Clinical Trials

Monitoring and Morphologic Classification of Pediatric Cataract Using Slit-Lamp-Adapted Photography

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Purpose: To investigate the feasibility of pediatric cataract monitoring and morphologic classification using slit lamp–adapted anterior segmental photography in a large cohort that included uncooperative children.

Methods: Patients registered in the Childhood Cataract Program of the Chinese Ministry of Health were prospectively selected. Eligible patients underwent slit-lamp adapted anterior segmental photography to record and monitor the morphology of their cataractous lenses. A set of assistance techniques for slit lamp–adapted photography was developed to instruct the parents of uncooperative children how to help maintain the child’s head position and keep the eyes open after sleep aid administration.

Results: Briefly, slit lamp–adapted photography was completed for all 438 children, including 260 (59.4%) uncooperative children with our assistance techniques. All 746 images of 438 patients successfully confirmed the diagnoses and classifications. Considering the lesion location, pediatric cataract morphologies could be objectively classified into the seven following types: total; nuclear; polar, including two subtypes (anterior and posterior); lamellar; nuclear combined with cortical, including three subtypes (coral-like, dust-like, and blue-dot); cortical; and Y suture. The top three types of unilateral cataracts were polar (55, 42.3%), total (42, 32.3%), and nuclear (23, 17.7%); and the top three types of bilateral cataracts were nuclear (110, 35.8%), total (102, 33.2%), and lamellar (34, 11.1%).

Conclusions: Slit lamp–adapted anterior segmental photography is applicable for monitoring and classifying the morphologies of pediatric cataracts and is even safe and feasible for uncooperative children with assistance techniques and sleep aid administration.

Translational Relevance: This study proposes a novel strategy for the preoperative evaluation and evidence-based management of pediatric ophthalmology (Clinical Trials.gov, NCT02748031).

Introduction

Monitoring and classification of morphology is a fundamental and critical issue for pediatric cataracts. Lens opacities in pediatric cataracts have a wide range of phenotypes.1 The nucleus can be the primary structure affected in some eyes. In other eyes, the fetal nucleus remains clear, but the cortex is involved, displaying various patterns of opacities.1–3 Small, mild, or eccentrically placed cataracts are frequently managed by observation, while dense and central opacities require immediate surgical removal, as they are considered amblyogenic.4 Such preoperative monitoring and judgments are frequently based on clear evaluations and recordings of cataract morphologies, which are difficult to complete in children who do not cooperate during the examination at regular follow-up visits.1,3,5

Currently, it is common to evaluate pediatric cataracts based on the appearance of the lens at the time of clinical presentation using handheld photographic equipment6 or during surgery under general anesthesia using the operating microscope. Although
handheld photographic equipment is simple and convenient, it often fails to provide precise assessments and to produce high-quality images of cataract morphology, making it more suitable for preliminary screening than for vital clinical decision making. Moreover, the high risk caused by general anesthesia is unnecessary for children who do not require surgery, especially for younger infants with immature cardiovascular, pulmonary, thermoregulatory, and nervous systems. Therefore, it is crucial to find a method of recording, classifying, and monitoring cataract morphologies that is more feasible, comprehensive, and safe in a large cohort of children with pediatric cataracts, including uncooperative children.

An attractive alternative is external imaging of opacity in the pediatric clinic but not at the time of surgery. The use of photographic images to grade age-related cataracts has a long history and has led to the successful adoption of various grading systems. These systems have greatly promoted the standardization of cataract classifications, enhanced the reproducibility of clinical judgment and improved decision-making regarding treatment.

However, for pediatric cataracts, conventional slit-lamp color photographs have reportedly been obtained for only a representative sample of a small group of children. To our knowledge, there has been no attempt to construct and evaluate a practical clinical procedure for an extensive range of pediatric cataract morphologic classifications in a large cohort that includes uncooperative children. Our strategy is an attractive alternative to provide objective preoperative assessments and precise treatment decisions for pediatric cataracts, and it represents a fresh paradigm for the evidence-based management of pediatric ophthalmology.

