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CASE REPORT

Early Mandibular Distraction to Relieve Robin Severe Airway Obstruction in Two Siblings with Lymphedema–Distichiasis Syndrome

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Abstract Although micrognathia and cleft palate have been reported in patients with Lymphedema–distichiasis syndrome (LDS), the classic Robin sequence with glossoptosis and airway obstruction has not been previously described in patients with genetically confirmed LDS. Here we report on two female siblings with LDS confirmed by a *FOXC2* mutation who presented at birth with severe airway obstruction related to Robin sequence. Respiratory obstruction was successfully managed by early distraction osteogenesis. Our report highlights the unusual occurrence of Robin sequence in LDS patients and advises distraction osteogenesis to resolve breathing problems in LDS patients who present with Robin related severe airway obstruction.

Keywords Airway obstruction · *FOXC2* · Lymphedema–distichiasis · Mandibular distraction · Magnetic resonance imaging · Pierre Robin sequence

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Introduction

Lymphedema–distichiasis syndrome (LDS) is a rare, highly penetrant autosomal dominant disorder characterized by late onset lower-limb lymphedema, and distichiasis, a congenital abnormality in which extra-eyelashes grow from the Meibomian glands and protrude into the cornea causing irritation [1]. Following the first description made by Campbell in 1945, several additional manifestations with variable expression have been reported such as ptosis, varicose veins, congenital heart disease, spinal extradural cysts, and cleft palate with or without Pierre Robin sequence (PRS) [2].

Pierre Robin sequence was described in 1923 by the French stomatologist, Pierre Robin, as a range of findings consisting of breathing problems in patients with glossoptosis and associated microagnathia. In a later manuscript Robin mentioned that patients with PRS could have an associated cleft palate [3]. PRS with or without cleft palate may be present as an isolated entity, as a component of a known syndrome, or associated with other malformations that have not been characterized as a known syndrome. More than 40 syndromes with PRS have been described [4] the most common of which involve connective disorders.

Micrognathia and cleft palate have been reported in 4 % of patients with LDS suggesting that PRS may be an associated feature of LDS [5]. However, the lack of airway obstruction in most patients with LDS, micrognathia, and cleft palate, raises the question of whether the clinical manifestations in these patients are enough to fulfill the diagnosis of PRS. For example, Temple et al., described the case of an infant with LDS presenting with cleft palate and micrognathia but no breathing problems [6]. In a large group of 18 families with LDS, Brice et al. [5] described cleft palate in three boys from different families, one case

associated with PRS but, again, made no mention about possible breathing problems. In 2001, Fang et al. [7] identified inactivating mutations in the *FOXC2* gene in two unrelated families with LDS, making molecular diagnosis possible. After this discovery, Tanpaiboon et al. described a boy with LDS confirmed by a *FOXC2* mutation who presented with ankyloglossia, glossoptosis, micrognathia, and cleft palate. Again, the diagnosis of PRS neglected to include airway or feeding problems [6].

Here we describe two Italian sisters with LDS confirmed by a *FOXC2* mutation who presented with the classic triad described by Pierre Robin, i.e., micrognathia, glossoptosis and airway obstruction, associated with cleft palate, in whom the respiratory obstruction was severe to the point to require surgical treatment. Our report thus emphasizes the association between LDS and PRS and advises distraction osteogenesis to resolve breathing problems in LDS patients who present with PRS related severe airway obstruction.

