Pediatric uveitis: EYE-Q and metrics beyond visual acuity

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Abstract: Pediatric uveitis is an inflammatory ocular disease that can lead to sight-threatening complications. Pediatric patients have distinct challenges in the diagnosis and management of uveitis, secondary to difficulties in performing ophthalmic examinations in young children, delayed diagnosis due to lack of adherence with recommended screening schedules, medication side-effects, and increased burden of disease into adulthood. Measurement of outcomes in pediatric uveitis has traditionally relied upon the ophthalmic examination and general quality of life (QOL) measures. However, the ophthalmic examination does not take into account the impact of uveitis on a child's QOL and general QOL measures do not adequately assess the specific effects of vision. Several vision-related quality of life (VR-QOL) instruments have been used to measure outcomes in both adults and children including: the National Eye Institute Visual Function Questionnaire (NEI VFQ-25), Vision-related Quality of Life of Children and Young People (VQoL_CYP), the Children's Visual Function Questionnaire (CVFQ), and the Effect of Youngsters' Eyesight on Quality of Life (EYE-Q). However, the NEI VFQ-25 is not a valid or applicable measure in children, and the VQoL_CYP and CVFQ are not uveitis specific and may not characterize disease specific burdens. The EYE-Q is the only uveitis-specific pediatric questionnaire that measures visual functioning and VR-QOL in 5–18 years old children and adolescents with uveitis. It has been shown to be a valid and reliable assessment tool in several cohorts of children with uveitis. A comprehensive assessment of the impact of uveitis on a child that includes a vision-specific measure, such as the EYE-Q, allows for better understanding of the true burden of uveitis in children. For this review, we describe traditional outcome measures in uveitis studies, general QOL measures and vision-specific measures in adults and in children.

Keywords: Uveitis; health-related quality of life (HR-QOL); vision-related quality of life (VR-QOL)

Introduction

Pediatric uveitis is an inflammatory ocular disease that can lead to sight-threatening complications. Noninfectious etiologies of uveitis are the most common cause of pediatric uveitis in the United States (1). The incidence of uveitis is estimated to be five in 100,000 children and the prevalence ranges from 13–30 cases per 100,000 children (1-4). In North America, the most common systemic disease association is juvenile idiopathic arthritis (JIA) (5,6). Juvenile idiopathic arthritis-associated uveitis (JIA-U) predominantly affects the anterior uvea, is bilateral, non-granulomatous, with a chronic and insidious course (7). Uveitis not associated with a systemic disease is classified as idiopathic and is at least as common as JIA-U (8,9).

Uveitis can also be seen in the setting of other systemic inflammatory diseases including *HLA-B27* disease, Behcet's disease, sarcoidosis, and vasculitides (10).

Pediatric patients have distinct challenges in the diagnosis and management of uveitis, secondary to difficulties in performing ophthalmic examinations in young children, delayed diagnosis due to lack of adherence with recommended screening schedules, medication side-effects, and increased burden of disease into adulthood (11,12). Measurement of outcomes in pediatric uveitis has traditionally relied upon the ophthalmic examination and general quality of life (QOL) measures. However, the ophthalmic examination does not take into account the impact of uveitis on a child's QOL and general QOL measures do not adequately assess the specific effects of vision. A comprehensive assessment that includes vision-specific measures allows for better understanding of the true impact of uveitis in children. For this review, we describe traditional outcome measures in uveitis studies, general QOL measures and vision-specific measures in adults and in children.

The ophthalmic examination, visual acuity (VA), and traditional outcome measures in uveitis

The ophthalmic examination is one of the primary measures of outcomes in children with uveitis and influences therapeutic decision-making. Anterior chamber (AC) cells indicate ocular inflammation, VA indicates visual impairment, and the presence or development of ocular complications indicates ocular damage.