Methods

Patients

This study included all the registered children with a diagnosis of unilateral/bilateral pediatric cataracts from the Childhood Cataract Program of the Chinese Ministry of Health (CCPMOH) who were treated between January 2011 and April 2014 at the Zhongshan Ophthalmic Center (ZOC), one of the largest eye hospitals in China. Children with a history of premature birth or any previous surgeries, diagnosis of microphthalmia, micro-, or megalocornea, keratoconus, glaucoma, traumatic or complicated cataracts, vitreous or retinal diseases, lens dislocation or contraindications for pupil dilation, and sedation were excluded.

Ethical Approval

The research protocol was approved by the institutional review board/Ethics Committee of Sun Yat-sen University (Guangzhou, China). Written informed consent was obtained from at least one family member of each participating child, and the tenets of the Declaration of Helsinki were followed throughout the study. To allow the confidential evaluation of the slit lamp, straps, specific transformable bed equipment, and sleep aid usage, our study was registered with the Clinical Research Internal Management System of ZOC and ClinicalTrials.gov (NCT02748031).

Slit Lamp Adapted Anterior Segmental Photography

All eligible pediatric patients underwent pupil dilation with compound tropicamide eye drops three times (once every 10 minutes) before the examination or administration of sleep aid medication. Then, the children underwent slit lamp–adapted anterior segmental photography (BX900; Haag-Streit AG, Küniz, Switzerland) for each cataractous lens, including one diffuse light image, one slit-light image across the cataract, and one retro-illumination image. The images were screened and morphologically classified separately by two pediatric ophthalmologists; a third ophthalmologist was consulted if the previous two physicians had different opinions.

Special Requirements for Uncooperative Children

Because infants and young children show poor compliance with slit lamp–adapted photography, we developed several specific techniques and strategies as follows:

1. Flying-baby posture: for infants with an immature spine and low weight (mostly under 1 year
and less than 10 kg), the mother held the infant with one hand on the haunch and another hand on the abdomen, and the head position was adjusted by a technician (Fig. 1A);

2. Strap technique: for children with a mature spine and moderate weight (from 1–2 years and less than 20 kg), the mother held up the child using straps, and the head position was adjusted by a technician (Fig. 1B);

3. Special transformable bed: for children who were too heavy to be held up by their parents, even with straps (mostly older than 2 years and more than 20 kg), a transformable bed (our patented product) was used to support the child, and a technician helped adjust the head position (notes: permissions have been received to use patient likeness in the figure).

4. Sedation: we performed slit lamp–adapted photography on sleeping children immediately after administering oral chloral hydrate or a retention enema, with chloral hydrate or intranasal dexmedetomidine (if chloral hydrate was contraindicated or failed) as a sleep aid. The safety of this sleep-aid administration strategy was preliminarily demonstrated in our previous studies\textsuperscript{30,31} and was approved by the institutional review board/Ethics Committee of Sun Yat-sen University. Informed consent was obtained from least one family member of each child before sedation. Sleep-aid administration was conducted with monitoring by an anesthesiologist in all instances. More details can be found at
our completed clinical trial for the sedation of pediatric cataract patients, NCT02077712) regarding children who were uncooperative during regular examinations in the clinic. All examinations were performed by three experienced pediatric ophthalmologists (H.T.L., J.J.C., and Z.L.L.) using the same procedures.

Statistical Analysis

The consistency between the classifications provided by the two researchers was calculated using pairwise comparisons by taking the number of times a researcher was in agreement with another researcher over the total number of pairwise comparisons. The ages of the included children were expressed as the mean ± standard deviation (SD). $\chi^2$ test was used to assess sex-related and laterality-related differences in the distribution of the morphologic types. All statistical tests were two-tailed, and a $P$ value below 0.05 was considered statistically significant, which were performed using SPSS software, version 18 (SPSS, Inc., Chicago, IL).

Results

Study Population

Among all the registered patients from CCPMOH, 438 patients diagnosed with pediatric cataracts were finally included. All 438 (288 [65.8%] males) children were Han Chinese. The mean age of the 438 included patients was 7.64 months ± 4.21 months, and no differences in age distribution based on sex were noted ($P = 0.71$).

