Bardet–Biedl syndrome: expect the unexpected, suspect the unsuspected

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This is the first reported description of Bardet–Biedl syndrome (BBS) with the combination of a malacic bifid epiglottis and anterior laryngeal web. Anaesthesia for BBS has numerous concerns and these are reviewed, focusing on features that manifest not only in BBS but across a spectrum of syndromes that impact airway management. Congenital laryngeal anomalies (CLA) are rare and usually present preoperatively with upper airway obstruction and stridor. In asymptomatic infants, CLA may cause unexpected airway problems under anaesthesia which can be mistaken for more common occurrences, such as laryngospasm. Preoperative dysphonia may be the only clue to suspecting the presence of a CLA. The combination of obesity, polysyndactoly/brachydactyly and even subtle craniofacial abnormalities should always alert the anaesthetist to the possibility of a CLA and difficult airway.

Keywords: anterior laryngeal web, Bardet–Biedl syndrome, bifid epiglottis, laryngeal anomalies, paediatric anaesthesia, paediatric obesity, stridor, craniofacial syndromes, upper airway obstruction

Introduction

Bardet–Biedl syndrome (BBS) is a rare autosomal recessive ciliopathy (MIM 209900),1,2 distinct from Laurence–Moon–Biedl syndrome.3,4 Renal disease5,6–10 and cardiovascular manifestations6,9,11–13 account for the greatest morbidity and mortality in BBS. Patients with BBS may present for multiple surgical procedures, the majority related to manifestations or complications of the disease.13,14

Craniofacial and airway abnormalities are not considered diagnostic in BBS,9 yet there is increasing recognition of the pattern, frequency, associated morbidity and anaesthetic challenges.5,12,13,15 We describe the unexpected finding of a bifid epiglottis and anterior laryngeal web in a 15-month-old child with BBS who developed upper airway obstruction (UAO) and stridor during anaesthesia for club foot correction. A clinical review of BBS is provided, highlighting features that may occur across a spectrum of syndromes and have implications for airway management.

Case report

The patient presented with dysmorphism at birth and was diagnosed with Bardet–Biedl syndrome. Abnormalities included: hypogonadism, bilateral hydrenephrosis with multiple cortical cysts, polydactyly of the left hand and both feet, syndactyly of the right little toe, and bilateral club feet (Figure 1a–b). Renal function, cardiac echocardiography and ophthalmic assessment were normal. The patient was noted to have micrognathia, but no other dysmorphic facial features.

Assessment at one year identified no new abnormalities but indicated developmental delay, although he was able to crawl and ‘say words’. Birth weight was on the 5th percentile (2.49 kg) but by one year this had increased to > 95th percentile (13 kg), whilst he was on only the 25th percentile for height (73 cm).

At the current admission, he was 15 months old and had no respiratory, airway or feeding problems although he was noted to have a ‘soft cry’. Renal function and cardiorespiratory examination were normal. He weighed 14.4 kg (> 95th percentile) with significant truncal, limb, facial and neck adiposity. He had subtle facial dysmorphism including a round face, bitemporal narrowing and deep-set eyes. Although previously reported, examination did not confirm significant micrognathia.

The patient was booked for a bilateral club foot repair and received 300 mg of paracetamol syrup and clear sweet fluids two hours preoperatively. The primary airway plan was inhalational induction and airway maintenance with a supraglottic airway device (SGAD) and pressure support ventilation (PSV). A difficult airway management cart was available in the theatre complex, including a paediatric flexible fibre-optic bronchoscope (FOB) and an Airtraq® Size 1 (Prodol Meditec S.A., Vizcaya, Spain).

Routine monitoring was placed in theatre and the child was induced on the mother’s lap with oxygen, air and sevoflurane. After transfer to the operating table he developed UAO and stridor, assumed to be laryngospasm due to light anaesthesia. A jaw thrust plus continuous positive airway pressure (CPAP) manoeuvres were ineffective but intravenous access was gained without difficulty and signs abated after 10 mg of propofol and insertion of an SGAD (size 2 iGel® (Intersurgical, Wokingham, UK)). Antibiotic prophylaxis and ketamine 0.2 mg/kg were administered, and a caudal block was performed in the right lateral with 14 mL of 0.25% bupivacaine. On PSV the child developed two additional episodes of stridor and inadequate tidal volumes, which were attributed to a dislodged SGAD and accumulation of airway secretions. No episode was associated with desaturation, haemodynamic instability or aspiration.

Direct laryngoscopy (DL) was performed at the end of surgery to ascertain whether there were any abnormalities of the upper airway. A size 2 straight blade obtained a Cormack–Lehane (CL) grade 2 view, with a percentage of glottic opening score16 (POGO) of < 20%. This revealed a bifid epiglottis with features of laryngomalacia (malacic), which was folded down over the larynx and prolapsing into the laryngeal inlet on inspiration and which could not be lifted, as the blade kept slipping through the defect. After changing to a curved blade and with significant external laryngeal manipulation (ELM) a CL grade 1 view, POGO...
100% score was obtained and a Grade 1 anterior laryngeal web was identified (see Figures 2 to 4).

