Original article

Central nervous system demyelinating disease-associated uveitis☆

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ABSTRACT

Objective: To describe the epidemiology, clinical features and visual prognosis in uveitis associated with demyelinating disease (DD) of the CNS.

Methods: A clinical, retrospective, and descriptive study was performed. Data regarding age at presentation, gender, time from onset was recorded, as well as type of uveitis, complications, treatment and initial and final visual acuity (BCVA) on all patients with DD-associated uveitis diagnosed in our Unit between January 2009 and June 2011.

Results: Five women and 4 men were finally included (1.3% of 697 with uveitis). There was associated multiple sclerosis in 78% of cases. Mean age at presentation was 36.6 years for uveitis and 40 years for DD. The uveitis preceded the DD in 3 cases (33%). Typically, uveitis was bilateral (89%), chronic (89%), intermediate (89%), and associated with previous inflammation (29%), with synechiae (65%), and granulomatous (44%). The most frequent complications were cataract (71%) and macular edema (53%). Besides local treatment, uveitis was managed with systemic steroids (78%), immunosuppressants (44%), and surgery (41% of eyes). After a mean follow up of 5 years, 47% of the eyes had a worse BCVA, among which, 12% lost ≥3 Snellen lines. The only patient treated with interferon (IFN) remained stable without treatment for the last 7 years.

Conclusions: DD-associated uveitis typically affected young adult women with intermediate–anterior uveitis of chronic, bilateral and synechiae type. Complications are common and there is a risk of visual loss, despite treatment. IFN therapy may be an effective alternative to be investigated.

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Uveitis asociadas a enfermedad desmielinizante del sistema nervioso central

RESUMEN

Objetivo: Describir la epidemiología, características clínicas y pronóstico visual de las uveitis asociadas a enfermedad desmielinizante (ED) del SNC.

Métodos: Estudio retrospectivo, descriptivo de serie clínica. Se recogieron la edad de presentación y el sexo, el tiempo de evolución, el tipo de uveitis, las complicaciones, el
Uveitis  
Esclerosis múltiple  
Enfermedad desmielinizante  
Oftalmología  
Mielitis transversa aguda

tratamiento instaurado y la agudeza visual (AVmc), basal y final, de todos los pacientes con uveitis asociada a ED diagnosticada en nuestro Servicio entre enero de 2009 y junio de 2011. Resultados: Se incluyó a cinco mujeres y cuatro hombres (1,3% de 697 uveítis atendidas). Asociaron esclerosis múltiple un 78%. La edad media de presentación de la uveitis fue de 36,6 años y de la ED, 40 años. La uveitis antecedía a la ED en 3 casos (33%). La uveitis fue, típicamente, bilateral (89%), crónica (89%) e intermedia (89%) y asociada a inflamación anterior (29%), sinequienne (65%) y granulomatosa (44%). Las complicaciones más frecuentes fueron: catarata (71%) y edema macular (53%). Además del tratamiento local, la uveitis se manejó con esteroides sistémicos (78%), inmunosupresores (44%) y cirugía (41% de ojos). Tras un seguimiento medio de 5 años, un 47% de los ojos empeoró su AVmc, perdiendo 3 líneas de Snellen en un 12%. La única paciente tratada con interferón (IFN), permaneció estable sin tratamiento durante los últimos 7 años.

Conclusiones: La uveitis asociada a ED afecta típicamente a mujeres adultas jóvenes con uveitis intermedias-anteriores, crónicas, bilaterales y sinequientes. Las complicaciones son frecuentes y existe riesgo de pérdida visual, a pesar del tratamiento. La terapia con IFN podría ser una alternativa eficaz a investigar.

