



Published in final edited form as:

Int Ophthalmol Clin. 2015 ; 55(2): 93–101. doi:10.1097/IIO.0000000000000067.

Quality of life Metrics in Pediatric Uveitis

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Abstract

Uveitis can lead to vision loss and blindness in children. It can significantly impact a child's vision related quality of life and daily function. Outcome studies in pediatric uveitis focus on the clinical ocular exam and general measures of quality of life whereas in adults, measures of visual function are incorporated. Adequate vision can affect a child's daily activities and is crucial for daily function in the home and school. A comprehensive approach that incorporates all aspects of disability could improve the assessment of outcomes and may help us better understand the impact of visual impairment on children with uveitis.

Pediatric uveitis is an inflammatory ocular disease that can lead to severe ocular complications, vision loss, and permanent blindness. Non-infectious uveitis can occur as a primary disease with no associated systemic conditions (idiopathic uveitis) but can also be related to autoimmune diseases such as juvenile idiopathic arthritis (JIA), sarcoidosis, and Behcet's disease. JIA is the most common systemic disease associated with childhood uveitis in North America wherein 10–20% of children will have uveitis¹. For children with JIA considered at high risk for developing uveitis, regular ophthalmology screenings are recommended every 3–4 months until 7 years of age to screen for disease development². The impact of eye disease on a child's quality of life and function has been understudied.

Vision related quality of life and function

Adequate vision is a crucial component of a child's daily activities such as in reading, writing and being able to see the board. Poor vision can have a negative impact on quality of life and function and can adversely affect one's social, emotional, mental and physical well-being. Quality of life is known to be an important construct, particularly related to chronic disease. It is defined by the World Health Organization as an "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns"³. Visual function can be assessed by measuring the degree of visual impairment experienced in activities of daily living. Significant impairment would lead to difficulty in performing tasks which rely on vision. Since uveitis sequelae often result in compromise of visual function, outcomes studies in children with uveitis should account for visual disability.

Uveitis can be chronic with frequent relapses and recurrences. Ocular symptoms vary depending on disease etiology, and many children with JIA-associated uveitis are

asymptomatic until complications present. Common symptoms include eye redness, pain, blurry vision, glare and photosensitivity which can be secondary to ongoing inflammation or to complications such as cataracts, glaucoma, and macular edema. Unfortunately, visual handicap can have long standing effects into adulthood⁴.

The need for local and systemic treatment can present an additional challenge in young children. Medications include frequent eye drops (mydriatics and intraocular steroids), ocular injections, and systemic immunosuppressive therapy administered by injections or infusions. Interestingly, although these can potentially affect quality of life and function, a study in adults with uveitis demonstrated that those on systemic therapy had similar vision related and health related quality of life as those not on systemic therapy⁵. However, the effects of medication for uveitis in children are virtually unknown. In addition, regularly scheduled physician and treatment visits (with ophthalmologists and rheumatologists as well as frequent blood draws to monitor medication related toxicity and disease activity) commonly lead to missed school days and reduced productivity. Activities of daily living related to the school and home are unfortunately affected. Therefore, further investigation into the effects of chronic disease and long term management by various subspecialists, which may ultimately impact a child's quality of life and function, is essential.

To date, studies examining outcomes in pediatric uveitis have consisted of the clinical ophthalmology exam (visual acuity, slit lamp examination) from the Standardized Uveitis Nomenclature criteria, and measures of general quality of life such as the Pediatric Quality of Life Inventory (PedsQL)^{6, 7}. In children with JIA and uveitis, measures of physical function such as the Childhood Health Assessment Questionnaire (CHAQ) are often incorporated⁸⁻¹⁰. However, current assessments of outcome may result in an underestimation of the impact of uveitis since they do not account for vision specific limitations. Furthermore, the clinical exam may not completely describe visual performance since other measures of function such as color vision, contrast sensitivity, and visual field are not always included.¹¹ The addition of a vision specific instrument may capture aspects of visual functioning that would otherwise not be assessed by current evaluations.