The patient was awakened uneventfully with no further episodes of airway obstruction, stridor or respiratory distress in the recovery room or overnight in a high care observation unit. The mother was counselled regarding the findings and the patient was referred for otorhinolaryngology (ENT) consultation. He was discharged well on day three postoperatively.

Clinical review of BBS

Molecular mechanisms, genetics and diagnostic criteria

Advances in molecular research have identified dysfunction of cilia (micro-tubule based intracellular organelles), as causative in all six cardinal features of BBS. Cilia are responsible for transduction of molecular signals between cells during development and are implicated in the aetiology of a variety of
different craniofacial syndromes that share features with BBS, leading to the proposal of a new classification of ‘craniofacial ciliopathies’.18

Twenty-one genes19 have been identified, and testing confirms the diagnosis in 80% of patients, improving surveillance and earlier interventions to minimise complications.2,4,11,12 As a pleiotropic disease, genotypes and related phenotypes vary widely in expression, onset and clinical severity.2,6,9,12,13–21 As not all features are congenital, diagnosis may be delayed, especially in the absence of polydactyly.7 The disease or full extent of the abnormalities may therefore be unrecognised when patients present to theatre.

Diagnosis remains primarily clinical and Beale’s modified diagnostic criteria, comprising primary and secondary features, have been widely adopted (Table 1).3 Numerous additional non-diagnostic features are described, although the association may be unreliable in some.2,4,9,12,13,15,22–24

**Anaesthetic challenges**

Anaesthetic concerns for BBS patients have been reviewed13,14 and are summarised with additional source material in Table 2. Anaesthetic morbidity is related to the manifestation of BBS rather than the disease per se,13,14 hence references from BBS patients and non-BBS paediatric patients with similar phenotypic manifestations are reviewed. Further discussion will focus on features, especially rare airway anomalies, that may result in difficult airway management.

**Table 1:** BBS modified diagnostic criteria and frequency2,4,5,6,9,10,12,15,25,26

| Feature | Prevalence (%) |
|---------|----------------|
| Primary features: | |
| Rod-cone dystrophy | 90–100 |
| Obesity | 72–100 |
| Polydactyly | 63–93 |
| Hypogonadism in males/genital anomalies | 59–98 |
| Learning disabilities | 50–61 |
| Renal anomalies | 20–80 |
| Secondary features: | |
| Brachydactyly/syndactyly | 46–100 |
| Developmental delay | 50–91 |
| Speech disorder/delay | 54–81 |
| Ataxia/poor coordination/imbalance | 40–86 |
| Left ventricular hypertrophy/congenital heart disease (including ventricular septal defects and aortic valve lesions)4,5,6,9 | 10–50 |
| Diabetes mellitus | 6–48 |
| Hepatic fibrosis | 53\(^a\) |
| Dental crowding/hypodontia/small roots/high arched palate | 51 |
| Strabismus/cataracts/astigmatism | |
| Polysyndactyly (nephrogenic diabetes insipidus) | |
| Mild spasticity (especially lower limbs) | |

Notes: Four primary features are required to be present, or three primary plus two secondary features. Modified from Beales et al.3

**Diagnostic features with potential for difficult airway management**

**Obesity**

Obesity >95th percentile for age and gender significantly increases the risk of co-morbidities.29 Obesity has been associated with 79 genetic syndromes.27 There is increased risk of airway events in older obese children, but data on difficult intubation are conflicting.29,30,12,35,36 and studies on anaesthetic implications in children aged under two years are lacking.31 Obesity in BBS usually manifests by 2–3 years of age,2,9,11 but rapid weight gain may occur in the first year of life9,39 as demonstrated in our case. Obesity is central in adults,13 but diffusely distributed in children.2,13 Intravenous access is more difficult in BBS and obese children in general,14,58 but was not problematic in the case presented. Obesity did impact in the following ways: (i) difficulty with identification of traditional landmarks for caudal block although our block was successful; (ii) degree of craniofacial dysmorphism was obscured by facial and neck adiposity; and (iii) airway adiposity may have contributed to upper airway obstruction. Similar problems are confirmed in the literature.2,3,5,14,29

**Orthopaedic manifestations**

Polydactyly is often the only sign present at birth and clue to the diagnosis of BBS.2,24 Of interest is that our patient’s mother had chosen not to have the extra digits removed as she said it made her child ‘unique’. There are many additional orthopaedic manifestations including club foot, although this association may be incidental.1,9,12,13,20 Frequencies of polydactyly/brachydactyly/syndactyly vary widely in different BBS populations but are common.3,9,15,18,26 These are associated with several other syndromes which have craniofacial or airway abnormalities, especially bifid epiglottis,18,26,29–41 and if present in an undiagnosed child should alert the anaesthetist to an underlying syndrome with potential airway problems.

