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Stridor in an Infant with Multiple Pterygium Syndrome: a Case Report

Stridor pri novorojenčku s sindromom večkratnih pterigijev: prikaz primera

ABSTRACT

KEY WORDS: multiple pterygium syndrome, Escobar syndrome, webbing, arthrogryposis, bilateral vocal fold immobility

Multiple pterygium syndrome is a very rare congenital inherited condition. The clinical presentation involves joint contractures and excessive webbing (pterygia). The disease exists in two forms differentiated by severity: lethal multiple pterygium syndrome and the non-lethal milder Escobar syndrome. In patients with Escobar syndrome, webbing usually occurs on the skin of the neck, fingers, forearms, inner thighs, and back of the knees. This case report intends to describe the laryngological features of the Escobar syndrome, the work-up and approach in the case of an affected neonate presenting with congenital stridor, multiple webbing, joint contractures, and feeding difficulties.

IZVLEČEK

KLJUČNE BESEDE: sindrom, Escobarjev sindrom, pterigij, artrogripoza, obojestranska okvara gibljivosti glasilk

Sindrom večkratnih pterigijev je zelo redka dedna bolezen. V klinični sliki se kaže s številnimi skrčenji sklepov in nastankom pterigijev. Bolezen obstaja v dveh oblikah, ki se razlikujeta glede na klinični potek: letalna oblika sindroma in Escobarjev sindrom, ki ima lažji klinični potek. Pri bolnikih z Escobarjevim sindromom pterigiji nastanejo na koži vratu, med prsti, na notranjosti rok in nog ter za koleni. V prikazu primera predstavljamo laringološke posebnosti, ki se lahko pojavijo pri Escobarjevem sindromu, in opisujemo klinični pristop k diagnostični obravnavi novorojenčka s kongenitalnim stridorjem, številnimi pterigiji, sklepnimi skrčenji in motnjo hranjenja.

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INTRODUCTION

In the last few decades, over 150 different conditions have been identified as the cause for congenital contractures. All of them are quite rare *(1)*. On the basis of observed malformations, multiple pterygium syndrome (MPS) was first described in 1902, but was not identified as a distinct syndrome until 1978 *(2)*. The phenotypic features are extensive webbing across major joints and contractures, small stature, minor facial anomalies, ptosis of eyelids, inner canthal folia, micrognathia with downturning corners of the mouth, limb anomalies, finger contractures, camptodactyly, syndactyly, equinovarus and/or rocker bottom feet, scoliosis, vertebrae and/or rib anomalies, and genital anomalies like cryptorchidism and absence of labia majora *(3)*.

CASE PRESENTATION

We present a firstborn child of a non-consanguineous couple, in whom fetal ultrasound identified an aortic valve stenosis and increased nuchal translucency. An amniocentesis and karyotyping were performed in the 16th week of pregnancy and the results showed a normal male karyotype. Shorter leg bones were additionally identified on the morphologic ultrasound. Further genetic testing was performed, but initially suspected autosomal dominant achondroplasia was not identified. The pregnancy was terminated in the 40th week by Caesarean section because of a breech neonatal position. Birth was uncomplicated (appearance, pulse, grimace, activity and respiration (APGAR) 8/8, weight 2,990 g, body length 43 cm, head circumference 37 cm), and the child's mother's tests for hepatitis B virus infection and toxoplasmosis were negative.

Otorhinolaryngological Examination

The child had inspiratory and biphasic stridor at birth, as well as tachypnea. Breath sounds were more pronounced when agitated. Nasal continuous positive airway pressure (CPAP) was initially applied, however, he had desaturation spells up to 70% SpO_2 (saturation of oxygen) in cases of distress with agitation and crying. After five days on CPAP, the Airvo™ nasal high-flow system (8 l O_2/min and 21% O_2) was initiated successfully.

