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Case report

Prenatal diagnosis of Lowe syndrome in a male fetus with isolated bilateral cataract

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ABSTRACT

Background: Lowe syndrome is a rare disease characterized by the association of congenital cataract, hypotonia, followed by global psychomotor delay and intellectual disability, as well as progressive renal dysfunction, and renal failure occurring at around 20 years of age.
Case presentation: We discuss the case of a male fetus diagnosed with isolated bilateral cataract on the sonography performed at 21 + 5 weeks of gestation, confirmed by a fetal MRI at 23 weeks of gestation.
After ruling out infectious etiologies, a genetic consult was conducted at 26 weeks of gestation, and an amniocentesis was realized to search for a chromosomal cause, Norrie's disease and Lowe syndrome by Sanger analysis. A c.1351G > A (p.Asp451Asn) hemizygous mutation in *OCRL* gene was identified, inherited from the mother, which led to the diagnosis of Lowe syndrome in the fetus.
Conclusions: This is the first case of Lowe syndrome diagnosed prenatally on an isolated cataract, which allows the discussion of a more extensive etiological research when a male fetus is diagnosed with isolated bilateral cataract, by including notably a systematic analysis of the *OCRL* gene.

1. Introduction

Lowe syndrome is a very rare disease (prevalence of 1/500,000) characterized by the association of congenital cataract, neurological damage with hypotonia, moderate to severe intellectual disability, and proximal tubulopathy evolving to renal failure usually before the age of 20 [1]. It is an X-linked disease, caused by pathogenic variations of the *OCRL* gene [2].

Congenital cataract is a type of cataract that presents at birth or during early childhood. It has an estimated prevalence of 1–6 cases per 10,000 live births. A recent systematic review identified 62.3% of cases of isolated bilateral congenital cataract, while 22.7% were associated with another ocular anomaly and 17.3% with a syndromic condition [3]. Approximately 50% of all congenital cataract cases may have a genetic cause, and such cases are quite heterogeneous [4], including inherited nonsyndromic cataracts, cataracts arising from chromosomal aberrations, rare syndromic (isolated) cataracts arising from genetic anomalies, including for example Lowe syndrome, Norrie's disease, or congenital disorder of glycosylation.

Lowe syndrome is a known cause of prenatal cataract [5, 6], but molecular testing is not usually performed during pregnancy when a fetus only presents an isolated bilateral cataract with no associated signs of neurological or renal damage.

In this case report, we present a case of a prenatal diagnosis of Lowe syndrome in a male fetus with an isolated bilateral cataract.

2. Case report

This case is about the third pregnancy of a non-related couple with no prior medical history. The first two daughters of the family have had no

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health issues. Family history includes only a cataract occurring after 70 years old in the paternal grandmother and great-grandmother of the fetus.

In the first trimester of pregnancy, serum markers and sonography did not show any particular risk. Serum markers were 0.55 MoM (Multiple of Median) for β-HCG, 2.10 MoM for AFP and 0.78 MoM for oestradiol, leading to an evaluated trisomy 21 risk of 1/1100. The nuchal translucency was 1.2 mm for a cranio-caudal length of 74 mm.

The second trimester sonography, realized at 21 + 5 weeks of gestation, showed a eutrophic fetus (occipito-frontal circumference: 221.8 mm (50–90th percentile), abdominal perimeter: 210.3 mm (90–97th percentile), femoral length: 45.5 mm (<90th percentile)), male sex, no abnormalities in amniotic fluid quantity, but a bad visualization of the eye's lenses. A fetal MRI performed at 23 weeks of gestation confirmed the bilateral cataract without any anatomic malformations and with normal measurements.

A control sonography performed at 24 + 5 weeks of pregnancy revealed an isolated bilateral cataract, without any anomaly of ocular globe growth or associated anomalies (Figure 1a), compared to the normal aspect at 24 WG (Figure 1c). It was confirmed by sonography at 32 WG (Figure 1b).

Two MRI control performed at 25 and 30 weeks of gestation showed a normal brain evolution (Figure 3a–c), without any visible anomalies and confirmed an apparently isolated cataract (Figure 2a and c), compared to the normal aspect (Figure 2b and d).

