Discrepancies in assessing anterior chamber activity among uveitis specialists

Running Title: Anterior chamber activity discrepancies

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Abstract

Purpose To evaluate current practices in anterior chamber (AC) inflammation assessment amongst uveitis specialists.

Methods Uveitis specialists were invited to participate in an electronic survey designed to understand their practice in assessing AC inflammation.

Results Sixty-five ophthalmologists participated in the survey. Of them, 69.2% (n = 45) reported using the current Standardization of Uveitis Nomenclature (SUN) guidelines of a 1 x 1-mm slit beam when grading AC cells. Only 38.5% (n = 25) reported routinely counting the number of cells. In the management of uveitis, 98.5% (n = 64) valued flare assessment, but 84.6% (n = 55) did not use laser flare photometry. In total, 36.9% (n = 24) agreed that laser flare photometry would change their management, while 16.9% (n = 11) did not see its usefulness. The remaining participants were undecided.

Conclusion A number of issues limit the clinical assessment of AC inflammation. Different classifications are still being used despite efforts to standardize practice. While the value of flare is widely recognized, the role of laser flare photometry remains controversial.

Keywords Anterior chamber flare; Anterior chamber cells; Anterior chamber activity grading; Laser flare photometry

Introduction

The breakdown of the blood-aqueous barrier in anterior uveitis results in the release of inflammatory cells and proteins into the aqueous humor. Anterior chamber (AC) activity can manifest as the presence of aqueous cells and flare, leading to the formation of a hypopyon, and also of fibrin in some cases. These features not only assist in the diagnosis of uveitis, but also determine the severity of the disease, providing useful information regarding response to therapy.

The assessment of anterior chamber activity is essential to any ophthalmic exam. However, the practice of examining AC activity remains varied among ophthalmologists. The 2 main reasons for this are the use of different systems in grading AC cells and the continued debate on the usefulness of assessing aqueous flare.

Traditionally, AC inflammation is assessed using slit-lamp biomicroscopy. A beam of light is cast posterior to the cornea to examine for any signs of inflammation. For decades, Hogan et al's [1] grading systems were the most widely adopted classifications. Using a 'wide beam and narrow slit' on slit-lamp biomicroscopy, they classified AC activity as shown in Tables 1 and 2.

Over time, the system for the grading of AC inflammation was gradually modified. Currently, a number of different grading systems exist [2-5]. These classifications began to specify the size of the slit beam used: 3 x 1-mm and 2 x 1-mm slit beams were reportedly being used [6, 7].

In 2005, the Standardization of Uveitis Nomenclature (SUN) group was set up with the aim of achieving a consensus on clinical data reporting in the field of uveitis [5]. One of the outcomes attained was the agreement in grading of AC cells and flare. A 6-step grading system was agreed for the cellular reaction, as documented in Table 3. In comparison with previous systems, there was a minor change in the number of cells that qualified for each grade. The group also agreed on the use of a smaller, 1 x 1-mm slit beam. In the grading of AC flare (Table 4), a 4+ grade was added to the original Hogan et al classifications.

Many clinicians use cell counts as the benchmark to assess AC inflammation. The usefulness of flare grading, on the contrary, has been questioned. This is because the clinical assessment of flare is qualitative in nature. Some clinicians also believe that flare is an indicator of chronicity rather than of activity [8]. However, it has been argued that cells and flare are both useful markers in grading AC activity because they can both present in varying degrees. The presence of flare may even manifest prior to that of AC cells in active disease [9].

Clinically assessing flare is also highly observer-dependent. Previous publications have shown the level of discordance amongst clinicians in grading flare and have highlighted the importance of the clinician's experience level in the accurate grading of flare [11-13]. Additionally, a wide variation of laser flare photometry readings for each step on the clinical scale has been reported, emphasizing the lack of sensitivity when depending solely on the observer's eye [12, 13]. Therefore, laser flare

