Case Report

Newborn with bilateral congenital cataracts: Never forget congenital rubella syndrome

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Abstract

A term, growth-restricted newborn presented with a sepsis-like picture, persistent pulmonary hypertension and bilateral cataracts. Initial review of prenatal and family history, as well as microbiological investigations were noncontributory. Following lenticular extraction, viral examination of the lenses confirmed the presence of rubella. Congenital rubella syndrome (CRS) presents with a constellation of signs and symptoms that overlap with many other conditions. The presence of bilateral cataracts in a newborn is a rare finding and this case is used to review the broad etiology of congenital cataracts. We propose a structured diagnostic approach for clinicians, remembering that CRS is a rare but possible etiology. The early diagnosis of CRS in this case, allowed us to initiate appropriate management and preventive measurements.

Keywords: *Bilateral cataracts; Congenital; Rubella*

Congenital cataracts are a rare finding in neonates, occurring in 4.24/10,000 live births (1). About half of the bilateral congenital cataracts (BCC) are inherited, either as an isolated trait or as part of a multisystemic condition or chromosomal abnormality. Other cases are associated with maternal exposures during pregnancy, including infections, medications, and irradiation (2,3). Congenital rubella syndrome (CRS) is a cause of bilateral congenital cataracts that presents with a constellation of ophthalmologic, cardiac, auditory, and/or neurologic findings that overlap with many other conditions, therefore, it should be kept in the differential diagnosis.

CASE PRESENTATION

A term male neonate born by uncomplicated spontaneous vaginal delivery developed respiratory distress at 5 minutes

of life requiring intubation and transfer to our centre with a diagnosis of persistent pulmonary hypertension and sepsis. He was born to a primigravid following an uneventful pregnancy other than hypothyroidism that was medically treated. Her serology was documented as protective: hepatitis B, HIV, and syphilis all nonreactive. The rubella IgG titer was interpreted as protective, though the value was in the indeterminate range (6.7 IU/mL; protective range ≥ 10 IU/mL). Ultrasounds were reportedly normal. She initially denied illnesses, sick contacts, international travel, or exposures to substances during pregnancy. However when specifically asked, she recalled a generalized maculopapular rash and mild fever for 2 to 3 days during her first trimester. Family history was noncontributory for consanguinity, inherited conditions or congenital abnormalities including ocular malformations.

On physical examination, the infant was nondysmorphic and symmetrically small (growth parameters <third centile). Pertinent findings included a 3/6 systolic murmur along the left sternal border, respiratory distress, and bilateral membranous cataracts (Figure 1A). There was no hepatosplenomegaly or rash, and he had normal muscular tone. He was extubated after 5 days, but required supplemental oxygen for the majority of his 30-day hospitalization. Infectious workup was negative for bacterial causes and ruled out congenital infections with cytomegalovirus, herpes simplex virus, toxoplasma, and parvovirus B19. Rubella IgG was positive (224.7 IU/mL), but

polymerase chain reaction (PCR) testing of urine and nasopharyngeal swabs were negative.

Other investigations revealed periventricular and thalamostriate vessel calcifications in the brain, an atrial septal defect, patent ductus arteriosus, and profound sensorineural hearing loss. His newborn screening (including galactosemia) and a chromosomal microarray were normal.

At 6 weeks of age, he underwent cataract surgery where microphthalmia and anterior segment dysgenesis were evidenced. The extracted cataract tested positive for rubella by PCR and further testing confirmed 2B rubella genotype,

Figure 1. Patient ophthalmological photos showing findings of congenital rubella syndrome. (A) Membranous cataract prior to surgery. (B) View of the salt and pepper retinopathy

Figure 2. Etiological classification of congenital and infantile cataracts. ROP Retinopathy of prematurity.

which is limited to Asia and Europe isolates. At that time, additional results were available including a positive rubella IgM and low IgG avidity. Repeat urine and nasopharyngeal rubella PCR testing were negative at 3, 4, and 6 months.

In follow-up in the infectious diseases clinic, further history from the mother revealed she was never vaccinated against rubella and had travelled to India early in her first

trimester when she developed the mild febrile illness. At the patient's 2-year visit, all growth parameters remained below the third percentile, he had cochlear implants and global developmental delay. He had salt and pepper retinopathy in this right eye with 20/160 vision and could only fixate and follow with his left eye due to macular atrophy (Figure 1B).