AC cells

Quantifying the number of inflammatory cells in the AC is traditionally used as a marker of uveitis activity. In 2005, the Standardization of Uveitis Nomenclature (SUN) Working Group developed a standardized scoring system that grades the number of inflammatory cells in the AC of the eye identified on slit lamp examination (13). The scores range from 0 to 4+, with each grade corresponding to a larger number of AC cells. Grade 0 is considered inactive and 0.5+ and greater represent increasing levels of inflammatory activity (13). Holland *et al.* showed that an AC cell grade ≥1+ was the strongest predictor of new complications during follow up (14). An additional study conducted by Thorne *et al.* showed that an AC grade of ≥0.5+ was associated with an increased risk of vision impairment (VA 20/50 or worse) and blindness (VA 20/200 or worse) (15).

AC flare

AC flare is the reflection of light from proteins in the aqueous humor during slit-lamp examination. This has been used as both a measure of uveitis activity and of tissue damage. The presence of AC flare has been shown to be associated with AC cells, keratic precipitates and complications of uveitis such as band keratopathy, posterior synechiae, and cataract (16). AC flare was associated with increased risk of vision loss and development of new vision-threatening complications (such as glaucoma), this risk was independent of the presence of AC cells (16). Thorne *et al.* also reported that AC flare was associated with a significantly increased risk of loss of VA of 20/50 or worse (15). Flare is typically detected using slit-lamp examination but estimates of flare can vary between examiners and between visits. The use of laser flare photometry is a more objective technique however this tool is expensive, time-consuming, and not frequently performed in most normal clinic settings (17).

VA

VA has traditionally been used as one of the main outcome measures in uveitis studies and is typically the only visual function measure routinely tested in clinic for uveitis. Therefore, VA is often used as a proxy for visual function, however it does not take into account other factors that contribute to visual function such as color vision, contrast sensitivity, and visual field (18). Despite this, most studies in children with uveitis have used VA as a primary outcome measure (3,8,19,20). Additionally, VA alone is not a complete representation of how visual impairment affects a child's everyday life. This supports the use of more comprehensive QOL measures to understand the true impact of uveitis in children.

Ocular complications

The presence or the development of new ocular complications remain an important outcome measure that can reflect both disease activity and accrued disease damage. Ocular complications that can occur secondary to uveitis include: synechiae, cataract, cystoid macular edema, band keratopathy, and glaucoma among others.

Structural complications have been statistically associated with vision impairment (VA <20/50) and blindness (VA <20/200) in several studies in children with uveitis (7,21,22). Additionally, new or worsening ocular complications can indicate poorly controlled inflammation.

General health-related quality of life (HR-QOL) measures in adults with uveitis

Evaluating general HR-QOL is important in the assessment of chronic diseases, including uveitis. HR-QOL is defined as a person's general perceived health status incorporating their overall physical, mental, and emotional wellbeing and is not disease specific (23). One of the more commonly used general health questionnaires used in adults with rheumatic diseases is the Medical Outcomes Study 36 Item Short Form (SF-36). This questionnaire measures health in eight domains including: general health, physical functioning, role limitations due to physical health, mental health, role limitations due to emotional health, vitality, bodily pain, and social functioning (23). The SF-36 has been used in numerous adult studies to assess HR-QOL related to uveitis.

Murphy *et al.* describes a cohort of patients with uveitis who underwent vision-related quality of life (VR-QOL) and general HR-QOL evaluation using the Vision Core Measure 1 (VCM1) questionnaire and the SF-36 questionnaire respectively. Patients who had reported significant impairment of vision on the VCM1 had significantly worse SF-36 scores than those who did not, representing increased difficulties in overall physical and mental functioning as vision impairment worsened (18). Another study conducted by Schiffman *et al.* compared visual functioning and general health status between a uveitis cohort and healthy control population using the SF-36. The physical and mental component summary scores from the SF-36 were significantly lower in patients with uveitis compared to the healthy population (24). Another cohort of patients with uveitis were compared to a population of individuals with normal vision, and patients with uveitis have significantly reduced mental health and HR-QOL outcomes as assessed by the SF-36 (25). A more recent study of adult patients with non-infectious uveitis reported significantly lower scores compared to controls on the SF-36 domains of role limitations due to physical problems, general health, vitality, and pain (26).