Patient 1

The proband was an infant girl, the first child of two non-consanguineous parents with several members on the paternal side of the family diagnosed with lower-limb lymphedema and blepharitis. Information provided by the father suggested that cleft palate and mild to moderate micrognathia with no breathing problem were also a dominant trait in the family. The baby girl was born in a community hospital by cesarean section at 41 weeks gestation because of fetal decelerations. Her birth weight was 3260 g, Apgar scores were 8/4/10 at 1, 5 and 10 min. On physical examination, there were facial anomalies including micrognathia, retrodisplacement of the tongue causing airway obstruction, and cleft palate, which were consistent with a diagnosis of PRS; mild ptosis and low set ears were also noted. A few minutes after delivery the baby girl went into acute respiratory distress and required urgent intubation, which proved difficult owing to her micrognathia and cleft palate. She was referred to our pediatric intensive care unit (PICU) on her second day of life for management of micrognathia and subsequent respiratory distress. She was extubated at 5 days old to perform a fiberoptic aiway endoscopy and exclude other causes of obstruction in addition to epiglottis collapse due to severe glossoptosis. A three-dimensional computed tomography (CT) facial scan was also performed and confirmed severe micrognathia (Fig. 1a). During the following days an oral airway was used to maintain the upper airway patent. Clinical condition worsened until it was decided to resume endotracheal intubation. Given the severity of obstructive apneas and the persistent need for endotracheal intubation, several surgical options were proposed to her parents to relieve airway obstruction. After being informed about the possible advantages and disadvantages of each surgical option (tracheostomy, glossopexy, and mandibular distraction) her parents opted for distraction osteogenesis. At 13 days old, the patient underwent bilateral mandibular osteotomies and neonatal external distraction devices were applied (KLS Martin, Inc., Jacksonville, FL, USA) [8]. Sixteen days after surgery, when distraction was completed, the baby girl was extubated and assisted with non-invasive ventilation for 4 days. During the postoperative period, no complications developed except for generalized edema that responded to diuretics but delayed time of extubation. To resume oral feeding earlier, the baby girl was encouraged to suckle on a dummy soon after extubation and bolus feeds were gradually introduced. The girl was discharged at 49 days of life at which time she had been completely weaned from nasogastric feeding and no apneic episodes reported. Before palate closure at 9 months an overnight polysomnographic study disclosed an apnea–hypopnea index of 5.6 events per hour. During follow-up, her parents reported that the child had recurrent otitis media and gastroesophageal reflux and delayed clearing, which was confirmed by 24-h esophageal pH monitoring. Eye examination showed a double row of eyelashes (distichiasis) on both lower eyelids with no signs of corneal irritation (Fig. 2). The family history of lymphedema and cleft palate led us to a suspected diagnosis of LDS. Genetic testing in the proband and several other affected family members identified a segregating *FOXC2* mutation (i.e., c.595insC). At the age of 3 and 8/12 years her neuromotor development is normal, she shows adequate growth of the mandible, and no signs of lymphedema. A facial CT scan acquired at 2 years of age is shown in Fig. 1b.

Patient 2

Patient 2, the proband's sister, was born at the 38th week gestation by cesarean section after an uneventful pregnancy and her birth weight was 3255 g. Villocentesis identified the familial *FOXC2* mutation. A prenatal US showed a small mandible, later confirmed by magnetic resonance (MR) imaging (Fig. 3). Because of the sister's history of PRS and the difficulties in securing the airway at birth, delivery was planned in a level III obstetric unit. Apgar scores were normal, 8 at 1 min and 9 at 5 min, but within an hour after delivery, the patient manifested signs of airway obstruction (retractions, stridor, and desaturation). She was initially admitted to the neonatal unit where she was treated with an oral airway and prone position. On the fifth day of life she was referred to our PICU owing to difficult airway management. She had severe obstructive apneas which were managed with positive airway pressure through