A nasolaryngoscopy and bronchoscopy under general anesthesia and spontaneous breathing were performed 14 days after birth. These examinations showed that the nasal cavity and choanae were patent, there was no adenoid hypertrophy and the epiglottis had a normal shape. Vocal folds were white and smooth but in an adducted paramedian position and there was no visible abduction on inspiration. Mild inspiratory collapse of the arytenoid mucosa was observed, the subglottis was normally shaped and there was no tracheomalacia. An X-ray of the thorax did not show pulmonary abnormalities.

An awake nasolaryngoscopy 27 days after birth showed a paramedian position of the vocal folds, with adduction of folds during crying, but no abduction movement on inspiration. There were no signs of laryngomalacia. Nocturnal polygraphy was performed with the Airvo™ high-flow system (8 l O_2/min and 21% O_2). It showed a normal breathing and heart rate for the age, mean SpO_2 98% (range: 95–98%), no central apneas and an apnea–hypopnea index (AHI) of 1/hour. The child was discharged with the Airvo™ high flow system (8 l O_2/min and 21% O_2) that he used during the day and at night time. Regular nocturnal polygraphies were performed. Based on the results without the Airvo™ system at the age of seven months (breathing frequency 26–32/min, mean SpO_2 98% and range: 95–100%, heart rate 115–125/min, AHI 1/hour), a period of only nocturnal use of Airvo™ was suggested. Re-evaluation of nocturnal polygraphy without the Airvo™ system after six months showed no sleep-

related breathing disorder (breathing frequency 28–30/min, SpO2 mean 97% and range: 96–99%, heart rate 90–105/min, AHI 0/hour), therefore, Airvo™ support was stopped. Yearly follow-up polygraphies remained good.

Feeding difficulties were initially observed with easy fatigue. Placement of a nasogastric feeding tube was indicated because of failure to thrive. A fiberoptic endoscopic evaluation of swallowing (FEES) at two months of age showed no pathological swallowing function or aspiration and oral feeding rehabilitation was successfully initiated. A combination of oral and nasogastric tube feeding was necessary until the age of four months.

Disease Presentation

Multidisciplinary assessment was carried out, concerning *(4)*:

- cardiology:
  - Bicuspid aortic valve stenosis (gradient 30 mmHg) was successfully dilated (balloon dilation) at two months of age. Ibuprofen conservative therapy for Bottal duct closure was successful.
- neurology:
  - General hypotonia was described with minimal spontaneous movement of the limbs. Facial expressions were minimal, but there was no facial muscular paresis. Limb reflexes were absent.
  - Head ultrasound and electroencephalogram (EEG) were normal.
  - Bilateral vocal fold immobility (BVFI) can be a sign of an underlying systemic neurologic condition. MRI scan would be useful in detecting such a cause. Based on the nasolaryngoscopic findings, which showed normal adduction of vocal folds, a neurological cause was improbable.
- gastro-enterology:
  - Ultrasound showed abdominal meteorism with normal peristalsis and anatomic structures.
- urology:
  - The patient underwent surgery for a left-sided inguinal hernia and bilateral cryptorchidism.
- genetic assessment:
  - Facial features: high nasal root, mild hypertelorism, downward slant eyes, ptosis of the right upper eyelid, normal iris, blepharophimosis, epicantus inversus, high arched palate without palatal schisis, small jaw, low set ears. Short neck with webbing and fibromatosis was documented on ultrasound. Webbing of skin was present in the axillae, elbow and inguinally.
  - Metabolic disorders were absent.
  - At the first genetic assessment based on clinical features, MPS or Freeman-Sheldon syndrome was suspected. Genome sequencing showed two genetic variants of the Cholinergic Receptor Nicotinic γ-Subunit gene (the CHRNG gene). One variant (c. 753–754del) is a known pathologic gene variant, the other (c. 250G>A) is a gene variant of unknown function. The child has inherited one variant from each parent. Based on the genetic testing and the clinical signs the most probable diagnosis is MPS Escobar type.

