Title: Quality of Life and Functional Vision in children with glaucoma.

Running head: Quality of Life in children with glaucoma

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Abstract

Objective: To evaluate the effect of glaucoma on functional vision and vision and health-related quality of life in children up to the age of 16 years.

Design: Cross-sectional observational study

Participants: 119 children aged 2 to 16 years (mean 9.4, SD 4.56) with glaucoma and their parents.

Methods/Interventions: Completion of three validated instruments for children to assess (i) functional visual ability (FVA) with the Cardiff Visual Ability Questionnaire for Children (CVAQC), (ii) vision -related quality of life (VR-QoL) with the Impact of Vision Impairment for Children (IVI-C) and (iii) health-related quality of life (HR-QoL) with the PedsQL™ V 4.0.

Main Outcome Measures: Cardiff Visual Ability Questionnaire for Children, Impact of Vision Impairment for Children and PedsQL™ scores.

Results: Scores for FVA, VR- and HR-QoL are reduced in children with glaucoma: median CVAQC score -1.24 (interquartile range IQR -2.2 to -0.11, range: -3.00 higher visual ability to +2.80 lower visual ability), mean IVI-C score 67.3 (SD 14.4) (normal VR-QoL = 96), median PedsQL™ self-report 78.8 (IQR 67.4-90.2), parent report 71.2 (IQR 55.7-85.8) and family impact score 74.3 (IQR 56.9-88.5) (normal HR-QoL = 100). Psychosocial PedsQL™ subscores are lower than physical subscores. Older children report less impairment on CVAQC, IVI-C and PedsQL™ than younger children. Parents state greater impact on their child's HR-QoL than children themselves.

Conclusions: Glaucoma and its management have a marked impact on a child's functional visual ability and quality of life. Children with glaucoma report HR-QoL scores similar to those described by children with severe congenital cardiac defects, liver transplants or acute lymphoblastic leukemia.

Precis (35 words)

Childhood glaucoma not only impacts a child's vision, but also severely affects their quality of life and that of the family**.**

Introduction

Childhood glaucoma (CG) is a rare, but significant and potentially sight-threatening condition associated with elevated intraocular pressure (IOP). [1] [2] Common causes of childhood glaucoma are primary developmental defects of the aqueous drainage pathways leading to primary congenital glaucoma (PCG), and more extensive ocular maldevelopment and/or systemic disease such as Axenfeld-Rieger anomaly, aniridia, phakomatoses along with acquired glaucoma after lensectomy for congenital cataract. CG poses significant management challenges and visual outcomes may be disappointing. [3] [4] [5] Primary treatment for PCG is surgical but secondary glaucomas often also require surgical intervention to control intraocular pressure (IOP) should topical medications fail. [6] Surgical success is often compromised by aggressive postoperative inflammation and scarring, potentially leading to multiple surgical interventions. [6] Children often require topical medication to control IOP prior to and after surgery, which may cause discomfort and be a burden to families. Correction of ametropia and amblyopia in young children require additional monitoring and treatment. Furthermore, examinations under anesthesia (EUA) may be necessary in infants and young children for accurate assessment.

The diagnosis of glaucoma in a child can be very stressful for the child and for the parents/caregivers (henceforth referred to as “parents”), siblings and extended family members for many reasons. Glaucoma is a chronic, sight threatening condition with an uncertain prognosis which requires lifelong treatment and follow up. Associated visual impairment may have a significant impact on the child’s development, education, social integration and independence. Treatment may involve multiple operations often when the patient is a neonate or infant. A decision to proceed to incisional or laser surgery may be made during an EUA, so children and parents face the anxiety of not knowing whether the child will wake up in discomfort or pain. The challenges associated with assessing and controlling glaucoma in children also result in numerous hospital appointments requiring parents to take time off work and absences from school as the child grows older, affecting education.

Secondary glaucoma may be associated with systemic disease requiring treatment, which may further compound these absences. Furthermore, buphthalmos, a physical manifestation of glaucoma in infancy, may further highlight a child's difference from their peers especially if unilateral, as may a port wine stain. Lastly, the potential financial burden on the family should not be underestimated. In some countries, medical expenses may have to be paid for by the family. Loss of earnings due to hospital visits affects parents everywhere.

