Visual function and quality of life in children and adolescents with anophthalmia and microphthalmia treated with ocular prosthesis

Beatrice Casslén,1 Ylva Jugård,2 Rezhna Taha Najim,1 Marie Odersjö,3 Alexandra Topa4,5 and Marita Andersson Grönlund1,6

1Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
2Department of Ophthalmology, Södra Älvsborg Hospital, Region Västra Götaland, Borås, Sweden
3Department of Otolaryngology, Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden
4Department of Clinical Genetics and Genomics, Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden
5Department of Laboratory Medicine, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
6Department of Ophthalmology, Sahlgrenska University Hospital, Region Västra Götaland, Mölndal, Sweden

ABSTRACT.

Purpose: To evaluate health-related quality of life (HR-QoL), vision-related (VR-)QoL and perceptual visual dysfunction (PVD) among individuals with anophthalmia (A) and microphthalmia (M) treated with ocular prosthesis.

Methods: The study comprised 15 individuals (mean age 6.6 years; range 1.7–14.1) with unilateral A or M. Three validated instruments measuring HR-QoL and VR-QoL were used: The Pediatric QoL Inventory (PedsQL), consisting of physical and psychosocial self-report and parent-proxy report (2–18 years); Children’s Visual Function Questionnaire (CVFQ); and Effects of Youngsters’ Eyesight on Quality of Life (EYE-Q). Perceptual visual dysfunctions (PVDs) were assessed by history taking according to a specific protocol.

Results: A/M children and their parents showed low HR-QoL scores (PedsQL total score: 66.3; 69.6) compared with controls (83.0; 87.61) (p = 0.0035 and <0.0001, respectively, unpaired t-test). No differences were found between A/M children and parents, but parents tended to underestimate their children’s emotional state. A/M children with subnormal visual acuity (VA) for age scored lower in physical health compared with A/M children with normal VA (p = 0.03, Mann–Whitney U-test). No significant VR-QoL differences between A/M children and references or between A/M children with subnormal or normal VA for age were found. More A/M children than controls exhibited PVDs in ≥1 area (7/11 versus 4/118; p < 0.0001, Fisher’s exact test).

Conclusion: A/M individuals show poor HR-QoL and increased PVDs. No difference in QoL was found between children and parents, though the children tended to score lower in emotional well-being. A/M children with subnormal VA showed lower physical health score. These problems indicate the necessity of a thorough multidisciplinary assessment and follow-up of children with A/M.

Key words: anophthalmia – microphthalmia – patient-reported outcome measures – quality of life – visual perceptual dysfunction

Introduction

Anophthalmia (A) and microphthalmia (M) are severe congenital ocular defects equivalent to a total absence or a smaller-than-normal size of the ocular globe. These rare malformations may have variable effects on vision, and often result in significant disability (Shah et al. 2011). In England in 2011, the incidences of A and M per 100 000 infants were estimated at 0.4 and 10.0, respectively (Dharmasena et al. 2017). A/M is often associated with other defects, both ocular and general. When M is associated with additional ocular features in the affected eye, it is termed complex microphthalmia (Verma & Fitzpatrick 2007; Bardakjian et al. 2010; Plaisancié et al. 2019). Changes in the M eye or fellow eye in children with A/M include ocular developmental disorders such as coloboma, retinal
dysplasia and optic nerve abnormalities (Schittkowski & Guthoff 2010; Plaisancié et al. 2019). Both A and M may also occur as syndromic conditions with additional malformations affecting the face and other organ systems (Morrison et al. 2002; Verma & Fitzpatrick 2007; Schittkowski & Guthoff 2010; Chambers et al. 2018). Growth deficiency and extraocular defects involving, for example, heart, kidneys, brain, oesophagus and hearing have been reported in 33–95% of individuals with A/M (Forrester & Merz 2006; Slavotinek 2011; Shah et al. 2012).

