Relevance of erythrocyte sedimentation rate and C-reactive protein in patients with active uveitis

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Abstract

Purpose To relate erythrocyte sedimentation rates (ESR) and C-reactive protein (CRP) values to different uveitis entities.

Methods A retrospective study of patients with a first episode of active uveitis visiting the Erasmus University Medical Center, uveitis clinic, Rotterdam, the Netherlands, was performed. Levels of ESR and CRP were determined within 2 weeks and 1 week after onset of uveitis, respectively. Uveitis had to be of unknown origin at that moment. The specific etiologic groups were related to ESR and CRP values.

Results The majority of patients with uveitis had ESR and/or CRP values within the normal limits and no association of ESR and/or CRP with the specific cause of uveitis was observed. However, elevation of ESR ≥ 60 mm/h and/or CRP ≥ 60 mg/L was mostly seen in patients with systemic immune-mediated diseases (8/59, 14% of all with immune-mediated diseases) or systemic infectious causes (7/38, 18% of all infectious uveitis). Patients with ocular toxoplasmosis typically exhibited normal ESR and CRP (9/11, 82%) while patients with endogenous endophthalmitis had elevated ESR and/or CRP in 6/7, 86%. Sarcoidosis-associated uveitis showed predominantly elevated ESR (13/24, 54%; range 20–59 mm/h in 11/13, 85%). Human immunodeficiency virus–positive patients had more often elevated ESR values when compared to the remainder of patients (9/11, 82% vs. 64/163, 39%, 18%, P = 0.009). The cause of uveitis was established in 19/20 (95%) of patients with ESR ≥ 60 mm/h and/or CRP ≥ 60 mg/L.

Conclusions The majority of patients with first attack of uveitis had ESR and CRP within the normal limits. Elevated levels of ESR and CRP reflected systemic involvement and high levels of both values were associated with established uveitis cause.

Keywords Erythrocyte sedimentation rate • C-reactive protein • Uveitis • Diagnostics

Introduction

Uveitis is an intraocular inflammation of multiple causes, which may result in permanent visual loss [1–4]. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), both non-specific markers of inflammation, are usually included in the initial diagnostic workup. However, the clinical value of these parameters in the adult uveitis population is not known. Earlier investigations showed that ESR and CRP are within the normal range in a majority of patients with anterior uveitis [5]. In contrast, a recent report on juvenile idiopathic arthritis (JIA)-associated uveitis in a pediatric population showed that elevated ESR predicted the development of uveitis in patients with JIA [6]. However, it remains debatable whether ESR and CRP have any diagnostic value in evaluation of uveitis in adult patients having a first uveitis attack of unexplained origin.

Herein, we investigate the values of ESR and CRP during the first episode of active uveitis, determined within a short period after the onset in adult patients and relate the results to specific etiologic categories and clinical characteristics of uveitis.
Materials and methods

The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines were used to ensure the reporting of this observational study and this study followed the Tenets of the Declaration of Helsinki [7].

We conducted a retrospective cross-sectional study at the ophthalmology department of the Erasmus Medical Center (Rotterdam, the Netherlands). All medical records of patients referred with new uveitis of unknown origin investigated between 2010 and 2017 were reviewed and 174 patients were identified who fulfilled our inclusion criteria. The onset of uveitis was defined as the first time active inflammation was documented by an ophthalmologist. ESR had to be determined ≤2 weeks and CRP values ≤1 week after the onset uveitis (as ESR normalizes within weeks and CRP levels within 7 days after resolution of tissue injury) [8]. Exclusion criteria included age less than 18 years and patients with first mild anterior uveitis episode as these patients do not undergo diagnostic screening according to our guidelines. The ESR and CRP values were arbitrarily stratified to three subgroups (normal ESR < 20 mm/h, elevated ESR between 20 and 60 mm/h, highly elevated ESR ≥ 60 mm/h) and normal CRP < 10 mg/L (as defined in our laboratory), elevated CRP between 10 and 60 mg/L and highly elevated CRP ≥ 60 mg/L).