Published data on the impact of glaucoma on children and their families is scarce partly due to a paucity of suitable instruments in children to measure functional visual ability (FVA) (i.e. an individual's use of their given vision in activities of daily living) and quality of life (QoL) (i.e. an individual's subjective impression of various aspects of their life such as physical, emotional, social and schooling), as it relates to their vision (VR-QoL) and health (HR-QoL). Three previous studies have used validated tools to explore QoL in children with glaucoma and their parents. Children with glaucoma report lower VR-QoL scores than healthy children [7] and better visual acuity is associated with higher VR-QoL. [8] Glaucoma surgery in children is associated with an improvement in the quality of life of their parents. [9] No study has assessed HR-QoL or FVA in children with glaucoma. Our main objective was therefore to explore FVA, VR-QoL and HR-QoL in children with glaucoma and their parents.

Methods

This work presents an analysis of children with glaucoma who took part in a larger cross-sectional observational study of quality of life in children with developmental eye defects, approved by the National Research Ethics Committee South Central – Oxford A (14/SC/1052). It adhered to the tenets of the Declaration of Helsinki.

Between 25 June 2014 and 03 June 2015 we enrolled children age 2-16 years with primary or secondary glaucoma who attended clinics at Moorfields Eye Hospital, London, UK. Exclusion criteria were: inability to communicate in English, surgical intervention (incisional or laser) within one month of date of completing

questionnaires (before or after). We screened the notes of all children attending our pediatric glaucoma clinics in advance to identify those who met the inclusion criteria. These children were then approached consecutively for inclusion in the study. For those who did not wish to take part, we noted the reasons given. Age-appropriate written information material was provided; we addressed any questions before obtaining written consent and assent.

We recorded age at study participation, gender and ethnic background. From the medical notes, we recorded ocular and systemic diagnoses, age at diagnosis of the eye condition (primary glaucoma, or eye defect causing secondary glaucoma), and best corrected visual acuity (BCVA) with both eyes open in logMAR on the day of study participation. Where visual acuity was recorded as "counting fingers", we noted a BCVA of 2.1 logMAR, for "hand movements only" we noted 2.4 logMAR, for "perception of light" 2.7 logMAR, and for "no perception of light" or "ocular prosthesis/artificial eye", 3 logMAR. [10] Details of previous and current treatment were recorded. The number of previous glaucoma-related surgical interventions performed in the operating room only were noted, as these were considered more significant than clinic procedures due to factors such as the potential traumatic experience of hospital admission, anesthesia and postoperative pain. The sum of interventions to the right and left eye including incisional surgery (angle surgery, trabeculectomy and glaucoma drainage device surgery), laser treatment, bleb needling, and removal of sutures and/or subconjunctival injections performed under EUA. The number of general anesthetics for both surgical procedures and examinations under anesthesia, and the number of current topical medications (sum of eyedrop applications per day right and left eye) were also noted.

Main outcome measures

To evaluate functional vision, children from the age of 5 years completed the Cardiff visual ability questionnaire for children (CVAQC). [11] The CVAQC was developed to assess the difficulty in performing activities in children's daily lives in the developed world following extensive work with focus groups of children with and without sight

impairment to determine the relevant questions. The tool was validated in children with visual impairment. It is self-report tool consisting of 25 questions with answers selected on a four-point scale ("very easy" to "very difficult") which cover the areas of education, near and distance vision, getting around, social interaction, entertainment and sports. [11] For example, children were asked "Because of your eyesight and with your glasses and low vision aids if you use them, how difficult do you find it to walk in a crowded place ?" or "Because of your eyesight and with your glasses and low vision aids if you use them, how difficult do you find it to watch television ?". Using a Rasch conversion calculator provided by the developers of the CVAQC tool, we transformed the raw CVAQC scores into logarithmic scores. The resulting scores range from -3.00 (higher visual ability) to +2.80 (lower visual ability).

To assess VR QoL, a subgroup of children aged 8 years and older enrolled after 01 August 2014, when required agreements and permissions were granted, completed the Impact of Vision Impairment for Children (IVI-C) tool. [12] The IVI-C tool was validated in visually impaired and normally sighted children. It entails 24 questions with 5 possible answers plus an additional option of "no, for other reasons". We scored the IVI-C responses using the relevant scoring sheet which allocates values between 0 and 4 to the responses from "never" to "always" to questions covering areas of school (aspects of school life and classroom activity), mobility (travel and access to the environment), interaction (with non vision impaired peer group and people in broader community) and emotion (the emotional impact of visual impairment on day-to-day life). For example children were instructed to give an answer which best described what they did and felt most of the time in response to a questions such as "Do you find it difficult to go down stairs or to step off the footpath ?", "Are you confident in places you don't know ?" and "Can you find your friends in the playground at lunch and play time?". We did not allocate a score when the response "no, for other reasons" was selected. As the tool comprises 24 items, the resulting raw scores range from 0 to 96, with the highest score indicating normal VR-QoL. No Rasch conversion table is available for this tool as yet, and we did not carry out a Rasch transformation on our data, as the sample size

was small.

