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Eye Abnormalities in Fryns Syndrome

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Abstract

Fryns syndrome is a rare, generally lethal, autosomal recessive multiple congenital anomaly (MCA) syndrome first described in 1979. Patients with the syndrome present with the classical findings of cloudy cornea, brainmalformations, diaphragmaticdefects, and distal limb deformities. Over 70 patients have been reported revealing a wide variety of phenotypic features. Although initially considered a major feature of Fryns syndrome, cloudy cornea has been relegated as a minor diagnostic sign and not commonly reported in patients since the original description. However, eye findings per se are not uncommon. Abnormal eye findings occasionally reported in Fryns syndrome potentially result in amblyopia and blindness, profoundly affecting neurologic outcome of those who survive the neonatal period. We reviewed 77 reported patients with Fryns syndrome and summarized the abnormal eye findings identified in 12 of the reported cases. In addition, we contribute three new patients with Fryns syndrome, one of which demonstrated unilateral microphthalmia and cloudy cornea.

Keywords

Fryns syndrome; autosomal recessive; eye findings

INTRODUCTION

Fryns syndrome first described in 1979 in two stillborn female siblings is an autosomal recessive multiple congenital anomaly (MCA) syndrome. Several classical findings are noted including cloudy cornea, brain anomalies, diaphragmatic defects, and distal limb deformities [Fryns et al., 1979]. Over 70 cases have been reported revealing a wide range of variability in phenotypic expression modifying the syndrome's earliest description [Ayme et al., 1989; Davis and Samarakkody, 2002]. The definition of Fryns syndrome and features required for the diagnosis clearly influences the number of reports and clinical variability. Although initially considered a major feature of Fryns syndrome, cloudy cornea has not been reported frequently in this syndrome. In addition to cloudy cornea, other ocular

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findings have been reported including hypertelorism, microphthalmia, Bowman irregularities, thickened posterior lens capsule with vacuolization of lens fibers, and retinal dysplasia with rosettes and gliosis [Cursiefen et al., 2000]. Retinal gliosis and cloudy cornea may occur in an estimated one-fifth to one-third of those affected with this rare often lethal disorder [Van Hove et al., 1995].

Major criteria for diagnosis of Fryns syndrome typically include postero-lateral diaphragmatic defects with lung hypoplasia, distal limb hypoplasia, and craniofacial dysmorphism. Minor malformations are plentiful and have been documented in all organ systems; often contributing to significant morbidity [Fryns and Moerman, 1998; Ramsing et al., 2000]. Chromosome studies in patients presenting with Fryns syndrome are generally normal although the constellation of birth defects may resemble conditions with known chromosomal abnormalities such as 12p tetrasomy and chromo-some 1q duplication [Clark and Fenner-Gonzales, 1989; Enns et al., 1998]. The incidence of Fryns syndrome is estimated at 1 in 12,000 live births [Fryns, 1990]; however, the prevalence may be increasing secondary to improved surgical intervention and intensive care management of the newborn with the syndrome [Fryns et al., 1989; Vargas et al., 2000].

Although purported to be the most frequent nonchromosomal MCA syndrome associated with congenital diaphragmatic hernia (CDH), accounting for 4–10% of cases, CDH has not been a feature in 14 reports of Fryns syndrome [Van Hove et al., 1995; Davis and Samarakkody, 2002]. Lack of CDH is associated with milder lung hypoplasia, fewer complex cardiac malformations, and mitigated neurologic impairment [Van Hove et al., 1995]. Marked developmental retardation is reported in all survivors with this syndrome [Neville et al., 2002]. Autosomal recessive is the most likely inheritance pattern for Fryns syndrome [Davis and Samarakkody, 2002]. Herein, we reviewed 77 reported cases of Fryns syndrome and summarized the abnormal eye findings identified in 12 of the cases and contribute three new patients.