Learning difficulties are found in one-fifth of cases (Morrison et al. 2002; Rainiger et al. 2014). The complex aetiology of A/M involves several genes and chromosome aberrations, but in many cases, a precise cause is difficult to establish. Various genes important for eye development, including SOX2, OTX2, STRA6, GDF6, RAX, PAX6, BCO1, HCCS, BMP4, SHH, CHX10, SIX6, FOXE3 and SMOC1, have been shown to be associated with these congenital malformations (Verma & Fitzpatrick 2007; Bardakjian et al. 2010; Slavotinek 2019). Although mutations in known causative genes currently explain less than 40% of cases (Bardakjian et al. 2010; Bardakjian & Schneider 2011; Slavotinek 2011), the majority of A/M cases occur sporadically, with a wide variation in phenotypic outcomes due to variable expressivity and incomplete penetrance that complicates the interpretation of the inheritance pattern and the possibility of predicting the long-term outcome (Morrison et al. 2002; Verma & Fitzpatrick 2007; Schneider et al. 2009). Recent progress, particularly in DNA sequencing, provides a greater diagnostic capability for genetic counselling in A/M patients. This will help early identification of patients in need of additional care and subsequent provision of appropriate treatment and genetic counselling (Williamson & FitzPatrick 2014; Chassaing et al. 2014; Searle et al. 2018).

Because of the wide phenotypic spectrum associated with A/M, the assistance of a multidisciplinary team is vital and will contribute to improving the patients’ quality of life (QoL). Intervention with prostheses not only serves a cosmetic purpose, but also stimulates orbital growth and hence may prevent facial asymmetry. In recent years, studies have suggested a relationship between visual disabilities in general and impaired QoL in children due to limitation of their independence and of many daily life activities (Chak et al. 2007; Angeles-Han et al. 2010; Dahlmann-Noor et al. 2017). However, a lack of vision-specific patient-reported outcome measures (PROMs) means that the impact of A/M on QoL is poorly understood. Although several studies have dealt with QoL in children and adolescents with anophthalmia, to our knowledge there is only one previous study regarding QoL in children with microphthalmia (Dahlmann-Noor et al. 2018). The aim of our study was to further evaluate health-related (HR-)QoL and vision-related (VR-)QoL in relation to visual function and perceptual visual dysfunctions (PVDs) among A/M children and adolescents treated with ocular prostheses.

Methods

Study population

Of the 59 children and adolescents treated with ocular prostheses at Department of Otolaryngology, Sahlgrenska University Hospital in Gothenburg, Sweden, by the same certified dental technician (CDT)/anaplastologist (MO) during 2000–2012, 22 children under the age of 18 years were diagnosed with A/M and they were all invited to participate in the study. Four cases declined participation, two did not respond to the invitation, and one family chose to only participate with the retrospective medical record part of the study. Thus, the participants in this prospective cross-sectional observational study were 15 children and adolescents (eight boys and seven girls) with a mean age of 6.6 years (range 1.7–14.1 years), diagnosed with unilateral A (n = 3) or M (n = 12) and treated with ocular prostheses.

Methods

The children and the adolescents (in appropriate age for each questionnaire) and their parents individually completed three validated instruments measuring health-related quality of life (HR-QoL) and vision-related quality of life (VR-QoL): The Pediatric Quality of Life Inventory (PedsQL); the Children’s Visual Function Questionnaire (CVFQ); and the Effects of Youngsters’ Eyesight on QoL (EYE-Q). Visual acuity (VA) was measured, and PVDs were assessed by history taking according to a specific protocol. The A/M individuals underwent an extensive ophthalmological examination including ultrasound of the orbit and genetic assessment, which will be presented in detail elsewhere.

Health-related quality of life

The Pediatric Quality of Life Inventory

The PedsQL questionnaire measures HR-QoL in children from 2 years of age and consists of 23 items regarding physical and psychosocial (emotional, social and school) functioning. It includes both a self-report for individuals aged 5 years and over and a parent-proxy report for those aged 2–18 years. A 5-point scale is utilized, from 0 (never having a problem) to 4 (almost always a problem). Raw scores range from 0 to 4 and are then reversed and linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25 and 4 = 0) so that a higher score indicates a better QoL (Varni et al. 2001). Psychosocial health, physical health and total summary score are computed as the sum of the items divided by the number of items answered. In the self-report section, for children aged 5–7 years the Likert scale is reworded and simplified to a 3-point scale with each response anchored to a happy-to-sad face scale (Varni et al. 2001; Varni et al. 2002; Petersen et al. 2009). Our results were compared with previously published scores for healthy controls for both children (n = 401) and parents (n = 717) (Varni et al. 2002).