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Introduction

Demyelinating diseases (DDs) of the central nervous system (CNS) comprise a group of inflammatory diseases characterized by the degradation of the myelin sheaths that cover neurons. The maximum expression of this entity is multiple sclerosis (MS), although systemic inflammatory diseases such as systemic lupus erythematosus, Adamantiades-Behçet disease or Sjögren syndrome can also produce DD.1,2 It is believed that the etiology is self-immune. Several antigens have been identified as candidates for triggering the process.3

Intraocular inflammation associated to MS can express in the form of optic neuritis, intermediate uveitis (IU), periphlebitis, anterior uveitis and (AU) which can be granulomatous or non-granulomatous, panuveitis, choroiditis or an overlapping of the above. It has been demonstrated that MS patients have a higher risk of developing uveitis (OR = 3.2, 95%; CI 1.7–5.7), probably because they share target antigens, genetic vulnerabilities or alterations in the immunological homeostasis.4–6 About 1% of MS patients exhibit uveitis and 1% of uveitis will associate MS.7 However, a deliberate search for subclinical periphlebitis in MS patients will reveal that this disease can be found in 20–44% of cases.8

There is a certain controversy in the literature about the incidence, the most frequent form, the chronology of presentation of MS and the visual prognosis of said uveitis. Specific uveitis subgroups could be precursors for the development of MS and as they probably share etiopathogenic mechanisms both could respond to the same treatment which, if established at an early stage, could prevent neurological and visual sequels.9

This paper analyzes the clinic characteristics and the visual prognosis of 9 patients with uveitis associated to DD that were attended in the Institut Clinic d’Oftalmologia (ICOF) of the Barcelona Hospital Clinic.

Subjects, material and methods

A retrospective search for patients with uveitis and DD was made in the uveitis database of the Institut Clinic d’Oftalmologia (ICOF) between January 2009 and June 2011. The classification of uveitis was made on the basis of the International Uveitis Study Group (IUSG)10 in what concerns location (anterior, intermediate, posterior or panuveitis), the biomicroscopic type (granulomatous or non-granulomatous) and duration (acute, chronic or recurring). The neurological diagnosis of DD was made by the Neurology Service of the same hospital. On the basis of clinic, paraclinic and analytical criteria, DD was classified as MS, according to the McDonald revised criteria,11 or another DD of the CNS.

As this was a retrospective, descriptive and non-interventionist study, it was not deemed appropriate to request the approval of the Ethics Committee of our institution although this paper complies with all the other requirements of the 1983 Helsinki Revised Declaration.

After the identification of patients their clinical records were reviewed in depth, recording demographic, clinic, ophthalmological and therapeutic data to a database for subsequent statistical study. Absolute and relative frequencies were calculated together with the mean values and ranges utilizing Excel (Office 2003, Windows XP, Microsoft Ibérica, Madrid, Spain).

Results

Out of 697 patients with uveitis attending in the ICOF between January 2009 and June 2011, 9 (1.3%) also exhibited CNS DD diagnosis and were included in the study. Of said 9 patients, 7 were finally diagnosed with MS (7/689, 1%), one case with self-immune transversal myelitis and one case of idiopathic DD (multiple demyelination brain plates without dissemination in space and time).
### Table 1 – Characteristics, required treatments and visual acuity of patients with uveitis and demyelinating disease.

