Title: Functional vision and quality of life in children with microphthalmia /anophthalmia /coloboma – a cross-sectional study

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Abstract

Purpose: This study aimed to determine the child's and parental perception of functional visual ability (FVA), vision- and health-related quality of life (VR-, HR-QoL in children with microphthalmia/anophthalmia/coloboma (MAC).

Methods: Between 25 June 2014 and 3 June 2015 we carried out a cross-sectional observational study at a single tertiary paediatric eye care center at XXX, enrolling 45 children age 2 to 16 years with MAC attending our clinics, and their parents. To assess FVA, VR- and HR-QoL we asked participants to complete three validated tools, the Cardiff Visual Ability Questionnaire for Children (CVAQC), the Impact of Vision Impairment for Children (IVI-C) instrument, and the PedsQL^{TM} V 4.0. The main outcome measures were the FVA, VR- and HR-QoL scores, reported by children and parents.

Results: In children with MAC, FVA is moderately reduced, with median CVAQC score -1.4 (IQR -2.4 to 0.4; range -3.0 = higher FVA to +2.8 = lower FVA). VR-QoL and HR-QoL are greatly reduced: IVI-C median score 63 (IQR 52 to 66; normal VR-QoL = 96), PedsQL^{TM} median: self-report score 77 (IQR 71 to 90; normal HR-QoL = 100), parental report score 79 (IQR 61 to 93), family impact score 81 (67 to 93). Psychosocial well-being scores are lower than physical well-being scores. Parents and children have a different perception of the impact of the condition on the child's HR-QoL.

Conclusions: Microphthalmia/anophthalmia/coloboma (MAC) have a significant impact on a child's FVA and QoL similar to that described by children with acute lymphoblastic leukaemia and chronic systemic conditions. Healthcare professionals need to be aware of the psychosocial impact, as children and families may benefit from psychosocial support.

Introduction

Microphthalmia/anophthalmia/coloboma (MAC) form a spectrum of rare congenital eye malformations. The estimated prevalence of anophthalmia is 0.6–4.2, microphthalmia 2–17 and coloboma 2–14 per 100,000 live births. [1] [2] In most children the condition is bilateral, and in around a third of children it is part of a syndrome associated with extra-ocular abnormalities such as brain, craniofacial, cardiac, renal and urogenital defects. [1] [2] [3]

The extent of the malformation determines the visual acuity in children with MAC. Vision is often poor, and children with bilateral MAC often have severe sight impairment and require developmental support. [4] It is estimated that MAC is responsible for approximately 15 to 20% of severe visual impairment and blindness in children worldwide.[5] There is scarce published literature on the clinical management of MAC. The growth of the orbital cavity and the development of the maxilla can be significantly affected in the absence of a normal sized globe. Therefore, in infants, orbital conjunctival conformers of progressively increasing size are applied to expand the orbital tissues; fitting and exchanging expanders may require multiple anesthetics. Cases of marked orbital asymmetry may require orbital reconstruction surgery to reduce cosmetic disfigurement.

Despite the burden of MAC and its management on children and their families, no study has explored functional visual ability (FVA), vision- and health-related quality of life (VR-, HR-QoL) in this population. Two studies of adults with MAC reported low HR-QoL, increased anxiety and psychosocial impact from feelings of shame, shyness, sadness and fear. [6] [7]

Validated tools to measure FVA, VR- and HR-QoL in children include the Cardiff Visual Ability Questionnaire for Children for FVA, [8] Impact of Vision Impairment for Children (IVI-C) instrument for VR-QoL, [9] and PedsQL™ V 4.0 for HR-QoL.[10] [11] The aim of the present study is to describe the impact of MAC on FVA, VR- and HR-QoL from a child's perspective. Parental views on the impact of MAC on their child's and family's HR-QoL are also assessed.

Material and Methods

This work presents an analysis of children with MAC who took part in a larger cross-sectional observational study of quality of life in children with developmental eye defects, approved prospectively 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 3 June 2015 we enrolled children age 2-16 years at XXX. Exclusion criteria were inability to communicate in English and surgical intervention within one month of date of completing questionnaires (before or after). We screened the notes of all children attending clinics in advance to identify those who met the inclusion criteria. We consecutively approached these children and families. For those who did not wish to take part, we noted the reasons given. We gave parents and children age-appropriate information material and addressed any questions. Parents gave written consent, and children could sign an assent form.

Data collected

We recorded age at study participation, gender and ethnic background, ocular and systemic diagnoses, laterality and best corrected visual acuity (BCVA) with both eyes open in logMAR on

the day of study participation. Where BCVA was recorded as “counting fingers” we assigned a value of 2.1 logMAR, for “hand movements”, 2.4 logMAR, for “light perception” 2.7 logMAR, and for “no light perception” or “ocular prosthesis/artificial eye”, 3 logMAR. [12] We also recorded details of previous and current treatment, such as number of previous surgical interventions, and number of general anesthetics.