Depression and anxiety are known to occur among patients with chronic diseases. Several studies have shown the importance of depression and anxiety screening among adult patients with uveitis. A study of an adult uveitis cohort from Brazil with bilateral vision impairment found that anxiety and depression symptoms were found in 65% and 33% of patients, respectively, when assessed using the Hospital Anxiety and Depression Survey (HADS) (27). An additional study of an adult uveitis cohort from Turkey evaluated rates of anxiety and depression using the Beck Depression Inventory II (BDI-II) and State-Trait Anxiety Inventory (STAI) and found 37% of patients screened positive for depression and 53% screened positive for anxiety. They found a correlation between rates of depression and lower VA. Patients reporting anxiety were found to be younger and had an earlier age at disease onset. Depression was also found to be associated with impairment in HR-QOL (on SF-36) (28).

General measures and measures specific to anxiety and depression are likely important in assessing the disease burden of uveitis. However, even the combination of general outcome measures, anxiety and depression assessments, and the ophthalmic examination do not sufficiently describe functioning related to eye disease in a uveitis population.

VR-QOL measures in adults with uveitis

The National Eye Institute Visual Function Questionnaire (NEI VFQ-25) is a 25 item questionnaire presented in a Likert scale format asking patients to grade the severity of visual symptoms and their difficulty with vision-related tasks. Subscales of the questionnaire include: general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, color vision, peripheral vision, and driving. This questionnaire underwent validity and reliability testing in an adult cohort of patients with varying eye diseases such as: age-related macular degeneration, diabetic retinopathy, glaucoma, and cytomegalovirus retinitis (29). Since that time, the questionnaire has been used to assess patient reported visual outcomes in numerous uveitis studies. Assessment of VR-QOL was performed using the NEI VFQ-25 in the VISUAL-1 and VISUAL-2 adalimumab clinical trials for adults with noninfectious intermediate, posterior, and panuveitis. Analysis of these trials showed that adalimumab provided statistically significant and clinically meaningful improvements in VR-QOL for adult patients with noninfectious uveitis (30).

VR-QOL was also measured in a longitudinal trial comparing fluocinolone acetonide implant *vs.* systemic

steroid therapy for treatment of noninfectious uveitis. Initial VR-QOL as measured by the NEI VFQ-25 was lower in patients with worse baseline VA and visual field testing. Both treatment groups showed improvement in VR-QOL using the NEI VFQ-25 questionnaire after 3 years of follow up (31).

Another study compared VR-QOL in patients with uveitis to patients with diabetic retinopathy and healthy controls using the NEI VFQ-25. Patients with uveitis had lower VR-QOL than both healthy subjects and patients with diabetic retinopathy. Further analysis determined that lower VR-QOL scores were predicted by poor VA, ocular comorbidities, and female sex (32).

Numerous studies of adults with uveitis have shown significantly decreased VR-QOL compared to normal, healthy populations (18,24,25,32,33). In addition, many patients who were diagnosed with uveitis as children continue to have active disease or suffer complications from disease into adulthood. A study of adult patients who were diagnosed with JIA as children reported that a previous history of uveitis had a significant negative effect on VR-QOL, even in patients with normal VA (34). Taken together, these results support ongoing longitudinal assessments of VR-QOL in adult patients with uveitis.

General HR-QOL measures in children with uveitis

General HR-QOL measures have been used to evaluate outcomes in many pediatric diseases including diseases such as JIA and uveitis. HR-QOL measures should represent the patient's lived experience in the context of their health condition. However, the lived experience of young children with a chronic health condition is often reported by a parent proxy. It has been reported in several studies that discordance exists between patient and parent report of HR-QOL in chronic illness using measures such as the Pediatric Quality of Life Inventory (PedsQL) and Child Health Questionnaire (CHQ) (35,36). Therefore, pediatric HR-QOL measures must take into account the cognitive development of the child and ideally include both a child and parent reported measure to take into consideration both perspectives.