Safety and Feasibility

Pupil dilation and slit lamp–adapted photography were successfully completed in all 438 children, including 260 (59.4%, 260/438) uncooperative children with our assistance techniques and equipment, after sleep aid administration. Specifically, the assistance techniques were used in the following proportions: flying-baby posture (141, 54.2%), strap technique (97, 37.4%), and special transformable bed (22, 8.4%). All 746 slit-lamp images of the 438 pediatric patients were successfully diagnosed and classified.

Figure 2. Flow chart of patient selection, examination and analysis. A total of 438 patients diagnosed with pediatric cataracts were finally included, containing 260 (59.4%, 260/438) uncooperative children with our assistance techniques and equipment, after sleep aid administration. Specifically, the assistance techniques were used in the following proportions: flying-baby posture (141, 54.2%), strap technique (97, 37.4%), and special transformable bed (22, 8.4%). All 746 slit-lamp images of the 438 pediatric patients were successfully diagnosed and classified.
patients’ parents had a brief instruction, and all eight remaining parents had special situations (e.g., physical challenge). Sedation was conducted in 246 patients (94.6%, 246/260) using chloral hydrate and 14 patients (5.4%, 14/260) using dexmedetomidine. There were no cardiopulmonary accidents or other complications during the slit lamp–adapted photography using chloral hydrate or dexmedetomidine. Therefore, our strategy is considered a safe and feasible application of slit lamp–adapted anterior segmental photography for uncooperative children.

**Morphologic Classification and Monitoring**

Among the slit-lamp images of the 438 pediatric patients, there were 130 (28.9%) unilateral cataracts and 308 (68.5%) bilateral cataracts; thus, a total of 746 images were finally included. In our cohort, pediatric cataract morphologies could be classified into seven types and 10 subtypes by considering the lesion location (representative images are presented in Fig. 3).32

All 746 images of 438 pediatric patients were successfully diagnosed and classified. The consistency between the classifications provided by the two researchers was 98.1% (732/746), and all discrepancies were resolved after further discussion and consultation with the third ophthalmologist. Among 308 bilateral patients, only six patients (2.0%, 6/308) had a different type of morphology. Three patients were nuclear/lamellar, two patients were total/nuclear + cortical (dust-like), and one patient was nuclear/cortical.

**Morphologic Distribution**

To avoid duplication, all the right eyes of bilateral patients were included in the analysis of the distribution of cataract types. In decreasing order, the numbers of cataract types and subtypes were total (144, 32.9%), nuclear (133, 30.4%), polar (94, 21.5%, including two subtypes [anterior 35, 8.0% and posterior 59, 13.5%]), lamellar (42, 9.6%), nuclear combined with cortical (21, 4.8%, including three subtypes [coral-like 7, 1.6%, dust-like 12, 2.8%, and blue-dot 2, 0.5%]), cortical (2, 0.5%), and Y suture (2, 0.5%). The proportions of various types and subtypes among all included patients are summarized in Table 1.

Further analysis was conducted to investigate the relationship between laterality and cataract morphology. As shown in Fig. 4, the top three types of unilateral cataracts were polar (55, 42.3%), total (42, 32.3%), and nuclear (23, 17.7%); the top three types of bilateral cataracts were nuclear (110, 35.8%), total (102, 33.2%), and lamellar (34, 11.1%). Additionally, no sex-related differences in cataract morphology type distributions were observed ($P = 0.64$). The polar type of cataract (both anterior and posterior subtypes) was most likely to be categorized as unilateral (58.5%, 55/94), while the most likely laterality categorization of other types or subtypes of cataract was bilateral.

**Discussion**

Although the use of photographic images to grade age-related cataracts has a long history and has led to the successful adoption of various grading systems,14,15 the standardization of the cataract state,16,33 enhanced reproducibility of clinical judgment,16,34 and improved decision-making regarding treatment35; few studies have investigated the recording, classification, and monitoring of morphologies in large pediatric cataract series in the clinic.

