ORIGINAL ARTICLE

Intermediate uveitis, an ophthalmological manifestation of systemic disease

Uvéite intermédiaire, une manifestation ophtalmologique annonçant une maladie associée


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Intermediate uveitis; Cancer; Systemic diseases; Infections

Summary
Purpose. — Intermediate uveitis is frequently indicative associated with systemic disease. In addition to the initial evaluation of the patient with intermediate uveitis, we sought to determine the role of longitudinal follow-up in improving the diagnosis of systemic disease associated with intermediate uveitis.
Method. — Retrospective analysis of a cohort of 51 patients with intermediate uveitis followed for 5 to 13 years.
Results. — Upon initial evaluation, an underlying disease associated with the intermediate uveitis was found in nine out of the 51 patients. Among the remaining patients, after at least 5 years of follow-up, eight new associated diagnoses were revealed (primarily inflammatory diseases and cancers).

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**Introduction**

Intermediate uveitis (IU) are defined by the inflammation of the vitreous including, posterior cyclitis, pars planitis and hyalitis [1]. They give account for up to 20% of the whole uveitis [2] and often remain unexplained since an associated diagnosis is found in only 15 to 30% of the cases depending on the diagnostic criterias [3–5]. Most frequently, multiple sclerosis (MS) and sarcoidosis are found when IU occurs, but Behcet disease, inflammatory bowel diseases, tuberculosis or Lyme disease are also known to be associated with IU. Nevertheless, costly diagnostic procedures do not seem to be useful [3–5].

The goal of the present study was to determine if longitudinal follow-up of patients with IU improved the discovery rate of associated diagnosis. In our 650 patient’s uveitis file, we identified 62 IU. We followed 51 of these patients or contacted referred ophthalmologists or physicians in order to know if IU preceded the appearance of a defined pathology. We also studied the course of uveitis, relapsing trend, complications and functional sequela.

**Patients and method**

**Patients**

Among 650 patients with uveitis followed at our center, 62 were diagnosed with IU according to defined international criteria [1]. This rate of 9,5% of IU is slightly inferior to historical published series. However, other recent cohorts also reported lower frequencies [4]. Patients with Fuch’s disease were excluded. Among the 62 patients with IU, 11 were lost of follow-up and were not included in the study. We report then on 51 patients, eight of them suffering from typical pars planitis. All respond to the IU SUN definition. None has associated anterior or posterior uveitis, but OCT was not available when cohort started.

**Initial evaluation of IU**

Patients were referred to our uveitis center by their referent ophthalmologist. An internal medicine specialist and an ophthalmologist evaluated them. All received the same extensive check-up (Appendix S1).

**Follow-up**

Follow-up was performed by our center or by referent ophthalmologists and physicians in charge of the patients between 1993 and 2000. A standardized form (Appendix S2) was designed to collect detailed information about diagnosis and course of uveitis: occurrence of general or systemic diseases, uveitis relapses, complications, sequela of uveitis. The follow-up extended from 6 years to 14 years.

**Results**

**Patients**

Patients were caucasian coming from the East of France. Sex ratio was 1 (26 males and 25 females). Mean age was 38 years old (15 years old to 78 years old). Eight patients displayed features of pars planitis as recommended by the Standardisation of Uveitis Nomenclature working group. The definition identifies a subgroup of IU with snowbank or snowball formation without associated infection nor systemic disease. Our patients with pars planitis were younger (middle age: 25 years old vs 38 years old for overall uveitis). Seven of the eight patients (87,5%) displayed a bilateral uveitis compared to 27 of the 43 remaining cases (62%).

**Conclusion.** — These results suggest that the initial work-up of the patient with intermediate uveitis is not sufficiently sensitive and that careful follow-up of these patients considerably improves the diagnosis of associated disease.

