CASE REPORT

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PELIZAEUS-MERZBACHER DISEASE AS A RARE CAUSE OF STRIDOR IN AN INFANT WITH SEVERE REFLUX AND HYPOTONIA

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Abstract

Stridor is high-pitched, noisy breathing that occurs as a result of a narrowed airflow. It is considered as a respiratory emergency in which if left untreated, may lead to death. The most common cause of stridor in paediatric is laryngomalacia (LM). Nevertheless, other causes of persistent stridor in infant have to be ruled out, in the case of failed surgical therapy. Here, we report a rare case of a three-month-old infant boy with persistent stridor since birth who had undergone aryepiglottoplasty for LM at day ten of life and was referred back to the hospital due to worsening of stridor with signs of respiratory distress and subsequently he was diagnosed with Pelizaeus-Merzbacher Disease (PMD). This is the first report to discuss on PMD as a rare differential diagnosis of stridor.

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Introduction

Congenital stridor occurred due to the narrowed or partially blocked airway mostly caused by laryngomalacia (LM) and can be established by a combination of highly suggestive history, clinical presentation as well as endoscopic evaluation to confirm the diagnosis [1]. Although the pathophysiology of LM is not very well understood, few literatures have proposed factors such as mechanical, anatomical and neurological play an important role in the development of LM [2]. Typically, most of the cases only required close monitoring until the age of two years old, nevertheless, there is a small percentage of the patient will have a severe form of LM requiring surgical intervention [3]. When the infant presented with persistent stridor despite surgical intervention, other associated findings such as gastroesophageal reflux (GER), hypotonia, failure to thrive, seizure, abnormal neurological manifestations and pneumonitis must not be overlooked.

Pelizaeus-Merzbacher Disease (PMD) is a rare X-linked recessive hypomyelinating leukodystrophy

which is caused by a mutation in the proteolipid protein 1 (PLP1) gene. It is characterized by developmental delay, abnormal eye movements, progressive hypotonia and involuntary movements. Due to the rarity of the disease, PMD is usually suspected by similar clinical findings in the siblings who had been diagnosed as PMD or if the mother is the carrier. Kimia Najafi et al., had concluded, clinical manifestations have been accepted as being the mainstay of the diagnosis in most of the conditions [4]. However, despite neurological findings in physical examination, abnormal myelination in magnetic resonance imaging (MRI) of the brain together with cytogenetic studies may support the diagnosis of PMD. Although stridor is not commonly

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presented in PMD, progressive hypotonia may affect pharyngeal and laryngeal muscles which will lead to persistent stridor and severe reflux esophagitis.

Case Summary

A three-month-old infant boy who had a history of underwent aryepiglottoplasty for LM at day ten of life, had attended to our emergency department with a symptom of rapid breathing associated with worsening of stridor for the past one day duration. Mother claimed the existing stridor had gradually become louder since two months duration after discharged from the hospital and there was the presence of deep chest recession on the patient. Otherwise, there was no episode of vomiting, no seizure, no cyanosis, no cough or runny nose, no fever, no recent trauma or fall, no interrupted bottle feeding, no foreign body ingestion and no obvious abnormal movement of the infant except for the hyperextension of the back and bilateral upper limbs which occurred intermittently since birth.

The patient was born term via elective caesarean section for multiple indications such as advanced maternal age with gestational diabetes mellitus and one previous scar. His birth weight was 2.9 kg. He had a history of intubation at 30 minutes post-delivery for 18 days of duration, due to desaturation and subsequent scope revealed intubation granuloma with features of mild LM. Hence, direct laryngoscopy, bronchoscopy and aryepiglottoplasty were performed to him with no complications. The patient was observed in the neonatal intensive care unit for almost four weeks of life and the weight had reached 3 kg. He was then discharged home after no other episodes of desaturations and was able to breathe independently despite having soft stridor.

On examination, the infant was pink, active on handling with severe back arching (opisthotonus) posture and remarkable muscle wasting (Figure 1). There was presence of inspiratory stridor, tracheal tug with deep subcostal and intercostal recession. There was no other physical dysmorphism such as downward slanting of eyes, low set of ears, arched eyebrows, broad nasal

root, epichantal folds, strabismus or cleft lips/palates were noticed. Saturation was 98% under nasal prong oxygen 3L/min. Other vital signs were normal. Lungs had transmitted sounds bilaterally with equal air entry. His current weight, length and head circumference at presentation was 3.5 kg, 55 cm and 38 cm respectively, which indicated failure to thrive. Flexible fibre optic scopy was performed at the casualties and revealed pooling of secretions over bilateral pyriform fossa with bilateral arytenoids mildly inflamed and edematous. Both vocal cords were normal, mobile and symmetrical. The epiglottis was omega in shaped but not floppy. Laryngeal inlet and subglottic were both patent and no stenosis. Chest and neck radiograph were done and revealed clear lung fields with no sign of pneumonia and normal trachea patency with no prevertebral widening. Full blood counts were normal.

