Prenatal Diagnosis of Fetal Cataract: Case Report and Review of the Literature

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Key Words

Fetal • Ultrasound • Eye • Lens • Cataract • Congenital abnormalities • Aneuploidy

Abstract

Objectives: To report a case of prenatally diagnosed fetal cataract and conduct a systematic review of previously reported cases. **Methods:** Review of the literature based mainly on Pubmed search using specific keywords in order to list cataract causes diagnosed prenatally and in early childhood, isolated or associated with microphthalmia. **Results and Discussion:** A differential diagnosis list and specific prenatal diagnosis testing are suggested in order to offer the best management of this rare fetal condition.

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Background

Cataract is defined by the presence of any lens opacity. The incidence of congenital cataract ranges from 1 to 6 newborn infants out of 10,000 births [1].

Cataract development is strongly linked to the embryonic ocular development. The lens differentiates from the surface ectoderm before the sixth week of gestation, explaining the absence of cataract in case of late first-trimester fetal infection [2, 3].

A large number of genes causing congenital cataract have been mapped or cloned, but most of them are not yet

used in clinical practice. Several ocular development genes may be affected, thereby inducing a lens proteins synthesis default such as the major intrinsic protein, which plays a role in the cortical and nuclear formation of the lens [4–6]. A genetic cause is responsible for 30% of unilateral cataracts and 50% of bilateral cataracts. The transmission mode may be autosomal dominant, recessive, or X-linked. A neomutation is found in 25% of cases. In general, autosomal dominant transmission is associated with symmetrical and bilateral cataracts without systemic anomalies. A similar prevalence is observed in both sexes for unilateral and bilateral forms [7–9].

When a fetal cataract is observed, an early treatment should be started immediately after birth in order to prevent severe amblyopia or glaucoma.

Objectives

The improvement of ultrasound imaging allows the diagnosis of fetal ocular anomalies that could be easily missed in the postnatal period. Fetal ultrasound of the orbital region should also be offered when there is a family history of congenital ocular anomaly [10]. When a fetal cataract is observed, it is important to list the differential diagnosis possibilities and to offer the specific prenatal testing.

The following case report of fetal cataract associated with microphthalmia confirms the difficulty for prenatal diagnosis and management.

Fig. 1. Ultrasound cataract diagnosis at 30 weeks of gestation.

Fig. 2. Ultrasound of orbital region at 30 weeks of gestation with highly echogenic lens (full arrow); behind the lens, the primitive vitreous is visible (dashed arrow).

As differential diagnosis references were difficult to find, the aim of this paper is to report both diagnostic and therapy management algorithms for this severe fetal condition.

Data Sources

For the literature review, we searched the Pubmed database, without any restriction of publication date or journal, with recognized experts and cross-referencing relevant material.

Most causes of cataract in early childhood were identified using the following key words, which were combined using all possibilities: fetal, prenatal and congenital in association with cataract, lens, eye, ocular, orbit, small eye and microphthalmia, ultrasound. Among them, we checked those diagnosed prenatally. For each cause, a new search was done through Pubmed to complete the table data.

Results

Case Report

A 26-year-old pregnant woman was referred because the fetal lenses were not properly visualized during the morphological second trimester scan. At 27 2/7 weeks'

gestation, fetal ultrasound was normal, except for 2 highly echogenic lenses. Lens diameter was 5.8 mm, normal according to the literature [11–13].

Subsequent ultrasound assessment confirmed similar findings (fig. 1, 2). The patient's medical and family history was uneventful. No other fetal anomalies were evidenced. Then, no complementary invasive investigations were performed.

The pregnancy outcome was normal. The child was born vaginally at term with a birth weight of 2.995 kg and a length of 46.5 cm. Postnatal clinical examination revealed the presence of bilateral lower limbs clinodactyly (toes 4 and 5), low implantation of the ears, micropenis associated with a small right testicle. Development retardation and major axial hypotonia were also observed, with permanently clenched fists and positive Babinski's sign. Postnatal ophthalmological examination showed the additional presence of microphthalmia, not observed antenatally, with an ocular globe axis of 12 mm (5th centile: 16 mm; 95th centile: 21 mm) [14].

The combination of microphthalmia with fetal cataract, hypogenitalism and hypotonia suggested a final diagnosis of Micro syndrome [15].

This case report is interesting for several reasons. It confirms the difficulty for detecting microphthalmia prenatally and we could not find references about the differential diagnosis of fetal cataract associated with or without microphthalmia.