Assessment of vision related functioning and quality of life in adults with uveitis

Adults with uveitis have significantly decreased vision related functioning and health-related quality of life¹¹⁻¹⁴. Several studies have utilized the National Eye Institute Visual Function Questionnaire (NEI-VFQ) which measures the impact of visual impairment on vision-related functioning and has been validated in ocular diseases such as age-related macular degeneration, age-related cataract, diabetic retinopathy, and low vision from any cause¹⁵. Naik et. al evaluated the psychometric properties of both the NEI-VFQ and the Visual function Questionnaire Utility Index in adults with non-infectious intermediate and posterior uveitis enrolled in a phase 3 clinical trial of a Dexamethasone implant¹⁴. Both instruments were found to be reliable and valid measures in a uveitis population.

Comparisons between uveitis and normal populations have shown that adults with uveitis generally have worse health status and visual functioning^{12, 16}. Compared to the normal-

vision and US populations, adults with uveitis also had worse impairments in psychological functioning and well-being¹⁶. Within the uveitis population itself, uveitis specific characteristics can affect visual functioning- disease severity, visual acuity, bilateral involvement, location, active disease, chronic course, increased immunosuppressive therapy, and other medical comorbidities^{11, 12, 17, 18}. Gardiner et. al. noted correlations between vision related quality of life, measured by the Vision Specific Quality of Life questionnaire, with binocular VA and age wherein younger patients with decreased binocular VA had worse vision related quality of life.^{19, 20}. Interestingly, Tan et. al. found that disease activity was not a factor in determining quality of life, rather, the chronicity of uveitis was important¹⁸.

The importance of both the clinical exam (visual acuity) and a visual function measure has been demonstrated, and several studies replicate findings of the use of visual acuity as a predictor of visual function^{13, 18, 19, 21}. Small to moderate correlations between visual acuity and the NEI-VFQ imply that adults with better visual acuity have improved vision related functioning¹³. In fact, Individuals who experienced greater impairments in visual acuity (VA between 20/40 and 20/200, or a VA equal or worse than 20/200) had worse visual functioning.¹⁴ Both visual acuity and health related measures are generally considered to be reflective of the better-seeing eye²¹. Naik et. al. confirmed that the better seeing eye had low to moderate correlations with visual acuity when his group looked at differences in the NEI-VFQ25 scores and visual acuity in the general US population, a normal-vision reference group and a uveitis population¹⁶. In contrast, other studies observed that worse eye visual acuity is predictive of vision related quality of life, and not better eye visual acuity^{11, 22}.

Visual acuity has been used as a proxy for visual function in uveitis but other components of the clinical ocular examination such as contrast sensitivity, visual field testing, or color vision may be necessary. In a cohort of patients with severe uveitis needing systemic immunosuppression, the majority (80%) had a visual acuity of 20/25 or better and no patients were legally blind^{11, 22}. Color vision was not significantly affected, but the patients had visual field loss. Aside from visual acuity of the worse eye, contrast sensitivity was also predictive of vision related quality of life^{11, 22}. Gardiner looked at correlations between tests of visual function and vision related quality of life and also noted that visual acuity and contrast sensitivity correlated with vision related quality of life although binocular VA had the greatest effect¹⁹. Naik et. al. demonstrated significant correlations between vitreous haze and visual functioning¹⁶. Hence, the addition of other components of the clinical ocular examination may provide a more accurate assessment of uveitis impact on vision related function and quality of life.