Vision-related quality of life

Children’s Visual Function Questionnaire

The CVFQ was designed for use with parents of young children (≤7 years) and evaluates the impact of visual impairment on children and their families (Felius et al. 2004). In children <3 years, an age-specific 34-item version was used, which excluded questions irrelevant to this age group, while in children ≥3 years, a 39-item questionnaire was used. The CVFQ contains six QoL-related domains: general health, general vision, competence, personality, family impact and general well-being.
treatment difficulties. Parents respond on a 5-point Likert-type scale with the additional answer option of ‘not applicable to my child’. Each response correlates with a score between 1 (‘best’) and 0 (‘worst’) (Birch et al. 2007). We compared our A/M children with a previously published reference group (n = 33) with no underlying eye disease (Petersen et al. 2009).

**Effects of Youngsters’ Eyesight on Quality of Life**

The EYE-Q, which was used to complement the ophthalmic examinations, is a vision-specific instrument that consists of 13 self-reported items for individuals aged 8–18 years. For 12 of these items, the questionnaire assesses difficulty performing tasks using a 5-point Likert scale with the following response formats: 1 (not hard/never), 2 (a little hard/rarely), 3 (hard/sometimes), 4 (very hard/often) and 5 (cannot do). The items were rescaled, with scores ranging from 0 to 4 and higher scores indicating better QoL. The 13th item deals with other things that are difficult to do in relation to the child’s vision and uses a yes or no alternative. Patients answering ‘yes’ are then asked to describe their problems (Angeles-Han et al. 2010; Angeles-Han et al. 2011; Angeles-Han et al. 2015).

**Visual acuity**

Visual acuity was measured using different methods appropriate for the age and capability of each child, specifically the Kays, Cardiff, Lea, HVOT and KM charts (Hedin et al. 1980; Hyvärinen et al. 1980; Kay 1983; Hedin & Olsson 1984; Adoh & Woodhouse 1994; Moutakis et al. 2004). Values of VA were noted in decimal format and then transformed to logarithm of the minimum angle of resolution (logMAR). Since these methods are not always applicable in visual impaired individuals, we used ‘fix and follow’, ‘hand movements’ and ‘counting fingers’ for some participants. Visual acuity (VA) in the non-A/M eye was used in the analysis to categorize the best corrected visual acuity (BCVA).

**Perceptual visual dysfunction**

Perceptual visual dysfunctions (PVDs), also known as visual perceptual problems, were assessed with a structured history taking according to age and VA, using a questionnaire consisting of twelve questions concerning cognitive visual problems in five areas: recognition, orientation, depth perception, movement perception and simultaneous perception (Grönlund et al. 2006; Raffa 2016). An age- and sex-matched control group was used, consisting of 118 healthy individuals (mean age 9.5; range 4.0–18.1 years).

**Statistical analyses**

Means, standard deviations (SD), medians and ranges were calculated for descriptive purposes. For comparison between two groups, the unpaired t-test and the Mann–Whitney U-test were used for ordered and continuous variables, and Fisher’s exact test was used for dichotomous variables. The Wilcoxon signed-rank test was used to compare the difference between parent and child/adolescent reports. All correlations were analysed using Spearman’s rank correlation coefficients, and test results were considered significant if p < 0.05. The controls for VA and PVDs were selected and matched regarding age and sex from a group of healthy Swedish children aged 4–15 years (Grönlund et al. 2006) and another control group aged 13–18 years using a population matching method (Pocock & Simon 1975). Controls were chosen using the minimum of the maximum t-test score of this group against the A/M group concerning age and sex.

**Ethical approval**

The study was approved by the Research Ethics Board at the University of Gothenburg, Sweden. All participants signed an informed consent, and all procedures were performed according to the Declaration of Helsinki.

**Results**

The 15 individuals with A/M treated with ocular prosthesis are described in Table 1 in terms of features such as sex, age, A/M, isolated or syndromic condition, VA, abnormal ocular findings in the fellow eye/ the A/M eye, VR-QoL and HR-QoL.

**Health-related quality of life**

The results of the PedQL questionnaires (total score, physical health and psychosocial health) reported by seven A/M children/adolescents and 15 parents compared with healthy controls (Varni et al. 2001) are summarized in Table 2. Seven individuals in the study group had both self- and parent-proxy report completed. There was no difference in total, psychosocial or physical QoL when comparing those seven adolescents’ self-reports with their parents’ proxy report (Table S1). Self-reports from children with A/M (divided into normal and subnormal VA for age) and parent-proxy reports divided according to their child’s VA are shown in Table 3.