Main outcome measures

To assess FVA, children from the age of 5 years completed the CVAQC. [8] The CVAQC was developed with focus groups of children with and without sight impairment and validated in children with visual impairment to assess difficulties in performing activities of daily life. The CVAQC is designed for completion by the child, and was validated in children with visual impairment. It consists of 25 questions with answers selected on a four-point scale which cover education, near and distance vision, getting around, social interaction, leisure and sports. Using a Rasch conversion calculator provided, we transformed the raw scores into logarithmic scores. The resulting scores range from -3.0 (higher FVA) to +2.8 (lower FVA).

To evaluate 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 IVI-C tool. [9] The IVI-C 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”, covering areas of school, mobility, interaction and emotion. We scored the IVI-C responses using the relevant scoring sheet which allocates values between 0 and 4, and 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.

For HR-QoL, we used age-specific versions of the PedsQL™ Inventory (www.pedsql.org), which allow children aged over 5 years of age to express their views on different aspects of their physical and emotional state and their social and school life. [10] [11] Furthermore, parents completed two questionnaires, one regarding their child ("parental report") and one about the impact on the condition on the family ("family report"). The parental report was specific to the age of the child and consisted of 21-23 questions covering children aged 2-4, 5-7, 8-12 and 13-18 years. The family report contained 36 questions. Children from the age of 5 self-administered the questionnaire (PedsQL™ administration guidelines) and answers were given on a Likert scale from 0 to 4. We calculated the PedsQL™ scores following 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. Scores range from 0 to 100, with 100 indicating normal HR-QoL.

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

Statistics

We aimed for an overall sample size of 50, the smallest sample size required for Bland Altman limits of agreement analysis. Where data were missing for individual items in the PedsQL™ and

IVI-C, we adjusted the denominator accordingly. For the CVAQC, the Rasch-analysis based calculator takes into account missing data.

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, BCVA in better eye, sum of surgical interventions, sum of general anesthetics and CVAQC, IVI-C and Peds QL^{TM} scores using Spearman rank correlation, and relationships with uni/bilaterality using the Mann Whitney test. Agreement between parent and child PedsQL^{TM} scores was assessed using Bland-Altman techniques. Statistical significance was set at the 5% level and all tests conducted were two-tailed. We did not adjust for multiple comparison testing in our exploratory investigations of associations, but would urge readers to review these as hypothesis generating rather than confirmatory. [13]

We approached 62 families of children with MAC who met the inclusion criteria. Sixteen declined to take part because of perceived lack of time. We enrolled 46 children, and removed one dataset as the child did not have MAC, resulting in the analysis of 45 datasets.

The proportion of missing data was low. No data were missing for age, gender, diagnoses, laterality and BCVA. Ethnicity was unknown in 13.3%. Questionnaire response rates were high (Supplementary Material 1).

Results

The median (interquartile range, IQR) age of participants was 6.4 (3.7 to 9.9) years (Table 1). 27 participants (60%) were female. 73% of participant were White, 4% Asian or Asian British, 2% Black or Black British, 2% mixed, 4% other, ethnicity was unknown in 13%.

Microphthalmia was isolated in 23 children (51%), associated with coloboma in ten (22%) and with cataract in nine (20%). Two children developed glaucoma, one following lensectomy. Three children (7%) had anophthalmia. The condition was bilateral in 20 cases (44%). Table 1 summarizes clinical and participant characteristics.

Eighteen children aged 5-16 years completed the CVAQC. The median of the Rasch transformed scores indicated moderate impairment of FVA (Table 2). There was no evidence of an association between CVAQC score and age or any other clinical factors such as BCVA or bilaterality of the condition (Table 2, Fig. 1).

Eleven children and young people age 8-16 years completed the IVI-C tool. The median score indicated markedly reduced VR-QoL (Table 2). There was no evidence of an association between IVI-C and age or any other clinical factors such as BCVA or bilaterality of the condition (Table 2, Fig. 1).

24 children completed the PedsQL^{TM} self-report and were found to have a median score significantly lower than healthy children (Table 2). There was evidence of an association between self-report scores and the total number of surgical socket interventions (Spearman's rho correlation coefficient SRCC -0.43, p=0.04, n=23; Suppl. Material 2) but no evidence of an

association with age (Fig. 1) or clinical factors (Suppl. Material 2). Self-reported scores for psychosocial well-being were lower than those for physical well-being (Table 2); the mean difference was -7 (CI -14 to -0.4).