<table>
<thead>
<tr>
<th>No</th>
<th>Sex</th>
<th>DD-CNS</th>
<th>Uveitis/ DD onset age</th>
<th>Uveitis/DD evolution time</th>
<th>Laterality</th>
<th>Type</th>
<th>Complications</th>
<th>Treatments</th>
<th>VA1 (RE/LE)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>MS</td>
<td>48/48</td>
<td>5y/5y</td>
<td>BE</td>
<td>IU</td>
<td>MS BE</td>
<td>PDN + AZA</td>
<td>0.8/0.8</td>
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<td></td>
<td></td>
<td>CATA BE</td>
<td>TCA IV × 3 BE</td>
<td>0.2/0.7</td>
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<td></td>
<td>Atrofa ON BE</td>
<td>Anti-VEGF BE</td>
<td>(48)</td>
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<td>Nv iris RE</td>
<td>Ozurdex RE</td>
<td>0.95/0.95</td>
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<td></td>
<td></td>
<td>PVO</td>
<td>IFN</td>
<td>(18)</td>
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<tr>
<td>2</td>
<td>F</td>
<td>MS</td>
<td>13/20</td>
<td>16y/9y</td>
<td>BE</td>
<td>IU</td>
<td>PVO</td>
<td>PDN + CyA</td>
<td>0.8/0.4</td>
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<td></td>
<td>CATA BE</td>
<td>TCA ST × 2 BE</td>
<td>0.4/0.3</td>
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<td>RD LE</td>
<td>VPP + L RE</td>
<td>(168)</td>
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<td>VPP + SO + FACO + IOL</td>
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<td>(48)</td>
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<tr>
<td>3</td>
<td>M</td>
<td>MS</td>
<td>24/34</td>
<td>22y/12y</td>
<td>BE</td>
<td>IU + AU</td>
<td>PVO</td>
<td>PDN</td>
<td>0.5/0.8</td>
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<td>CATA BE</td>
<td>TCA ST × 1 RE</td>
<td>0.3/0.6</td>
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<td></td>
<td>ATROFA ON BE</td>
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<td>(48)</td>
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<tr>
<td>4</td>
<td>F</td>
<td>MS</td>
<td>45/52</td>
<td>15y/10y</td>
<td>BE</td>
<td>IU</td>
<td>MS BE</td>
<td>PDN + CyA</td>
<td>0.9/0.85</td>
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<td>Anti-VEGF BE</td>
<td>0.85/0.95</td>
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<td></td>
<td>CATA BE</td>
<td>VPP + ERM BE</td>
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<td>FACO + IOL LE</td>
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<td>(96)</td>
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<tr>
<td>5</td>
<td>F</td>
<td>MS</td>
<td>48/38</td>
<td>2y/12y</td>
<td>RE</td>
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<td>(CD)</td>
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<td>6</td>
<td>M</td>
<td>CIS</td>
<td>72/69</td>
<td>5y/9y</td>
<td>BE</td>
<td>AU</td>
<td>CATA BE</td>
<td>PDN</td>
<td>0.2/0.9</td>
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<td>ATROFA ON BE</td>
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<td>7</td>
<td>M</td>
<td>STTM</td>
<td>38/38</td>
<td>7y/7y</td>
<td>BE</td>
<td>IU</td>
<td>MS BE</td>
<td>PDN</td>
<td>0.16/0.3</td>
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<tr>
<td>8</td>
<td>F</td>
<td>MS</td>
<td>22/21</td>
<td>19y/20y</td>
<td>BE</td>
<td>IU</td>
<td>MS RE</td>
<td>PDN</td>
<td>0.1/0.8</td>
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<td>0.2/0.9</td>
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<td>FACO + IOL RE</td>
<td>MTX</td>
<td>(96)</td>
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<td>CD/0.1</td>
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<tr>
<td>9</td>
<td>M</td>
<td>MS</td>
<td>20/NA</td>
<td>14y/NA</td>
<td>BE</td>
<td>IU</td>
<td>MS BE</td>
<td>PDN</td>
<td>0.16/0.3</td>
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<td>CATA BE</td>
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<td></td>
<td>OHT BE</td>
<td>FACO + IOL RE</td>
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</table>

**Abbreviations:** y, years; anti-VEGF, anti-vascular endothelium growth factor drug in intraocular injection; BE, both eyes; SO, silicone oil; VA1, initial visual acuity; VA2, final visual acuity; AZA, azathioprine; CATA, cataract; CIS, clinically isolated syndrome; CyA, cyclosporin A; L, left eye; M, male; MS, multiple sclerosis; F, female; FACO + IOL, lens phacoemulsification and intraocular lens implant; OHT, ocular hypertension; IFN, interferon; L, lensectomy; RE, right eye; LE, left eye; PVO, persistent vitreous opacities; Ozurdex, sustained release dexamethasone intraocular device; PDN, prednisone; TCA, peri- or intraocular triamcinolone acetonide; AU, anterior uveitis; IU, intermediate uveitis; VPP, pars plan vitrectomy plus lensectomy.

