

# Fryns syndrome: a lethal mesoectodermal birth defect with variable expression in a pair of monozygotic twins

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## ABSTRACT

**We report a pair of twins with variable expressions of Fryns syndrome, both of whom died in the neonatal period. The syndrome is characterised by craniofacial dysmorphism, diaphragmatic hernia and distal limb hypoplasia. With this report, there are a total of 83 cases reported in the literature and this further serves to illustrate the clinical variability of this disorder.**

**Keywords: congenital diaphragmatic hernia, craniofacial dysmorphism, Fryns syndrome, limb hypoplasia, monozygotic twins**

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## INTRODUCTION

Fryns syndrome is an autosomal recessive, genetically-determined condition with variable expression.<sup>(1,2)</sup> As originally described, the major diagnostic criteria include abnormal facies, small thorax with widely-spaced hypoplastic nipples, distal limb and nail hypoplasia, and diaphragmatic hernia with pulmonary hypoplasia.<sup>(3)</sup> More than 70 cases have been reported since the first report in 1979, 86% of which have been associated with an early lethal outcome.<sup>(4)</sup> We report a pair of twins with Fryns syndrome, with one of the twins having characteristic coarse hirsute facial appearance, bilateral cleft lip and palate, cardiac and renal anomalies, dilated bowel, distal limb abnormalities, and the other twin having unilateral cleft lip palate, frontal encephalocoele, polymicrogyria and nail hypoplasia. However, diaphragmatic hernia, which is considered a cardinal feature in this condition, was absent in the second twin.

## CASE REPORTS

A 26-year-old mother delivered a pair of identical twins, a product of first-degree consanguinity, by spontaneous vaginal delivery at term. There was polyhydramnios. Karyotyping was normal and alpha-foetoprotein was in the normal range.

## Twin 1

The first twin was a male neonate who weighed 1,800 g. The Apgar scores were 3 and 5 at one and five minutes, respectively. The child was electively intubated in view of worsening respiratory distress due to congenital diaphragmatic hernia (CDH). Clinical examination revealed multiple congenital anomalies associated with left CDH suggestive of Fryns syndrome. They included coarse facial features, hirsutism, hypertelorism, microphthalmia, corneal clouding, broad nasal root, absent malformed right ear, malformed left ear with absent external auditory canal, very short neck, and a scaphoid abdomen due to the large CDH with herniation of bowel in the thoracic cavity (Fig. 1). The limb abnormalities included nail bed hypoplasia, simian crease in right hand, and increased space between first and second toes (Fig. 1d). Echocardiography show a large ventricular septal defect and an atrial septal defect. The left pulmonary artery could not be visualised. Cranial ultrasonography (US) revealed dilated lateral ventricles, while renal US was normal.

## Twin 2

The second twin was a male neonate who weighed 2,100 g. The Apgar scores were 5 and 6 at one and five minutes, respectively. Clinical examination revealed multiple congenital anomalies suggestive of Fryns syndrome. They included coarse facial features, hirsutism, hypertelorism, microphthalmia, corneal clouding, broad nasal root, bilateral cleft lip and palate, and nail bed hypoplasia (Fig. 2a). Echocardiography revealed a large ventricular septal defect. The central nervous system abnormalities included a frontal encephalocoele, malformations of gyration and sulcation, particularly around the central sulcus, corpus callosum agenesis and absent septum pellucidum (Fig. 2b). Congenital diaphragmatic hernia was not present. Clinical examination and US of abdomen did not show any abnormality of the genitourinary tract.

Twin 1 died at eight hours of age after withdrawal of life support following failure of maximal medical