75 photometry is regarded as a more objective method of flare assessment and has also
76 been found to better use the information gathered from flare assessment [10].
77
78 The discordance in AC activity assessment not only has significant clinical
79 implications but also is an important aspect to consider when conducting research.
80 This paper aims to identify standard practices and areas of differences in assessing
81 AC activity amongst uveitis specialists from across the world.
82
83
84 **Methods**
85
86 Uveitis specialists from various leading tertiary eye referral centers across the world
87 were invited to participate in the study's survey. Electronic copies of the survey were
88 mailed to the participants. The survey questions posted are shown in Appendix 1.
89 When compared with previous grading systems, the change in the slit beam size
90 specified in the SUN classification was the most significant modification. Hence,
91 question 1 was aimed at determining the different sizes used by the participants.
92 Question 2 examined if it was a common practice to count cells. While this practice is
93 time-consuming and its clinical implications are uncertain, it would still produce the
94 most accurate and consistent grading. Questions 3 to 6 sought to determine
95 participants' perspectives about the usefulness of flare and flare photometry.
96
97 The Fisher exact test was used to determine the association between responses and the
98 participants' geographical locations. The statistical analysis was performed using R
99 version 3.02 (R Foundation for Statistical Computing, Vienna, Austria).

Approval for the study was obtained from the local ethics review board in accordance with the Declaration of Helsinki.

Results

We received 65 responses out of 180 invitations (36.1%). Forty of the respondents were from Asia; 15, from Europe including the UK; and 10, from the United States. The results are presented in Figures 1 to 6.

A total of 69.2% of the participants (n = 45) reported using the current SUN guidelines to use a 1x 1-mm slit beam in their grading of AC inflammation; 7.7% (n = 5) reported using a 2 x 1-mm slit beam; and 21.5% (n = 14), reported using a 3 x 1-mm slit beam (Fig. 1). One of the participants reported not using the slit lamp for grading AC flare. As the participant thought that the question was in reference to flare grading alone, none of the provided options were selected in the returned response to question 1.

A total of 38.5% (n = 25) of the participants reported that they counted the number of cells when grading; 21.5% (n = 14), that they rarely did so; and 4.6% (n = 3), that they never did so (Fig. 2). A significant number of participants (84.6%, n = 55) did not use laser flare photometry in their practice (Fig. 3). However, the majority (98.5%, n = 64) reported seeing the value of flare assessment in the management of uveitis (Fig. 4). Specifically, half of the participants (49.2%, n = 32) found flare to be

of ‘very significant’ value (Fig. 4), while the majority (72.3%, n = 47) agreed that it was a useful marker of disease activity (Fig. 5).

When asked if the availability of laser flare photometry would alter their management, we received a mixed response. A total of 36.9% (n = 24) felt that the use of laser flare photometry would be a useful addition to the assessment of their patients and would likely change their management. Only 16.9% (n = 11) did not see any use in laser flare photometry. The remaining participants (46.2%, n = 30) were undecided (Fig. 6).

Table 5 displays the breakdown of the responses according to the specialists’ geographical location. Asia had a lower proportion of participants who always count the number of cells on the slit lamp than did the UK/Europe and the United States ($P < 0.001$). The UK/Europe had a higher proportion of participants who use laser flare photometry than did Asia and the United States ($P = 0.004$). Asia had a lower proportion of participants who considered flare assessment in uveitis management to be of very significant value than did the UK/Europe and United States ($P = 0.001$). The responses of the 3 groups for the remaining questions did not differ significantly.

Discussion

AC cell grading is an integral part of any ophthalmic examination. However, clinical grading has been marred by interobserver disparity [11]. On the basis of our results, it

is apparent that differences in examination methods are a contributing factor toward this disparity.

The SUN classification resulted in the standardization of the slit beam size, which considerably changed the grading of cells as compared with previous classifications [5]. However, our results indicate that a significant number of uveitis specialists do not follow this system, choosing instead to use different-sized slit beams and not to count the number of cells routinely. The specialists from Asia, in particular, appear to count cells less frequently than do their western counterparts (Table 5). The grading of AC cells is such a fundamental activity, one that is so ingrained in a clinician's daily practice, that the need to make any adjustments might not be deemed necessary. For this very reason, some clinicians may not even be aware of the differences in grading systems. This finding is noteworthy because the use of different systems can result in clinically significant interobserver differences.