A genetic counseling session was given to the family at 26 weeks of gestation, after ruling out infectious etiologies by maternal serum screening including toxoplasmosis, rubella and cytomegalovirus. During the genetic consultation, we inquired about exposures to infectious diseases, specifically maternal rashes and fever during pregnancy, travel history, pets at home and sick contacts, vaccination history. Moreover, there was no use of medications nor ionizing radiations exposure. This was a sporadic case of apparently isolated bilateral cataract, within the limits of what antenatal imaging can reveal. We discussed with the couple the fact that bilateral congenital cataracts could be either isolated, or associated with other ocular malformations, or part of a syndromic pattern. We explained that the ultrasound and MRI scans did not identify any malformation, growth anomaly or amniotic fluid quantity suggestive of a syndromic form. As the couple wanted to rule out as many syndromic aetiologies as possible, especially those with a risk of associated neurodevelopmental disorder or severe visual impairment. This couple was considering asking to terminate the pregnancy, as the French law allows, without an upper limit if the fetus had a severe impairment. An amniocentesis was offered to rule out a chromosomal abnormality, as well as certain rare but serious monogenic pathologies. At the time, the laboratories experts in genes which can cause prenatal cataract were contacted. Two laboratories agreed to perform the analysis in a very short time frame allowed by the pregnancy. We were thus able to propose the analysis of the *OCRL* and *NDP* genes. We further performed an amniocentesis to search for a chromosomal anomaly, Norrie's disease by Sanger sequencing analysis of the *NDP* gene and Lowe syndrome by Sanger sequencing analysis of the *OCRL* gene. Results of Sanger sequencing of the 24 coding exons of *OCRL* gene were available at 31 weeks of gestation, and revealed an hemizygous pathogenic variation of *OCRL* gene, c.1351G > A (p.Asp451Asn), which confirmed the diagnosis of Lowe syndrome.

This variation was predicted as pathogenic by bioinformatic software. It is located in the catalytic site of the protein, a very preserved functional domain during species' evolution. Previously, it had already been discovered in two other children with Lowe syndrome, and had also been considered pathologic. One of the two prior diagnosis had been a child who had also presented prenatal bilateral cataract and Lowe syndrome with neurological and typical renal features.

Following the diagnosis, the family asked for a medical termination of pregnancy which was performed at 32 weeks of gestation.

Further investigations revealed that the fetus' mother was a carrier of the mutation. We therefore informed her about other family members who could possibly carry the gene mutation. However, no other concerned woman accepted to perform the molecular screening.

3. Discussion

In this case report, we present a diagnosis of Lowe syndrome in a male fetus with only an isolated bilateral cataract as a clinical sign.

It is the first time, to our knowledge, that such a diagnosis is made in this context. We systematically listed all reported cases of Lowe's syndrome with antenatal manifestations (Table 1). In the literature, a case in 2013 is presented, which diagnoses Lowe syndrome with an isolated bilateral cataract as the first clinical sign [7]. An MRI was performed at 26 weeks of pregnancy and led to the discovery of a frontal periventricular cavity communicating with the anterior horn. The couple decided to follow with the pregnancy, and the diagnosis was made after birth, due to the fact that the patient began to present a Fanconi-type tubulopathy, which led to the analysis of gene *OCRL*. In 2018, a prenatal Lowe syndrome was diagnosed with the association of a bilateral cataract and hypoplasia of the gyrus on the MRI [8]. Cases of Lowe syndrome presenting isolated cataract have also been reported, but with only post-natal diagnosis [9, 10], which confirms the possibility of a phenotype first limited to an isolated bilateral cataract in prenatal Lowe syndrome.

This diagnosis is important to receive before birth, given the risk of intellectual deficiency (only 25% of *OCRL* patients will have an IQ > 70, 25% will have a mild to moderate mental retardation, and 50% will have severe to profound mental retardation [11]), and renal disease, starting with albuminuria due to proximal renal tubular dysfunction, with a progressive glomerulosclerosis leading to end-stage renal disease, usually between the second and fourth decade of life [12]. In the light of the prior articles, we can say that while the phenotype of Lowe syndrome is variable, it is severe in most cases, with a lifespan not exceeding 40 years