The following data were extracted from patients’ records: age, gender, localization of uveitis, laterality, and human immunodeficiency virus (HIV) status. All immunosuppressive medications as well as co-morbidities were registered. Definitive anatomical classification was determined according to the Standardization of Uveitis Nomenclature (SUN) Working Group, by reviewing the whole follow-up period [9]. The cause of uveitis was determined after the diagnostic examinations were completed. The diagnosis of definitive ocular sarcoidosis was given to patients that had histologically proven evidence and in all other cases; the criteria from the International Workshop on Ocular Sarcoidosis (IWOS) were used [10]. For the diagnosis of tuberculosis (TB)-associated uveitis, a positive culture for mycobacteria in any fluid/tissue sample was needed. Patients with a positive tuberculin skin test (Mantoux test) or interferon gamma release assay (IGRA) test with otherwise unexplained uveitis and no other indications of active tuberculosis were labeled as of unknown origin. All other specific diagnoses were performed according to current diagnostic criteria [10–16].

All statistical analyses were performed using SPSS software (version 22.0, Chicago, IL, USA) and a P value of < 0.05 was considered statistically significant. Specific groups were categorized as mentioned above and compared with each other according to gender, anatomical localization of uveitis, age, and etiology. Continuous variables were described by mean and range, categorical variables with proportions, and compared using the Mann-Whitney U test. Categorical variables were compared using the chi-square test or Fisher’s exact test.

Results

The results of ESR and CRP measurements are shown in Table 1. Specific diagnoses in our cohort are depicted in the Supplemental Table. A majority of patients was diagnosed with associated non-infectious systemic diseases (59/174, 34%) and had non-anterior uveitis (141/174, 81%). Slight female preponderance was observed (96/174, 55%).

Immunosuppressive medication (required for other causes than uveitis) was used by 17/174, 10% patients. Patients suffering from diabetes mellitus (DM) and patients using immunosuppressive medication more often had elevated ESR values (P = 0.018 for both, chi-square test), compared to the remainder of patients. No significant differences in ESR and CRP levels were found for gender, race, localization, or laterality of uveitis (all P values > 0.05, chi-square test). Furthermore, elevated values of ESR and/or CRP were not significantly associated with any of the etiologic categories.

Concordance and discrepancies between ESR and CRP are depicted in Table 2. A majority of patients had both ESR and CRP values within the normal limits (91/174, 52%). Elevation of only one of the parameters was seen in 50/174, 29%. Elevated levels of both parameters were found in 33/174, 19% patients.

The median ESR and CRP of patients with uveitis of established cause were higher than the median ESR and CRP of patients with unknown uveitis (17.0 mm/h, range 1–120 mm/h vs. 11.0 mm/h, range 1–140 mm/h for ESR and 3.4 mg/L, range 0.4–262.0 mg/L vs. 1.9 mg/L, range 0.3–229.0 mg/L for CRP; P = 0.015 for both, Mann-Whitney U test).

Out of 20 patients with either ESR ≥ 60 mm/h and/or CRP ≥ 60 mg/L, the cause of uveitis could be determined in 19/20. Fifteen had either non-infectious systemic disease or systemic infection, which was also a cause of uveitis (Table 3). The remaining five patients had uveitis limited to the eye, but had a concurrent systemic disorder, which explained their highly elevated ESR and/or CRP but was not related to the cause of uveitis (such as multiple myeloma in a patient with infectious uveitis).

A majority of patients with infectious uveitis had ESR and CRP values within the normal limits (17/38, 45%) or only ESR ≥ 20 mm/h (14/38, 37%), see Table 2. Discrepant results were more often noted in this group (17/38, 45% vs. 33/136, 24% P = 0.024, chi-square test). Patients with toxoplasmosis exhibited normal ESR values in 9/11, 82%, and all had CRP values within the normal limits. Patients with endogenous endophthalmitis exhibited CRP ≥ 10 mg/L in 5/7, 71%.
Patients with non-infectious uveitis commonly had ESR and CRP values that were both within the normal limits (28/59, 47%; Table 2). If elevated (N = 31), the parameters were most often elevated simultaneously (15/31, 48%). Of the patients with HLA B27-associated uveitis without systemic involvement, 2/8, 25% exhibited CRP ≥ 10 mg/L and 1/8, 13% had both ESR ≥ 20 mm/h and CRP ≥ 10 mg/L. Two patients had HLA B27-associated uveitis with systemic involvement of which one had high elevation of CRP ≥ 60 mg/L and ESR ≥ 59 mm/h and the other exhibited normal values. Sarcoidosis-associated uveitis was found in 9/11, 82% HIV-positive patients, out of which 4/9, 44% had CMV retinitis and 4/9, 44% had syphilitic uveitis. ESR ≥ 60 mm/h together with HIV positivity was observed in 4/11, 36% (2 with CMV retinitis, one with syphilitic uveitis, and one with sarcoidosis-associated uveitis). Only one of the HIV-positive patients exhibited normal values of both ESR and CRP; this patient was diagnosed with CMV retinitis.