DISCUSSION

The diagnosis of arthrogryposis or multiple joint contractures (as seen in MPS) can usually be made on a prenatal ultrasound. The most common detailed findings are fixed flexion joint deformities, micrognathia, altered amniotic fluid volume, limb deformities, cerebral ventriculomegaly, dysmorphic features, and growth retardation *(5)*. The classic facies of MPS shows micrognathia, short and webbed neck, low set ears, long philtrum and downturning mouth *(6)*.

In children with arthrogryposis, airway anomalies such as vocal fold immobility, glossoptosis, supraglottic narrowing and laryngomalacia have been described with

a high risk of airway compromise. Dysphagia is common with possible aspiration pneumonia and poor nutrition *(7)*.

Stridor is an abnormal audible high-pitched breath sound, resulting from a partially obstructed or stenotic upper airway. It is a warning sign of potentially dangerous underlying airway disease and must be investigated. Generally, the main causes of congenital stridor are laryngomalacia, vocal fold immobility, congenital subglottic stenosis, laryngeal webs, tracheomalacia and subglottic hemangioma. Laryngomalacia accounts for 60–70% of cases, and BVFI is the second most common cause. Unilateral vocal fold immobility is usually due to recurrent laryngeal nerve injury during birth, surgical trauma or compression from mediastinal masses, while BVFI results from neurological disorders *(8)*.

The manifestation of interest in the presented clinical case is BVFI, not initiated by a neurologic cause but probably due to an underlying fixation of the cricoarytenoid joints in a patient with arthrogryposis. BVFI is a recognized source of stridor and respiratory distress, and a vocal fold in a paramedian adducted position can present as a medical urgency at birth that leads to stridor and breathing difficulty *(9)*.

A careful diagnostic evaluation needs to be done when facing a child with MPS and BVFI *(10)*.

Many practitioners examine the upper airways of a child with an awake flexible nasolaryngoscopy, however, an examination under general anesthesia provides the opportunity for better visualization of the entire airway system. A flexible nasolaryngoscopy or bronchoscopy and a direct rigid laryngoscopy can be performed. These enable the visualization of the airway during sedation and spontaneous breathing. A dynamic obstruction in the upper airway and movement of the vocal folds during breathing can be visualized on a flexible nasolaryngoscopy. Direct rigid laryngoscopy is the method of choice to diagnose the presence of laryngotracheal clefts, and in cases of BVFI, allows palpation of the arytenoids to assess the mobility of the cricoarytenoid joints. After the diagnostic endoscopy, it is possible to proceed with surgical intervention if needed during the same procedure. Therefore, a combination of flexible and rigid endoscopy is often performed *(11)*.

Laryngeal electromyography is a well-established instrument for evaluating adult patients with cricoarytenoid joint dysfunction. It is an adjunct to the clinical investigations and palpation of arytenoids under direct laryngoscopy, mostly useful in recurrent laryngeal nerve damage, centrally correctable lesions, and idiopathic BVFI *(7, 12)*.

In general, when confronted with a patient with BVFI, an MRI is used to evaluate the brain and spinal cord, in case an underlying neurological or cerebral condition is suspected *(3)*.

Mutations in the CHRNG gene can result in both the non-lethal Escobar variant MPS, and the lethal MPS (fatal in 2nd or 3rd trimester). Lethal MPS follows an autosomal and an X-linked recessive inheritance pattern *(13)*. The CHRNG gene provides instructions to make the γ-protein component (subunit) of the acetylcholine receptor (AChR). The AChR is found in the membrane of skeletal muscle cells and is critical for signaling between nerve and muscle cells, which is necessary for movement. A lack of signaling results in the inactivation of the muscular neural motor plate, leads to akinesia, and joint contractures (with pterygia) before birth, and may also result in cricoarytenoid fixation. In contrast to other forms of BVFI, this is a direct result of restricted joint motion *(14, 15)*.