For HR QoL, age-specific versions of the PedsQL™ Inventory (www.pedsql.org) enable children aged 5-18 years to express their views on different aspects of their physical and emotional state and their social and school life.[13 14] Parents completed two questionnaires, one about the child ("parental report") and another about the impact on the family ("family report"). The parental report is specific to the age of the child and usually consists of 23 questions covering children aged 2-4 years (21 questions), 5-7 years, 8-12 years and 13-18 years. The family report contains 36 questions. Children from the age of 5 up to 16 self-administered the questionnaire (PedsQL™ administration guidelines) and gave answers on a 5-point Likert scale from 0 ("never a problem") to 4 ("always a problem") to questions such as "It is hard to keep up when I play with other kids" or "I worry what will happen to me".

We calculated the PedsQL™ scores as detailed in the scoring instructions. If items were left blank, we adjusted the denominator, using the number of completed items instead of the number of total items. It is recommended to remove questionnaires from the analysis if 50% or more of the items have been left blank; this did not occur in our sample. PedsQL™ scores range from 0 to 100 providing physical functioning, psychosocial (school, social, emotional) functioning and summary total scores with a score of 100 indicating normal HR-QoL.

All questionnaires were completed on the same day, during a regular clinic appointment. When children needed help completing the questionnaires, they were assisted by a member of the research team or play leaders, but not by family members.

Statistics

We aimed for a sample size of 100 children to allow for a limits of agreement comparison (Bland-Altman plot) of parent and child scores for the PedsQL™ questionnaire. Demographic and clinical data, CVAQC, IVI-C scores and PedsQL™ scores were transferred to a dedicated database in Microsoft Office Excel by a member of the research team. Calculation of scores and data transfer were double-checked by a second member of the team.

Where data were missing for individual items in the PedsQL™ and IVI-C, we adjusted the denominator accordingly. For the CVAQC, a Rasch-analysis based calculator transforms raw data into standardized scores, and this takes into account missing data.

Analysis was carried out in SPSS v23 (IBM) and Stata (V14). Where data were missing, datasets were excluded from the relevant analyses. We applied descriptive statistics throughout, reporting means and standard deviations for normally distributed data or median and interquartile range (IQR) for data not normally distributed. We assessed relationships between age at participation, age at diagnosis, unilateral / bilateral disease, BCVA in better eye, sum of surgical interventions, sum of eyedrops, sum of general anaesthetics and CVAQC, IVI-C and Peds QL™ scores using Spearman rank correlation and assessed whether differences observed between groups were statistically significant using the Rank Sum test or independent t-test. Agreement between adult and child PedsQL™ scores was assessed using Bland-Altman techniques. Statistical significance was set at the 5% level and all tests conducted were two-tailed.

Enrollment

We approached 158 consecutive children with glaucoma and their families who met the inclusion criteria; 30 declined because of a perceived lack of time to complete the questionnaires. We enrolled 128 children (Fig 1). We removed six children who had undergone incisional surgery or laser treatment within four weeks of study participation. One child who developed glaucoma after extensive trauma related injury and surgery along with another child with multiple non-glaucoma surgical interventions had significant visual loss

unrelated to secondary glaucoma and so were excluded on the basis that their complex ophthalmic history prior to glaucoma management may have influenced their responses leading to a different impact on our main outcome measures. We also excluded one dataset, as neither parents nor child completed the questionnaires after having given consent. The statistical analysis was carried out on the remaining 119 datasets (Fig 1).

Missing data

The proportion of missing data was low. No data were missing for age, gender, diagnoses, laterality, BCVA and number of daily eye drops. Ethnicity was unknown in 14 participants (11.76%). Age at diagnosis of the eye condition could not be determined exactly in 2 children (1.7%). Five children had previous surgical interventions at other centers, and information about previous number of operations and general anesthetics was incomplete (4.2%). For all questionnaires administered, response and completion rates were high (Supplementary Material).

CVAQC and IVI-C response rates were 85.87% and 90.91%, respectively. CVAQC and IVI-C scores both contain a "for other reasons" category; selection of this category is taken into account during calculation of the scores. The response rate for the PedsQL^{TM} self-report was 96.74%, parent report 97.48% and the family report was 98.32%. The proportions of fully completed questionnaires were 94.38%, 92.24% and 94.02%, respectively.