The median PedsQL^{TM} parental report score about the child was also reduced. There was an association between parental report scores and number of previous operations (SRCC -0.45, p=0.002, n=43) and anesthetics (SRCC -0.34, p=0.02, n=43) (Suppl. Material 2).

The PedsQL^{TM} family report (n=45) median score was also reduced and with the same associations as the parental report, namely previous operations (SRCC -0.416, p=0.005, n=44) and anesthetics (SRCC -0.35, p=0.02, n=44) (Suppl. Material 2).

Overall PedsQL^{TM} parent report scores were higher than self-report scores (Table 2), with a mean difference of -4 (CI -9 to 1) (Fig. 1). The mean difference between parental and self-scores on the PedsQL^{TM} physical subscale was -4 (CI 11 to 2, and on the psychosocial subscale, -4 (CI -10 to 2).

Discussion

This is the first report of FVA, VR- and HR-QoL in children with MAC. Previous studies reported increased anxiety and feelings of shame, shyness, sadness and fear in adults with MAC but these studies included also non developmental MAC such as post-traumatic or post-infectious forms of anophthalmia. [6] [7] The reduction in HR-QoL in children with MAC we report here is similar to levels reported by children with acute lymphoblastic leukaemia and

chronic diseases. [14] [15] In addition, VR-QoL is profoundly reduced, whilst FVA is moderately reduced. A greater number of surgical interventions is associated with worse HR-QoL scores reported by both children and parents. No other associations were found, however, our sample size may have limited our ability to find associations had they existed. In contrast to previous findings [16] [17] we found parents reported MAC to have less of an impact on their child's HR-QoL than young children themselves. Parents may be underestimating the impact of facial disfigurement and placing more emphasis on visual impairment in a group where most cases were unilateral.

A strength of our study is that children completed the questionnaires by themselves, or were supported by play specialists eliminating parental perceptions influencing the children's answers.

Our study has some limitations. MAC are rare conditions, and although we enrolled participants over one year, only 62 families could be approached, a quarter of which declined to take part. Selection bias may arise from families stopping attending clinics as their child gets older. We have no data to estimate this proportion of these families, but consider the overwhelming majority of parents eager to provide the best healthcare for their child. However, our teenage group only included three young people. Selection bias may also have arisen from limiting enrollment to a single site, and to English-speaking families only. Lack of a control group of normal-sighted children may be considered a limitation, however, the questionnaires we used were specifically developed for the age range of children we included. In addition, CVAQC was developed for children with visual impairment, leading to an expected ceiling effect if used in

252 normal sighted children. For both IVI-C and PedsQL^{TM} a normative database of healthy children
253 is available.
254
255 Furthermore, the use of number of surgical procedures as a proxy of painful treatment episodes
256 may be less valid than using validated pain scales, but has been used in similar studies before. [15]
257 Similarly, the number of general anesthetics (including EUAs, as these are often arranged on the
258 understanding that should findings indicate a need for additional surgery, this will be carried out
259 under the same anesthetic) as a proxy for episodes of emotional upset and anxiety is not as valid
260 as using a validated scale measuring anxiety, but has previously been used by others. [18]
261
262 Whilst logMAR visual acuity is a well-established measure of visual function, it is not always
263 possible to use logMAR methods in children with visual impairment, and "hand movements" or
264 "counting fingers" at a specified testing distance are occasionally used. Complete blindness, "no
265 perception of light", or "artificial eye/ocular prosthesis" can also not be expressed in logMAR. In
266 order to allow a quantitative analysis, we followed a published approach of using logMAR
267 values of 2.1 to 3 in these cases. [12] This conversion was required in 8 cases (17.8%, 7 cases of
268 NPL, one of PL) and may have led to an underestimation of logMAR acuity.
269
270 Within the limits of the study design, that is selection bias which may have led to inclusion of a
271 higher proportion of more treatment-adherent families and the limitation of enrolling participants
272 at a single site in a highly developed country, our findings can be generalized to other children
273 with MAC who receive care in similar settings.
274

Conclusions

MAC have a profound impact on the life of affected children and their families. Healthcare professionals need to be aware of these emotional and practical difficulties. Children and families may benefit from support to address psychosocial problems and difficulties with children's activities of daily living.

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References

[1] Skalicky SE, White AJ, Grigg JR, Martin F, Smith J, Jones M, et al. Microphthalmia, anophthalmia, and coloboma and associated ocular and systemic features: understanding the spectrum. JAMA Ophthalmol 2013;131:1517-24.

[2] Williamson KA, FitzPatrick DR. The genetic architecture of microphthalmia, anophthalmia and coloboma. Eur J Med Genet 2014;57:369-80.