**Vision-related quality of life**

Children’s Visual Function Questionnaire All parents (n = 10) of the A/M children aged 0–7 years filled in the CVFQ questionnaire and they subscored as follows: general health (0.88), general vision (0.52), competence (0.88), personality (0.87), family impact (0.69) and treatment (0.79). When comparing the result of the mean total score (0.77; SD 0.19) with those of parents of healthy children (0.85; SD 0.12) (Felius et al. 2004), it was slightly lower, however, not statistically significant. Table 3 presents the CVFQ total and general vision score, divided into children with normal or subnormal VA according to age.

**Effects of Youngsters’ Eyesight on Quality of Life**

Five A/M children (age 8–18 years) completed the EYE-Q questionnaire. Mean (SD) outcome scores were 3.15 (1.06) in the total group, 3.67 (0.53) among children with normal VA (n = 3), and 2.38 (1.18) among children with subnormal VA (n = 2). Four A/M children reported difficulties when answering the 13th item of the EYE-Q: the first child reported reading issues; the second reported difficulties in biking, being out in the dark alone, recognizing people and recognizing things; the third reported difficulties with reading, participating in ball games and other games, and impaired colour vision; and the fourth child reported difficulties with walking in the forest and running.
Perceptual visual dysfunction

Perceptual visual dysfunctions (PVDs) were reported in 11 of the A/M children. Four A/M children were excluded due to young age (1.1–2.1 years). Seven of these 11 children and adolescents exhibited PVDs in one or more areas (median 2; range 1–4), compared with 4 of the 118 age- and sex-matched healthy controls (p < 0.0001, CI 33.3–85.6). The most frequently reported area of PVDs among A/M children was depth perception (n = 5), followed by simultaneous perception (n = 3), movement perception (n = 3), recognition (n = 1) and orientation (n = 1). Figure 1A presents results in the study group divided according to normal versus subnormal VA for age. In A/M children with normal VA (n = 7), five reported PVDs in one or more area, whereas in A/M children with subnormal sight (n = 4), two reported PVDs in one or more area. Perceptual visual dysfunction (PVD) in A/M children with isolated (non-syndromic) and syndromic condition is displayed in Fig. 1B.

Discussion

Our results show that children and adolescents with A/M have worse self-reported and parent-reported HR-QoL and more PVDs than healthy individuals. Moreover, A/M individuals with a subnormal VA had lower scores in physical health than A/M children with normal VA.

In this study, both self-reported and parent-reported HR-QoL were significantly lower among A/M children in all PedsQL categories compared to healthy individuals with no underlying eye disease. These findings are comparable with results reported by children with severe systemic diseases such as congenital heart defects, children who have undergone liver transplants and those who have survived childhood lymphoblastic leukaemia and CNS tumours (Eiser et al. 2003; Limbers et al. 2011; Knowles et al. 2014). Additionally, several studies examining self-assessed and parent-assessed HR-QoL in children with different ophthalmological diagnosis such as congenital cataract, glaucoma and microphthalmia, anophthalmia and coloboma (MAC) reported similarly reduced levels (Chak et al. 2007; Castaneda et al. 2016; Dahlmann-Noor et al. 2017; Tailor et al. 2017; Dahlmann-Noor et al. 2018). In the present study,

Table 1. Demographic and clinical data, and the vision-related (VR) and health-related (HR) quality of life (QoL) scores of the 15 study individuals with A/M.

