Reminder of important clinical lesson

Branchio-oto-renal syndrome with obstructive sleep apnoea

Arjun Chavan,¹ Aravind R T Shastri,² Robert I Ross-Russell¹¹Paediatrics Department, Addenbrookes Hospital, Cambridge, UK;²Paediatric Cardiology Department, Royal Brompton Hospital, London, UK

Correspondence to Dr Arjun Chavan, arjuns@gmail.com

Summary

Branchio-oto-renal (BOR) syndrome is a rare autosomal dominant disorder characterised by branchial arch anomalies, otological and renal abnormalities. To the best of our knowledge, upper airway obstruction has not been hitherto reported in BOR. The authors report a 19-month-old girl with BOR syndrome with features of severe airway obstruction needing tracheostomy.

BACKGROUND

This case report illustrates that even in an antenatally diagnosed infant with a known genetic phenotype, who is failing to thrive from upper airway obstruction, an increased awareness may lead to early intervention and better outcome. Whether the significant airway involvement in this case is the result of an intrafamilial phenotypic variation occurring from the genetic phenomenon of anticipation is uncertain. Sleep studies (especially if including video recording) can be a useful adjunct in deciding the medical and surgical management of individual cases, and monitoring progress.

CASE PRESENTATION

A 19-month-old girl with branchio-oto-renal (BOR) syndrome was referred to the paediatric respiratory team in view of snoring, feeding difficulties and faltering growth. Her mother and brother were both known to have BOR syndrome with mutation c.821delG of EYA1 gene on chromosome 8q (a novel mutation). She was born at full term with the suggestion of BOR in 3-D ultrasound at 28 weeks of gestation. Physical examination at birth revealed cup shaped ears, bilateral ear pits and a left sided branchial fistula, typical of BOR syndrome (figure 1).

Analysis of cord blood sample confirmed the same mutation as her mother. Hearing screen showed evidence of significant bilateral mixed hearing loss, although postnatal renal ultrasound was normal.

Her birth weight was 4.46 kg on the 98th centile but subsequently dropped to the 2nd centile by 6 months. She had repeated episodes of upper respiratory tract infection, feeding difficulties and snoring at nights which were attributed to laryngomalacia. An ear, nose, throat review at 9 months of age showed a horseshoe shaped epiglottis with large arytenoids and a laryngeal inlet that tended to close dynamically with forcible inspiration. It was thought that no intervention was required at this stage and that she would outgrow her symptoms.

At 16 months of age she underwent successful excision of her branchial fistula. Postoperatively on the ward she was noted to have significant snoring and desaturations at night. She underwent a sleep study which was markedly

abnormal with several episodes of desaturations of 1–2 min duration and arterial saturation (SaO₂) down to 70% (figure 2). There was also video evidence of severe airway obstruction with asynchrony between chest and abdomen. In retrospect mother felt that such episodes occurred several times at night. An MRI of the brain was normal.

SUMMARY OF INVESTIGATIONS

- ▶ 3-D ultrasound at 28 weeks of gestation: suggestive of BOR.
- ▶ Cord blood sample: BOR syndrome with mutation c.821delG of EYA1 gene on chromosome 8q (a novel mutation).
- ▶ Direct laryngoscopy at 9 months of age: horseshoe shaped epiglottis with large arytenoids and a laryngeal inlet that tended to close dynamically with forcible inspiration.
- ▶ Sleep study at 16 months of age: markedly abnormal with several episodes of desaturations of 1–2 min duration and arterial saturation (SaO₂) down to 70%.
- ▶ MRI of the brain (to exclude central causes of apnoea): normal.

OUTCOME AND FOLLOW-UP

She underwent an aryepiglottoplasty and release of retroflexed epiglottis with a view to improve upper airway airflow. This produced some improvement in her symptoms, but she was readmitted a month later with frequent nighttime episodes of profound desaturation. A further sleep study day confirmed very significant hypoxic episodes with evidence of CO₂ retention. A trial of nasopharyngeal airway was unsuccessful and we therefore undertook a tracheostomy. Following the procedure, episodes of desaturations completely disappeared and a sleep study 3 weeks later was entirely normal. At follow-up 1 month later she was noted to be well, with no symptoms and good weight gain (9th centile).

In summary, this girl with BOR syndrome had features of obstructive sleep apnoea (OSA). Sleep studies and video monitoring helped to make the initial diagnosis. She has been managed successfully by tracheostomy at 18 months of age following a difficult respiratory course since birth.

DISCUSSION

BOR syndrome is a rare syndrome with an estimated incidence of 1 in 40 000 children.^{1 2} Chang *et al* have described major and minor criteria for the full spectrum of BOR, major criteria being second branchial arch anomalies, deafness, preauricular pits, auricular deformity and renal anomalies. Minor criteria include external auditory canal anomalies, middle ear anomalies, preauricular tags, inner ear anomalies facial asymmetry and palate abnormalities.

Figure 1 Frontal view showing typical phenotypic features taken with informed consent.

In the absence of a family history, three or more major criteria or two major and two minor criteria are required to make the diagnosis but only one major criterion is required if there is positive family history.¹

It is inherited as an autosomal dominant condition with 40% of the mutations reported as affecting the EYA1 gene on chromosome 8.¹ Our case did not have renal involvement and in such situations it is sometimes termed branchio-oto (BO) syndrome. Many families with BOR and BO show linkage to same EYA1 gene suggesting that they may be allelic phenotypes of mutations in this single gene.³ The EYA1 gene is expressed very early, between the 4th and 6th weeks of human development. Deafness relates to abnormalities in the three ossicles of the middle ear derived from the first and second branchial arches, while the branchial fistulae relate to abnormalities of the second, third and fourth arches.⁴

Although BOR syndrome has been associated with retrognathia and short or cleft palates, OSA in our case is probably related to branchial arch anomalies giving rise to a very floppy larynx and laryngeal inlet. The fourth branchial arch gives rise to structures forming the intrinsic muscles of soft palate, laryngeal inlet (thyroid and epiglottic cartilages) and to the vagus and superior laryngeal nerves. The internal and external laryngeal nerves are derived from the superior laryngeal nerve and innervate all the structures of larynx except the adductors of the vocal cords which are innervated by the recurrent laryngeal nerve.

To the best of our knowledge, severe upper airway obstruction has not previously been reported in BOR syndrome. In this family an older sibling and the mother had the same genetic mutation but no evidence of upper airway involvement. All of the affected had characteristic floppy pinnae, preauricular pits which were repaired, mixed deafness and no evidence of renal involvement. This type of

Figure 2 A snapshot of the sleep study showing significant desaturation.

intrafamilial phenotypic variation within BOR families is well known.⁵ Whether the significant airway involvement in this case is the result of such an intrafamilial phenotypic variation occurring from the genetic phenomenon of anticipation is uncertain.²

Learning points

- To the best of our knowledge, upper airway obstruction has not been hitherto reported in BOR.
- Sleep studies (especially if including video recording) can be a useful adjunct in deciding the medical and surgical management of individual cases, and monitoring progress.
- Chronic severe airway obstruction in itself can be one of the causes of failure to thrive.
- It may be useful to be aware of the genetic phenomenon of anticipation in any well-described syndrome.

Competing interests None.

Patient consent Obtained.

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