CLINICAL REPORTS

Patient 1 was a 36-week, large for gestational-age white female born to an unrelated couple. The 29-year-old mother had a history of three prior spontaneous abortions. A sibling had no reported malformations. Delivery by caesarian section was complicated by marked respiratory distress requiring intubation and ventilatory support. Chest radiographs showed a left diaphragmatic hernia with large amounts of bowel loops in the left chest. Echocardiography demonstrated coarctation of the aorta, while a head ultrasound detected a right hemisphere abnormality. Physical findings included facial dysmorphism with right microphthalmia, corneal clouding, hypoplastic right side of face, frontal bossing, flat nasal bridge, low-set right ear, and mild nail hypoplasia. Surgical options and prognosis issues were discussed with the family, who desired no heroic intervention. The patient subsequently expired shortly after extubation on the first day of life. Findings at autopsy included hypoplastic bilateral lungs, a posterior-lateral diaphragmatic defect, aortic isthmic coarctation, patent ductus arteriosus/foramen ovale, and pancreatomegaly. The ocular findings noted at autopsy included the right microphthalmia with cloudy cornea and a hypoplastic right optic nerve. Neuropathologic examination showed the right side of the

brain to be underdeveloped, as compared to the left. Multifocal white and deep gray matter microcalcifications, microscopic focal cerebellar cortical dysplasia and patchy cerebral, cerebellar and brainstem white matter gliosis were observed. A dilated third ventricle, less prominent uncus, and shallow parietal groove were noted. Chromosomal studies reported a normal 46,XX karyotype.

Patient 2 was a 32-week, appropriate-for-gestational age white female who was born by vaginal delivery to a 26-year-old primigravid and an unrelated father secondary to premature rupture of membranes. An ultrasound at 28 weeks gestation demonstrated a left diaphragmatic hernia and polyhydramnios. Amniocentesis at that time revealed a normal 46,XX karyotype. Apgar scores at delivery were 1 at 1 min and 2 at 5 min. A head ultrasound revealed absence of the roof of the third ventricle with enlargement of the lateral and third ventricles. The patient was maintained on high frequency ventilation, but was unable to ultimately convert to conventional support. She expired at the age of 1 week secondary to respiratory failure. External dysmorphic features included narrow palpebral fissures; low-set, posteriorly rotated ears; a webbed, short neck; wide nipples with a hypoplastic right nipple; and abnormal thumb insertion. In addition to the above findings, at autopsy the lungs were found to be bilaterally hypoplastic. The ductus arteriosis and foramen ovale were patent. Skeletal abnormalities included markedly shortened cervical vertebrae with complex segmentation anomalies, including butterfly and hemivertebrae. Neuropathologic findings included nodular anterior cervico-medullary neuroglial heterotopia, congenital cerebral aqueductal stenosis with moderate hydrocephalus, and partial agenesis of the corpus callosum.

Patient 3 was a 37-week, small-for-gestational-age black female born by cesarean section secondary to breech presentation. The 28-year-old mother and father had a nonconsanguineous relationship. Two older children by the couple were normal. Respiratory distress requiring aggressive intervention and obvious dysmorphia was present at birth. A right diaphragmatic hernia was evident on chest radiograph. Critical aortic stenosis/atresia with retrograde filling of the aortic arch, mitral valve stenosis/atresia with no evidence of forward flow through the valve, and a large ventricular atrial defect were diagnosed by echocardiogram. Facial dysmorphia included severe cleft lip/palate, upward-slanting palpebral fissures, and low-set, posteriorly rotated ears. The anus was imperforate, and a sacral dimple was present. Fingers were tapered and toenails were hypoplastic. Chromosomal analysis was normal (46,XX). Given her poor prognosis and the family’s request, comfort measures were continued while supportive care was withdrawn. The patient expired shortly thereafter.