[3] Roos L, Jensen H, Gronskov K, Holst R, Tumer Z. Congenital Microphthalmia, Anophthalmia and Coloboma among Live Births in Denmark. Ophthalmic Epidemiol 2016;23:324-30.

[4] Bardakjian T, Weiss A, Schneider A. Microphthalmia/Anophthalmia/Coloboma Spectrum. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al., editors. GeneReviews(R). Seattle (WA)2015.

[5] Shah SP, Taylor AE, Sowden JC, Ragge NK, Russell-Eggitt I, Rahi JS, et al. Anophthalmos, microphthalmos, and typical coloboma in the United Kingdom: a prospective study of incidence and risk. Investigative ophthalmology & visual science 2011;52:558-64.

[6] Ahn JM, Lee SY, Yoon JS. Health-related quality of life and emotional status of anophthalmic patients in Korea. Am J Ophthalmol 2010;149:1005-11 e1.

[7] Goiato M, dos Santos D, Bannwart L, Moreno A, Pesqueira A, Haddad M, et al. Psychosocial impact on anophthalmic patients wearing ocular prosthesis. Int J Oral Maxillofac Surg 2013;42:113-9.

[8] Khadka J, Ryan B, Margrain TH, Court H, Woodhouse JM. Development of the 25-item Cardiff Visual Ability Questionnaire for Children (CVAQC). Br J Ophthalmol 2010;94:730-5.

[9] Cochrane GM, Marella M, Keeffe JE, Lamoureux EL. The Impact of Vision Impairment for Children (IVI_C): validation of a vision-specific pediatric quality-of-life questionnaire using Rasch analysis. Investigative ophthalmology & visual science 2011;52:1632-40.

[10] Varni JW, Seid M, Knight TS, Uzark K, Szer IS. The PedsQL 4.0 Generic Core Scales: sensitivity, responsiveness, and impact on clinical decision-making. J Behav Med 2002;25:175-93.

[11] Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care 2001;39:800-12.

[12] Day AC, Donachie PH, Sparrow JM, Johnston RL, Royal College of Ophthalmologists' National Ophthalmology D. The Royal College of Ophthalmologists' National Ophthalmology Database study of cataract surgery: report 1, visual outcomes and complications. Eye (Lond) 2015;29:552-60.

[13] Cipriani V, Quartilho A, Bunce C, Freemantle N, Dore CJ, Ophthalmic Statistics G. Ophthalmic statistics note 7: multiple hypothesis testing-to adjust or not to adjust. Br J Ophthalmol 2015;99:1155-7.

[14] Limbers CA, Neighbors K, Martz K, Bucuvalas JC, Webb T, Varni JW, et al. Health-related quality of life in pediatric liver transplant recipients compared with other chronic disease groups. Pediatr Transplant 2011;15:245-53.

[15] Bansal M, Sharma KK, Vatsa M, Bakhshi S. Comparison of health-related quality of life of children during maintenance therapy with acute lymphoblastic leukemia versus siblings and healthy children in India. Leuk Lymphoma 2013;54:1036-41.
[16] Chak M, Rahi J. British Congenital Cataract Interest Group. The health-related quality of life of children with congenital cataract: findings of the British Congenital Cataract Study. Br J Ophthalmol 2007;91:922-6.
[17] Upton P, Lawford J, Eiser C. Parent-child agreement across child health-related quality of life instruments: a review of the literature. Qual Life Res 2008;17:895-913.
[18] Freedman B, Jones S, Lin A, Stinnett S, Muir K. Vision-Related quality of life in children with glaucoma. J AAPOS 2014;18:95-8.

Figure legends

Fig. 1 Box plots of median and interquartile range (IQR) for Cardiff Visual Ability Questionnaire for Children (top left), Impact of Vision Impairment for Children (top right) and PedsQL^{TM} self-report scores (bottom left) of children with MAC. Bottom right: Bland Altman plot showing agreement between parental and child self-report PedsQL^{TM} total scores.

Table legends

Table 1. Age at study participation and at diagnosis and clinical characteristics.

Table 2. Scores for functional visual ability (FVA), vision- and health-related quality of life (VR-QoL, HR-QoL) reported by children according to age and parents. Possible CVAQC scores (FVA) range from -3.00 (higher FVA) to +2.80 (lower FVA). IVI-C scores range from 0 to 96 (severe reduction to normal VR-QoL). PedsQL^{TM} scores range from 0 to 100 (severe reduction to normal HR-QoL). Children reported markedly reduced FVA and VR-QoL. All HR-QoL scores were significantly reduced as reported by both children and parents (self-, parental, family report) and psychosocial more than physical scores.

Supplementary Material:

1) Table "Response 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 rates were high.

2) Statistical significance and strengths of associations. In bold those associations that reach significance with $p<0.05$.