| Patient (age group) | No./sex/age | A/M/RE/LE | VA of distance (logMAR) | Bin VA at near (logMAR) | Abnormal ocular findings in fellow eye | PedsQL total score | Self-report/parent-proxy report score (0–7 years) | CVFQ total score (0–7 years) | EYE-Q total score (8–18 years) |
|---------------------|-------------|-----------|-------------------------|-------------------------|--------------------------------------|---------------------|-------------------------------------------------|-----------------------------|---------------------------------|
| Age ≤ 4 years       | #1/m/1.7    | I M/RE    | NA/0.25 (0.6)           | NA                      | Nystagmus                            | NA/63.0             | 0.55                                            | NA                          | NA                              |
|                     | #2/m/1.7    | S A/RE    | NA/fix and follow†      | NA                      | Ptosis                               | NA/63.0             | 0.72                                            | NA                          | NA                              |
|                     | #3/f/1.7    | I M/LE    | 0.63 (0.2)/NA           | NA                      | Shallow anterior chamber             | NA/76.1             | 0.89                                            | NA                          | NA                              |
| Age 5–7 years       | #4/f/2.8    | S A/LE    | 0.8 (0.1)/NA            | NA                      | None                                 | NA/71.7             | 0.70                                            | NA                          | NA                              |
|                     | #6/f/2.8    | S M/RE    | 0.63 (0.2)/NA           | 0.4 (0.4)               | None                                 | NA/62.0             | 0.82                                            | NA                          | NA                              |
|                     | #5/f/4.6    | I M/RE    | NA/0.8 (0.1)            | 0.2 (0.70)              | None                                 | NA/95.2             | 0.82                                            | NA                          | NA                              |
|                     | #7/m/4.7    | I M/RE    | NA/0.8 (0.1)            | 0.5 (0.30)              | None                                 | NA/75               | 0.74                                            | NA                          | NA                              |
| Age 8–12 years      | #8/m/6.1    | I M/LE    | 0.5 (0.30)              | NA                      | Nystagmus                            | 89.2/85.9           | 0.85                                            | NA                          | NA                              |
|                     | #9/m/6.1    | I M/RE    | NA/0.25 (0.6)†          | 0.3 (0.50)              | Myopia                               | 30.5/3.3            | 0.76                                            | NA                          | NA                              |
|                     | #10/f/7.7   | I M/LE    | 1.0 (0.0)/NA            | 0.9 (0.05)              | None                                 | 92.9/97.5*          | 0.89                                            | NA                          | NA                              |
| Age 13–18 years     | #11/f/9.6   | I M/RE    | NA/1.0 (0.0)            | 0.65 (0.20)             | None                                 | 79.8/70.4           | NA/41                                           | NA                          | NA                              |
|                     | #12/m/10.1  | S M/RE    | NA/0.1 (1.0)†           | 0.1 (1.0)               | Iris and postsegment coloboma, including optic disc, nystagmus | 0/62.0              | NA/21                                           | NA                          | NA                              |
|                     | #13/m/10.6  | S M/RE    | NA/1.25 (0.1)           | —                      | —                                    | 70.6/63.0           | 0.43                                            | NA                          | NA                              |
|                     | #14/m/12.1  | S A/RE    | NA/1.0 (0.0)            | 1.0 (0.0)               | None                                 | 50.0/47.8           | 0.48                                            | NA                          | NA                              |
|                     | #15/m/14.1  | S M/RE    | NA/0.1 (1.0)†           | 0.1 (1.0)               | Iris and postsegment coloboma, nystagmus | 52.2/57.5           | NA/36                                           | NA                          | NA                              |

— = no information available, A = anophthalmia, CVFQ = Children’s Visual Function Questionnaire, EYE-Q = Effects of Youngsters’ Eyesight on Quality of Life, f = female, ft = feet, I = isolated M/A (non-syndromic), LE = left eye, logMAR = logarithm of the minimum angle of resolution, m = male, M = microphthalmia, NA = not applicable, PedsQL = Pediatric Quality Of Life Inventory, RE = right eye, S = syndromic, VA = visual acuity.

† Considered to have subnormal VA for age. VA was measured using Kays, Cardiff, Lea, HVOT and KM chart methods. Since these methods are not always applicable in visually impaired individuals, we used ‘fix and follow’, ‘hand movements’ and ‘counting fingers’ for some participants.

Visual acuity

Five children were considered having a subnormal VA for age and the remaining ten individuals to have a normal VA (Table 1). VA did not correlate with either PedsQL total score or CVFQ (total and general vision scores).
psychosocial PedsQL subscores appeared more affected than physical subscores in both self-report and parent proxy. These findings are similar to those of previous studies among children with cataract, glaucoma and MAC (Chak et al. 2007; Castañeda et al. 2016; Dahlmann-Noor et al. 2017; Tailor et al. 2017; Dahlmann-Noor et al. 2018). We also found that A/M children reported a greater impact on HR-QoL in all categories compared with parent proxy, although the differences were not significant. Hence, it is possible that children with A/M experience a greater impact of A/M on HR-QoL than perceived by their parents. These findings are similar to those of a study among children with MAC (Dahlmann-Noor et al. 2018). In contrast, several previous reports have described that parents of children with glaucoma and cataract state a greater impact on HR-QoL than the children themselves (Chak et al. 2007; Dahlmann-Noor et al. 2017; Tailor et al. 2017).