**Discussion**

In this retrospective, cross-sectional study, the majority of patients with a first active episode of uveitis of unknown origin presented with normal ESR and CRP values. Moreover, no significant relationship between the levels of these biomarkers and specific causes of uveitis was found.

Earlier investigations of ESR and CRP in uveitis patients also demonstrate normal values in a majority of patients with anterior uveitis, but none of these previous studies defined the time window in which ESR and CRP were determined in relation to the onset of uveitis, while both biomarkers are susceptible for changes within short periods [5, 8, 17]. Biomarkers like ESR and CRP are commonly assessed during the diagnostic workup of new uveitis patients for potential detection of infections or systemic immune-mediated disease-causing uveitis [1–4, 18–21]. Elevated levels of ESR are due to a higher plasma protein levels (e.g., fibrinogen, gamma globulins) and CRP is an acute phase protein released after tissue injury caused by infections or other sources of inflammation [8, 22].

Though a majority of patients with infectious uveitis in the present study exhibited normal ESR and CRP values, increased values were predominantly encountered in systemic infections. The high levels of ESR and CRP were found in patients with endogenous endophthalmitis, an ocular inflammation that occurs concurrently with bacteremia. In contrast, these inflammatory parameters were nearly always normal in

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### Table 1

| Total \( N = 174 \) | ESR\(^a\) | CRP\(^b\) |
|------------------|----------|----------|
|                  | \(< 20 \ (N = 101)\) | \(20–59 \ (N = 57)\) | \(\geq 60 \ (N = 16)\) | \(< 10 \ (N = 131)\) | \(10–59 \ (N = 33)\) | \(\geq 60 \ (N = 10)\) |
| Total            | 174      | 101/174 (58%) | 57/174 (33%) | 16/174 (9%) | 131/174 (75%) | 33/174 (19%) | 10/174 (6%) |
| Diabetes mellitus| 17/174 (10%) | 5/17 (29%) | 9/17 (53%) | 3/17 (18%) | 12/17 (71%) | 5/17 (29%) | 0 |
| Immune suppressive medication\(^b\) | 17/174 (10%) | 5/17 (29%) | 7/17 (41%) | 5/17 (29%) | 12/17 (71%) | 2/17 (12%) | 3/17 (18%) |
| Human immunodeficiency virus positivity\(^c\) | 11/174 (6%) | 2/11 (18%) | 5/11 (45%) | 4/11 (36%) | 10/11 (91%) | 0 | 1/11 (9%) |

**Anatomical localization**

| Anterior         | 33/174 (19%) | 18/33 (55%) | 10/33 (30%) | 5/33 (15%) | 23/33 (70%) | 8/33 (24%) | 2/33 (6%) |
| Intermediate     | 2/174 (1%)   | 1/2 (50%)   | 1 (50%)     | 0          | 2/2 (100%) | 0         | 0 |
| Posterior        | 45/174 (26%) | 32/45 (71%) | 12/45 (27%) | 1/45 (2%)  | 37/45 (82%) | 8/45 (18%) | 0 |
| Panuveitis       | 86/174 (49%) | 48/86 (56%) | 30/86 (35%) | 8/86 (9%)  | 65/86 (76%) | 15/86 (17%) | 6/86 (7%) |
| Scleritis        | 8/174 (5%)   | 4/8 (50%)   | 4/8 (50%)   | 2/8 (25%)  | 4/8 (50%)   | 2/8 (25%)  | 2/8 (25%) |
| Non-infectious systemic disease | 59/174 (34%) | 33/59 (56%) | 20/59 (34%) | 6/59 (10%) | 39/59 (66%) | 14/59 (24%) | 6/59 (10%) |
| Infectious uveitis | 38/174 (22%) | 20/38 (53%) | 11/38 (29%) | 7/38 (18%) | 31/38 (82%) | 4/38 (11%) | 3/38 (8%) |
| Established clinical entity | 24/174 (14%) | 14/24 (58%) | 8/24 (33%) | 2/24 (8%)  | 17/24 (71%) | 7/24 (29%) | 0 |
| Unknown          | 53/174 (30%) | 34/53 (64%) | 18/53 (34%) | 1/53 (2%)  | 44/53 (83%) | 8/53 (15%) | 1/53 (2%) |