Further questions could also be posed regarding the incongruities in AC inflammation assessment. For instance, the rationale behind the use of a specific slit size was not provided in the SUN publication. To date, the advantage of using a 1 x 1-mm slit beam over a 3 x 1-mm slit beam has not been clarified. In all the available grading systems, the ideal location of the slit beam in the AC is similarly not specified. The number of fields a clinician needs to scan in the AC before being able to grade the AC cells accurately is also unclear. Moreover, whether the AC activity should be assessed in a dilated or a nondilated pupil has not been specified in any of the published guidelines.

Besides these differences, the inherent shortcoming of the clinical grading of cells also lies in the fact that it is a nonlinear and semiquantitative system. Although laser cell photometry technology has been described as an objective alternative, the difficultly in differentiating pigments from cells and the technical complexities involved in using this device have limited its usefulness [14].

Uveitis is a common disease and is frequently encountered by ophthalmologists from other subspecialties. It is possible that the discrepancies in the assessment of AC inflammation could be larger between each group of clinicians. While the exact merits of each grading system are unknown, it is more important that a standardized grading system is acknowledged and adhered to. This not only would allow for continuity of care to be preserved in the follow-up of patients but also would maintain the accuracy of data collection in research settings.

The majority of the ophthalmologists who participated in our survey agreed that flare is a marker of activity. Participants also generally agreed that flare had a role to play in the diagnosis and management of uveitis. However, most of the participants indicated that they do not use laser flare photometry. This is surprising given that the flaws in the conventional method of assessing AC flare have been widely reported [9, 11, 12, 15]. For example, in Kempen et al's [11] study, although interobserver AC flare grading demonstrated a good agreement rate, most cases were graded 0.5+ to 1+, even in cases with severe uveitis. This finding suggests a wide range of flare activity between grades 0.5+ and 1+ and highlights a possible flaw in the current classification. This finding is supported by that of Agrawal et al [13], who observed a wide range of laser flare readings within each clinical grade of flare.

Laser flare photometry is far superior to the clinical assessment of AC flare on slit-lamp biomicroscopy in terms of precision and reproducibility [12, 13, 16]. It can also play an important role in improving disease management [13, 17, 18]. In fact, Guex-Crosier et al [19] observed that when the laser flare readings of patients with Behçet's disease were followed up, a 20% rise in laser flare readings was seen as the earliest sign of recurrence, even before the onset of AC cells. However, our results indicate that many uveitis specialists are still unsure of whether laser flare photometry will change their management practices. As the assessment of flare remains highly valued, further evidence is needed to support the use of laser flare photometry.

We believe this study has demonstrated a disparity in the assessment practices of uveitis specialists and hope that it raises questions that will initiate further research and discussion in this area.

A limitation of this study is the lack of follow-up questions addressing the reasons for the participants' responses. For instance, it would be informative to find out participants' rationales behind their use of different grading systems. Also, it would be particularly useful to determine why some participants did not use laser flare photometry. For the participants from Asia, the smaller proportion who valued flare assessment could explain the lack of flare photometry use (Table 5). Lack of equipment availability or financial constraints could also be a plausible reason. Follow-up questions would certainly have enabled a better understanding of participants' views towards laser flare photometry.

Given the larger proportion of participants from Asia, the differences found among the different regions may also be skewed and require broader confirmation. Furthermore, whether these differences are specific to individual countries remains uncertain, because we did not analyze the participants by country owing to the small sample size.

In summary, the clinical assessment of AC inflammation is a fundamental part of an ophthalmic examination. It is imperative to use a standardized clinical grading scale, especially in the assessment of AC cells. While the current literature recognizes the value of assessing AC flare, its evaluation on the slit lamp is not ideal. Laser flare photometry has long been studied and remains the only objective quantitative method for examining aqueous inflammation. However, no consensus on the use of this method has been reached, and many uveitis specialists still refrain from its use.
Further research needs to be conducted to determine the exact role of laser flare photometry in the management of uveitis.

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Figure Legends

Fig. 1 Size of slit beam used

Fig. 2 Frequency of counting the number of anterior chamber cells

Fig. 3 Percentage of respondents using laser flare photometry

Fig. 4 Significance of flare in management of uveitis

Fig. 5 Percentage of respondents who consider flare a useful marker of disease activity

Fig. 6 Percentage of respondents who think laser flare photometry can change uveitis management