Three of the more commonly used HR-QOL measures in children, specifically in children with uveitis, include the PedsQL, the CHQ, and the Childhood Health Assessment Questionnaire (CHAQ). The PedsQL is a validated general QOL questionnaire for children aged 2–18 which evaluates QOL in numerous domains including: physical, social, emotional and school (37). The CHQ is an internationally recognized HR-QOL questionnaire for children aged 5–18 that assesses a child's physical, social, and emotional well-being (38). The CHAQ is a questionnaire that evaluates physical functioning domains including: dressing, arising, eating, walking, hygiene, and activity and was initially validated in a cohort of children with JIA (39).

The PedsQL and CHAQ have been suggested for use as outcome measures in clinical studies evaluating children with JIA-U. The Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC) enrolled children with JIA-U and proposed outcome measures to validate their applicability for future clinical studies. The PedsQL and CHAQ were used as measures of overall well-being and significant improvements in patient-reported PedsQL and CHAQ scores were noted at 6 months when compared to baseline values, suggesting improvement in physical functioning and QOL (40). Based on the results of this prospective study performed by the MIWGUC, consensus was reached on the recommended items to be selected for defining response to treatment. Measures selected include not only AC cells, AC flare, and the new occurrence of structural complications, but also include ophthalmologist and rheumatologist global assessment of disease activity, patient and parent global assessment of disease activity, and changes in both general HR-QOL and VR-QOL measures (40).

Additionally, a double-blind randomized control trial examining the efficacy of adalimumab in JIA-U used the CHAQ and CHQ as secondary end points to measure physical functioning and HR-QOL between adalimumab and methotrexate vs. methotrexate alone groups. Adalimumab did meet its primary trial end point of decreased rate of treatment failure compared to methotrexate alone, however there were no significant differences between CHAQ or CHQ scores between the two groups at baseline or over the course of the study (41). This might suggest that the more general QOL questionnaires do not fully assess the impact of eye disease or the response to treatment.

As in adults, chronic diseases can have significant impact on the mental health of children. However, anxiety and depression have not been well characterized in this cohort and studies are needed. The PedsQL has questions pertaining to emotional wellbeing but does not specifically evaluate for anxiety or depression in children. The Revised Childhood Anxiety and Depression Scale (RCADS) is one of the more widely used, brief screening tools evaluating

symptoms of depression and anxiety in children (42). The RCADS has been used in the evaluation of overall QOL in a cohort of children with JIA and uveitis and in contrast to adults with uveitis, children with uveitis did not report clinically significant anxiety or depression (43). This may be secondary to the cohort of children all having inactive disease with normal, preserved VA at the time of questionnaire completion.

VR-QOL measures in children with uveitis

There are very few studies that have evaluated the QOL in children with uveitis. As in adults, outcome measures include: VA, slit lamp examination, and general QOL assessments. However, like the adult measures, none of these take into account the effect uveitis and vision impairment have on everyday life for children with uveitis.

Several vision-specific measures exist for use in children with vision impairment however they are general measures and are not disease specific. The Cardiff Visual Ability Questionnaire for Children (CVAQC) is used to assess visual function in children 5–18 years of age (44). The Impact of Vision Impairment on Children (IVI_C) and the Vision-related Quality of Life of Children and Young People (VQoL_CYP) are both measures of VR-QOL (44). However, their use in children with uveitis would likely not capture the full effects of the disease because they do not take into account the specific effects of disease-related ocular complications or treatment regimens (45). Additionally, discordance exists in child and parent reports for children with visual impairment when examining VR-QOL and visual function measures, again stressing the importance of both child and parent measures (46).

