Uveitis and Psychological Stress

**ABSTRACT**

Uveitis is an inflammatory condition affecting the eye and is often associated with systemic autoimmune disease. A role for the involvement of psychological stress in autoimmune disease has been widely demonstrated. However, uveitis is not classified as an autoimmune disease, and a definite or direct cause has yet to be identified, although infection may be involved. Many uveitis patients retrospectively report stressful life events occurring prior to the onset or recurrence of uveitis. However, only a small number of studies have explored the potential association between psychological stress and uveitis, and their findings are somewhat contradictory, many showing that the experience of uveitis itself results in stress. The present article reviews what is currently known about the relationship between uveitis and psychological stress.

**Introduction**

Stress can be defined as environmental events (real or perceived) that perturb one’s psychological or physiological homeostasis or balance and can be categorised by its duration: Acute stress lasts for minutes to hours, whereas chronic stress persists for several hours a day for a number of days or months. Chronic stressful life events such as relationship breakdown and bereavement have been shown to have far-reaching health effects. Uveitis is an inflammatory condition affecting the eye. This inflammation is often associated with systemic autoimmune disease, which itself has been shown to relate to psychological stress and physiological stress mechanisms. However, uveitis is not classified as an autoimmune disease, and a definite or direct cause has yet to be identified, although it can be caused by infection in some cases. Many uveitis patients retrospectively report stressful life events occurring prior to the onset or recurrence of uveitis. However, few studies have explored the relationship between uveitis and psychological stress, and their findings are somewhat contradictory. This review summarizes and discusses the current knowledge regarding the potentially bidirectional relationship between uveitis and psychological stress.

**Stress mechanisms and disease**

In humans, perceived physical or psychological stress results in the activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympatho-adrenal medullary (SAM) axis, which results in the production of the stress hormones cortisol and catecholamines, respectively. Although there is a clear anti-inflammatory role for cortisol and catecholamines released during stress, it is also true that dysregulated production of these factors, such as in the instance of chronic stress, can influence autoimmune disease. Cortisol can be highly immunosuppressive, which can also increase the risk of infection when excessively secreted in response to stress. Indeed, the presence and involvement of stress hormones is well characterised in many diseases and disorders. Whether this extends to uveitis is unknown.

**Uveitis**

Uveitis is a heterogeneous group of inflammatory disorders, predominantly affecting the uveal tissue (choroid, iris and ciliary body) of the eye. Ocular inflammation can cause serious damage in the eye, badly affecting sight and, in severe cases, can cause increased intraocular pressure and permanent visual loss. The ocular environment, like other immune-privileged sites, such as the brain, testes, placenta and uterus, cannot tolerate collateral damage occurring during the immune response triggered in uveitic disease. However, ocular immunopathology is closely regulated, with multiple mechanisms limiting immune-mediated inflammation. Despite these mechanisms, inflammation still occurs among some vulnerable individuals, but thus far, the cause underlying the onset and recurrence of uveitis is unknown. There is some evidence of immune dysregulation in uveitis, including dysregulation of regulatory T lymphocytes (Tregs), which are known to have a role in maintaining immune

*continued on the next page*
Uveitis and Psychological Stress

Continued from page 11

tolerance. Human and animal studies have shown that psychological stress can alter the number and function of T cells and their subtypes, including Tregs. For example, chronic stress at work among nurses was related to increased expression of the IL-2 receptor on CD4+CD25 T cells. Similarly, the stress of unemployment was related to a decreased proliferation of lymphocytes following stimulation.

