

Management of cataract surgery in Lowe syndrome

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Abstract

• **AIM:** To evaluate the ophthalmic and anesthesiologic management of cataract surgery in children with Lowe syndrome receiving lens removal, the development and management of secondary glaucoma.

• **METHODS:** This retrospective case series included 12 eyes of 6 children with genetically verified Lowe syndrome receiving cataract removal. Information regarding the type and duration of surgery and total anesthesia time were recorded. Additionally, intra- and postoperative complications were noted as well as clinical examinations such as visual acuity and funduscopy.

• **RESULTS:** All children received simultaneous bilateral cataract surgery at the mean age of 8.98 ± 3.58 wk. Lensectomy combined with posterior capsulotomy and anterior vitrectomy was performed in all children. The mean time for cataract surgery per eye was 35.83 ± 8.86 min, whereas the total time of surgery was 153.33 ± 22.11 min. The mean extubation time and duration at recovery room was 42.33 ± 22.60 min and 130.00 ± 64.37 min, respectively. During surgery, a decrease of oxygen saturation below 93% was found in only one child. During the postoperative follow-up, nystagmus (6 children) and strabismus (5 children) was commonly found in contrast to no case of visual axis opacification. Secondary glaucoma developed in five eyes of three children, which was treated with topical eye drops in only one child. A trabeculectomy was performed in both eyes of one child, whereas removal of sychia and an iridectomy in one eye of one child.

• **CONCLUSION:** Bilateral simultaneous cataract surgery under general anesthesia is a safe surgical procedure in Lowe syndrome children. The glaucoma screening with intraocular pressure measurements is crucial in the postoperative management of Lowe syndrome patients to avoid additional visual impairment.

• **KEYWORDS:** Lowe syndrome; congenital cataract; pediatric cataract surgery

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INTRODUCTION

The Lowe syndrome, also known as oculocerebrorenal syndrome, is a rare systemic disorder which involves several organ systems such as the eyes, the central nervous system and the kidneys^[1]. The prevalence is estimated at 1 in 500 000 children^[2]. It is an X-linked recessive disorder^[1], showing a key mutation in the *OCRL* gene. This gene encodes for the enzyme OCRL-1, which is essential for cell functions such as protein trafficking, signaling and actin cytoskeleton polymerization. Dysfunction of this enzyme leads to an accumulation of the substrate phosphatidylinositol-4,5-bisphosphate and impairs the intracellular pathways^[2-3]. Upon birth, Lowe syndrome should be suspected if children show bilateral dense congenital cataract and infantile congenital hypotonia. Furthermore, a positive family history of male relatives is highly indicative. The definite diagnosis is then established on the results of the physical exam findings, laboratory findings and molecular genetic testing.

Nervous system abnormalities, already present at birth, show severe central hypotonia and loss of the deep tendon reflexes which may complicate the vital functions (breathing) at birth. Hypotonia can slowly improve with age, but normal motor function and strength will not be achieved. Also, mental retardation is found in the majority of patients and many will develop maladaptive behaviors such as temper tantrums or irritability as well as seizures or febrile convulsions^[4-5].

Kidney dysfunction may not be present at birth but rather develop during the first few months of life. Typically, a proximal renal tubular dysfunction of the Fanconi type is found in these patients, which include low molecular-weight proteinuria, aminoaciduria, bicarbonate and potassium wasting, renal tubular acidosis and proteinuria. Chronic renal failure slowly develops due to glomerulosclerosis associated with chronic tubular injury between the second and fourth decade of life^[6-8].

Congenital cataract will initially present as bilateral lens opacities during physical examination of the newborn^[9]. Next to the congenital cataract, ophthalmic abnormalities include congenital glaucoma, nystagmus and keloids. Glaucoma is found in about 50% of patients^[10]. Therefore, also typical glaucomatous changes such as corneal haze, increased corneal diameter or buphthalmos combined with lens opacities should be suspicious for Lowe syndrome.

The initial approach is the cataract removal under general anesthesia. During surgery a complete ophthalmic examination will be carried out including assessment for glaucomatous changes^[9].

Ophthalmologists often examine babies only a few weeks of age, since parents or pediatricians found bilateral lens opacities. Prompt cataract removal is necessary to allow visual development. Therefore, a good cooperation between ophthalmologists and pediatricians is essential for the initial diagnosis and subsequently treatment and supportive therapy in these patients.