Regardless of our small study population, we observed a trend towards differences in PedsQL emotional health scores between A/M children and their parents. However, our small sample size likely limited our possibility to find statistical significance if it indeed exists. Further discordance between child–parent agreement regarding social issues has been found in children with cataract (Castañeda et al. 2016). Previous studies by Rasmussen (2010) regarding eye-amputated patients treated with ocular prosthesis revealed a low HR-QoL in comparison with healthy individuals, especially regarding the patient’s own feelings about their social relations, emotional problems and mental health problems. Similar results have been reported in adult anophthalmic patients (Ahn et al. 2010; Goiato et al. 2013).

In the present study, parents of children with a subnormal VA for age tended to associate their child’s visual impairment with poor physical health rather than poor psychosocial health. Besides physical health, children with subnormal vision also tend to report lower scores in school functioning, compared to A/M children with a normal VA. A study by Hiatt et al. found that poor VA among children with congenital cataract was associated with psychosocial problems. Hiatt (1998) also found that children treated for bilateral cataracts with a poor VA outcome experienced more psychosocial problems, including social problems and attention deficit, compared to children with a good visual outcome.

Regarding social and emotional questions such as getting along with other children, another child does not want to be his/her friend or getting teased by other kids, children’s response and parent’s response showed that the majority of all children experienced these problems. However, seven out of the nine children who presented these issues were assessed as having a syndromic condition with additional extraocular problems, which may affect their psychosocial well-being.

All VR-QoL questionnaires were carried out according to age, and so there were only a few A/M children in each age group. This small sample size made it difficult to compare data with

### Table 2. PedsQL questionnaire answered by 7 of 8 age-suitable children/adolescents (mean age 9.7 years) with microphthalmia/anophthalmia and 15 suitable parents of study group, compared with healthy controls and their parents.

| Variables                  | Study group Child/adolescent | Healthy controls Child/adolescent | P-value     | Difference between the groups Mean (95% CI) |
|----------------------------|------------------------------|-----------------------------------|-------------|------------------------------------------|
| PedsQL: total              | 66.3 (21.4)                  | 83.00 (14.79)                     | 0.0035      | −16.70 (−27.87; −5.53)                   |
| Mean (SD)                  | n = 7                        | n = 401                           |             |                                          |
| PedsQL: physical health    | 68.3 (30.9)                  | 84.41 (17.26)                     | 0.0164      | −16.11 (−29.25; −2.96)                   |
| Mean (SD)                  | n = 7                        | n = 400                           |             |                                          |
| PedsQL: psychosocial       | 61.1 (17.1)                  | 82.38 (15.51)                     | 0.0004      | −21.28 (−32.92; −9.64)                   |
| Emotional                  | 59.6 (20.1)                  | 80.86 (19.64)                     | 0.0048      | −21.26 (−35.99; −6.54)                   |
| Social function            | 67.9 (21.4)                  | 87.42 (17.18)                     | 0.0032      | −19.52 (−32.45; −6.59)                   |
| School function            | 60.0 (8.9)                   | 78.63 (20.53)                     | 0.0171      | −18.63 (−33.92; −3.33)                   |
| PedsQL: total Parent       | Parent                       | Parent                            | <0.0001     | −18.01 (−24.35; −11.67)                  |
| Mean (SD)                  | 69.6 (13.9)                  | 87.61 (12.33)                     |             |                                          |
| n = 15                     | n = 7                        | n = 717                           |             |                                          |
| PedsQL: physical health    | 73.8 (20.2)                  | 89.32 (16.35)                     | 0.0003      | −15.52 (−23.94; −7.10)                   |
| Mean (SD)                  | n = 15                       | n = 717                           |             |                                          |
| PedsQL: psychosocial       | 68.1 (16.3)                  | 86.58 (12.79)                     | <0.0001     | −18.48 (−25.08; −11.89)                  |
| Mean (SD)                  | n = 15                       | n = 717                           |             |                                          |
| Emotional                  | 70.3 (17.8)                  | 82.64 (17.54)                     | 0.0072      | −12.34 (−21.33; −3.35)                   |
| Social function            | 77.0 (20.9)                  | 91.56 (14.20)                     | 0.0001      | −14.56 (−21.92; −7.20)                   |
| School function            | 68.2 (19.5)                  | 85.47 (17.61)                     | 0.0003      | −17.27 (−26.64; −7.90)                   |
| n = 15                     | n = 7                        | n = 716                           |             |                                          |
| n = 14                     | n = 611                      |                                   |             |                                          |