Potential role of stress and the HPA axis in uveitis

The theory that psychological stress may affect ocular health emerged in the 1970s and 1980s. An early paper attempted to attribute the onset of postpartum uveitis to an increase in the level of corticosteroids during pregnancy followed by a rapid decrease after delivery. In contrast, it has been more recently suggested that pregnancy and its associated corticosteroid level changes influence inflammatory disease activity, including uveitis, in a positive way. Nevertheless, local corticotrophin-releasing hormone (CRH) has been shown to impact negatively upon inflammatory diseases, including rheumatoid arthritis and ulcerative colitis. Further, CRH has been found in the peripheral accessory immune cells in the animal model of experimental autoimmune uveoretinitis (EAU). Immunoactive CRH (IrCRH), a peptide that works as a pro-inflammatory cytokine in the inflammatory site, was detected in the cytoplasm of inflammatory cells infiltrating the iris, ciliary body, vitreous, retina and choroid in this model. The intensity of the IrCRH staining was positively correlated with the severity of the disease graded via histopathological examination. Further, mice immunized with retinoid-binding protein developed uveitis, but had reduced disease severity when injected with anti-CRH treatment compared to placebo or late-treated animals. Thus it appears that IrCRH is associated with the severity of the disease and could be involved in the induction of experimental uveitis. Whether or not these findings extend to human uveitic eyes is not yet known. It should be noted, however, that biologically significant levels of active glucocorticoids have been demonstrated in human aqueous humor due to the absence of cortisol binding protein.

In another ocular condition, central serous chorioretinopathy (CSC), human studies have found an association between the occurrence of disease and high cortisol levels, and there is evidence that psychological stress and a lack of coping mechanisms could be involved. Based on these findings, ophthalmologists surmised that corticosteroids should be one of the contraindications in treating CSC after using it to treat this condition previously. However, uveitis differs from CSC in its pathology, thus it would be surprising if the above discovered facts were also applicable in uveitis. The link between HPA axis and ocular disease has been addressed in another ocular condition, retinal vasculitis, but there were no differences in the levels of serum cortisol and DHEA-S levels between patients and control subjects. A recent review discussed potential mechanisms of HPA and SAM axis involvement in ocular diseases and gave examples, such as the cortisol dysregulation in CSC and other ocular conditions, but their involvement in uveitis is less well established.

Stress and uveitis studies

In clinical practice, there is much anecdotal evidence to suggest a potential relationship between stress and uveitis. When questioned by ophthalmic health professionals, patients commonly report stressful life events at the time of, or prior to, the onset and flare-up of uveitis. However, such observations may reflect the patient’s beliefs about the cause of their disease or experimenter effects (i.e., being asked about stressful events in the context of their disease recurrence may cause patients to report greater stress than would be the case in a blind study). A limited number of studies have, therefore, attempted to systematically investigate the association, if any, between psychological stress and recurrence of uveitis. Due to the heterogeneity of uveitis, both in terms of its pathologic features and its aetiology, these studies have tended to focus on the recurrence rates of idiopathic acute anterior uveitis (AAU). Details of these studies are shown in Table 1. These studies were identified through searching PubMed for articles with the keywords “psychological stress and uveitis, stress and uveitis, psychological stress and iritis, stress and iritis, and psychological stress and eye” in the Title or Abstract.