Said group comprises 5 females and 4 men with a mean age at uveitis onset of 36.6 years (13–72) and 40 years at DD onset (20–69). In 3 cases, uveitis expressed before DD, in a further 3 cases it expressed after DD, in 2 cases both expressed at the same time and in one case this is unknown. All cases except one were bilateral (Table 1).

In 8 patients uveitis was intermediate, 2 of which associated significant anterior inflammation. Only in one patient it was considered that uveitis was predominantly anterior. During the study period 511U cases were diagnosed, of which 8 (16%) were related to DD. Uveitis was generally of the granulomatous type in 47% of eyes and synechating in 65%. Its course was chronic in 8 patients (89%) and self-limited in one (Table 2).

The most frequent ocular complications were cataracts in 12/17 eyes (71%) and macular edema in 9/17 eyes (53%) of 5 patients (Table 3).

The medical treatment for controlling the intraocular inflammation was oral prednisone in 7/9 (78%) patients. Immunosuppressants had to be associated in 3 patients (azathioprine in one case and cyclosporine in 2). One patient was treated with methotrexate and a further one with subcutaneous interferon (IFN) due to the baseline MS. During the uveitis exacerbation periods, peri- or intraocular triamcinolone injections were necessary in 8/17 eyes (47%) of 5 patients. In 4 eyes of 2 patients intraocular anti-VEGF were injected and in 3 eyes of 2 patients dexamethasone sustained release intravitreal devices were placed (Ozurdex™) as a consequence of resistant macular edema.
Despite due eyes FACO T
Table RD, Cataract Complication Eyes/n
Table demyelinizing 0
T able of Immunosuppressant a.
Table 3 - Complications during 11.8 years (R: 2-22) of mean duration of uveitis.

In addition, 7/17 eyes (41%) of 4 patients required surgery due to inflammatory complications. In 6/17 (35%) eyes of 30 patients, pars plana vitrectomy was performed associated to cataract surgery in 4 of the 6 vitrectomized eyes (one lensectomy and 3 phacoemulsification and intraocular lens implant). One patient with macular edema was vitrectomized in both eyes with simultaneous epiretinal membrane peeling and was intervened in a second surgery for left eye cataracts. Despite the treatments the macular edema relapsed in both eyes (patient 4) (Table 4).

Table 4 - Medical and surgical treatments applied.

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Patients or eyes/n (%)</th>
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<tbody>
<tr>
<td>Prednisone or</td>
<td>7/9 (78)</td>
</tr>
<tr>
<td>Immunosuppressant or</td>
<td>4/9 (44)</td>
</tr>
<tr>
<td>IFN sc</td>
<td>1/9 (11)</td>
</tr>
<tr>
<td>TCA ivit/perí</td>
<td>8/17 (47)</td>
</tr>
<tr>
<td>Ozurdex ivit</td>
<td>3/17 (18)</td>
</tr>
<tr>
<td>Anti-VEGF ivit</td>
<td>4/17(24)</td>
</tr>
<tr>
<td>FACO + IOL, phacoemulsification and intraocular lens implant; IFN, interferon; ivit, intravitreal; peri, periocular; sc, subcutaneous; TCA, triamcinolone acetonide; or, oral pathway; VPP, vitrectomy pars plana.</td>
<td></td>
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</tbody>
</table>

Fig. 1 - Vision lines gained or lost (Snellen decimal) after 60 months mean follow-up.

Best corrected visual acuity (BCVA) at treatment baseline was equal or under 1/10 in 3/17 (18%) eyes of 2 patients and equal or under 5/10 in 8/17 (47%) eyes of 6 patients. After a mean follow-up period of 60 months (R: 4–168), 2/17 (12%) eyes of 2 patients exhibited a BCVA equal to or under 1/10 and 8/17 (47%) eyes of 6 patients remained with BCVA equal to or under 5/10. During the same follow-up period, BCVA improved in 7/17 (41%) eyes of 5 patients, with the improvements being of 3 or more lines in 2/17 (12%) eyes of 2 patients. On the other hand, in the same period 8/17 (47%) eyes of 5 patients experienced worsening of their vision, of which 2/17 eyes (12%) of 2 patients had a worsening of 3 or more lines. One patient maintained vision in the area of 10/10 and remained stable in both eyes during the 18 months of the follow-up (patient 2) (Fig. 1).