CI = confidence interval, PedsQL = Pediatric Quality of Life Inventory, SD = standard deviation. PedsQL child self-report available from ≥5 years old and parent-proxy report available from 2–18 years old, answered by all 15 appropriate parents. Higher score indicating better quality of life. Confidence intervals were computed based on the unpaired t-test.
Table 3. Health-related (HR) and vision-related (VR) quality of life (QoL) questionnaires answered by children/adolescents with microphthalmia and anophthalmia and their parents, divided into those with a normal age-based visual acuity (VA) and those with a subnormal VA for age.

| Variable                      | Study group Children/adolescents with normal VA for age (n = 10)* | Study group Children/adolescents with subnormal VA for age (n = 5)* | p-Value | Difference between groups Mean (95% CI) |
|-------------------------------|---------------------------------------------------------------|-----------------------------------------------------------------|--------|---------------------------------------|
| PedsQL; total                | 73.2 (17.9)                                                   | 37.4 (10.5)                                                      | 0.29   |                                       |
| Mean (SD)                    | n = 4                                                         | n = 3                                                           |        |                                       |
| PedsQL; physical health      | 78.1 (16.3)                                                   | 22.9 (32.4)                                                     | 0.03   | 55.2 (7.95; 102.5)                    |
| Mean (SD)                    | n = 4                                                         | n = 3                                                           |        |                                       |
| PedsQL psychosocial          | 69.6 (19.2)                                                   | 43.0 (0.2)                                                      | 0.07   |                                       |
| Mean (SD)                    | n = 4                                                         | n = 3                                                           |        |                                       |
| Emotional                    | 65.0 (26.5)                                                   | 53.3 (13.0)                                                     | 0.52   |                                       |
| Social function              | 71.3 (29.5)                                                   | 56.7 (4.7)                                                      | 0.44   |                                       |
| n = 4                                                                       | n = 3                                                           |        |                                       |
| School function              | 66.3 (4.8)                                                    | 55.0 (7.1)                                                      | 0.05   | 11.3 (−0.15; 22.75)                   |
| n = 4                                                                       | n = 3                                                           |        |                                       |
| Parents to children/adolescents with normal VA for age (n = 10)*             | 72.2 (15.1)                                                   | 64.3 (12.7)                                                     | 0.22   |                                       |
| Mean (SD)                    | n = 5                                                         | n = 5                                                           |        |                                       |
| PedsQL; physical health      | 80.3 (17.5)                                                   | 60.6 (22.7)                                                     | 0.12   |                                       |
| Mean (SD)                    | n = 5                                                         | n = 5                                                           |        |                                       |
| PedsQL Psychosocial          | 69.8 (17.5)                                                   | 64.7 (16.6)                                                     | 0.81   |                                       |
| Mean (SD)                    | n = 5                                                         | n = 5                                                           |        |                                       |
| Emotional                    | 72.0 (20.4)                                                   | 67.0 (14.8)                                                     | 0.58   |                                       |
| Social function              | 81.5 (19.4)                                                   | 68.0 (25.1)                                                     | 0.42   |                                       |
| n = 9                                                                       | n = 5                                                           |        |                                       |
| School functioning           | 74.3 (17.7)                                                   | 63.7 (27.3)                                                     | 0.50   |                                       |
| n = 9                                                                       | n = 5                                                           |        |                                       |
| CVFQ, general vision         | 0.5 (0.2)                                                     | 0.6 (0.2)                                                       | 0.13   |                                       |
| n = 7                                                                       | n = 3                                                           |        |                                       |
| CVFQ, total                  | 0.8 (0.1)                                                     | 0.8 (0.1)                                                       | 1.0    |                                       |
| n = 7                                                                       | n = 3                                                           |        |                                       |