Wilson et al.36 described a video-documented assessment of cataract types among unilateral infantile cataracts and demonstrated a higher than previously realized rate of posterior capsule involvement among the study population. However, such an assessment is available during surgery, making it difficult to be extended to the context of follow-up situations.36 Forster et al.3 obtained slit-lamp color photographs as a representative sample ($n = 13$) using retro- and direct illumination. These images were developed on Kodak color film, scanned using a Nikon Coolscan 4000ED at a maximum of 4000 dpi, and then compressed with intensity profiles computing. The authors did not report the mean age of their patients, but they noted that cataract photographs were frequently obtained under general anesthesia.3

Compared with those studies, our work remains a pioneering investigation that has demonstrated the safety and feasibility of pediatric cataract monitoring and morphologic classification by slit lamp–adapted anterior segmental photography in pediatric clinic with our assistance techniques and equipment in a large cohort (CCPMOH). Multiple evidences were provided to ensure the safety of our sleep-aid administration. First, no cardiopulmonary accidents or other complications occurred during examination. Second, the safety of our sedation drugs has been validated in several clinical trials30,31 and outpatient setting.37 Third, the sedation was conducted with monitoring by an anesthesiologist in all instances.
Table 1

<table>
<thead>
<tr>
<th>Cataract type (Subtype)</th>
<th>Slit-lamp images</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td><img src="image1" alt="Total slit-lamp images" /></td>
</tr>
<tr>
<td><strong>Nuclear</strong></td>
<td><img src="image2" alt="Nuclear slit-lamp images" /></td>
</tr>
<tr>
<td><strong>Polar (Anterior)</strong></td>
<td><img src="image3" alt="Polar (Anterior) slit-lamp images" /></td>
</tr>
<tr>
<td><strong>Polar (Posterior)</strong></td>
<td><img src="image4" alt="Polar (Posterior) slit-lamp images" /></td>
</tr>
<tr>
<td><strong>Lamellar</strong></td>
<td><img src="image5" alt="Lamellar slit-lamp images" /></td>
</tr>
<tr>
<td><strong>Nuclear + cortical</strong></td>
<td><img src="image6" alt="Nuclear + cortical slit-lamp images" /></td>
</tr>
<tr>
<td><strong>(Coral-like)</strong></td>
<td><img src="image7" alt="Nuclear + cortical slit-lamp images" /></td>
</tr>
<tr>
<td><strong>(Dust-like)</strong></td>
<td><img src="image8" alt="Nuclear + cortical slit-lamp images" /></td>
</tr>
<tr>
<td><strong>(Blue-dot)</strong></td>
<td><img src="image9" alt="Nuclear + cortical slit-lamp images" /></td>
</tr>
<tr>
<td><strong>Cortical</strong></td>
<td><img src="image10" alt="Cortical slit-lamp images" /></td>
</tr>
<tr>
<td><strong>Y suture</strong></td>
<td><img src="image11" alt="Y suture slit-lamp images" /></td>
</tr>
</tbody>
</table>

Figure 3. Representative slit-lamp images of 10 types and subtypes of congenital cataract morphologies. Considering the lesion locations, the pediatric cataract morphologies could be objectively classified into seven types (or 10 subtypes): total; nuclear; polar, including two subtypes (anterior and posterior); lamellar; nuclear combined with cortical, including three subtypes (coral-like, dust-like, and blue-dot); cortical; and Y suture.
Therefore, it is worthwhile to achieve precise evaluation and monitoring of pediatric cataracts with sedation for uncooperative children. However, it is acknowledged that sedation in a setting of anesthesiology supervision might be challenge for some primary care hospitals and more evidences from large population were required to further confirm the safety of drugs.