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Intermediate uveitis associated diseases

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Type of IU and number of associated diagnoses.</th>
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<tbody>
<tr>
<td></td>
<td>Number of cases</td>
</tr>
<tr>
<td>Pars planitis</td>
<td>8</td>
</tr>
<tr>
<td>Non pars planitis IU</td>
<td>43</td>
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</table>

<table>
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<tr>
<th>Table 2</th>
<th>Diagnoses, which were found to be associated with IU.</th>
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<tr>
<td>Associated diagnosis</td>
<td>Initial check-up (9/51)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>ENT contiguous infections</td>
<td>2</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>1</td>
</tr>
<tr>
<td>Lyme</td>
<td>1</td>
</tr>
<tr>
<td>Inflammatory diseases</td>
<td></td>
</tr>
<tr>
<td>MS</td>
<td>1</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>0</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1</td>
</tr>
<tr>
<td>Masquerade uveitis</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>0</td>
</tr>
<tr>
<td>Prostatic cancer</td>
<td>1</td>
</tr>
<tr>
<td>Allergy</td>
<td></td>
</tr>
<tr>
<td>Spider</td>
<td>1</td>
</tr>
</tbody>
</table>

Initial diagnosis and follow-up

Among the 51 patients who were followed up, the initial check-up found an associated diagnosis in only nine of them (17.6%, Tables 1 and 2). The follow-up allowed identification of associated diagnosis in eight patients, increasing the number of associated diagnosis to 17/51 patients (33%, Table 2). Associated diagnosis was made after a mean time of 31,375 months (one to 120 months). The link between IU and the late associated diagnosis is suggested by a relative short period of time between the two events like during the tuberculosis case and the cancer cases, or by already known associations (MS cases). The link is also suggested by the disappearance of the feature of IU after the cure of the associated pathology (as for patient suffering from recurrent IU cured after tonsillectomy for contiguous infection). Taking into account both initial and late diagnosis, IU was associated with inflammatory diseases in five cases (three MS, one rheumatoid arthritis, one and ulcerative colitis), infections seven cases (two tuberculosis, one Lyme disease, one toxoplasmosis, two sinusitis and one tonsillitis) cancers cases (two ocularcerebral lymphomas, two prostate cancers) and allergic disease one case.

Complications and sequelae

The overall relapse rate was 52% (26 of 51 patients). In the subgroup pars planitis, this rate increased to 75% (six of eight patients). Blindness of the sick eye occurred in three cases and a decrease of visual function persisted in 20 cases. The most frequent ophthalmologic complications were cystoid macular edema (eight in 51), glaucoma (two in 51), vitreous traction with or without retinal detachment (three in 51, Table 3).

Discussion

During IU, three diagnostic situations can be described: typical pars planitis (which is usually isolated), IU with an associated diagnosis and IU without associated diagnosis. Literature analysis on IU is impaired by the confusion between pars planitis and IU without associated diagnostic that must be distinguished on the basis of ophthalmologic signs.

If we exclude pars planitis, we found at entry 20.9% (nine over 43) of IU with an associated pathology. Prolonged follow-up allowed to find associated diagnosis in eight other patients increasing the diagnostic rate up to 39.5% (17/43).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Complications occurring during IU.</th>
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<tr>
<td>IU complications</td>
<td>Number (percentage)</td>
</tr>
<tr>
<td>Macular cystoid oedema</td>
<td>8 (15.6%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>5 (9.8%)</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>3 (5.8%)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>2 (3.9%)</td>
</tr>
</tbody>
</table>
This rate is higher than previously reported in historical series (diagnostic rate between 15,8 and 31,3%) [3,6], showing the interest of a careful follow-up of these patients which would lead to rapid diagnosis.