CVFQ = Children’s Visual Function Questionnaire.
* Where numbers differ from the number of children and parents in the group, they are given separately for each category; CI = confidence interval; PedsQL = Pediatric Quality of Life Inventory; SD = standard deviation. Child self-report available from ≥5 years old, answered by 7 out of 8 suitable children. Higher mean scores indicate better quality of life. Bold indicates statistical significance. The Mann–Whitney U-test was used for continuous variables. Calculation of confidence interval for continuous variables is based on bootstrapping of 10 000 replicates picking the 2.5 and 97.5 percentiles of the 10 000 mean differences as CI.

larger healthy reference groups. No statistical analysis was carried out regarding VR-QoL except in CVFQ, where no statistically difference was found comparing A/M children with healthy children or regarding subnormal/normal VA of the children with A/ M and CVFQ mean total score. On the contrary, no differences were found when comparing A/M children to children with other eye diseases (Birch et al. 2007).

Previous studies of paediatric patients with optic pathway gliomas, retinopathy of prematurity, congenital bilateral cataract and glaucoma have found an association between worse VA and poorer VR-QoL (Ye et al. 2007; Lopes et al. 2009; Avery & Hardy 2014; Freedman et al. 2014; Messa et al. 2015). Moreover, Avery and Hardy noted lower competence scores in children with a more profound vision loss diagnosed with optic pathway gliomas and reported that children with two visually impaired eyes showed increased social difficulties compared to those with only one eye affected (Avery & Hardy 2014). These results indicate that children with impaired vision in both eyes might experience not only difficulties with performing daily life activities, but also negative effects on their participation in and enjoyment of social activities.

Our study showed a high proportion of reports of PVDs among A/M individuals compared with healthy controls, regardless of VA and presence of an isolated or syndromic condition. In healthy controls, all four children who reported PVDs in any area had a normal VA. The most frequently reported area of PVDs among A/M children was depth perception, which may have been due to the visual function of only one eye.

One strength of our study resides in the use of validated tools to assess QoL. We included both children and their parents, in order to gain the best perspective of the impact of A/M on QoL. A limitation is the small numbers of children and parents within each age category. Because of the low number of participants who completed the VR-QoL questionnaires, we cannot provide conclusive evidence that lower VA would reduce VR-QoL in this cohort of patients. If associations do exist, the small sample size is likely to have limited our possibility to find them.

In conclusion, this study supports our clinical findings of a decreased HR-QoL among A/M children, and shows that their parents also perceive this
Perceptual visual dysfunctions (PVDs) in A/M children and adolescents with normal or subnormal visual acuity for age

![Diagram A](image1)

Subnormal visual acuity (n = 4)  Normal visual acuity (n = 7)

Perceptual visual dysfunctions (PVDs) in non-syndromic and syndromic A/M children and adolescents

![Diagram B](image2)

Syndromic (n = 7)  Non-syndromic/isolated (n = 4)

Fig. 1. Perceptual visual dysfunctions (PVDs) among microphthalmic and anophthalmic individuals in the study group, divided according to subnormal and normal visual acuity according to age (A) or divided into isolated or syndromic condition (B). The figures show children who either showed no PVDs, or exhibited problems in one or more of the five areas tested, as recorded by structured history taking.

decrease. We found that A/M individuals had worse HR-QoL than healthy individuals in all respects and that A/M children particularly experienced a negative impact on psychosocial well-being. When comparing A/M participants with normal and subnormal VA for age, we found that having a lower VA negatively affected physical health and to some extend school functioning. A/M children and adolescents also reported a higher incidence of PVDs compared to sex- and age-matched controls. In consequence, all children born with A/M require a complete assessment by a multidisciplinary team. It is important to examine each A/M individual thoroughly and initiate treatment with ocular prosthesis. An examination of the fellow eye is necessary to assess the potential development of VA. A clinical genetic assessment is recommended to look for further associated abnormalities, to perform genetic analysis and provide genetic counselling to the patient and his/her family. HR-QoL and VR-QoL evaluations are needed to identify and address these psychosocial problems and other additional problems among these individuals. Finally, our results indicate that A/M children need thorough eye
examinations, individual assessment and suitable strategies to manage their diagnosis. Early evaluation of HR-QoL and PVDs could be important to identify the patients who need further support and may in the long run prevent a low QoL among these individuals.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. The seven microphthalmic and anophthalmic children/adolescents with both child-self reports and parent-proxy reports of the PedsQL questionnaire completed.