Table 1. Main genetic syndromes that can present with congenital cataracts

Chromosomal disorders			
Trisomy 21			
Trisomy 13			
Trisomy 18			
Unbalanced translocations/deletions/duplications*			
Metabolic diseases	Gene	Location	Inheritance
Galactosemia	GALT	9p13.3	AR
Refsum disease	PHYH	10p13	AR
Zellweger syndrome	PEX1	7q21.2	AR
MELAS	MT-TL1 and others	mtDNA	MT
Craniofacial disorders	Gene	Location	Inheritance
Smith-Lemli-Opitz	DHCR7	11q13.4	AR
Marshall syndrome	COL11A1	1q21.1	AD
Nance-Horan	NHS	Xp22.2-p22.1	XLD
Dermato-ectodermal disorders	Gene	Location	Inheritance
Rothmund-Thompson	RECQL4	8q24.3	AR
Cockayne syndrome	ERCC8	5q12.1	AR
CNS disorders	Gene	Location	Inheritance
Marinesco-Sjogren	SIL1	5q31.2	AR
Warburg Micro syndrome	RAB3GAP1	2q21.3	AR
Martsolf syndrome	RAB3GAP2	1q41	AR
Skeletal disorders	Gene	Location	Inheritance
Stickler syndrome	COL2A1/**	12q13.11	AD
Chondrodysplasia punctate	ARSE	Xp22.33	XLR
Renal disorders	Gene	Location	Inheritance
Lowe Syndrome	OCRL	Xq26.1	XLR
Limb disorders	Gene	Location	Inheritance
Rubinstein-Taybi	CREBBP/EP300	16p13.3/22q13	AD
Bardet-Biedl	17 genes		AR/DR/Triallelic
Oculo-dento-digital dysplasia	GJA1	6q22.31	AD
Miscellaneous	Gene	Location	Inheritance
Myotonic dystrophy	DMPK	19q31.32	AD

AD Autosomal dominant; AR Autosomal recessive; DR Digenic recessive; mtDNA Mitochondrial DNA; MT Maternal inheritance; XLD X-linked dominant; XLR X-linked recessive.

*Cataracts have been described in patients with deletion 5p- and other unbalanced translocations.

**Other genes also implicated including COL9A1/COL9A2 and COL11A1.

DISCUSSION

A recent systematic review and meta-analysis identified 62.3% of BCC cases presented in isolation, whereas the remainder were associated with other ocular disorders (22.7%) or existed as part of a systemic disorder (17.3%) (1). A variety of genetic and nongenetic etiologies have been identified, as summarized in Figure 2.

The majority of the 47 documented genetic causes of isolated cataracts (4) are inherited in an autosomal dominant fashion, however, autosomal recessive and X-linked modes of inheritance have also been reported (4). Table 1 lists the more commonly identified genetic syndromes associated with congenital cataracts. The diagnosis can be challenging, requiring a

thorough and systematic approach (Figure 3) including metabolic, genetic (such as gene panels and next-generation sequencing), and infectious investigations (5).

Among nongenetic causes of cataracts, congenital infections are the most frequently identified etiology (3,6,7). Following the introduction of universal rubella vaccination in Canada, the number of CRS cases significantly decreased (8). Susceptibility to rubella virus, however, is still a risk for pregnant women who are from or who travel to parts of the world where universal rubella vaccinations programs have not been nationally implemented, including many African, south-Asian and Indonesian countries (9). Therefore, CRS must remain on the differential diagnosis for congenital cataracts. In our case, the mother's

Figure 3. Diagnostic approach to congenital/infantile cataracts.

indeterminate serology likely reflected a recent infection that she acquired during the first trimester prior to her prenatal serologic testing.

Among adults, rubella infection is asymptomatic in 25 to 50% of the cases. Those with symptoms may have a self-limited febrile illness associated with rash, tender adenopathy or arthralgias. Pregnant women may also experience pregnancy loss or fetal growth restriction (10).

The virus is readily detected by PCR, from nose, throat, and urine, but can also be found in the blood and cataract tissue (11). The likelihood of obtaining a positive result from the nasopharynx or urine is greater if samples are collected close to the time of rash onset. Furthermore, 50% of the affected infants may not shed virus beyond 3 months of age. Therefore, negative PCR results alone are not sufficient to rule out a suspected case of CRS and serologic testing is also required (12). CRS is confirmed if rubella-specific IgM is detected within the first 3 months of life or a stable/rising rubella-specific IgG titre is seen over the first 7 to 11 months of life (13). An infant with CRS should be considered very contagious as they may shed the virus for up to a year. Appropriate contact precautions are indicated if they are hospitalized during this period (14,15).

CONCLUSION

Though BCC can be a diagnostic challenge, having a standardized approach allows the engagement of relevant specialists for optimal patient care. The finding of CRS necessitates urgent evaluation by a paediatric ophthalmologist and microbiological investigations. This case highlights the importance of rubella immunization, as the spread of rubella and CRS remain ongoing issues in regions with low vaccination rates.

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Informed consent has been obtained to publish this case report.

Contributors' Statements: ICF and DC examined the patient, initiated genetic, imaging, and metabolic investigations; conceptualized and drafted the initial manuscript; corresponded with all co-authors; and made the final revisions. JW examined the patient following the admission to the neonatal intensive care unit and followed the baby in the outpatient Infectious Diseases clinic. She participated

in drafting the manuscript, reviewed the literature, and revised the final manuscript. KM performed the ophthalmologic examination and carried out the cataract surgery as well as provided the lens for histopathological and virology investigation. He participated in writing the manuscript and in reviewing the literature. He provided photos and reviewed the final version. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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