CASE REPORT

Congenital glaucoma and paradoxical microphthalmos in Neu-Laxova syndrome: a case report

Felix PY Lai[1,2,3], Stephanie KY Chu[1,2,3], Tracy HT Lai[1,2,3], Emily WH Tang[1,2,3], Kenneth KW Li[1,2,3]

[1] Department of Ophthalmology, United Christian Hospital, Hong Kong SAR, China

[2] Department of Ophthalmology, Tseung Kwan O Hospital, Hong Kong SAR, China

[3] Department of Ophthalmology, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

Correspondence and reprint requests:
Dr Emily WH Tang, Department of Ophthalmology, United Christian Hospital, Hong Kong SAR, China.
Email: etang1222@gmail.com

Abstract

Neu-Laxova syndrome (NLS) is characterized by multiple congenital anomalies and distinctive facial features such as proptosis and ectropion. Most NLS cases result in stillbirth or early postnatal death. NLS-associated ocular manifestations have not been widely documented. We report on a case of NLS with unilateral glaucoma and, paradoxically, bilateral microphthalmos and dense cataracts, despite having normal intraocular pressures in the first 3 months of life. At age 1 year, the patient developed glaucoma in the right eye, which was refractory to topical and systemic medications, as well as repeated transscleral cyclophotocoagulation. At age 2 years, the patient underwent definitive lens aspiration and Ahmed glaucoma valve implantation and achieved satisfactory outcomes. We recommend repeated intraocular pressure assessment in patients with NLS, particularly during their first year of life, even when initial measurements are normal. To our knowledge, this is the first reported case of NLS-associated congenital glaucoma with, paradoxically, microphthalmos.

Key words: Cataract, congenital, with microcornea or slight microphthalmia; Hydrophthalmos; Microphthalmos; Neu-Laxova syndrome

Introduction

Neu-Laxova syndrome (NLS) is a rare autosomal recessive genetic disorder caused by deficiencies of serine metabolism and characterized by ichthyosis, intrauterine growth restriction, microcephaly, limb deformities, and abnormal facial features such as severe proptosis with ectropion, hypertelorism, and flattened nose.[1,2] Most NLS cases result in stillbirth or early postnatal death owing to respiratory failure and sepsis. We present a genetically confirmed case of NLS with novel ocular findings of congenital glaucoma and, paradoxically, microphthalmos.

Case presentation

In February 2020, a female baby was born to consanguineous Pakistani parents. Prenatal ultrasound at 39 weeks of gestation revealed intrauterine growth restriction, microcephaly, cataracts, polyhydramnios, and abnormal limb posture. The baby was delivered at full term via spontaneous vaginal delivery and had a low birth weight of 1525 g. She was not breathing at birth and required resuscitation. She had multiple anomalies, including ichthyosis, microcephaly, flattened nasal bridge, generalized edema, limb deformities, and bilateral dense white cataracts **(Table).**

Confirmatory genetic testing identified a homozygous

Table. Systemic abnormalities in our patient.
Systemic abnormality
Neurology
Microcephaly
Retrocerebellar cyst (suspected Dandy-Walker variant)
Musculoskeletal system
Multiple joint contractures
Teratological bilateral hip dislocation
Congenital vertical talus
Respiratory
Respiratory distress syndrome
Bilateral lung hypoplasia
Pneumonia
Tracheostomy required
Cardiovascular system
Ventral septal defect
Patent foramen ovale
Secundum atrial septal defect
Patent ductus arteriosus (closed)
Hepatobiliary
Thrombosis in portal vein (resolved)
Skin
Ichthyosis
Ear
Failed brainstem auditory evoked response test
Eye
Congenital cataract
Glaucoma

variant in the PHGDH (phosphoglycerate dehydrogenase) gene, consistent with NLS type 1 (OMIM 256520) and PHGDH deficiency (OMIM 601815). Both parents were heterozygous carriers of this variant.

Ocular examination at age 1 month revealed normal intraocular pressure (IOP) of 18 mmHg in the right eye and 19 mmHg in the left eye. Both corneas were clear, and bilateral dense white cataracts were present **(Figure a)**. Both eyes were microphthalmic, with cornea diameters (horizontal × vertical) measuring 8.5 × 9.0 mm in the right eye and 8.0 × 9.0 mm in the left eye. Her pupils dilated poorly after administration of phenylephrine and tropicamide eye drops, and the fundus could not be viewed due to media opacities. Bedside ultrasound did not show any intraocular mass. The axial lengths were 18.2 mm in the right eye and 15.8 mm in the left eye. The ocular condition was stable in her first 3 months of life.