To better understand the effects of uveitis and its treatment on children and their parents Sen and colleagues performed semi-structured interviews with 10 patient/parent pairs of children with JIA-U. Patients and parents commonly reported concerns included: negative emotional reactions to treatment, missing school for treatment, side effects of treatment, worrying about poor vision, trouble reading at school, feeling excluded from activities, and bullying (45). A separate study by Parker *et al.* also performed patient/parent interviews in a population of children with chronic anterior uveitis. They describe fear of vision loss and blindness, burden of examination and treatment regimens, and drug toxicities as particular stressors for children with uveitis and their families (47). Since most general HR-QOL measures and general VR-QOL measures do not address these disease-specific concerns, it justifies the inclusion of uveitis-specific measures to assess these important areas of concern for children with uveitis. Current adult vision-specific QOL measures such as the NEI-VFQ contain many items that are not applicable to the daily life of a child affected by uveitis, such as questions asking about cooking, driving, and working.

Given the great need for a child uveitis-specific VR-QOL measure, Angeles-Han *et al.* created the Effects of Youngsters' Eyesight on Quality of Life (EYE-Q) questionnaire. This uveitis-specific questionnaire consists of 27 items assessing both visual functioning (i.e., near, far, color, and night vision, photosensitivity, functionality, and visual aids) and VR-QOL (i.e., medication use, activities, feelings) related to uveitis. Each question is answered on a 3-point Likert scale with the response format assessing level of difficulty in performing each task. The questionnaire was determined to be both a valid and reliable measure in several single center cohorts (48,49). In a cohort of 120 children aged 8–18 years old with and without ocular diseases including uveitis, there were significant associations between the EYE-Q and PedsQL scores. EYE-Q scores were associated with worsening VA and bilateral disease (48). Thus the EYE-Q was able to detect differences in normal and impaired eyes and differences in the severity of vision impairment suggesting it is a valid measure of VR-QOL (48). The PedsQL scores were not significantly associated with VA suggesting it is likely a poor measure of VR-QOL.

A subsequent study using the EYE-Q examined QOL in 57 children with JIA, JIA-U, and uveitis alone. Children with visual impairment (VA 20/50 or less) in their better seeing eye had worse EYE-Q scores. However, PedsQL and CHAQ scores did not correlate with VA (49). Thus the EYE-Q was able to differentiate children based on underlying visual impairment suggesting that the EYE-Q may be a more useful and sensitive tool in the measurement of visual outcomes in childhood uveitis compared with general measures (49).

In another cohort of 40 children with JIA-U and other non-infectious uveitis not related to JIA, the EYE-Q, PedsQL, CHAQ, and RCADS were used to evaluate the impact of topical and systemic medication on HR-QOL, mental health, and VR-QOL. The parents of children with uveitis who require topical therapies report worse VR-QOL scores using the EYE-Q. There were no differences noted for child reports using the EYE-Q, likely related to parental responsibility for instilling topical drops. Additionally, the other measures including the PedsQL, CHAQ, and RCADS

did not appreciate differences based on treatment regimen. These findings suggest the importance of including uveitis-specific disease measures to accurately evaluate the burden of disease and treatment which can include complex topical therapy regimens (50).

The EYE-Q contains several items that are school specific and the questionnaire is only validated for children age five and up leaving a population of non-school aged children with uveitis without a patient reported outcome tool. The Children's Visual Function Questionnaire (CVFQ) could be used in this population as it measures VR-QOL by parent reports for children less than age seven (51). However, the questionnaire is not specific to uveitis and to date has not been evaluated in children with uveitis. There is currently no uveitis specific QOL measure evaluating non-school aged children with uveitis and this remains an important area for future outcome measure development.

Conclusions

Comprehensive outcomes assessments could bolster the impact of future clinical studies in uveitis. These assessments should optimally include measures of disease activity, severity, and damage in combination with patient reported outcome measures that measure both general and disease specific domains for a disease such as uveitis. Patient reported outcome measures in pediatrics should be age appropriate and optimally include child reports in addition to parent reports. Future studies evaluating uveitis-specific questionnaires, such as the EYE-Q, in larger cohorts will be useful. Future development of outcome measures that include children less than five would help capture a large population of non-school aged children who develop uveitis.

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Footnote

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