**ESR** erythrocyte sedimentation rate, **CRP** C-reactive protein

\(^a\) ESR had to be determined < 2 weeks of onset, CRP within < 1 week of onset

\(^b\) Indicated for other causes than uveitis

\(^c\) HIV was tested in 62 patients, out of which 11/62 (18%) were found positive
Table 2  Concordance and discrepancies in erythrocyte sedimentation rate and C-reactive protein in patients with uveitis

|                      | Total N= 174 | Concordant results ESR and CRP<sup>a</sup> | Discrepant results ESR and CRP<sup>a</sup> |
|----------------------|--------------|------------------------------------------|------------------------------------------|
|                      |              | CRP < 10 mg/L and ESR < 20 mm/h N=91      | ESR ≥ 20 mm/h and CRP ≥ 10 mg/L N=33      |
|                      |              | ESR ≥ 20 mm/h but CRP < 10 mg/L N=40     | CRP ≥ 10 mg/L but ESR < 20 mm/h N=10    |
| Age at onset of uveitis (years) Mean (±SD) | 45.8 (±17.1) | 43.1 (±17.3) | 5.9 (±15.6) | 51.7 (±15.9) | 46.6 (±20.7) |
| Localization |                      |                                            |                                         |
| Anterior uveitis | 33/174 (19%) | 16/33 (48%) | 8/33 (24%) | 7/33 (21%) | 2/33 (6%) |
| Intermediate uveitis | 2/174 (1%) | 1/2 (50%) | 0 | 1/2 (50%) | 0 |
| Posterior uveitis | 45/174 (26%) | 29/45 (64%) | 5/45 (11%) | 845 (18%) | 3/45 (7%) |
| Panuveitis | 86/174 (49%) | 44/86 (51%) | 17/86 (20%) | 2186 (24%) | 4/86 (5%) |
| Scleritis | 8/174 (5%) | 1/8 (13%) | 3/8 (38%) | 3/8 (38%) | 1/8 (13%) |
| Laterality |                      |                                            |                                         |
| Unilateral | 83/174 (48%) | 43/83 (52%) | 15/83 (18%) | 20/83 (24%) | 5/83 (6%) |
| Bilateral | 91/174 (52%) | 48/91 (53%) | 18/91 (20%) | 20/91 (22%) | 5/91 (5%) |
| Gender |                      |                                            |                                         |
| Females | 96/174 (55%) | 50/96 (52%) | 16/96 (17%) | 25/96 (26%) | 5/96 (5%) |
| Males | 78/174 (45%) | 41/78 (53%) | 17/78 (22%) | 1578 (19%) | 5/78 (6%) |
| Race |                      |                                            |                                         |
| Caucasian | 110/174 (63%) | 59/110 (54%) | 22/110 (20%) | 23/110 (21%) | 6/110 (5%) |
| Non-Caucasian | 64/174 (37%) | 32/64 (50%) | 11/64 (17%) | 1764 (27%) | 4/64 (6%) |
| Non-infectious systemic disease |                      |                                            |                                         |
| Sarcoidosis<sup>b</sup> | 24/59 (41%) | 10/24 (42%) | 6/24 (25%) | 724 (29%) | 1/24 (4%) |
| HLA B27-associated uveitis | 10/59 (17%) | 6/10 (60%) | 2/10 (20%) | 0 | 2/10 (20%) |
| Miscellaneous<sup>c</sup> | 25/59 (42%) | 12/25 (48%) | 7/25 (28%) | 4/25 (16%) | 2/25 (8%) |
| Infectious |                      |                                            |                                         |
| Toxoplasmosis | 38/174 (22%) | 17/38 (45%) | 4/38 (11%) | 14/38 (37%) | 3/38 (8%) |
| Endogenous endophthalmitis | 11/38 (29%) | 9/11 (82%) | 0 | 2/11 (18%) | 0 |
| Miscellaneous<sup>d</sup> | 7/38 (18%) | 1/714 (14%) | 2/7 (29%) | 17 (14%) | 37 (43%) |
| Established clinical entity<sup>e</sup> | 20/38 (53%) | 7/20 (35%) | 2/20 (10%) | 11/20 (55%) | 0 |
| Unknown | 53/174 (30%) | 33/53 (62%) | 8/53 (15%) | 11/53 (21%) | 1/53 (2%) |