In our series, infections give account for 41% of the diagnosis associated with IU. Infectious causes can be divided into contiguous infections and systemic infections with probably different underlying pathogenic mechanisms. In two of our patients, sinusitis occurred at the same time that IU. In the last case, after five years of relapsing course, tonsillectomy apparently cured IU, linking IU with recurrent tonsillitis. However, the precise link between late contiguous infections and IU is unknown and literature remains very poor about contiguous ENT infection linked uveitis. Systemic infection was diagnosed after IU in only one case. In this patient, lymph node tuberculosis appeared a few months after uveitis. We should also mention that, despite the high incidence of Lyme disease in the geographic area of our study, we found only one patient with this diagnosis. Finally, between 1993 and 2000, molecular biology assays on ocular fluid analysis was not performed, but improve the diagnostic rate of infections [7].

Among the five patients who were diagnosed with an inflammatory disease, four were recognized during the follow-up. In two patients, the diagnosis of MS was made lately, up to 10 years after IU occurred. These results and others suggest that systematic gadolinium injected brain MRI should be performed in patients with IU in order to diagnose silent MS [8]. The fourth patient lately presented an unusual association with ulcerative colitis, which is usually linked with anterior HLA B27 uveitis or scleritis. However, even if inflammatory mechanism is implied for the two conditions, association is not enough to ensure a causality link and some observations could be fortuitous. Surprisingly, no patient had sarcoidosis, a classical cause of IU. However, one of the patients who were lost of follow-up had mediastinal hilar enlargement and blood angiotensin converting enzyme elevation at the initial work-up, making the diagnosis of sarcoidosis diagnosis highly likely. Moreover, between 1993 and 2000, Chest CT scan was not performed in the systematic IU investigations.

Cancers are also reported to be associated with IU. Mechanisms involve local malignancies, ocular metastasis and paraneoplastic syndromes. In our series, four patients had IU associated malignancy. In two of them, ocular lymphoma was diagnosed. Both were women, 76 and 79 years old respectively. The first case was diagnosed a few weeks after IU started, with vitreous pathergy showing lymphomatous cells. In the second case, IU preceded lymphoma for ten months. Patient deceased one year after IU onset. Two patients had prostatic adenocarcinoma. The first had known cerebral metastasis when IU occurred, possibly linked to ocular metastasis. In the other case, IU preceded cancer by six months, without cerebral metastasis, suggesting a paraneoplastic mechanism as it was described during cancer associated retinopathy driving to choriotireal atrophy [9,10]. Taking together, masquerade IU give account for 17,6% (three over 17) of all associated diagnosis in our IU patients.

Recent publication by Khairallah et al. interestingly focused on clinical presentation of IU, reported a 87 patients cohort [11]. They precised the visual prognostic factors (i.e., initial visual acuity and severe vitritis). However, they identified only 13,8% of systemic diseases associated to IU (infectious or inflammatory diseases). Our work usefully completes this work and underscores the importance of standardized IU check-up.

Secondary objective was to precise the long term course of IU. In our series, relapses are frequent (52%), mainly in the pars planitis group. The visual prognosis can also be severe (Table 3). Complications led to blindness in three patients, and some degree of loss of visual function in 20 cases. A recent retrospective study underscored the favorable visual outcome despite persistent inflammation. However, some patients evolved to blindness or visual impairment [12].

Our data emphasize the interest to follow the patients with IU for both ophthalmologic reasons (complications) and medical reasons. Indeed, if we consider patients at entry, our initial general evaluation missed an associated diagnosis in eight cases over 43 (18,6%). In elderly patient, masquerade syndrome (lymphoma and solid cancer) should be rule out. In these cases, the explanation probably resides in the lack of sensibility of the initial diagnostic procedures, and strongly urges to investigate the apparently idiopathic IU patients with brain MRI, thoracic CT scan and maybe molecular biology assays on vitreous liquid. The follow-up should be prolonged, as the mean time to associated diagnosis during unexplained uveitis follow-up is 31,375 months.

Thus, a future prospective study, distinguishing between pars planitis and other IU, with more accurate initial check-up and well defined follow-up is required to define the field of IU.

Disclosure of interest

The authors declare that they have no conflict of interest concerning this article.

Appendix A. Supplementary data

Supplementary data (Appendix S1 and S2) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfo.2012.05.007.

References

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