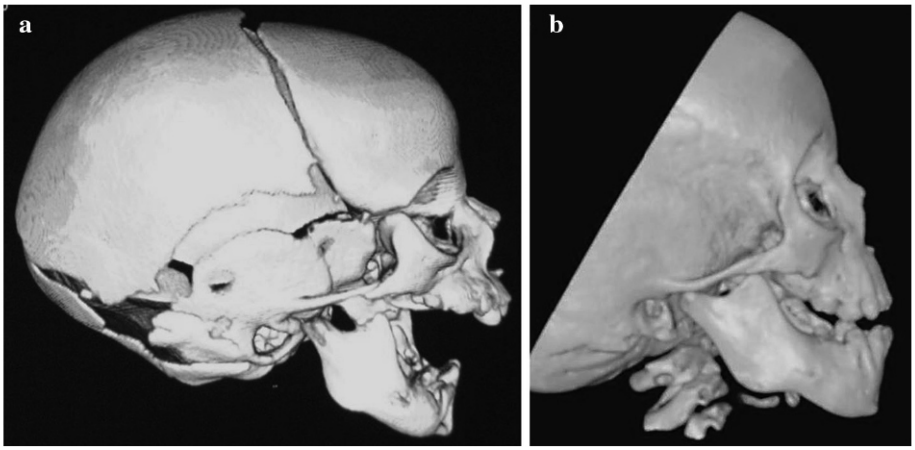

Fig. 1 **a** Preoperative three-dimensional computed tomographic (CT) scan in patient 1 demonstrating severe micrognathia. **b** Two-year follow-up three-dimensional computed tomographic (CT) scan in patient 1 demonstrating new bone growth along the mandible

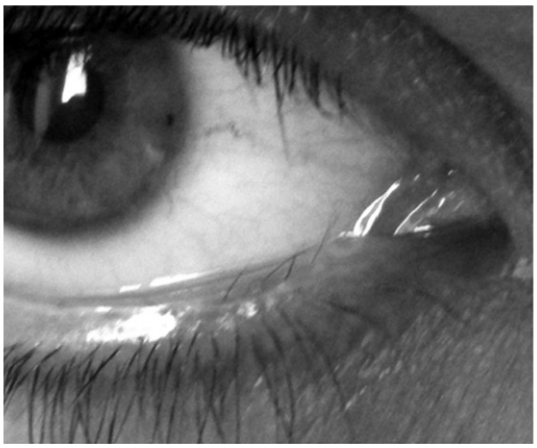

Fig. 2 Extra row of eyelashes on the lower eyelid (distichiasis) in patient 1

a nasopharyngeal tube but owing to progressive decompensation she underwent emergent endotracheal intubation. Before intubation, an airway endoscopy showed severe tongue retro-displacement and posterior pharyngeal space collapse with no further anomalies. A CT scan confirmed the small mandibular body and maxillomandibular discrepancy (Fig. 4a). The maxillofacial surgeon considered that these findings met the indications for mandibular distraction [8]. At 8 days of age, the patient underwent mandibular distraction. An eye examination showed a double row of eyelashes (distichiasis) on both lower eyelids with no signs of corneal irritation. Echocardiography showed a patent foramen ovale. The girl was kept intubated postoperatively for 18 days. During this time she manifested severe generalized edema predominantly involving the trunk, neck and forearms and was treated with diuretics and fluid restriction. The girl was weaned from nasogastric feeding at 2 months of life, and discharged. During follow-up, the parents reported noteworthy growth with no sign of lymphedema and a good neurodevelopmental outcome. She underwent palate closure

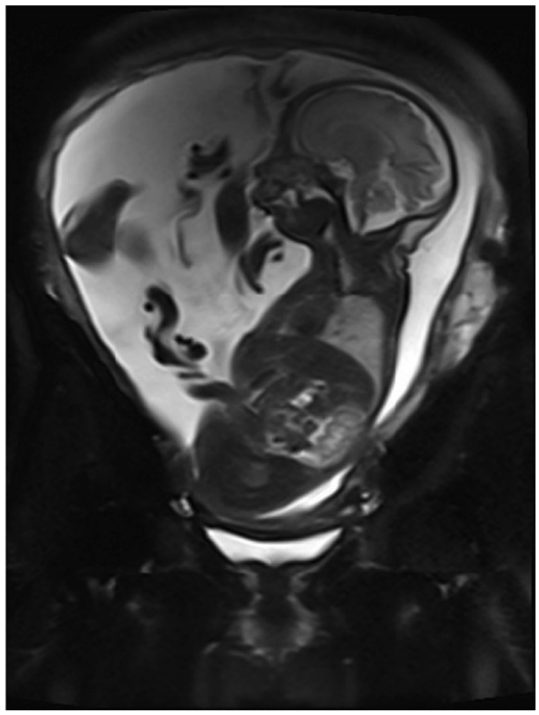

Fig. 3 Magnetic resonance imaging (MRI) scan at 29 weeks gestation in patient 2. T2w sequence acquired on sagittal plane. The *picture* shows a receded chin with a prominent upper lip on the profile view

at 15 months of life. An overnight polysomnographic study before palate repair disclosed an apnea–hypopnea index of 6.4 events per hour. A facial CT scan acquired at 2 years of age is shown in Fig. 4b.