In this study, we evaluated the initial diagnose process, surgical treatment and the postoperative functional development and complications of children with Lowe syndrome.

SUBJECTS AND METHODS

Ethical Approval This retrospective, case series was performed at the Department of Ophthalmology, Vienna. Ethics approval for retrospective chart review and analysis was obtained from the local ethics committee (EK: 1116/2019) and adhered to the tenets of the Declaration of Helsinki. Medical records of patients aged 0 to 18y with genetically verified Lowe syndrome who received cataract extraction were included to the study. The Ethics Committee did not ask for informed consent as this was a retrospective chart review.

Bilateral simultaneous cataract surgery was performed under general anesthesia in all cases.

During surgery, a complete ophthalmologic examination including ultrasound B-scans (Ocuscan; Alcon Laboratories, Fortworth, Texas, USA) for evaluation of axial eye length and the posterior segment, measurement of intraocular pressure (IOP) and keratometry was performed. Cataract surgery was performed through the aspiration of the soft lens material with a bimanual irrigation-aspiration system. Afterwards, a posterior capsulotomy was done using either a bent needle or the vitrector. All children remained aphakic and glass or contact lenses were prescribed for postoperative visual rehabilitation.

Outcome measures included descriptive data (age and gender), information on the cerebral and renal pathologies and the surgical procedure. Anesthesia outcomes, composed of duration of surgery and anesthesia (measured in minutes, min)—that is, total anesthesia time (intubation to extubation),

extubation time (time between the end of surgery and extubation), time in the recovery room, and events of oxygen decrease (below 93% was regarded as severe hypoxia)—were recorded. The type intra- (iris bleeding, expulsive bleeding, posterior capsule rupture, intraocular lens (IOL) problems, iris dislocation) and postoperative complications [glaucoma, visual axis obscuration (VAO), synechia, retinal detachment, endophthalmitis or enucleation] were analyzed as well as the number of surgical re-treatments.

Statistical Analysis Microsoft Excel[®] 2010 was used for collecting patients' data, which was then converted to SPSS[®] version 20 (SPSS, Inc., Chicago, IL, USA) for statistical analysis. Nominal data is given as numbers or percentages, whereas continuous data is given as means±standard deviations (SDs).

RESULTS

This study included twelve eyes of six male children. In all children initial diagnosis was made clinically, whereof in three boys at the Ophthalmic Department and in one child at the Neonatology Intensive Care Unit (NICU). Genetic testing in all children confirmed the diagnosis of Lowe syndrome.

Five boys were born at the gestational week 37 to 39, whereas one child was born premature at week 26⁺⁶ and had to be treated at the NICU. The mean birth weight was 2865.17±1007.38 gram (Table 1). In two children a congenital infection was found, whereof in one child an endocarditis and in the other sepsis. At pediatric examination, cerebral hypotonia was observed in all children. Renal changes varied within the study population. One child showed no renal changes, whereas renal calcinosis was found in three children, isolated proteinuria and hydronephrosis in one child each.

Ophthalmic Evaluation The mean age of the children at diagnosis of congenital cataract was 4.07±3.26wk (1-8wk). Lens surgery was performed at the age of 8.98±3.58wk (3-12wk). The mean follow-up was 4.80±5.32y (1.11 to 15.91y). In all children a lensectomy combined with posterior capsulotomy and an anterior vitrectomy was performed. No IOL was implanted at the initial procedure as well as during the follow-up. Evaluation of the eye characteristics showed a mean eye length, the corneal diameter and the IOP of 17.16±2.01, 10.38±0.41, and 10.63±1.49 mm Hg, respectively. In one eye of one child an iris bleeding developed during cataract surgery, whereas no intraoperative complication developed in the remaining eleven eyes (Table 2).