Discussion

According to our results, 1.3% of all uveitis and 16% of IU were associated to DD and MS in the majority of cases (78%). These data confirm those described previously in the literature in which approximately 1% of general uveitis and between 8% and 16% of IU were associated to MS.7,12,13

The disease predominantly affects women (5/7, 71% of patients with associated MS), young adults (mean age of 36.6 years) and uveitis can express several years before the appearance of the neurological symptoms (in our case, a mean of 8 years); it can appear simultaneously or several years later (5 on average). In general, our demographic and chronologi- cal data match those described in the literature,7,12,14,18 even though there are some series which include different data.19

The most frequent clinical form in our patients was chronic uveitis (8/9, 89%) intermediate uveitis (8/9, 89%) and bilateral uveitis (8/9, 89%), even though the inflammation frequently involved the anterior segment with cellular Tyndall (3/9 patients, 33%) and on some occasions with granulomatosus (4/9, 44%) and synechiatat forms (6/9, 67%). This clinical description of uveitis associated to MS is in close agreement with the majority of published series,12,14,15 even though other series consider AU as the most frequent anatomic form and panuveitis or retinal vasculitis as other frequent forms.16,19 It is likely that the confusion in some series about the anatomic type of uveitis is because the IUISG10 criteria are interpreted differently. Even though intraocular inflammation predomi- nates at the level of the anterior vitreous and of pars plana in the majority of cases, on some occasions it extends toward the iris and the ciliary body, causing associated chronic iritis.12,20,21 The synechiae and cataracts which appear in
many cases prevent visual contact with intermediate uvea, not even with indention, giving the image of a false isolated anterior uveitis. On the other hand, peripheral vasculitis (periphlebitis) is a typical sign of UI of any etiology. Peripheral vasculitis with vitritis and anterior chamber inflammation is not a diagnosis for panuveitis but for IU (if it is significant) associated to anterior uveitis. Posterior vasculitis which in the above case would lead to panuveitis diagnosis, as well as retinitis and choroiditis, are very rare in MS patients although some cases have been described.

Macular edema and cataracts are frequent complications and in some surgery cases is necessary as the only option for maintaining vision. In contrast with other series, none of the patients developed retinal or papillary neovessels and none required glaucoma filtering surgery. Only one of our patients developed ruberosis iridis which responded favorably to inter-chamber injection of bevacizumab (1.25 mg/0.05 ml). Possibly, relatively good local and systemic inflammatory control were able to halt said complications in our series.

With adequate medical and surgical treatments for this type of uveitis the visual prognosis was favorable because none of the patients reached legal blindness after 12 years (R: 2–22) of mean evolution of uveitis. However, up to 47% of eyes lost visual acuity within 5 years of follow-up and 12% lost 3 or more lines. In general, our prognostic data match those of other publications. In contrast, the visual results and the need for systemic maintenance treatment seem to be better in the series analyzed by MD Becker et al. after receiving treatment with interferon (IFN) type 1. In our series only one patient who exhibited significant bilateral IU and optic neuritis was treated with subcutaneous IFN due to the baseline MS. After 24 months of IFN treatment, it remains inactive and with a visual acuity close to 10/10 in both eyes for the past 7 years without needing baseline treatment. The positive results of IFN treatment for some uveitis, which is quite extended in Germany, are not very popular in our country perhaps due to the potential collateral effects of this treatment. However, as this is an infrequent entity, the series available to date, including those of this paper, are generally short and retrospective which means that the results obtained must be interpreted with a degree of caution.

In conclusion, uveitis, particularly the intermediate, synechiatating and bilateral types in young adult women, could be associated to MS or another DD. Even though the visual prognosis is usually favorable, steroid, immunosuppressants and surgical treatment are usually necessary. On the other hand, it would be interesting to carry out an in-depth research on the possible benefits of treatments with IFN type 1 in this type of uveitis.

Conflict of interests

No conflict of interest has been declared by the authors.

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REFERENCES