The analyses of treatment efficacy should also include the effects of treatment on an individuals' clinical status, quality of life and function. Murphy, et. al. demonstrated dynamic associations in visual acuity and vision related quality of life since both measures reflected clinical change over time after treatment, thus could potentially be used as treatment end points²². Lightman et. al. observed a sustained improvement in visual functioning after treatment with a dexamethasone intravitreal implant¹³. This improvement was specific to near vision, distance vision, peripheral vision, vision-specific social functioning initially at 8 weeks which was sustained at 6 months in distance vision and

vision-specific social functioning but now included vision-specific role difficulties, -dependency, -social functioning and -mental health. Frick et. al. examined vision-related function in cost-utility analyses and found stronger associations between vision-related function and health utility measures compared to visual acuity²¹. They concluded that the combination of visual acuity, generic quality of life and vision-related function measures may be better able to detect clinically important outcomes.

Of note, one study looked at the effects of the primary ophthalmological disease and associated comorbidities on quality of life²³. In their ophthalmology cohort, the subjects' ocular disease determined overall QOL rather than all of the diseases affecting the individual. Hence, in patients with several comorbidities, health related quality of life may be affected primarily by the disease that most adversely affects quality of life. This could have implications in the measurement of outcomes of individuals with uveitis and associated systemic diseases as focus may need to be more vision specific.

Depression can also occur in patients with chronic disease. Qian et. al. noted that almost 30% of their uveitis cohort were depressed²⁴. In fact, those patients who were depressed were more likely to have poorer self-reported visual function. The recognition of other factors that can affect a patient's quality of and function can help us better address and support the global needs of this population.

General outcome measures and the clinical ocular exam alone do not entirely measure functioning related to ocular disease in a uveitis population. They are likely complementary wherein each measure provides distinct information. Moreover, visual acuity itself may not be an adequate measure of uveitis outcomes, and measures of contrast sensitivity, color vision and visual field may be necessary in addition to vision specific quality of life and function instruments.

Assessment of vision related quality of life and function in children with uveitis

There is a scarcity of studies that have examined the impact of uveitis in children^{25–27}. Similar to adults, measurements in the pediatric population include an ophthalmologic examination (visual acuity, applanation tonometry, and slit lamp biomicroscopy), and general quality of life instruments (i.e. Pediatric Quality of life Inventory – PedsQL⁷). However, like adults, none of these take into account visual disability secondary to uveitis. The Multinational Interdisciplinary Working Group for Uveitis in Childhood proposed outcome measures that incorporate the clinical ocular exam based on SUN criteria, overall quality of life assessments (PedsQL, Child Health Questionnaire), and physical function measures (CHAQ), but they recognize the lack of a uveitis-related quality of life assessment questionnaire²⁸.

There are several challenges in the measurement of vision related quality of life and function in children. There is a lack of patient reported outcome (PRO) measures that are vision specific for pediatric use, and only one that is focused on a uveitis population^{26, 29–33}. Adult based measures such as the NEI-VFQ contain items that are inapplicable to a pediatric

population such as questions related to cooking and sewing, working, or picking out and matching clothes. Existing pediatric vision measures include the Children's Visual Function Questionnaire, which is limited to children < 7 years of age, and the LV-Prasad Questionnaire, which are not culturally optimal for a U.S. population^{29–31, 34}. Although current pediatric vision measures can differentiate between children with and without eye disease, they may not distinguish between variations in disease severity or clinically significant vision changes over time. Likewise, as reviewed elsewhere, many pediatric instruments focus on the impact of vision on function but not on the effects on health related quality of life or physical, emotional and social domains^{35, 36}.

A greater challenge is the paucity of vision specific PRO measures aimed at children less than 7 years of age which is essential since this age group is most vulnerable to developing uveitis²⁹. Many studies use parent-proxy reports which do not always accurately reflect the child's perspective and quality of life studies have showed discordance. Likewise, the importance of the ability to perform tasks in the home and school differ depending on age since children have distinct cognitive abilities that vary during growth and development.