The mean time for cataract surgery per eye was 35.83±8.86min, whereas the total time of surgery was 153.33±22.11min. Four children received an endotracheal tube, whereas two children a larynx mask. The mean extubation time and duration at recovery room was 42.33±22.60min and 130.00±64.37min, respectively. During surgery, a decrease of oxygen saturation

Table 1 General characteristics on birth, age and postoperative complications

Patients	Birth information			Age at diagnosis (wk)	Age at cataract surgery (wk)	Postoperative complications				
	Week of pregnancy	Body weight (g)	Body length (cm)			Re-treatment	Nystagmus	Strabismus	VAO	Glaucoma
1	38	3505	57	1.73	3.61	Yes (LE)	Yes	Esotropia	Yes (LE)	No
2	26 ⁺⁶	780	34	1.59	7.37	Yes (BE)	Yes	Exotropia	No	Yes (BE)
3	38 ⁺⁴	2960	51	8.96	12.13	No	Yes	No	No	No
4	38	2760	-	8.38	12.57	Yes (LE)	Yes	Esotropia	No	Yes (LE)
5	37 ⁺⁶	3238	53	1.73	5.63	No	Yes	Esotropia	No	Yes (BE)
6	39	3948	-	2.02	12.42	No	Yes	Esotropia	No	No

BE: Both eyes; LE: Left eye; VAO: Visual axis obscuration.

Table 2 Results of the eye examination and intraoperative complications at the initial cataract surgery as well as the results from the clinical assessment on the last follow-up examination

Patients	Operative notes			Visual acuity (logMAR)	Ophthalmic assessment	
	Eye length	Corneal diameter	Intraoperative complications		Intraocular pressure (mm Hg)	Postoperative intervention
1						
Right eye	-	-	No	1.0	14	-
Left eye	-	-	Bleeding during iridectomy	0.4	12	Removal of synechia
2						
Right eye	15.4	-	No	-	-	Trabeculectomy
Left eye	15.4	-	No	-	-	Trabeculectomy
3						
Right eye	16.83	10.5	No	-	12	-
Left eye	17.48	10.5	No	-	12	-
4						
Right eye	16.96	10.5	No	0.4	8	-
Left eye	17.11	10.5	No	0.4	9	Iridectomy
5						
Right eye	15.26	9.5	No	0.9	10	-
Left eye	15.46	10	No	0.9	10	-
6						
Right eye	20.85	10.5	No	0.7	12	-
Left eye	20.89	11	No	0.7	12	-

below 93% was found in only one child. Additionally, no serious complications such as asphyxia, malignant hyperthermia, cardiac and respiratory arrest or seizures were observed during surgery. One child, who showed a short period of insecure respiratory function during extubation, was transferred intubated to the recovery room. Extubation was then performed without complications. Afterwards, this child was brought to the pediatric intensive care unit for postoperative observation. All children left the hospital one to three days after cataract surgery, except the child who was born prematurely. This child remained at the hospital for another 43d because of the need for neonatal care.

During the postoperative follow-up, nystagmus was found in all children. Strabismus was seen in five children, whereof in four children an esotropia and in one child an exotropia. One child developed a VAO during the postoperative follow-up. Secondary glaucoma developed in five eyes of three children.

The maximum IOP was 21.75±10.49 mm Hg (10 to 40 mm Hg) during the follow-up. A trabeculectomy was performed in both eyes of one child four months after lens extraction, whereas a removal of synechia and an iridectomy in one eye of one child one year after lens surgery. In the third child, glaucoma was successfully controlled using topical IOP medication (beta-blocker).

At the last follow-up, the children showed a visual function of 0.61±0.88 logMAR (0.1-0.4 Snellen). No further surgical interventions were performed during the postoperative follow-up. However, in two children an examination under general anesthesia was performed for evaluation of glaucomatous changes.

During the follow-up one child, who was born prematurely and showed bronchopulmonary dysplasia, died at the age of 14.93mo due to recurrent respiratory infections (13.2mo after the cataract surgery).

DISCUSSION

From an ophthalmological point of view, Lowe syndrome is mainly characterized by bilateral cataract followed by infantile glaucoma and corneal kelloids. In addition, various diseases of the cerebrovascular system such as generalized hypotonia or intellectual impairment as well as renal changes such as renal tubular sclerosis or proteinuria have been described^[1]. The primary goal is established by the diagnosis *via* genetic testing in order to initiate adequate treatment and early intervention. In the ophthalmological field, cataract surgery and glaucoma management are the first priorities.

Within the demographic results we saw a male predomination of the study population, which is also described in the literature^[9]. About 95% of heterozygous females show specific cortical lens opacities in the shape of snowflakes already during the teenage years. However, cataract surgery is rarely required at a young age in female carriers^[11].