Table 1. Causes of fetal cataract already observed on prenatal ultrasonography

Syndrome	Frequency	Genetics and etiology	Principal ultrasonographic findings, in addition to cataract	Diagnosis
Facio-craniostenoses				
Apert syndrome [22–24]	1/160,000	AD; chrom. 10; FGFR2 gene	Acrosyndactyly with mitten hands and syndactyly of the feet; turribrachycephaly; clover leaf skull	US; causal mutation
Polymalformation and complex cranio-facial malformation syndromes				
Smith-Lemli-Opitz syndrome [25, 26]	1/20,000–1/30,000	AR; chrom. 11; DHCR7 gene	Microretrognathism; nasal anteversion; wide forehead; atrioventricular septum defect; renal hypoplasia; postaxial hexadactyly; IUGR affecting mainly the long bones; micropenis	US; maternal plasma with oestriol ↓; normal caryotype; from 13 W, AFP with 7-DHC ↑ and cholesterol ↓
Hallerman Streiff syndrome [27–29]	Rare	Sporadic; etiology unknown	Microcephaly; frontal bossing; micrognathia; bird head; beaky nose; teeth at birth; microphthalmia; small proportional stature	US
Rubinstein Taybi syndrome [30, 31]	1/125,000	AD/neomutation; CBP gene (chrom. 16) or EP300 (chrom. 22)	Large thumbs; large toes; small stature; antimongoloid palpebral fissures	US, difficult since not very specific
Musculoskeletal conditions				
Chondrodysplasia punctata syndrome [32, 33]	1/100,000	AR; PEX gene for peroxin 7; peroxysomal transfer ↓	Short femurs and humerus; proximal epiphyseal punctuations; congenital, early, bilateral, total cataract in almost 50% of the cases	US
Walker-Warburg syndrome [34–36]	1.2/100,000	AR; POMT1, POMT2, FKRP gene	Dandy-Walker malformation; hydrocephaly; lissencephaly; microcephaly; microphthalmia; retinal detachment	US; in utero muscle biopsy; genetic
Roberts syndrome [37, 38]	Very rare	AR probable; etiology unknown	Reductional anomalies of the limbs similar to phocomelia; round face; hypertelorism; microretrognathia; labiopalatine fissure	US; AC: premature centromere separation
Aneuploidism and chromosomal anomalies				
Trisomy 13 [39]	1/10,000		Holoprosencephaly; Fallot tetralogy; septal defect (VSD, ASD); omphalocele; hydronephrosis; club foot; cystic kidney; microphthalmia	US; fetal caryotype
Trisomy 18 [40]	1/8,000		Low ears; micrognathia; microphthalmia; omphalocele; septal defect (VSD, ASD); IUGR; overlapping fingers	US; fetal caryotype
Trisomy 21 [41, 42]	1/700		Nuchal translucency; mongoloid palpebral fissures; defect of nasal bones; cardiac (Fallot tetralogy), gastroduodenal (duodenal atresia), urinary (pyelectasis) anomalies; 40% has cataracts, but not necessarily in the antenatal period	US; fetal caryotype
Others [9, 41]	Triploidism, monosomy, deletion (5p), duplication			US; fetal caryotype
Cutaneo-dental disorders				
Nance Horan syndrome [43, 44]	Rare	Semi-dominant; chrom. X	In 100% of cases: male sex and congenital bilateral dense, most often total cataract. Also possible: microcornea (<10 mm in diameter); microphthalmia; long face; prognathism; large nose; large protruding ears; dental anomalies	US difficult; to our knowledge, only one publication exists on prenatal diagnosis of Nance-Horan syndrome
Metabolic disorders				
Zellweger syndrome [45–47]	1/50,000	AR	Prominent forehead; hypertelorism; mongoloid palpebral fissures; depressed nasal root; retrognathism; micrognathism; subcortical renal cysts; cardia defect; small stature; nuchal translucency; absent corpus callosum; abnormal neuronal migration (MRI)	US laborious; plasma and amniocytes: LCFA, with (C26:1) ↑ and (C26:0) ↑

Table 1 (continued)

Syndrome	Frequency	Genetics and etiology	Principal ultrasonographic findings, in addition to cataract	Diagnosis
Lowe's Oculo-cerebro-renal syndrome [48–50]	1/500,000	X-linked; recessive; OCRL1 protein gene, coding for Ptdlns(4,5)P2	Early congenital cataract in all patients affected; antenatal diagnosis of cataract is possible and has already been reported	US not very conspicuous; AFP: AC with Ptdlns(4,5)P2 ↓ and abnormal PCR mRNA of OCRL1
Infectious diseases				
Rubella [3, 51, 52]	First cause of congenital cataract	After the 6th W, the lens vesicle is separated, limiting viral access	Cardiac malformations (septal defects, pulmonary artery hypoplasia); microphthalmia; microcephaly; polycystic kidneys; IUGR; splenomegaly; hepatomegaly	US; serology; AFP (culture, PCR)
Varicella [9, 51]			Limb hypoplasia; microphthalmia; positional anomalies of the extremities; intracranial calcifications; polyhydramnios; hydrocephaly; highly echogenic liver	US; serology; AFP (culture, PCR)
CMV [51, 53]	2.3/100–4/100		Hepatosplenomegaly; microcephaly; IUGR; cerebral/hepatic calcifications; highly echogenic intestine; ventriculomegaly	US; serology; AFP (culture, PCR)
Herpes simplex [9, 51]			Microcephaly; microphthalmia; hydranencephaly; multicystic encephalomalacia; ascites; intrahepatic calcifications	US; serology; AFP (culture, PCR)