In view of the patient's uncertain life expectancy, the risks and benefits of eye examination under anesthesia and lens aspiration versus conservative treatment were discussed with her parents, who opted for conservative management. The possibility of poor visual prognosis and irreversible dense amblyopia was explained.

At age 1 year, the patient developed new-onset redness in her right eye. Examination found a high IOP of >50 mmHg. Digital pressure confirmed a tense globe with corneal edema. The corneal diameter had increased to 10.0 mm, whereas the left eye remained microphthalmic. The axial length had elongated to 23.5 mm, compared with 16.7 mm in the left eye. There was an acquired lower lid entropion, presumably due to buphthalmos **(Figure b)**. Bedside ultrasound again showed no intraocular mass. Maximal topical anti-glaucomatous therapy was initiated, including Cosopt (0.5% timolol and 2% dorzolamide) one drop twice/day, 0.005% latanoprost one drop/day, and oral acetazolamide 80 mg three times/day (the patient's body weight was 15.3 kg). However, IOP control remained suboptimal (at 39 to 45 mmHg). Given the poor visual potential, transscleral cyclophotocoagulation (TSCPC) using diode laser was performed under sedation three times over the following 7 months. After each TSCPC, the IOP would drop to the high teens for approximately a month before rebounding to 40 to 50 mmHg.

At age 2 years, the patient's right eye IOP was 47 mmHg **(Figure c)**, and a fourth TSCPC was planned under general anesthesia owing to COVID-19 infection control protocols. As the patient would face similar anesthetic risks for the repeated TSCPC or definitive glaucoma surgery, the options were discussed with her mother, and lens aspiration with Ahmed glaucoma valve implantation was performed under general anesthesia.

Intra-operatively, a dense cataract and diffuse posterior synechiae (almost 360°) without iris bombe were noted. The anterior chamber angle was difficult to assess due to corneal edema. The Ahmed glaucoma implant (FP7) was implanted, and a tube was inserted 1 mm posterior to the limbus and covered with a scleral patch graft. The patient was left aphakic, and primary posterior capsulorhexis was not performed to avoid the risk of tube blockage caused by vitreous humor.

The patient had an uneventful recovery except for hypotony on day 1 due to ciliary shutdown, which resolved spontaneously by day 2. On postoperative day 5, the cornea was clear, and the tube position was satisfactory and not touching the endothelium or iris **(Figure d)**. Fundal examination of the right eye revealed a cup-to-disc ratio of 0.8. The IOP remained normal for the first 6 postoperative months, after which anti-glaucomatous eyedrops were gradually resumed. At 4 years postoperatively, the patient's IOP remains stable on the maximum topical therapy.