Furthermore, four of the six children presented to the Ophthalmology Department within the first two weeks of life. Children with congenital cataract present very early to eye doctors, which demonstrates the special role of ophthalmologists in the screening process of newborns. Bilateral cataract requires, in general, further pediatric examination, since congenital infections (such as toxoplasmosis, rubella, cytomegalovirus, herpes simplex or other infections, *Coxsackievirus*, syphilis, Varicella-Zoster, HIV or Parvo-B19) or drug exposures have to be ruled out^[12]. Subsequently, a good cooperation and network between ophthalmologists and pediatricians is essential for the timely diagnosis and treatment, especially, if Lowe syndrome is suspected.

Different approaches in the management of pediatric cataract surgery are discussed in literature. Especially, the time point of cataract extraction for uni- and bilateral congenital cataract is discussed with regard to the functional outcome and avoiding postoperative complications^[13-15]. In Lowe syndrome, both eyes are predominantly affected, making surgery on both eyes necessary.

At our clinic, bilateral cataracts are treated in one session of general anesthesia but with special care taken *i.e.*, new equipment (two separate phako sets) or change of clothes and gloves. This has the advantage that the children do not need another operation and therefore the total anesthesia time can be significantly reduced. In a retrospective analysis of anesthesia times in pediatric cataract surgery, surgery times per eye and the total anesthesia time were similar to our study results, only extubation time and recovery room time were prolonged^[16]. This may be due to the fact that the anesthetists knew about the suspected diagnosis Lowe syndrome, and therefore general anesthesia was performed more cautiously, or due to the fact that the children took longer to wake up and breathe on their

own due to cerebral hypotension or delayed excretion due to the underlying renal pathologies. However, the children could be discharged from the inpatient area relatively quickly after the operation (on average 1-3d). Furthermore, the children did not experience any complications during anesthesia. One child showed prolonged weaning during extubation, but the tube could be removed in the recovery room without further complications.

Postoperative follow-up examinations revealed various complications such as nystagmus, strabismus and secondary glaucoma. Ma *et al*^[9] reported nystagmus strabismus and secondary glaucoma in 69.3%, 35.0%, and 54.7%, respectively. In our retrospective case series, all children showed nystagmus. Strabismus was seen in 83.33% of patients, whereas secondary glaucoma in 50%. All of the above are common postoperative complications in children with congenital cataract. But, due to the generalized muscular hypotonia in Lowe syndrome additional impairment of the ocular motility and fusion reflex resulting in a predisposition towards strabismus may be found. Further, secondary glaucoma in Lowe syndrome is often difficult to treat and might not be controlled with topical treatment and require surgical intervention^[9,17].

In our study, three children showed changes of the IOP two required surgery to control eye pressure. A similar finding was reported by Ma *et al*^[9], 55% of patients underwent glaucoma surgery to control eye pressure sufficiently. Secondary glaucoma is a serious complication following pediatric cataract surgery in any case. One of the main risk factor for the development of secondary glaucoma is, however, the age at cataract surgery^[18-19]. A delay of cataract surgery was shown to reduce the risk of secondary glaucoma development by 20% for each week of postponement^[20]. Furthermore, secondary glaucoma is associated with decreased visual function^[21]. As a result, timing of cataract surgery in Lowe patients should be adjusted to the timing of bilateral cataracts in general (12wk of life). Especially, since a good visual development is an important base for the general physical and mental development. Next to the vision therapy, many children with Lowe syndrome require supportive therapies in form of physiotherapy or psychotherapy. Therefore, early detection of bilateral cataract and subsequently treatment is essential for the optimal visual prognosis.

Within our case series, one child who was born prematurely showed persistent bronchopulmonary infections and died at the age of 14mo. In literature, the causes of death are related to the underlying renal disease, muscular hypotonia, epileptic seizures and infections, especially in the bronchopulmonary or gastrointestinal tract^[2].

A bilateral congenital cataract is challenging for the ophthalmologist, anesthesiologist and pediatrician. As a result,

an early diagnosis of Lowe syndrome is beneficial for the surgical management to increase the safeness of the surgery. Simultaneous bilateral cataract surgery showed no rise of complications in children with Lowe syndrome. A prolonged extubation time and stay at the recovery room was observed, but the children could be discharged one to three days after surgery.

The glaucoma screening with IOP measurements is crucial in the postoperative management of Lowe patients, since there seems to be a special association to Lowe syndrome causing an increased prevalence. Especially since a good functional outcome of children with Lowe syndrome is essential for the further general physical development.

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