Discussion

The present case report describing two sisters with genetically confirmed LDS who presented with micrognathia, cleft palate and severe airway obstruction, extends the

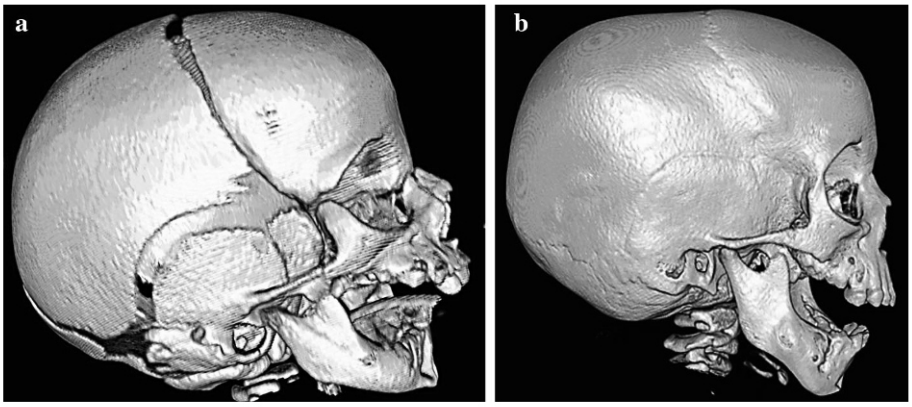

Fig. 4 **a** Preoperative three-dimensional computed tomographic (CT) scan in patient 2 demonstrating severe micrognathia. **b** Two-year follow-up three-dimensional computed tomographic (CT) scan in patient 2 demonstrating elongation of the mandible

clinical spectrum of LDS patients with PRS phenotype and, more importantly, suggests that early mandibular distraction can be a safe and effective surgical option in LDS patients to avoid tracheostomy.

The severe breathing problems secondary to micrognathia and glossoptosis described here although uncommon may represent a potentially life-threatening complication in neonates with LDS presenting with PRS phenotype. The literature includes only anecdotal reports on the association between LDS and PRS. O'Donnell et al. in 1993 were the first to describe in a series of 24 patients, with distichiasis evaluated for cryotherapy, the association of distichiasis and PRS, but no mention was done on the functional consequence of PRS. In one family Brice and colleagues describe the father of a child with LDS who required a tracheostomy in infancy for a "throat blockage" [5]. Although no medical records were available they speculated that he had PRS. Although tracheotomy continues to be held by many as the primary intervention modality for PRS patients, this technique is not without complications, including those encountered early such as bleeding, pneumothorax, or pneumomediastinum; as well as late complications such as recurrent airway infections, stomal granulation, interference with speech and language development, and feeding and swallowing difficulties [9]. More recently, other approaches to airway obstruction have been studied. In 2001, Denny et al. [10] demonstrated that mandibular advancement through distraction osteogenesis could improve airway dimensions and result in decannulation in tracheostomy-dependent children. Monasterio [11] and Sidman et al. [12], also showed excellent results using distraction to prevent the need for tracheostomy in neonates and children with mandibular hypoplasia with severe tongue-based obstruction.