Few studies have looked specifically at visual function or vision related quality of life in children with uveitis. Maca et. al. studied the health related quality of life of 37 adolescents who were 11–18 year old and diagnosed with uveitis that was inactive, had inactive systemic disease and good vision (defined as at least one eye with a logMAR VA better than 0.1). Their objective was to obtain "basic" data on the health related quality of life in uveitic adolescents and avoid negative stressors²⁵. Instruments utilized included the Inventory for Assessing the Quality of life in Children and Adolescents and the Children's Quality of life Questionnaire. Compared to healthy adolescents, adolescents with anterior or intermediate uveitis, bilateral disease, shorter duration of disease, and increased recurrences had worse quality of life which was similar to several studies in adults with uveitis. Sixty two percent were worried about going blind and more than 50% thought their parents were worried about their disease and well-being. In fact, these adolescents with inactive uveitis and good binocular vision still had impairment in their health related quality of life. Our group explored the impact of physical and visual disability on the QOL of 27 children with JIA and or uveitis and noted that there was a moderate correlation between visual function and overall QOL in children with uveitis, but not in those with JIA alone²⁶. Hence, a broader assessment of the consequences of uveitis in children is needed.

Uveitis specific questionnaires

To address the lack of a disease specific questionnaire, our group developed the first validated instrument to measure vision related quality of life and function in childhood uveitis entitled, the "Effects of Youngsters' Eyesight on Quality of Life" or EYE-Q^{26, 27}. This is a promising vision specific instrument that complements the ophthalmic exam and global measures in the assessment of visual outcomes in children with uveitis.

The EYE-Q is geared towards school-aged children 5 years old and above, and consists of parent reports and patient self-reports for children < 8 years of age. The questionnaire has 26 items and uses a five-point Likert scale with no visual analogue scale to be sensitive to

children with visual difficulties. Nineteen items measure near, far, color and night vision, photosensitivity, and functionality. Four items on QOL inquire about feelings regarding the use of medications, missing school for doctor visits, and lab draws. There is a question about the presence of common uveitis symptoms (eye redness, blurry vision, eye pain, and photosensitivity). Additionally, there is an item that inquires about the use of visual aids (special lamps, magnifying glass and large print material) and allows the child to specify other aids that may be used. There is a subjective assessment of vision severity where the child rates their eyesight as: 1 (excellent), 2 (good), 3 (fair), 4 (poor), 5 (very poor), or 6 (blind). A child-friendly, reliable and valid instrument that assesses visual functioning within the context of quality of life would enhance our understanding of the impact of complex, multi-system childhood diseases on a child's quality of life. Validation studies in a pediatric uveitis population are ongoing.

Measuring quality of life and function in children with uveitis associated with systemic diseases

Many children with non-infectious uveitis have co-existing autoimmune diseases. Since JIA is the most common systemic cause of childhood uveitis, it is important to consider the contribution of both musculoskeletal disability secondary to arthritis and visual disability from uveitis. Measures of arthritis and physical function in children with JIA include counts of painful, swollen and limited joints, and validated physical function questionnaires such as the Childhood Health Assessment Questionnaire (CHAQ¹⁰). *In a prospective cohort of patients with JIA and or uveitis, our group has demonstrated a correlation between the EYE-Q with visual acuity, but found that the overall measure of QOL (PedsQL) did not correlate with visual acuity³⁷ (published abstract)* In adult vitreoretinal patients, quality of life was mainly affected by the primary ocular disease rather than by associated morbidities.²³ Hence, similar to the assessment of outcomes in adults with uveitis, vision specific measures should be incorporated since general measures may not adequately assess outcomes.

Conclusion

Adults with uveitis have decreased quality of life and visual functioning which worsens with severe disease. Few studies look at vision specific quality of life and function in children with uveitis. Vision specific measures may reveal areas of vision that are not quantified by general measures or the ocular exam. Hence, pediatric uveitis outcome studies should include a comprehensive assessment of disability and consider the use of uveitis specific measures which may be a more clinically sensitive assessment of visual function and an important treatment end point in clinical trials. Understanding how uveitis impacts a child's life will enable us to better provide appropriate support for our young patients.

Acknowledgments

Grant Support:

Dr. Angeles-Han was supported by Award Number K23EY021760 from the National Eye Institute.

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