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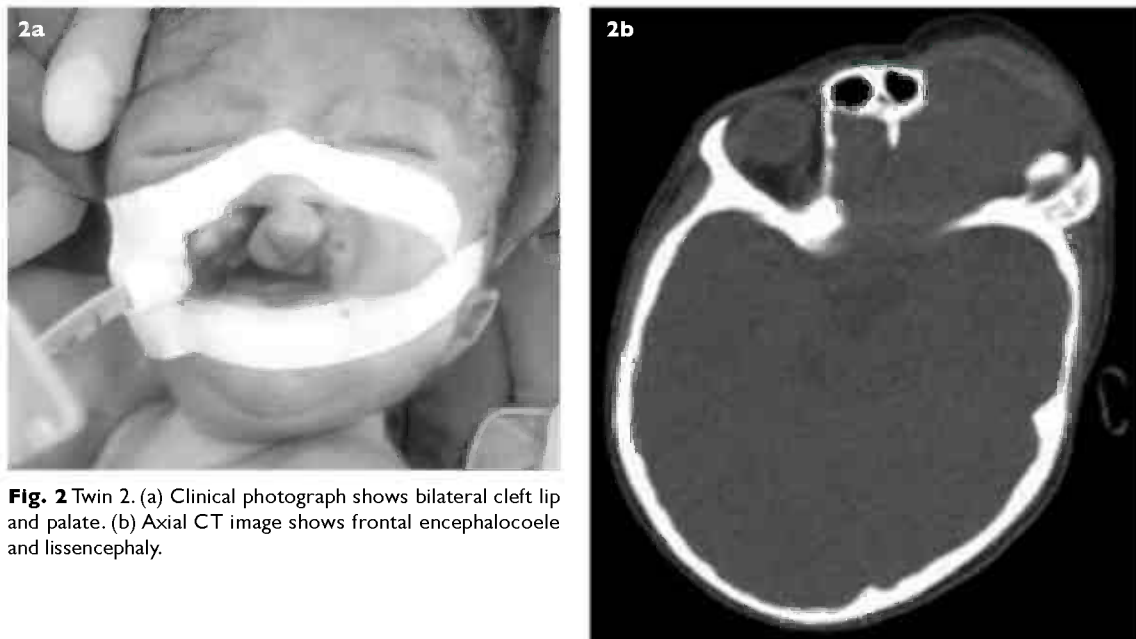
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**Fig. 1** Twin 1. (a) Clinical photograph shows bilateral cleft lip and palate, hirsutism, wide-spaced nipples, narrow thorax, and a scaphoid abdomen. (b) Clinical photograph shows generalised hirsutism. (c) Clinical photograph shows left ear malformation, with low set ears. (d) Clinical photograph shows a wide space between the first and second toes, and nail bed hypoplasia. (e) Chest radiograph shows herniation of bowel into the left hemithorax and significant mediastinum shift toward the right.



**Fig. 2** Twin 2. (a) Clinical photograph shows bilateral cleft lip and palate. (b) Axial CT image shows frontal encephalocele and lissencephaly.

therapy for pulmonary hypoplasia with severe persistent pulmonary hypertension of the newborn. Twin 2 died on the 15th day of life due to congestive cardiac failure. Autopsies of both twins were not done, according to the wishes of the mother.

## DISCUSSION

Fryns syndrome is an autosomal recessive, multiple congenital anomaly syndrome with an incidence of one in 10,000 births.<sup>(5)</sup> It is characterised by CDH, unusual facies and distal limb hypoplasia. The spectrum of distal limb hypoplasia includes short and broad hands, short digits, short or absent terminal phalanges, hypoplastic or absent nails, and clinodactyly.<sup>(6)</sup> A significant inter- and intrafamilial phenotypic variability, as well as discordant phenotype in monozygotic twins, have been reported.<sup>(2,7)</sup> In this report of monozygotic twins, Twin 1 exhibited the full blown phenotype of Fryns syndrome, while Twin 2 had discordant phenotypic expression. Complex neurological abnormalities are known to occur in Fryns syndrome; however, frontal encephalocele has not been previously described.

Diaphragmatic hernia is one of the major diagnostic criteria for Fryns syndrome, and a cause of lethality in most cases due to pulmonary hypoplasia was absent in one of our twins.<sup>(5)</sup> Fryns suggested that lung hypoplasia leading to absence of formation and outgrowth of the plicae peritoneales may be the primary event in the pathogenesis of the diaphragmatic hernia.<sup>(3)</sup> However, there have been similar reports of absence of diaphragmatic hernia in Fryns syndrome.<sup>(8-10)</sup> Some authors have suggested that absence of diaphragmatic defect in Fryns syndrome may represent a subpopulation of more mildly affected patients allowing survival beyond the neonatal period.<sup>(8,11)</sup> However, these survivors tend to have severe neurological impairment

and profound mental retardation. This report illustrates the great intrafamilial variation of this syndrome and high lethality attributable to lung hypoplasia.

In conclusion, Fryns syndrome is an apparently rare, autosomal recessive disorder with a high rate of stillbirth and early neonatal mortality. A significant inter- and intrafamilial phenotypic variability as well as discordant phenotype in monozygotic twins may be seen. Prenatal recognition of lethal anomalies with the routine use of US assists in determining which patients may survive.

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