It is well accepted that slit-lamp photography can produce quality images for cataract morphology analysis and recording.\textsuperscript{5,26} To date, it remains challenging to construct a simple method of grading the severity of pediatric cataracts to propose useful clinical guidelines for surgical intervention.\textsuperscript{21,36,38} Forster et al.\textsuperscript{3} described an 11-point ordinal classification scheme for the nine most frequently encountered types of pediatric cataracts. They subjectively ranked cataracts from major or “significant” (e.g., a total cataract) to minor or “insignificant” (e.g., anterior polar type) based on position, depth, and morphology.\textsuperscript{34} Consistent with conventional pediatric ophthalmologic practice, minor cataracts would be considered best left in situ, while major cataracts would ideally be removed as early as possible.\textsuperscript{21,38} Although Forster et al.\textsuperscript{3} concluded that the magnitude and severity of pediatric cataracts could be successfully characterized with the 11-point ordinal grading scale, this method largely depends on personal experience, and lacks evidence supporting its use to monitor patients who do not require surgery\textsuperscript{20} and to evaluate the relationship between cataract morphology and visual impairment.\textsuperscript{19} Therefore, it is imperative to develop a novel method to objectively evaluate these cataracts.

In the present study, our slit-lamp–adapted anterior segmental photography (BX900; Haag-Streit AG) provided high-quality digital images that could be saved electronically for recording and objective classification,\textsuperscript{11} which is more appropriate for use during long-term follow-ups in large series. In our study, all included patients (100\%) were successfully photographed, and a high proportion of patients (97.4\%) were successfully diagnosed and classified, including the 57.8\% of children who were uncooperative. In addition to the slit lamp–adapted anterior segmental photography process, we have developed assistance techniques for uncooperative children, along with our special equipment; these modifications have been determined to be safe and feasible in a busy pediatric clinical practice. Moreover, our pattern could serve as a valuable reference for evidence-based management of pediatric ophthalmology and could promote the application of artificial intelligence using these large-scale medical images.\textsuperscript{39}

The classifications and prevalence of pediatric cataracts are shown in Table 1 and Figure 4.

### Table 1. Clinical Details of 10 Congenital Cataract Types and Subtypes Classified

<table>
<thead>
<tr>
<th>Cataract Type (Subtype)</th>
<th>n (%)</th>
<th>Likely Cataract Laterality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>144 (32.9)</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Nuclear</td>
<td>133 (30.4)</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Polar</td>
<td>94 (21.5)</td>
<td>Bilateral</td>
</tr>
<tr>
<td>(Anterior)</td>
<td>35 (8)</td>
<td>Unilateral</td>
</tr>
<tr>
<td>(Posterior)</td>
<td>59 (13.5)</td>
<td>Unilateral</td>
</tr>
<tr>
<td>Polar</td>
<td>94 (21.5)</td>
<td>Bilateral</td>
</tr>
<tr>
<td>(Anterior)</td>
<td>35 (8)</td>
<td>Unilateral</td>
</tr>
<tr>
<td>(Posterior)</td>
<td>59 (13.5)</td>
<td>Unilateral</td>
</tr>
<tr>
<td>Lamellar</td>
<td>42 (9.6)</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Nuclear + cortical</td>
<td>21 (4.8)</td>
<td>Bilateral</td>
</tr>
<tr>
<td>(Coral-like)</td>
<td>7 (1.6)</td>
<td>Bilateral</td>
</tr>
<tr>
<td>(Dust-like)</td>
<td>12 (2.8)</td>
<td>Bilateral</td>
</tr>
<tr>
<td>(Blue-dot)</td>
<td>2 (0.5)</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Cortical</td>
<td>2 (0.5)</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Y suture</td>
<td>2 (0.5)</td>
<td>Bilateral</td>
</tr>
</tbody>
</table>

The polar type of cataract (both anterior and posterior subtypes) was most likely to be categorized as unilateral (58.5\%, 55/94), while the most likely laterality categorization of other types or subtypes of cataract was bilateral.