In 2000, one study provided evidence suggesting no link between stress and the recurrence of idiopathic AAU. The authors prospectively assessed patients presenting to the emergency department of a single ophthalmic center with recurrent AAU. Participants were invited to complete a questionnaire at the time of presentation based on the Holmes and Rahe stress scale and the Spielberger state-trait anxiety inventory. Patients were then asked to report on the form if they felt they had been under increased stress in the month preceding symptom onset. A control group consisting of patients with corneal foreign bodies, conjunctivitis and contact lens–related disease also completed the questionnaire. Using this method, no significant difference was found between 35 patients with recurrent AAU and 29 controls. Scores for both groups were also comparable with those published for normal adults of the same age and sex. Similarly, in
<table>
<thead>
<tr>
<th>Author</th>
<th>Participants</th>
<th>Psychological measures/method</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrim et al., 2006</td>
<td>42 AAU patients and 25 controls</td>
<td>Psychological questionnaires; GHQ, SRRQ. Items include measuring stressful life events in the proceeding month of the attack</td>
<td>Patients with AAU had higher GHQ scores than controls. Also, recurrent AAU patients had higher scores than the resolution group patients in stage 2</td>
<td>Clear relationship between stress and the recurrence of AAU in susceptible individuals</td>
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<td>Franke et al., 2005</td>
<td>51 AAU patients with uveitis and 51 parallel controls</td>
<td>Psychological questionnaires; (Coping Questionnaire) and Brief Symptom Inventory</td>
<td>AAU patients scored (1) higher on the Schedule of Recent Experiences, (2) lower different coping strategies, (3) higher psychological distress, (4) lower disease-specific quality of life</td>
<td>Supported the hypothesis that stressful life events are associated with the onset of diseases (uveitis) and that uveitis led to poor quality of life</td>
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<td>Maca et al., 2010</td>
<td>171 patients with B27-AU and 55 ethnicity- and age-matched controls</td>
<td>Psychological questionnaires (Beck Depression Inventory, Freiburg Questionnaire on Coping with Illness and Stress Coping Inventory)</td>
<td>Patients showed more depressive symptoms and more negative stress coping strategies. 57.9% of patients believed that psychological distress was a trigger for relapses, and 34.5% stated specific life events</td>
<td>Patients with B27-AU exhibited significant psychopathology concerning depression and disease coping</td>
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<td>Mulholland et al., 2000</td>
<td>35 patients with AAU and 29 controls (patients with other ocular problems)</td>
<td>Psychological questionnaires Holmes and Rahe life events scale and Spielberger state-trait anxiety inventory measured number of stressful life events in the proceeding month of the attack</td>
<td>AAU did not report a higher number of stressful life events or higher levels of anxiety compared with controls</td>
<td>Stress was not shown to be involved in triggering the recurrence of idiopathic acute anterior uveitis</td>
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<td>Secchi et al., 1987</td>
<td>60 AAU patients and 2 control groups: a) 15 patients from the first 60 who suffered relapses over 3–17 months vs. 45 who did not; b) 60 patients with medical diseases excluding ocular involvement</td>
<td>Semi-structured interviews/questionnaire (Paykel scale and symptom distress checklist), during active disease and follow-up second time point, measured stressful life events and psychological distress</td>
<td>No significant difference in scores between AAU group and controls</td>
<td>Neither life events nor psychological distress played a contributory role in this disease</td>
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<td>Yamamoto et al., 1996</td>
<td>116 uveitis patients followed over 2 years</td>
<td>Recurrence rate of uveitis before and after huge earthquake affected their living area</td>
<td>The post-quake uveitis rate was significantly higher than the pre-quake rate (10% vs. 3%)</td>
<td>Psychological stress due to the sudden changes in living conditions following the earthquake may have triggered the recurrences</td>
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</tbody>
</table>

*continued on the next page*
Uveitis and Psychological Stress

Continued from page 13

1987, another study, using standardized interviews to assess life events and psychological distress, found no relationship between stress and disease recurrence among 60 patients with idiopathic AAU.51

Conversely, a more recent study has shown a clear relationship between psychosomatic stress and recurrence of idiopathic AAU.52 Participants were 42 patients attending the emergency department with disease recurrence and 25 controls who completed the General Health Questionnaire (GHQ)53 and the Social Readjustment Rating Questionnaire (SRRQ).49 A follow-up postal survey, using the same questionnaires, was repeated at least three months later. This study showed that patients with recurrent AAU had significantly higher GHQ scores than controls (mean 6.8 versus 3.2, p = 0.01). However, some caveats exist; in particular, as the GHQ also includes somatic symptoms, social functioning, anxiety and depression, it is not strictly a measure of stress. Thus, the results of this study may be subject to confounding between the items on the questionnaire and the symptoms of AAU. It is also notable that no significant differences emerged for the SRRQ. However, these findings have been supported by a further questionnaire-based study where four different questionnaires were used to measure life events (Schedule of Recent Experiences), coping strategies (Essen Coping Questionnaire) and psychological distress (Brief Symptom Inventory).54, 55 When 51 patients with uveitis and 51 controls were compared, patients scored higher on the Schedule of Recent Experiences and lower regarding different coping strategies. They also demonstrated higher psychological distress and lower disease-specific quality of life, which they concluded may suggest that psychological stress and poor coping may precede uveitis,56 although true causality is impossible to determine in this study design.