Figure 1. Clinical photograph showing opisthotonus posturing with remarkable muscle wasting in the infant.

The patient was then admitted to the paediatric ward with nasal prong oxygen 3L/min for close observation and was started on anti-reflux medication. Throughout admission, the patient was dependent on the oxygen supply and developed desaturation each time weaning down of oxygen were attempted. Repeated flexible laryngoscopy was done bedside and revealed similar finding with resolved arytenoids oedema. The patient was subsequently arranged for emergency direct laryngoscopy and bronchoscopy under general anaesthesia. The intraoperative finding revealed normal supraglottic, glottic and subglottic structures with pattern trachea (Figure 2).

Figure 2. Clinical photograph (endoscopic view) showing intraoperative finding of normal vocal cords, supraglottis and subglottis.

The patient was then extubated well on day one post-operation and was put on optiflow oxygen. Initial multidisciplinary team (MDT) meeting between paediatric otolaryngologist and medical paediatric had proposed a differential diagnosis of likely Sandifer Syndrome given the presence of severe reflux esophagitis as well as generalized hypotonia. Hence, the patient was started on conservative management with feeding (small, frequent, anti-regurgitation formula), postural modification (lateral and head elevation) and anti-reflux medications such as syrup domperidone 1.8 mg QID and syrup pantoprazole 5 mg BD, and was planned to be kept in the ward until patient's weight reach up to 4 kg.

Upon follow up in the neonatal ward, the patient was told to have sudden rotatory nystagmus which had resolved spontaneously, worsening of the stridor as well as poor weight gain due to severe regurgitation. Second MDT was held together with the family to discuss on further investigation and management for the patient, eventually the mother had revealed that patient's elder brother had similar symptoms which had appeared earlier compared to the patient and he was diagnosed as PMD. The diagnosis of PMD in the patient's brother was confirmed at the age of 2 years old after the molecular genetic testing revealed hemizygous for PLP1 c.736G>A p.(Gly246Arg) likely pathogenic variant and abnormal myelination in MRI brain. Mother was found to be heterozygous for the c.736G>A PLP1 mutation and that confirmed she was the carrier of PMD. Currently, the patient's elder brother is 11 years old and had developed spasticity leading to joint deformities that restrict movement (Figure 3).

Figure 3. Clinical photograph showing features of spasticity leading to contracture in patient's elder brother who was diagnosed as PMD.

Electroencephalogram (EEG) was done for the patient twice and revealed a normal finding. Barium study revealed severe reflux disease with no obvious structural abnormalities. The patient was given an appointment for MRI brain to evaluate further on the working diagnosis. Tracheostomy and fundoplication surgery were offered to the parents during the subsequent meeting in view to maintain the airway as well as to reduce the severity of reflux esophagitis. The parents opted for tracheostomy after extensive counselling and meetings. The operation was uneventful with no post-operation complications. At present time, the patient was already discharged home, able to breathe via tracheostomy without needing any oxygen supplementation and on nasogastric tube feeding.

Discussion

Congenital anomalies account for 87% of cases of neonatal stridor, by which LM is the leading cause (60% of cases) [5]. Other differential diagnoses that should be considered including craniofacial anomalies, choanal atresia, encephalocele, turbinate hypertrophy, vocal cord paralysis, congenital or acquired subglottic stenosis,

laryngeal webs, cysts or clefts, papillomatosis, tracheomalacia, vascular ring, mediastinal masses, foreign bodies and GER or also known as reflux esophagitis. As for this patient, a diagnosis of LM was made previously at day ten of life due to presence of stridor post-delivery as well as the endoscopic finding intra-operatively, and aryepiglottoplasty (a variation form of supraglottoplasty) was performed. There were no other abnormalities seen except for the intubation granuloma and mild LM changes.

Unfortunately, after two months discharged from the neonatal ward, the patient develops worsening of stridor with regurgitation symptom, hence warrant us for further investigations. Repeated laryngoscopy revealed generalize hyperemia and pooling of saliva over both pyriform fossa, post cricoid region and vallecular, swelling of bilateral arytenoids which indicate a sign of reflux esophagitis. The epiglottis was omega-shaped but not floppy with normal vocal cords. The patient was started on anti-reflux medication with special anti-regurgitation formula milk. However, throughout admission, the patient's condition became worst especially for stridor loudness and regurgitation symptoms with failure to thrive. There were few literatures had written about the co-existing findings of reflux esophagitis in up to 80% of patients with LM and it has led to the surgical failure of supraglottoplasty [6]. A prospective study had been carried out to propose a relation between LM with the severity of GER, however significant scale of the group required to establish significant clinical implication and subsequent management.