The polar type of cataract (both anterior and posterior subtypes) was most likely to be categorized as unilateral (58.5\%, 55/94), while the most likely laterality categorization of other types or subtypes of cataract was bilateral. The top three types of unilateral cataracts were polar (55, 42.3\%), total (42, 32.3\%), and nuclear (23, 17.7\%); the top three types of bilateral cataracts were nuclear (110, 35.8\%), total (102, 33.2\%), and lamellar (34, 11.1\%). The polar type of cataract (both anterior and posterior subtypes) was mostly likely to be categorized as unilateral, while the most likely laterality categorization of other types or subtypes of cataract was bilateral. Nu + co, nuclear complicated with cortical cataracts.
cataract morphologies vary distinctly among different evaluation methods and series.\textsuperscript{1,3,5} The most common type of cataract in our series was total cataract (32.9\%, 144/438). Wilson et al.\textsuperscript{36} reported a lower proportion of total cataract (4\%). Similarly, Forster et al.\textsuperscript{3} collected data from three studies and found a 3\% prevalence of total cataract. Forster et al.\textsuperscript{3} also found that nontraumatic total cataracts were not common in industrialized countries. Another study of pediatric cataracts from the United States\textsuperscript{40} reported that only 4 of 199 cases (2\%) were classified as total. However, total cataracts are more common in developing countries. Johar and colleagues\textsuperscript{41} noted that total cataract was presented in 39 of 85 infant eyes (46\%) in western India. In a series from Nepal, 1804 of 2633 (68\%) cases were described as total cataract.\textsuperscript{42} Our current study was performed in China, a developing country similar to India, which may explain the similarly high proportion of total cataracts.

Another type of cataract that must be noted is nuclear cataract. Forster et al.\textsuperscript{3} reported a prevalence of nuclear involvement of approximately 10\%. Haargaard et al.\textsuperscript{5} reviewed the medical records of children (younger than 17 years) and reported that nuclear cataract accounted for 34\% of unilateral cataract cases and was the most common morphology in all major etiologic groups. In our cohort, 30.4\% (133/438) of cases consisted of nuclear cataract if laterality was not considered. However, the division of cases by laterality revealed that nuclear cataract represented 35.8\% (110/308) of bilateral cataracts but only 17.7\% (23/130) of unilateral cataracts. The different proportions of nuclear cataract can be partly explained by discrepant demographic characteristics and the improved slit-lamp photography equipment and techniques.\textsuperscript{3,12,27,28}

The results and interpretation of the current study should be understood within the context of its strengths and limitations. The study strengths include the large patient cohort (part of a national program\textsuperscript{11}), unified and strict inclusion criteria and evaluation protocols, innovative assistance techniques, and special equipment. The study weaknesses must also be acknowledged. Although a large cohort was used, patients with microphthalmia, micro-, or megalocornea, keratoconus, glaucoma, traumatic or complicated cataracts, vitreous or retinal diseases, any previous surgeries, or contraindications for pupil dilation, and sedation were excluded. Therefore, the study results cannot be directly generalized to all eyes with pediatric cataracts. Moreover, questions remain regarding categorization with the present two-dimen-

sional (2D) slit-lamp photography.\textsuperscript{3,36} For example, if a dense nuclear opacity was found with a posterior polar cataract, this type of cataract would always be missed in a 2D photo. An alternative to our current slit-lamp photography is the Scheimpflug camera, in which a tilted film plane and objective maintain focus for the entire slit image.\textsuperscript{6} We conducted another study combining our collected slit-lamp photos and three-dimensional (3D) Scheimpflug images using a Pentacam (Oculus, Wetzlar-Münchholzhausen, Germany) and proposed a novel category system for pediatric cataract. Although this 3D category system is more comprehensive, our slit-lamp adapted photography method has a wider range of applications and is easier to promote due to its low cost.\textsuperscript{43}

Despite the above limitations, this study represents a pioneering step in demonstrating the safety and feasibility of morphologic classification and monitoring using slit-lamp–adapted anterior segmental photography in a large cohort of pediatric cataract patients. The results have important potential implications for evidence-based medicine in pediatric ophthalmology, which is rapidly growing in worldwide importance. Our future work will focus on investigating dynamic changes in morphology with regular long-term follow-up among patients who do not require surgery, with the goal of elucidating the relationship between cataract morphology and visual impairment.

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*E.L., Z.L., and J.C. contributed equally to this work.*

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**References**