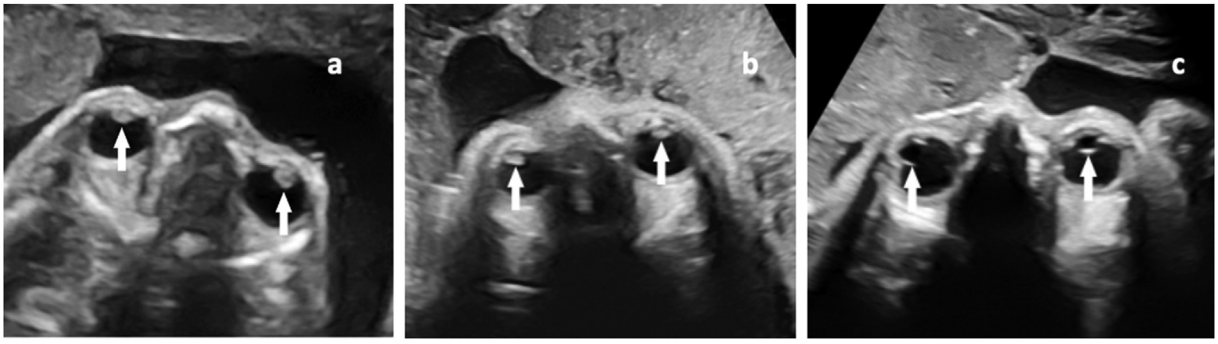

Figure 1. Sonography of our case at 24 + 5 weeks (a) and 32 weeks (b) of gestation confirming presence of an isolated bilateral cataract (→). Sonography of a normal fetus at 24 WG (c). Normal lenses (→) appear as thin hyperechoic circle located into the fetal orbits.

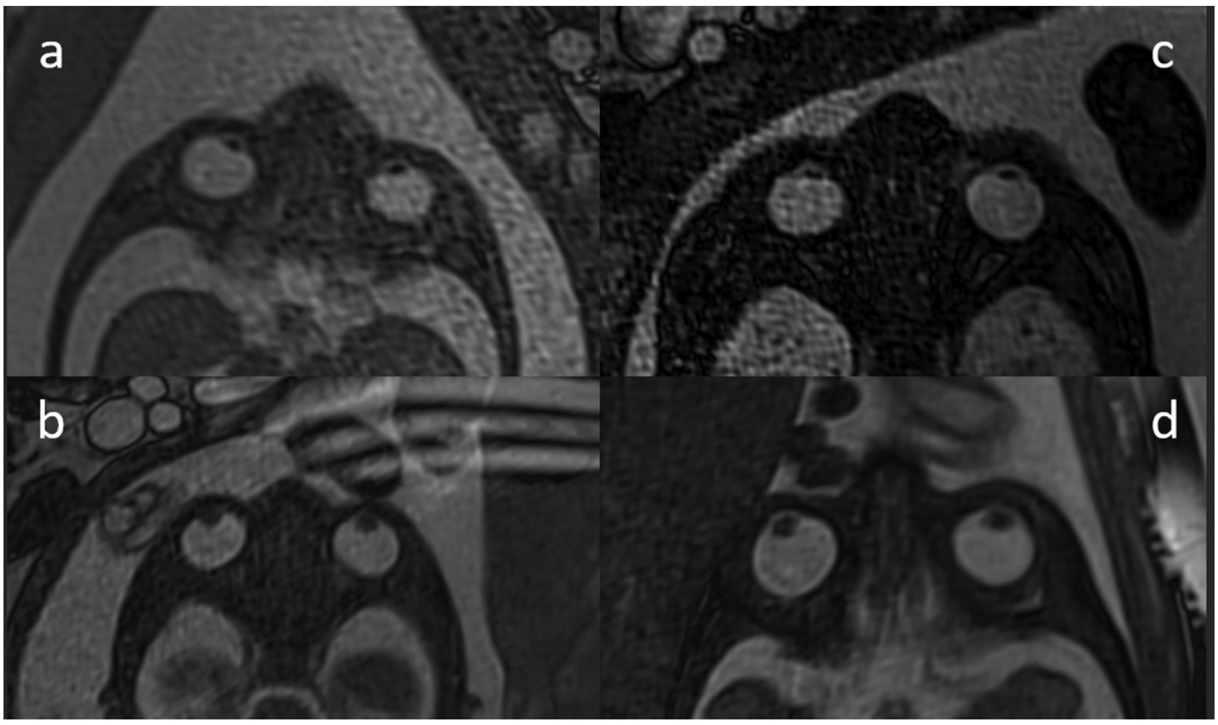

Figure 2. MRI of eyes (high resolution 3D T2 weighed image) showing abnormal size of crystalline of the fetus et 25 WG (a) in comparison to control at 26 WG (b). MRI of eyes (high resolution 3D T2 weighed image) of the fetus at 30WG (c) in comparison to control at 32 WG (d).