DISCUSSION

The above patients typify the phenotypic variability associated with Fryns syndrome. All three patients shared findings of diaphragmatic defects and respiratory decompensation; limb abnormalities including tapered fingers, hypoplastic nails, and/or abnormal thumb insertion; and craniofacial dysmorphism all consistent with the diagnosis of Fryns syndrome. Moreover, all had normal chromosome studies but significant morbidities contributed to their demise. At autopsy, Patients 1 and 2 demonstrated bilateral lung

hypoplasia, while no autopsy was performed on Patient 3. Of the group, Patient 3 was unique with multiple cardiac valve stenoses, ventricular/atrial septal defects, and imperforate anus. She was also a black infant, which has not been previously reported in the literature with Fryns syndrome. Patient 2 had congenital cerebral aqueductal stenosis, partial agenesis of the corpus callosum, and shortened cervical vertebrae with complex segmentation. Patient 1 was born with right microphthalmia, corneal clouding, and a hypoplastic right optic nerve with a neuropathologic exam showing underdevelopment of the right side of the brain.

Table I shows the eye abnormalities associated with Fryns syndrome. In our review of 77 reported cases, five were excluded from further investigation secondary to lack of chromosomal analysis. For example, three patients with microphthalmia were cited [Ayme et al., 1989; Henkel et al., 1993; Arnold et al., 2003] but only two patients were reported with normal chromosomes and included in Table I. The patient reported by Arnold et al. [2003] presented with microphthalmia (right) and anophthalmia (left), although Hall [2003] raised questions regarding the diagnosis of Fryns syndrome in this patient. In addition, we previously reported a newborn with anophthalmia [Pierson et al., 2002] and features consistent with Fryns syndrome. This large-for-gestational age infant at autopsy had no evidence of normal residual eye tissue in either orbital region.

Some eye anomalies are rare, such as anophthalmia, but identified in several MCA syndromes. For example, the Mendelian Inheritance in Man Database distinguishes 18 discrete combinations of anophthalmia and other malformations, while the London Dysmorphology Database delineates 46 syndromes with microphthalmia/anophthalmia [Steiner et al., 2002]. Moreover, distinction between anophthalmia and extreme microphthalmia is often blurred, with the former elucidated only by histological examination. The mode of inheritance is variable with autosomal dominant, autosomal recessive, sex-linked, and sporadic patterns reported [O'Keefe et al., 1987].

Fryns syndrome may have overlapping ocular features with other syndromes such as Matthew Wood syndrome. These two syndromes share normal chromo-some studies, ocular findings (e.g., anophthalmia and microphthalmia) and pulmonary anomalies. Matthew Wood syndrome is rare with only six reports in the literature and characterized by pulmonary agenesis, microphthalmia, diaphragmatic defect, and intrauterine growth retardation [Spear et al., 1987; Seller et al., 1996; Berkenstadt et al., 1999]. Two patients with Matthew Wood syndrome were siblings and had clinical anophthalmia and pulmonary hypoplasia but no diaphragmatic hernias. The combination of anophthalmia and pulmonary agenesis is rare, with only two clinical reports other than Matthew Wood syndrome described; one of which demonstrated frontal encephalocele [Ostor et al., 1978], and the other patient had hydrocephalus [Toriello et al., 1985]. Other Fryns syndrome reports did not show intrauterine growth retardation but had other multiple congenital anomalies including abnormal facies, optic nerve hypoplasia, an accessory spleen, and distal limb defects not reported in Matthew Wood syndrome.

Optic nerve hypoplasia has been reported in Fryns syndrome identified by magnetic resonance imaging and confirmed at autopsy [Cunniff et al., 1990; Van Hove et al., 1995]. There is a reported patient with optic nerve hypoplasia at the age of 33 months functioning

in the severe to profound range of mental retardation [Cunniff et al., 1990]. He required close inspection of objects and was observed to have frequent head movements from side to side. His visual problems were probably related to underdevelopment of post-chiasmatic optic tracts with subsequent limitation of true cognitive capabilities.

Amblyopia and blindness are also reported to occur with other ocular manifestations in Fryns syndrome and presented in Table I. Amblyopia can be defined as poor vision caused by abnormal visual development secondary to abnormal visual stimulation [Wright, 2003]. Children are at risk for developing amblyopia, which is considered to be in the spectrum of visual loss, between birth and age of 7 years [Keech and Kutschke, 1995].

