of eyes without steroid</th>
<th>( \lambda^2 ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSC</td>
<td>28</td>
<td>5</td>
<td>11.738 (p=0.001)*</td>
</tr>
<tr>
<td>NS</td>
<td>12</td>
<td>11</td>
<td>0.135 (p=0.713)</td>
</tr>
<tr>
<td>CC</td>
<td>6</td>
<td>4</td>
<td>0.000 (p=1.000)</td>
</tr>
<tr>
<td>Mixed</td>
<td>3</td>
<td>2</td>
<td>0.000 (p=1.000)</td>
</tr>
</tbody>
</table>

* Statistically significant
PSC = posterior subcapsular cataract, NS = nuclear sclerosis, CC = cortical cataract

Table 6. Distribution of intra-ocular pressure by age groups.

<table>
<thead>
<tr>
<th>IOP (mm.Hg)</th>
<th>Age Group (year)</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;19</td>
<td>20-39</td>
<td>40-59</td>
</tr>
<tr>
<td>≤15</td>
<td>6</td>
<td>148</td>
<td>182</td>
</tr>
<tr>
<td>16-21</td>
<td>0</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>&gt;21</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>166</td>
<td>196</td>
</tr>
</tbody>
</table>

* Number of eyes
IOP = intra-ocular pressure, mm.Hg = millimeters of mercury

Table 7. Relationship of intra-ocular pressure and corticosteroid administration.

<table>
<thead>
<tr>
<th>IOP (mm.Hg)</th>
<th>No. of eyes with steroid</th>
<th>No. of eyes without steroid</th>
<th>( \lambda^2 ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤21</td>
<td>254</td>
<td>190</td>
<td>2.824 (p=0.093)</td>
</tr>
<tr>
<td>&gt;21</td>
<td>4</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

IOP = Intra-ocular pressure, mm.Hg = millimeters of mercury

As chloroquine is tolerated better and less toxic than penicillamine, gold, levamasols, and systemic corticosteroid, an increasing number of patients with rheumatic disease are being treated with it. Corneal deposits, as described in 1958 by Hobbs and Calnan, were found to be antimalarial salts in the basal epithelium of the cornea. The pattern of deposition varies from diffuse punctate opacities to an aggregation of radial and whirling lines that converge on a zone just beneath the center of the cornea. Easterbrook reported that 95 per cent of patients receiving 250 mg of chloroquine daily developed corneal deposits. In the past, it was believed that keratopathy associated with chloroquine was not an indication to discontinue therapy and had no relationship to the development of retinopathy. However, a later report indicated that patients who demonstrated any significant corneal changes should be assessed carefully for any disturbance of macular function. Although macular lesion and visual field loss were described in a patient with SLE who was being treated with chloroquine in 1957, it was not until 1959 that a definite association between retinopathy and chloroquine was made by Hobbs. Depending on the definition of retinopathy and the method used for its detection, the reported incidence of chloroquine retinopathy varies widely from less than 1 per cent to more than 40 per cent. Various objective and subjective studies have been evaluated.
in an attempt to define early abnormalities and predict or prevent disease progression.

Visual field testing has been used to detect the presence of defects with antimalarial drug use, thereby, determining whether associated retinopathy exists(33). Various methods of testing have been employed, yielding a variety of results. Easterbrook and Trope compared automated, static and kinetic perimetry, and indicated that the automated perimetry (Humphrey10-2) yielded greater sensitivity in assessing macular function in patients and enhanced the use of a red target(34).

Color-vision testing is particularly useful for patients who do not handle visual-field testing well. Nozik et al(35) found that the defects of the pseudoisochromatic H-R-R color plates occasionally preceded the appearance of a scotomy in visual-field testing. However, when a pericentral or central scotoma does exist, difficulty in detecting the figures on the H-R-R plates can be noted. Easterbrook reported recently that the Ishihara color-vision test, which is available in most ophthalmology offices, would detect 25 per cent of patients with relative scotoma and 90 per cent of patients with absolute scotomas(36).

One study reported that the Amsler grid was a simple and inexpensive test that could be self-administered by any patient who cooperated and it was an excellent means of screening for early chloroquine retinopathy(6), since the detection of para-central scotomas correlated well with the Amsler grid and both static and kinetic perimetry(6). Another study also demonstrated that the Amsler grid could pick up very small early scotomas before they were detected by kinetic and static field testing(37).

The earliest abnormal fundus findings from chloroquine toxicity showed irregularity in the macular pigmentation and blurring of the foveal reflex(38). In time, the central, irregular pigmentation might become surrounded by a concentric zone of hypopigmentation, resulting in the classic bull's eye. With continued exposure to the drug, there may be more generalized pigmentary changes, vascular attenuation, and optic disc pallor(38). It should be noted, however, that there are reports of permanent visual field loss without noticeable macular changes or loss of the foveal reflex(5).

The incidence of retinopathy has been consistently reported to increase with both the dose and duration of chloroquine treatment, i.e. a daily dose of <250 mg, or cumulative dose of <100g, and duration of treatment if less than a year, which is associated with a very low incidence of retinopathy(39). However, the recommended dosage of 3.5 mg/kg/day for chloroquine, based on lean or ideal body weight by Mackenzie, was suggested(40). It is recommended that patients who receive chloroquine and have normal renal function need to be examined once a year if the dose is less than 3.0 mg/kg of ideal body weight, and every 6 months if the duration of treatment is longer than 10 years or the dose of chloroquine exceeds 3 mg(36).

Uveitis was found in both eyes of one patient who had JRA (Table 3). Two recent studies showed that the prevalence of uveitis in patients with JRA was 9 per cent and 9.3 per cent respectively(41,42).

In considering the ocular involvement revealed in this study, some separation of the changes might be made provisionally into those related to the disease and those due to previous or current treatment. The ocular involvement was probably related to diseases including dry eye and uveitis, and it presumably related to treatment that included posterior subcapsular cataract, glaucoma, and retinopathy.

It is important for ophthalmologists, internists, or other medical care providers to recognise ocular involvement in rheumatic disease patients. Quick recognition would lead to early diagnosis and treatment, which would in turn prevent associated ocular morbidities.

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