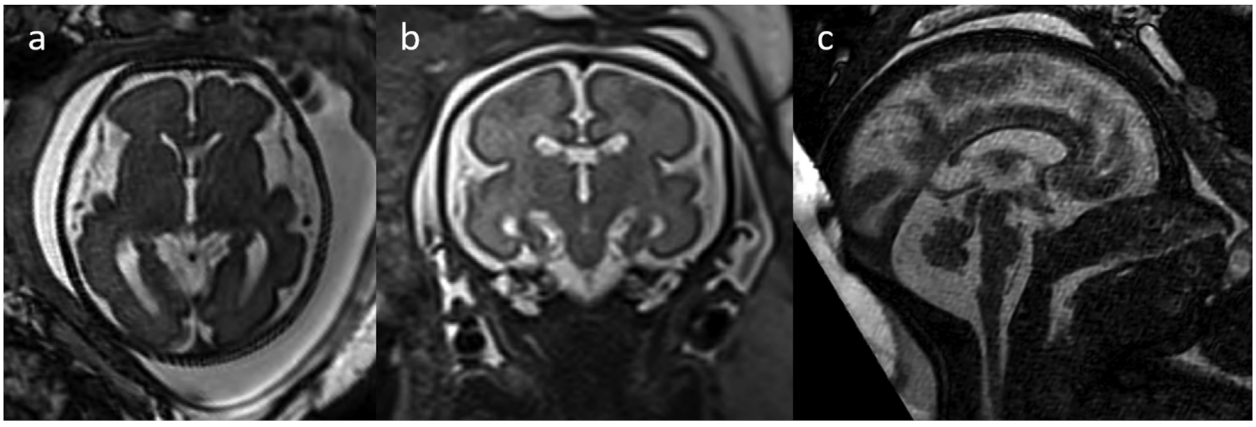

Figure 3. Normal brain MRI of the fetus at 30 WG: axial 2D HASTE T2-weighted image (a), coronal 2D HASTE T2-weighted image (b) and median line sagittal high resolution 3D T2-weighted image (c).

[13]. A possible argument against systematic testing for *OCRL* gene in prenatal bilateral cataract would be that it is a rare diagnosis, so the testing would rarely be positive. However, we argue that Lowe syndrome is of particular severity, so it remains an important diagnosis to make when possible.

With the evolution of sonography, the fetal lens can be identified as early as 13 weeks of gestation [14]. In France, the first sonography is done at 10 weeks of pregnancy and the second at 20 weeks of pregnancy, so by the time the second sonography is performed, fetal lens should be visible. If this is not the case, there should still be enough time to conduct thorough investigations on the etiology of the cataract before the birth. In France, termination of pregnancy is possible until delivery, if the mother asks for it, in the case that the fetus has an important probability to suffer from an untreatable and particularly severe disease. In the case of Lowe syndrome, the consequences are severe enough for a couple to decide to terminate the pregnancy for medical reasons.

In the light of this diagnosis and previous studies, we suggest widening the etiological search of an isolated bilateral cataract in male fetuses, by including a systematic analysis of the *OCRL* gene, after ruling out infectious etiologies. This case occurred when only Sanger sequencing analysis was possible to perform molecular analysis of the *OCRL* gene in France. Taking account of the seldom but severe diseases which present prenatal cataract as a first symptom and the fact that progress in molecular screening consisting in next generation sequencing makes it possible to offer panel or exome analysis, we are prompted to suggest that these investigations be proposed systematically in such cases, especially when there is no history of autosomal dominant non-syndromic congenital cataract in the family.

Table 1. Detailed information about antenatal reported cases of Lowe syndrome.

	Daskalakis et al 2010	Zephir et al 2016	Zhu et al 2017	Shalaby et al 2018		Our case
				Proband 1	Proband 2	
First trimester sonography	NA	NA	NA	NA	NA	No anomaly
Second trimester sonography	Bilateral lenticular opacities	Bilateral lenticular opacities	NA	NA	NA	Bilateral cataract
Third trimester sonography	NA	NA	Congenital cataract and enlarged posterior fossa	NA	NA	NA
Fetal MRI	No MRI	MRI at 26 weeks of pregnancy: bilateral cataract + frontal periventricular cerebral cavity	Hypoplasia of the gyrus	NA	NA	Bilateral cataract, normal brain evolution
Other clinical signs	Fanconi's syndrome at birth	NA	NA	Diagnosis of postnatal bilateral congenital cataract at birth + delayed speech	Postnatal congenital bilateral cataract + developmental delay + hypodontia	No other clinical sign
Diagnosis	Lowe syndrome (exact *OCRL* variant NA)	Lowe syndrome (exact *OCRL* variant NA)	Lowe syndrome: 633kb deletion encompassing gene OCRL on CMA	Lowe syndrome: *OCRL* pathogenic variant c.1964A > T	Lowe syndrome: *OCRL* pathogenic variant L c.1964A > T	Lowe syndrome: *OCRL* pathogenic variant L:c.1351G > A
Time of diagnosis	During neonatal period	Postnatal confirmation of pathogenic *OCRL* variant	NA	NA	At age of 19 years	31 weeks of gestation
Outcome	Baby delivered at 40 weeks of pregnancy	Couple decided to continue pregnancy, birth at 36 + 4 weeks of pregnancy	NA	NA	NA	Termination of pregnancy at 32 weeks of pregnancy

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Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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