Stress may also influence disease by association with other risk factors for uveitis such as depression and negative coping strategies. A more recent questionnaire-based study of patients with recurrent human leukocyte antigen-B27 (HLA-B27)–associated AAU has been conducted.57 A total of 171 patients with a history of HLA-B27–associated AAU and 55 healthy controls responded to a postal survey containing the Beck Depression Inventory, Freiburg Questionnaire on Coping with Illness and the Stress Coping Inventory. Patients with uveitis differed from healthy controls, by showing more depressive symptoms (31.6%) and by applying characteristic disease coping as well as negative stress coping strategies. Female patients with uveitis tended to react with depression while male patients tended to use negative stress coping strategies. A total of 57.9% of patients believed that psychological distress was a trigger for relapses, and 34.5% stated specific life events. Together, this group of patients had higher depression scores and used more negative disease and stress coping styles than patients without perceptions of distress.57 Despite these findings, it is difficult to determine a causal relationship from correlation studies, as it is possible that the experience of uveitis itself results in poor psychological well-being and quality of life.

On a wider scale, a group in Japan investigated the rate of recurrent endogenous uveitis before and after an earthquake which hit a crowded area in Japan that left many dead and tens of thousands homeless. Uveitis patients (N = 116) were monitored over two years, including the time of the earthquake, and results showed that the recurrence rate of uveitis among these patients was much higher after the earthquake than before (10% versus 3%). The authors suggested that the stress which these individuals underwent as a result of the difficult circumstances could be related to the increase in the rate of uveitis recurrence.58 However, it should be noted that many uveitis patients who participated in this study had underlying systemic autoimmune diseases. Also, it is possible that some unmeasured confounding variable related to the earthquake other than stress might underlie these findings, for example, the influence of environmental dust and contaminants, and causality cannot be inferred from such observational studies.

Conclusion

The vast majority of the above studies have utilized only questionnaires to evaluate or identify psychological stress; no studies have measured in detail other variables such as stress hormone profiles and rhythms. As such, there is a need to combine the measurement of these variables with the use of appropriate control groups including positive controls, such as patients’ relatives, and environmental controls, such as other eye patients attending the eye casualty as a disease control.59 One difficulty with such recruitment is that patients and their relatives attending A&E departments are normally stressed as a result of visiting the hospital, regardless of the reason for attending.

One of the key questions of this review was whether or not there is direct or indirect neuroendocrine involvement in the potential link between psychological stress and uveitis. If stress is related to the onset and recurrence of uveitis, the mechanisms of this association are yet to be identified. Ocular immunologists have established a role of immune cells in the activity of the disease; indeed, immune dysregulation in uveitis has been widely reported.23, 24, 26, 60 The relationship between such dysregulation...
and stress hormones should be investigated and the above observations could help explore this complex interplay, giving a clue to how stress might be related to uveitis.

Also the question whether uveitis can cause stress should be considered. Some reports show that living with uveitis can cause stress and can lead to poorer quality of life. Sources of anxiety and stress in uveitis include the symptoms (acute pain, redness, photophobia and visual loss), initial misdiagnosis and monetary expenses. Moreover, worse vision was shown to be correlated with the quality of life impairment and with impaired health-related quality of life in patients with intermediate uveitis.

In conclusion, there is no doubt that psychological stress and its different associated stress hormones have been found to be involved and modulate a variety of diseases and disorders via known and unknown mechanisms. However, despite much anecdotal and clinical evidence, the scientific evidence thus far regarding whether or not psychological stress could be a risk factor in the pathogenesis of uveitis is not clear, although distress as a result of uveitis seems to be demonstrated unequivocally. Further carefully designed longitudinal studies are necessary to demonstrate any causal association.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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References
Uveitis and Psychological Stress

Continued from page 15


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