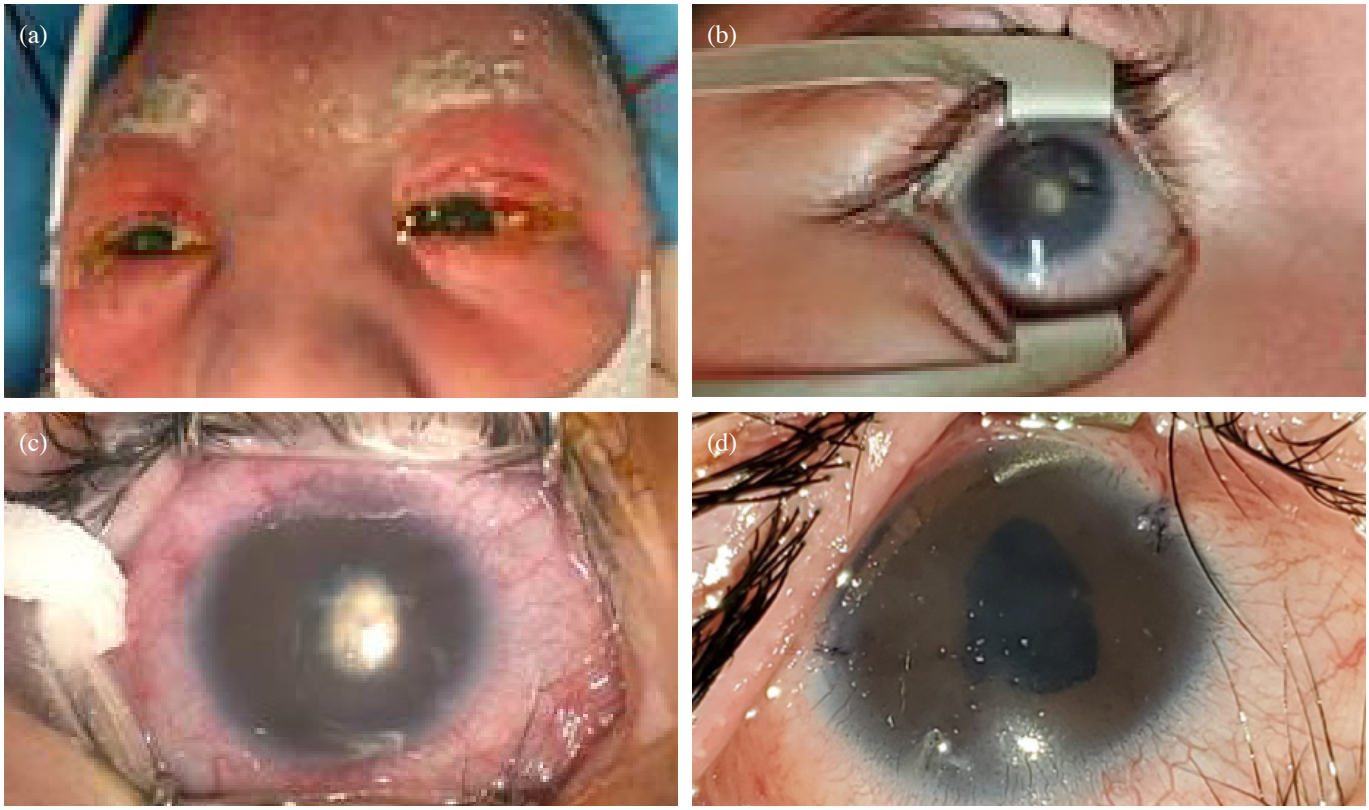

Figure. (a) Scaly skin lesions, microcephaly, flattened nasal bridge, and congenital cataract at birth, (b) corneal edema and buphthalmos in the right eye at age 1 year, (c) corneal edema, dense cataract, and extensive posterior synechiae in the right eye at age 2 years, and (d) the clear cornea and the Ahmed tube in the superotemporal region 5 days after lens aspiration with Ahmed glaucoma valve implantation.

Discussion

Studies of NLS-associated ocular conditions are limited. Craniofacial dysmorphism, proptosis, and exophthalmos are common features, exacerbated by associated eyelid abnormalities such as ectropion and hypoplasia or absence of lids.[1,3-5] Congenital cataract is less common and can be detected by prenatal ultrasound.[6,7] Other ocular issues reported include hypertelorism, microphthalmia, and the absence of eyebrows.[1,5,6]

Since 1971, fewer than 100 NLS cases have been reported worldwide. Most cases result in stillbirth or death in the early neonatal period.[8,9] At age 6 years, our patient is the oldest genetically confirmed NLS survivor reported to date and the first documented case of congenital glaucoma with, paradoxically, microphthalmos.

The mechanism of glaucoma in this patient remains undetermined. Microphthalmic eyes typically have normal or low IOP, similar to severe forms of persistent fetal vasculature with significant posterior segment involvement, which may undergo phthisis over time owing to the contraction of the hyaloid vessel remnant, which limits the globe's growth. In contrast, congenital glaucoma usually presents with large cloudy corneas and buphthalmos; gonioscopy typically reveals a characteristic Barkan's membrane, poorly differentiated trabecular meshwork, and high insertion of iris root secondary to trabeculodysgenesis.

Notably, pediatric glaucoma with microphthalmos is rare; typically these two conditions do not co-exist. Gonioscopy was not feasible in our patient because of significant corneal edema, and thus angle or lens-iris diaphragm abnormalities cannot be excluded. The posterior synechiae may be due to inflammatory adhesions of the iris to the lens following the three TSCPC procedures prior to the definitive surgery. The cataract was severe but not intumescent or swollen. The left eye remained microphthalmic. The reason why the right eye was more predisposed to glaucoma remains unclear.