ESR erythrocyte sedimentation rate, CRP C-reactive protein, SD standard deviation, HLA B27 human leukocyte antigen B27

<sup>a</sup> ESR had to be determined < 2 weeks of onset, CRP within < 1 week of onset

<sup>b</sup> 17/24 (71%) of sarcoidosis patients was biopsy confirmed

<sup>c</sup> Including patients with Vogt-Koyanagi-Harada syndrome (N = 6), multiple sclerosis (N = 4), Behçet's disease (N = 3), inflammatory bowel disease (N = 3), granulomatosis with polyangiitis (N = 2), reactive arthritis with uveitis (N = 2), acute disseminated encephalomyelitis (N = 1), Kikuchi disease (N = 1), relapsing polychondritis (N = 1), systemic lupus erythematosus (N = 1), systemic vasculitis not otherwise specified (N = 1)

<sup>d</sup> Including varicella-zoster virus (N = 5), cytomegalovirus (N = 4), syphilis (N = 4), herpes simplex virus (N = 3), rubella virus (N = 2), bartonella (N = 1), tuberculosis (N = 1)

<sup>e</sup> Including patients with acute multifocal posterior placoid pigment epitheliopathy (N = 3), birdshot chorioretinopathy (N = 2), toxic uveitis (N = 2), post-traumatic uveitis (N = 2), sympathetic ophthalmia (N = 1), serpiginous choroidopathy (N = 1), Fuchs heterochronic uveitis syndrome (N = 1), punctate inner choroidopathy (N = 1). The masquerade syndromes including lymphoma (N = 3), macular drusen (N = 2), human immunodeficiency virus-related microangiopathy (N = 1), macular dystrophy (N = 1), uveitis suspected to be caused by bacillus Calmette-Guérin intravesical immunotherapy for bladder cancer (N = 1), cotton wool spots (N = 1), Coats disease (N = 1)
Table 3 Patients exhibiting highly elevated erythrocyte sedimentation rate and/or C-reactive protein

| Erythrocyte sedimentation rate ≥ 60 mm/h and/or C-reactive protein ≥ 60 mg/L (N = 20) |  |
|---|---|
| Associated systemic disease | 2 Sarcoïdosis |
| 3 Reactive arthritis |
| 1 Granulomatosis with polyangiitis, |
| 1 Relapsing polychondritis |
| 1 Behçet’s disease |
| Infectious disease | 3 Endogenous endophthalmitis |
| 2 Cytomegalovirus retinitis |
| 1 Herpes simplex retinitis |
| 1 Varicella-zoster anterior uveitis |
| 1 Syphilis |
| 1 Tuberculosis |
| Clinical entity | 1 Masquerade syndrome |
| 1 Post-traumatic uveitis |
| Unknown | 1 |

*10 patients had ESR ≥ 60 mm/h, 4 patients had CRP ≥ 60 mg/L, and 6 patients both had ESR ≥ 60 mm/h and CRP ≥ 60 mg/L.

Not all patients had ESR and/or CRP values, were not available in our patients [27].

In conclusion, our study reflects that presence of uveitis alone is not sufficient to cause elevation of ESR and/or CRP as a majority of patients with a first uveitis episode had ESR and CRP values within the normal limits. In patients with highly elevated ESR and/or CRP, the presence of a systemic disease is very likely, and in consequence, the cause of uveitis is being established in a vast majority of cases.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study (retrospective study), formal consent is not required.

Disclaimer The sponsor had no role in the design or conduct of this research.

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