Results

Participants

The mean age (SD) of participants was 9.40 (4.56) years (Table 1). Fifty-seven participants (47.9%) were female. Seventy percent of participants were White, 4.2% Asian or Asian British, 5.9% Black or Black British, 0.84% mixed, 7.56% other; ethnicity was unknown in 11.76%.

Clinical details

Fifty-two participants (43.7%) had PCG, most commonly diagnosed before the age of two years. Glaucoma following lensectomy for infantile cataract (n=32, 26.9%) was the commonest cause of secondary glaucoma (Table 1). Glaucoma was bilateral in 89 cases (74.79%), and the mean age (SD) at diagnosis was 1.56 years (2.94). Further clinical data are summarized in Table 1.

Functional visual ability

Seventy-nine children age 5-16 years completed the CVAQC. The median of the Rasch transformed scores was -1.24 (IQR -2.2 to -0.11) indicating moderate impairment of FVA (-3.00 higher visual ability to +2.80 lower visual ability) (Table 2). Median scores were better in older children than in the younger age groups (Fig. 2). There was evidence of an association between CVAQC score with age, BCVA and bilateral glaucoma (Table 3).

Vision-related quality of life

Thirty children age 8-16 years completed the IVI-C. The mean score was 67.3 (SD 14.4) with 96 indicating normal VR-QoL (Table 2). The mean score was higher in older than younger children (Fig 2). There was evidence of an association between IVI-C score with age and BCVA (Table 3). Bilateral glaucoma was not associated with worse VR-QoL, but the sample size for this analysis was small (unilateral glaucoma n=10 with bilateral glaucoma n=20).

Health-related quality of life

The PedsQL^{TM} self report was completed by 89 children, with a median score of 78.8 (IQR 67.4-90.2) with 100 indicating normal HR QoL (Table 2). Self-report scores were higher in the older age groups than the younger ones but there was variability and overlap in score distribution (Fig 2). There was an association between self-report scores and BCVA but no association with laterality (Table 3) nor the number of daily eye drops,

operations and anesthetics (*p* value > 0.05, data not presented). The PedsQL™ parent report (n=116) median score was 71.2 (IQR 55.7-85.8) and family impact report (n= 117) median score was 74.3 (IQR 56.9-87.5) (Table 2). Parental HR-QoL scores were lower than child self-report scores, with a mean difference of -7.901 (confidence interval CI -11 to -4.8) (Fig.3).

The median "psychosocial wellbeing" subscores were lower than the "physical wellbeing" scores. Parent report scores were lower than self-report scores, with a mean difference of -8.24 (CI -12.4 to -4.1) for physical and -8.21 (CI -11.35 to -5.1) for psychosocial subscores (Table 2).

Discussion

The main aim of this study was to explore the effects of childhood glaucoma (CG) on functional visual ability, vision related QoL and health related QoL, as perceived by children and their parents. A strength of our approach is that we included both children and parents, and used multiple instruments to address these questions.

Our study demonstrates that most children with glaucoma have to apply numerous eyedrops and have undergone several surgical procedures and additional general anesthetics. Children with glaucoma report a significant reduction in their VR-QoL and HR-QoL compared to normal-sighted individuals, and decreased functional visual ability. Psychosocial HR-QoL is affected to a greater degree than physical HR-QoL. Although our study was not powered to detect associations, older children reported less impairment than younger children and better BCVA was associated with higher functional visual ability, VR- and HR-QoL (even when unilateral cases which may have skewed BCVA to better visual acuity were excluded). Bilateral glaucoma was associated with worse functional visual ability only. With regards HR-QoL, there was no association between the number of eye drops, surgical interventions or general anesthetics and PedsQL™ self-report scores, however our sample size is likely to have limited our ability to find associations had they existed.

The reduction in HR-QoL in children with CG we report here is comparable to levels reported by children with severe congenital heart defects, liver transplants and acute lymphoblastic leukemia. [15 16 17] A previous study exploring HR-QoL in children with congenital cataract and their parents reported similarly reduced levels [18]. The reporting of children with glaucoma stratified by age results in the novel finding which suggests that perceived HR-QoL is higher in older children than in younger children. Possibly child and family adjust over time, and children develop a better understanding of their condition and a greater range of coping strategies to deal with their condition and visual disability.

We found that parents report a greater impact of glaucoma on their child's HR-QoL than children themselves. A similar observation has been made in parents of children with cataract and other conditions.[18,19] This may be explained by parents having different expectations, and children themselves having a different benchmark for "normality".