Only a few articles describe patients with Escobar syndrome requiring a tracheotomy for upper airway obstruction *(6, 10, 16, 17)*. According to Shen et al., a trac-

heotomy for patients with BVFI due to cricoarytenoid fixation as seen in MPS should be considered when endotracheal intubation is necessary to keep airway patency, extubation is unsuccessful, or when severe complications related to BVFI and chronic respiratory insufficiency such as failure to thrive or recurrent aspiration pneumonia are present *(18)*.

In idiopathic cases unrelated to MPS, more than 50% of children with BVFI will have a spontaneous resolution in the first 12 months of life *(19)*. It is unclear whether this is the case in arthrogryposis. Recovery rates are unavailable in literature, but based on the etiology of cricoarytenoid articulation immobility, a full spontaneous recovery is usually not expected.

Watchful waiting can be considered in certain cases of BVFI. Non-invasive ventilation support techniques, such as CPAP and nasal high flow therapy systems have been successfully used in cases of dynamic mild airway obstruction, like in the presented clinical case *(19)*.

Endoscopic suture lateralization of one or both vocal folds with arytenoid abduction has been described in children and adults. Endoscopic arytenoid abduction lateropexy with alaryngeal suture is a quick, reversible, minimally-invasive vocal fold lateralizing technique, used for enlarging the posterior glottis. The arytenoid cartilage is lateralized to a normal abducted position. It might be a favorable option for neonates, since airway patency can be achieved in one step without irreversible damage to the glottic structures, and it can even be a long-term solution *(20)*.

However, different strategies and surgical techniques to increase the glottis area have emerged. Although they would possibly prevent tracheostomy, they involve a greater risk of laryngeal sequelae and postoperative aspiration or dysphonia. Cordotomy with or without arytenoidectomy has been often used in adults with BVFI and has been described in children as well. The procedure consists of an incision in the posterior third of the true vocal fold with a further partial or total arytenoidectomy. The procedure is irreversible, and an adverse effect on the voice is expected *(19, 21)*.

Recently, new endoscopic procedures have additionally emerged, like the endoscopic anterior and posterior cricoid split *(22)*. First, the posterior cricoid is incised using a laryngeal knife or CO_2 laser. Next, the anterior cricoid is incised through a mucosal incision made with a sharp sickle knife while exercising caution to avoid injury to the anterior commissure. After completing the anterior and posterior split, a non-compliant balloon is placed through the glottis and is expanded to put pressure and dilate the cricoid plate. The patient is then intubated with a half-size larger than the age-appropriate endotracheal tube for a period up to two weeks. After extubation, additional balloon dilation is performed if needed *(23)*. Furthermore, isolated endoscopic balloon dilation has been described as a successful treatment approach in cases of laryngeal stenosis. During the procedure, a telescope and the balloon catheter are introduced into the laryngeal lumen and dilated. A series of balloon dilations is usually needed, and in some cases the balloon itself could cause a partial cricoid split *(24)*. Endoscopic and open approach posterior cricoidotomy and cartilage grafting for laryngeal lumen augmentation have been described in isolated posterior glottic stenosis and in BVFI *(25, 26)*.

CONCLUSIONS

We have presented a rare case of congenital stridor caused by BVFI with cricoarytenoid joint fixation in a neonate with arthrogryposis in MPS. Congenital stridor is an abnormal audible high-pitched breath sound and results from a partially obstructed or stenotic upper airway. It is always

a warning sign of a dangerous underlying disease and must be investigated immediately. Stridor can be the presenting complaint in children with arthrogryposis, and early recognition of airway obstruction and feeding problems will avoid life-threatening complications and further developmental delay. Any procedure to establish a patent airway should ideally have a minimal impact on the ability to phonate and swallow. A conservative, but successful treatment approach should be used. Different surgical techniques to increase the glottis area in BVFI can be used to avoid tracheostomy, which has been the standard of care for a long time and is mandatory in cases of threatened airway and respiratory distress.

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