We recommend repeated IOP screening in patients with NLS before age 1 year, because an initially normal IOP can be falsely reassuring, as demonstrated in our patient who had a normal IOP at 1 and 3 months of age. Two cases of juvenile open-angle glaucoma with ichthyosis have been reported.[10,11] Further gene linkage-based analysis may clarify the association between NLS and ichthyosis and glaucoma.

Management and surgical decisions should balance the risks and benefits as well as the life expectancy and visual potential of our patient. We initially opted for a conservative

approach to avoid invasive procedures or general anesthesia, given the likely limited life expectancy. However, the IOP remained refractory despite repeated TSCPC. As general anesthesia was required during the COVID-19 period, we proceeded with definitive lens aspiration and Ahmed glaucoma valve implantation. The patient has maintained normal IOP with maximum medications for 4 years. An adult Ahmed glaucoma valve (FP7) was used because the axial length was 23 mm at the time of the surgery, with adequate orbital space and surgical exposure.

The pars plana is not fully formed until the age of 8 to 9 months.[12,13] In pediatric glaucoma, the site of tube insertion should follow the pediatric age references, rather than the axial length of the buphthalmic globe. In our patient, an insertion site of 1.5 mm post-limbus was first attempted in view of the axial length of 23 mm, but iris strand straddling occurred. A second site of 1 mm post-limbus was therefore chosen for tube insertion. Microphthalmos may lead to the atypical site of pars plana.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data analyzed in this study are available from the corresponding author upon reasonable request.

Ethics approval

The patient was treated in accordance with the tenets of the Declaration of Helsinki. The patient provided written informed consent for all treatment and procedures and for publication.

References

1. *Manning MA, Cunniff CM, Colby CE, El-Sayed YY, Hoyme HE. Neu-Laxova syndrome: detailed prenatal diagnostic and post-mortem findings and literature review. Am J Med Genet A 2004;125A:240-9.*
2. *Acuna-Hidalgo R, Schanze D, Kariminejad A, et al. Neu-Laxova syndrome is a heterogeneous metabolic disorder caused by defects in enzymes of the L-serine biosynthesis pathway. Am J Hum Genet 2014;95:285-93.*
3. *Neu RL, Kajii T, Gardner LI, Nagyfy SF. A lethal syndrome of microcephaly with multiple congenital anomalies in three siblings. Pediatrics 1971;47:610-2.*
4. *Aslan H, Gul A, Polat I, Mutaf C, Agar M, Ceylan Y. Prenatal diagnosis of Neu-Laxova syndrome: a case report. BMC Pregnancy Childbirth 2002;2:1.*
5. *Dwivedi T, Gosavi M. Neu Laxova syndrome. Indian J Pathol Microbiol 2019;62:149-52.*
6. *Kong CW, Li YY, Au SLK, et al. Long-surviving Neu-Laxova syndrome confirmed by whole exome sequencing: a case report. Hong Kong Med J 2024;30:328-30.*
7. *Barekatain B, Sadeghnia A, Rouhani E, Soofi GJ. A new case of Neu-Laxova syndrome: infant with facial dysmorphism, arthrogryposis, ichthyosis, and microcephalia. Adv Biomed Res 2018;7:68.*
8. *Carder KR, Fitzpatrick JE, Weston WL. What syndrome is this? Neu-Laxova syndrome. Pediatr Dermatol 2003;20:78-80.*
9. *Ozcan D, Derbent M, Seckin D, et al. A collodion baby with facial dysmorphism, limb anomalies, pachygyria and genital hypoplasia: a mild form of Neu-laxova syndrome or a new entity? Ann Dermatol 2013;25:483-8.*
10. *Angmo D, Patil B, Agarwal R, Mohanty K, Singh A. A unique case of JOAG with lamellar ichthyosis with rickets: a case report and review of the literature. J Glaucoma 2016;25:e280-3.*
11. *Ichhpujani P, Thakur S, Kumar S, Singh RB. Juvenile open angle glaucoma with nonbullous congenital ichthyosiform erythroderma. J Glaucoma 2018;27:e180-2.*
12. *Hairston RJ, Maguire AM, Vitale S, Green WR. Morphometric analysis of pars plana development in humans. Retina 1997;17:135-8.*
13. *Gan NY, Lam WC. Special considerations for pediatric vitreoretinal surgery. Taiwan J Ophthalmol 2018;8:237-42.*