Our study design is prone to some bias. Firstly, enrolling children attending a single site may induce selection bias. We reduced this as far as possible by approaching consecutive patients eligible for inclusion, of which 19% of families declined to take part citing time constraints. Some families may have stopped attending clinics due to dissatisfaction with the services, or unwillingness or inability to comply with intense treatment regimes. However, from clinical experience consider the overwhelming majority of parents to be eager to provide the best possible healthcare for their child. We limited inclusion to families able to communicate in English, which may induce selection bias. Lack of a control group of normally sighted children stratified by age may be considered a limitation as it may have helped determine whether the effect of age on the CVAQC and IVI-C was due to a better understanding of the questionnaire by older children. Although this is possible, these tools were completed by children within the age range for which they were developed and validated. In addition, all tools we used have either been specifically developed for children with sight

impairment leading to an expected ceiling effect if used in healthy children (CVAQC), or normative data are available from healthy children (IVI-C, PedsQL™). Whilst logMAR visual acuity is a well established measure of visual function, it is not always possible to use logMAR methods in children with sight impairment, and "hand movements" or "counting fingers" at a specified testing distance are still occasionally used. Complete blindness, "no perception of light", or "artificial eye/ocular prosthesis" can also not be expressed in logMAR. In order to allow a quantitative analysis, we used logMAR values of 2.1 to 3 in these cases. [10] This may have led to an underestimation of logMAR acuity, however this was only necessary in 3 children.

Within the limits of the study design, such as selection bias which may have led to inclusion of a higher proportion of more treatment-adherent families and the limitation of enrolling participants at a single site in a highly developed country, our findings can be generalized to other children with glaucoma who receive care in similar settings. But, it is possible that our study over- or underestimates the impact of glaucoma on children and their families due to the number of participants studied. Whilst treatment for glaucoma in adults is mainly medical and often successful at preserving vision, childhood glaucoma requires intensive management and frequent surgical interventions with dramatic impact on the life of affected children and also their families. It is important to highlight this multifaceted impact, and encourage its assessment to be part of the management of childhood glaucoma. More research is needed into childhood glaucoma specific instruments to better identify and measure the effect of glaucoma and its management on the quality of life on both children and their families. Along with clinical outcomes such as IOP control and visual acuity, the quality-of-life of children with glaucoma should be considered as a crucial outcome when evaluating treatment success and when comparing established with new interventions.

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393 **Figure legends**

394 **Fig. 1.** Enrollment, intervention and analysis flowchart (modified from CONSORT, www.consort-statement.org).

395 **Fig. 2.** Box plots of median and interquartile range (IQR) Cardiff Visual Ability for Children (left), Impact of Vision
396 Impairment for Children (center) and PedsQL™ self-report scores (right) of children with glaucoma. Overall,
397 there is a trend towards self-reported less impairment with increasing age, however there is considerable
398 variation in scores within age groups.

399 **Fig. 3.** Bland Altman plot showing agreement between parental and child self-report PedsQL scores. The fact so
400 many of the points lie below the y = 0 line highlights the point that parents tend to rate the impact on HR- QoL
401 greater than the children themselves.

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Table legends

Table 1. Age at study participation and at diagnosis and clinical characteristics (top); detailed diagnostic categories of study participants and laterality of glaucoma (bottom).

Table 2. Scores for functional visual ability (FVA), vision- and health-related quality of life (VR-QoL, HR-QoL) reported by children and parents according to age and laterality. Possible CVAQC scores (FVA) extend from -3.00 (higher FVA) to +2.80 (lower FVA). IVI-C scores range from 0 to 96 (severe reduction to normal VR-QoL); participants reported markedly reduced VR-QoL. PedsQL™ scores range from 0 to 100 (severe reduction to normal HR-QoL); scores were significantly reduced in all versions and subscales of the instrument (parent report, family report, self report, physical and psychosocial subscores).

Table 3. Statistical significance and strengths of associations. Younger age is significantly associated with reduced functional visual ability (CVAQC) and vision-related quality of life (IVI-C). Lower visual acuity is significantly associated with all outcome measures. Bilateral glaucoma is significantly associated with lower functional visual ability (CVAQC) and parent-reported and family health-related quality of life (PedsQL™).

Supplementary Material:

Table "Response and Completion Rates". Parents were asked to complete two questionnaires, and children from the age of 5 years were asked to complete two or three questionnaires. Response and completion rates were high.