Most cases of Pierre Robin airway compromise occur soon after birth. A prenatal diagnosis of micrognathia in infants with a history of disease potentially associated with PRS would be therefore advisable to plan delivery and improve neonatal outcome. Prenatal workup can now include advanced imaging techniques such as fetal US and MR imaging combined, as we did in our second case. Imaging findings suggesting PRS include appearances suggesting a receded chin with a prominent upper lip on the profile view with coexisting polyhydramnios (due to difficulty in swallowing) [13]. When micrognathia is detected as in our second patient, the baby should be delivered in a center that offers intensive neonatal care, has wide experience in treating airway malformations and undertaking difficult intubation. Neonates with small mandibles demonstrate a wide variation in the degrees of airway obstruction, feeding difficulty, and the need for treatment. Non-surgical options for airway management in PRS include prone positioning, nasopharyngeal cannula, and non-invasive ventilation. Because none of these suggested solutions worked in our two patients, after discussing the problem with the parents we opted for distraction osteogenesis for several reasons. First, we had achieved greater success in our unit with distraction than with other surgical techniques. In a small series of young patients with PRS, we have recently shown how mandibular distraction definitely corrected micrognathia eliminating the need for tracheostomy in 90 % of cases [8]. Equally important, mandibular distraction allowed for earlier oral feeding resumption and discharge without nasogastric feed [8]. The benefits of distraction osteogenesis are the consequence of increasing pharyngeal dimensions, repositioning the tongue, improving nasopharyngeal functions, and reducing nasorespiratory problems [14]. Despite its advantages, in patients such as ours, with syndromic PRS and with a deletion syndrome that potentially affects bone healing, distraction osteogenesis could have poor effectiveness. In patients with the *FOXC2* truncating mutation, surgical outcome might be compromised by severe alterations in tissue responses because *FOXC2* gene is a critical factor regulating cellular osteogenesis and angiogenesis [15], and several genes involved in skeletal development have

emerged as encoding critical elements for fracture repair [16]. Despite the truncating *FOXC2* mutation, distraction osteogenesis achieved a successful outcome in our patients, and bone repair appeared similar to that in patients with non-syndromic PRS treated at our institution [8]. Another concern arising when we decided to use distraction osteogenesis in our patients was that surgery could trigger lymphedema, as previously reported [5]. After surgery, both our patients had severe generalized edema that nevertheless responded to diuretics and fluid restriction. The lack of major surgery-related adverse effects in our two patients treated with distraction osteogenesis agrees with that previously reported for other syndromic patients with micrognathia phenotype. In their retrospective review, Al-Samkari [17] reported successful outcomes regarding upper airway and feeding management in patients with PRS independently of the syndromic status of the patients. Similarly, Taub et al., reported successful distraction for the hypoplastic mandible in patients with muscular dystrophy and amniotic band sequence, settings known to induce pathologic changes in the native bone [18, 19].

Another notable finding in our case was the high penetrance on the paternal side of the family for facial involvement (i.e., cleft palate and micrognathia), associated with c.595insC *FOXC2* mutation, which suggests some genotype–phenotype correlation. *FOXC2* is a gene expressed in the developing mesodermal mesenchyme in head, kidneys, bones, developing heart and vessels. Murine models deficient in the Mfh1, *FOXC2*-homolog gene, show abnormalities in the heart, aorta, vertebrae, head, also including cleft palate [20]. Given its role, it may be hypothesized that a truncating mutation such as c.595insC causing haplo insufficiency of *FOXC2* might result in poor mandibular growth and cleft palate. The previous description of an additional LDS patient with PRS features and sharing the same *FOXC2* mutation supports this hypothesis [21], even though it remains unclear why the typical PRS leading to airway obstruction occurs so rarely in LDS patients.

In conclusion, our report describing the classic PRS in two sisters with molecularly confirmed LDS, suggests extending the listed syndromes associated with PRS to include LDS. This information would allow for a prenatal diagnosis of PRS in infants with a history suggesting LDS and help plan careful delivery in units experienced in dealing with potentially difficult airways to improve neonatal outcome. The success we obtained with mandibular distraction, even though the *FOXC2* contains many regions with a potential role in bone healing, would also help those intending to use distraction osteogenesis to treat micrognathia and airway problems in infants with PRS related to LDS.

Conflict of Interest The authors have no financial interest to declare in relation to the content of this article.

Informed Consent Both parents gave their informed written consent to publication of their children's clinical data and pictures.

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