Corneal clouding has also been reported in nine Fryns syndrome patients in the literature, the cause of which is unknown. Corneal clouding has been ascribed to anterior segment developmental anomalies, congenital infections, trauma, corneal dystrophies, and corneal manifestations of metabolic disorders [Nischal, 2003]. Corneal clouding is also recognized as a sign of infantile glaucoma or buphthalmos [Hanssen et al., 1992]. This patient with Fryns syndrome also presented with megalocornea. Megalocornea may be either unilateral or bilateral. The cornea is typically of normal thickness. However, the intraocular pressure is elevated secondary to structural maldevelopment of the anterior segment and angle structures producing optic nerve damage and potential visual loss. Amblyopia, in this pediatric population, can sometimes lead to more severe loss of vision than caused by optic nerve damage itself. Opacification of the crystalline lens, reported in one patient with Fryns syndrome can be a source of considerable visual impairment in those who survive with Fryns syndrome.

Ocular histologic studies are not commonly reported in Fryns syndrome; the etiologies of atypical features remain unclear. Cursiefen et al. [2000] reported on one patient with cloudy cornea and normal histological corneal epithelium. An electron microscopic study showed absence of banded collagen fibrils in the Descemet’s membrane, demonstrating corneal endothelial dysfunction.

Hypertelorism, common in many MCA syndromes, is a nonspecific anatomical description reported in 29 patients with Fryns syndrome but not included in our summary table on eye abnormalities in Fryns syndrome. Severe hypertelorism is associated with exotropia. Hypertelorism may be secondary to arrest of the greater wings of the sphenoid fixating the orbits in a widely separated position [Miller and Newlin, 2003].

In summary, abnormal eye findings may occasionally be present in patients diagnosed with Fryns syndrome as illustrated in our review potentially resulting in amblyopia and blindness which profoundly affects neurologic outcome of survivors. The discussion of abnormal eye findings should not be minimized when describing Fryns syndrome and providing genetic counseling to families. Likewise, careful ophthalmic examination in future patients with Fryns syndrome who survive the neonatal period should be undertaken to detect lesions and provide appropriate treatment as well as to determine an accurate frequency of eye abnormalities in this classical genetic syndrome.

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TABLE I.

Eye Abnormalities in 12 Previously Reported Patients With Fryns Syndrome and our Three new Patients

	Our patients				
Eye abnormalities	**1**	**2**	**3**	**Number of eye abnormalities reported**	**Literature[a]**
Anophthalmia	−	−	−	2	N, O
Microphthalmia, unilateral	−	+	−	1	O
Microphthalmia, bilateral	−	−	−	1	E
Macrophthalmia	−	−	−	1	I
Corneal clouding, unilateral	−	−	−	1	G
Corneal clouding, bilateral	−	+	−	8	A(2), B, C, D, F, L, M
Attenuation of retinal arteries	−	−	−	1	B
Cataracts	−	−	−	1	J
Buphthalmos, unilateral	−	−	−	1	H
Megalocornea	−	−	−	1	H
Coloboma of the iris, unilateral	−	−	−	1	M
Coloboma of the iris, bilateral	−	−	−	1	M
Retinal dysplasia	−	−	−	2	E(2)
Hypoplastic optic tracts by MRI	−	−	−	1	K
Hypoplastic optic tracts at autopsy	−	−	−	1	G
Optic nerve, pallor	−	−	−	1	K
Prominent eye globes	−	−	−	1	M
Total number of abnormal eye findings seen in 12 of 77 reported patients				26	

[a]A: Fryns et al. [1979], B: Young et al. [1986], C: Samueloff et al. [1987], D: Moerman et al. [1988], E: Ayme et al. [1989], F: Bamforth et al. [1989], G: Cunniff et al. [1990], H: Hanssen et al. [1992], I: Ficcadenti et al. [1993], J: Riela et al. [1995], K: Van Hove et al. [1995], L: Cursiefen et al. [2000], M: Ramsing et al. [2000], N: Pierson et al. [2002], O: Arnold et al. [2003]. Two of two patients reported by Fryns et al. [1979] and two of eight patients reported by Ayme et al. [1989] were found with the specific eye findings listed.