Toxins

Corticosteroids, antipsychotic drugs such as chlorpromazine [54, 55]: harmful effects on lens but no publications of fetal cataract.
 Coumarin derivatives [56, 57]: punctuated chondrodysplasia, nasal hypoplasia, brachytelephalangic, microphthalmia, reports of cataract.

Idiopathic

Most fetal cataracts are idiopathic, but no accurate data are available on the percentage.

AD = Autosomal dominant; AR = autosomal recessive; chrom. = chromosome; US = ultrasound; AFP = amniotic fluid puncture; AC = amniocyte culture; 7-DHC = 7-dehydrocholesterol; AFP = α -fetoprotein; IUGR = intrauterine growth retardation; LCFA = long chain fatty acids.

Systematic Review of Cataract Already Observed on Prenatal Ultrasonography

Table 1 reports congenital cataract causes occurring in the fetus. It is important to notice that some disorders have never been reported prenatally and are therefore not included in the differential diagnosis, such as Steinert myotonic dystrophy, Turner syndrome [16, 17], Alport syndrome [18], Stickler syndrome and glucose-6-phosphatase dehydrogenase deficiency [19, 20]. Cataract due to in utero fetal irradiation may occur after some delay and then may not be identified during fetal life. Finally, only a single case of fetal cataract secondary to toxoplasma infection has been reported and we did not include it in the table [21].

Some disorders reported in table 1 can be associated with both fetal microphthalmia and cataract: Hallerman-Streiff, Walker-Warburg and Nance Horan syndrome; trisomy 13 and 18; rubella, varicella, herpes simplex fetal infection; coumarin derivatives used during

pregnancy. Other syndromes can present cataract and can be associated with microphthalmia, but up to now, these rare syndromes were confirmed only postnatally, such as Micro syndrome (mental retardation, microcephaly, hypogenitalism, hypotonia, atonic pupils, corpus callosum anomalies...) [15, 58], Martsolf syndrome (mental retardation, small stature, hypogonadism, microcephaly...) [58–60], clinical signs in the spectrum of phenotypes that range from Micro syndrome to Martsolf syndrome [61], cerebro-oculo-facio-skeletal syndrome [62, 63], and some chromosomal anomalies such as 46,XX,inv(2)(p21q31) [64].

One case of antenatal severe bilateral microphthalmia associated with cerebro-ocular-facio-skeletal syndrome was reported antenatally on ultrasound findings, mainly micrognathia, multiple joint contractures and rockerbottom feet. But so far, no prenatal cataract has been described though this may be part of the clinical picture [65].

Table 2. Proposal of management and differential diagnosis in cataracts detected on fetal ultrasonography, in combination with antenatal or postnatal microphthalmia

Table 2 summarizes a management proposal in case of US fetal cataract diagnosis in combination with microphthalmia. Microphthalmia could sometimes be missed on prenatal ultrasound, as in this case report. Microphthalmia can be associated with microspherophakia, defined by the presence of an abnormally small lens. According to our knowledge, isolated fetal microspherophakia has never been reported in the literature.

Discussion

This case report was the opportunity to review fetal cataract causes and to offer a management algorithm. The finding of associated ultrasound signs is important in order to focus on the final diagnosis, in this case, Micro syndrome. Prenatal orbital region ultrasound should be part of the level II fetal scan as it could detect fetal cataract and other ocular disorders, such as retinoblastoma [66, 67].

The prenatal diagnosis of ophthalmologic abnormalities ensures a postnatal follow-up. In case of unilateral cataract, treatment should be started as soon as possible as unilateral visual stimulation is dependant upon a more

rapid discontinuation of the cellular neuronal development. Moreover, a break in the neuronal density curve is observed from the fourth week of life in the newborn [68]. In bilateral forms, this break occurs only after 8 weeks. In the severe forms, surgery is then imperative within the following weeks. The aim of this early intervention is to limit the risk of amblyopia. Treatment of cataracts in the newborn includes etiologic findings, surgical treatment, treatment of amblyopia and long-term supervision. Long-term follow-up is essential, whether or not surgery is performed [9]. If the cataract is complicated by nystagmus, strabism or if amblyopia correction is not conclusive, visual prognosis is poor.

In conclusion, this case report and proposal of management algorithm should encourage ultrasonographers to perform an accurate examination of the eyes in order to detect ocular anomalies, such as cataract, microphthalmia or persistent hyperplastic primary vitreous [69].

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