The guarded information from the mother had makes the diagnosis a challenge to establish. Our consensus of provisional diagnosis during that time was severe reflux esophagitis to rule out Sandifer's syndrome given generalized hypotonia of the muscle, severe regurgitation with failure to thrive and inspiratory stridor. However, after a sudden onset of nystagmus appeared, mother revealed that patient's elder brother who is currently 11 years old was not diagnosed as cerebral palsy as per told earlier, instead he was diagnosed as PMD, and the mother was a confirmed carrier.

PMD is indeed, a very rare inherited disease involving the brain and spinal cord that predominantly occurs in male. It was first

described in 1885 by Friedrich Pelizaeus in a large family. Neuropathological studies published by Ludwig Merzbacher in 1910 demonstrated the near-complete absence of central nervous system (CNS) myelin, with an intact peripheral nervous system. The disease is caused by alterations (point mutations, duplications and rarely deletions) of the PLP1 gene, which was first described in 1989 (point mutations) and 1994 (duplications). It's allelic with one sort of the hereditary spastic paraplegia type 2 (SPG2) [7].

It is divided into classic (more common) and connatal (present since birth) types. Even though these two types of PMD differ in severity and prognosis, their features may overlap. The classic type of PMD disease typically experience weak muscle tone (hypotonia), involuntary movements of the eyes (nystagmus) and delayed development of motor skills, such as sitting or grasping objects within the first year of life [8]. Some individuals can walk with assistance. Despite these neurological problems, intellectual and motor skills develop throughout childhood, the development usually cease around adolescence and these skills are slowly regressing [9]. As the condition worsens, nystagmus usually disappears but other movement disorders develop, such as muscle stiffness (spasticity), imbalance gait (ataxia), head and neck tremors (titubation), involuntary tensing of the muscles (dystonia) and jerking (choreiform) movements [10].

The connatal type of PMD appears to be more severe form whereby the symptoms may begin in infancy and include problems with feeding, poor weight gain and slow growth, high-pitched breathing caused by an obstructed airway (stridor), nystagmus, progressive speech difficulties (dysarthria), severe ataxia, hypotonia and seizures [11]. As the condition worsens, the children will develop spasticity leading to joint deformities (contractures) which will cause restriction of movement that disabled walking or even use their both arms as manifested in patient's elder brother. They will also have impaired expressive language (unable to produce speech) with intact receptive language (able to understand speech).

As for this patient, the diagnosis of PMD is yet to be confirmed until the MRI brain is available. The diagnosis of PMD requires DNA sample to see any

mutation involving the PLP1 gene, with the help of clinical findings and abnormal myelination of cerebral white matters seen in MRI brain [12]. Nevertheless, Kimia Najafi et al., had reported a familial case of PMD involving patient's elder brother and maternal uncle. Similar clinical findings were reported among them, whereby both of the parents had normal phenotypes. The study has concluded that clinical manifestations have been accepted as being the mainstay of the diagnosis for most of the conditions. In fact, in many cases, the diagnosis of PMD was always delayed for many years as they were frequently misdiagnosed as cerebral palsy and sometimes, suspected only after the birth of another affected child in the family. In this case, since the mother was confirmed the carrier of PMD, all offspring of her will have a 50% risk of inheriting the c.736G>A mutation. Her sons will have a 50% risk of being affected and prenatal testing should be offered [13]. Moreover, a suspected PMD patient presenting in infancy may not show abnormal MRI findings until two years of age when the bulk of postnatal myelination is completed. However, a lack of the expected myelin changes in the pons and cerebellum of a newborn, or in the posterior limb of the internal capsules, optic radiations, or in the splenium of the corpus callosum of a three-month-old infant are helpful clues that are suggestive of leukodystrophy [14].

Conclusion

Although laryngomalacia is the commonest cause of stridor in an infant, the diagnosis of X-linked chromosomal disorder known as Pelizaeus-Merzbacher Disease (PMD) should be highly suspected in a male infant with a family background of PMD and mother is known to be the carrier. Abnormal myelination in MRI brain together with cytogenic molecular study, can confirm the diagnosis of PMD. After all, measures had to be undertaken in managing this kind of difficult case, which requires a holistic approach by the multidisciplinary team in terms of feeding and airway issues that will lead to the failure of management and imposed potential life-threatening to the patient. Parents should be counselled regarding the 50% possibility of affecting future offspring and prenatal genetic testing can be offered with appropriate genetic counselling.

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