**Non-diagnostic features with potential for difficult airway management**

(1) **Craniofacial features:**

A ‘typical’ BBS facies has been described,20 but marked phenotypic variation exists (Table 3).2,5,9,12,13,16,21 Preoperative abnormalities were identified in this case, but malar hypoplasia and mild retrognathia were underestimated. These features are likely to have contributed to upper airway obstruction and difficulty in obtaining a full glottic view. Craniofacial features may be subtle and therefore missed.3,12

(2) **Laryngeal anomalies (rare):**

Acquired lesions occur more frequently than congenital laryngeal anomalies (CLA) and are usually secondary to infection, surgery or intubation and are not reviewed here.52–44 CLA are mostly glottic but can be supra-glottic, infraglottic, or involve synchronous lesions. Laryngomalacia (LM) is the commonest lesion, occurring in 60–70% of cases.53,45–50 Laryngeal webs (5% of cases), and specifically bifid epiglottis (BE), are exceedingly rare,41,45–50 and almost always associated with a syndrome, craniofacial abnormalities or other organ (especially cardiac) defects.53,43,45–54

**Bifid epiglottis**

BE may have two separate leaflets (more commonly associated with syndromes) or a submucous cleft.24,43,54 BE has been described in only six children with BBS, half of whom were
Table 2: Anaesthetic concerns related to diagnostic features of Bardet–Biedl syndrome

| Feature(s)                                                                 | Implications                                                                                                                                 |
|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Blindness/learning disabilities/cognitive impairment/developmental delay/ | Multidisciplinary perioperative medical and allied team\(^{27}\)  
Reduced patient ability to cooperate or communicate  
Emotionally labile  
Difficult to establish rapport  
Difficultly with anaesthesia induction  
Ophthalmic/ENT surgery |
| deafness/behaviour problems\(^{3,14,27}\)                                |                                                                                                                                             |
| Polysyndactyly                                                            | Placement of lines if operating on hands/feet  
Difficulty with intravenous access  
Association of brachydactyly/polysyndactyly with bifid epiglottis\(^{24,26}\) |
| Brachydactyly/syndactyly                                                  |                                                                                                                                             |
| Obesity\(^{17,28–33}\)                                                   | Preoperative: screen for comorbidities  
Snoring/obstructive sleep apnoea (OSA) (OR 4.0)\(^{12}\)  
Dyslipidaemia, metabolic syndrome\(^{34}\)  
Accelerated cardiovascular disease  
Asthma (higher in both obesity and BBS)\(^{15,32}\)  
Intraoperative:  
Difficult airway management including\(^{28,32}\)  
airway obstruction major (OR 1.8)  
bag mask ventilation (OR 4.5)  
bronchospasm (OR 3.3)  
desaturation, critical airway events (OR 1.9)  
Divergent information on intubation difficulty  
Difficult intravenous access\(^{14}\)  
Difficult landmarks for regional anaesthesia\(^{14}\)  
Altered drug kinetics and dose calculations  
Opioid sensitivity with OSA  
Postoperative  
Unexpected hospital admission  
High care if co-morbidities significant |
| Renal anomalies\(^{6–8}\)                                                 | Preoperative  
Renal ultrasound  
Renal function tests  
Intraoperative  
Chronic kidney disease and attendant problems  
Urogenital surgery including kidney transplant  
Avoid nephrotoxic drugs  
Polyuria/polydipsia (nephrogenic diabetes insipidus) |
| Cardiovascular\(^{6,11,15}\)                                             | Preoperative:  
Cardiology cardiac evaluation, check blood pressure, electrocardiogram and echocardiogram and lipid profile  
Cardiac/hypertensive medication  
Intraoperative considerations for:  
Anaesthesia for congenital cardiac surgery or |
  | Congenital heart disease                                                |                                                                                                                                             |
  | Hypertension\(^{15}\)                                                   |                                                                                                                                             |
  | Left ventricular hypertrophy                                            |                                                                                                                                             |
  | Cardiomyopathy                                                          |                                                                                                                                             |

(Continued)
asymptomatic and half of whom had significant symptoms and morbidity related to the BE.22,24,45,56 Stevens et al.45 reviewed all cases of BE reported in the literature (n = 23) and suggest that BE may be under-recognised in BBS either as the disease had not been appropriately diagnosed or remained unrecognised in asymptomatic patients.45,54

Table 3: Craniofacial features in BBS patients

| Feature | Prevalence |
|---------|------------|
| Brachycephaly | 92% |
| Frontal balding in adult males | 92% |
| High-arched palate | 86% |
| Narrow palpebral fissures | 81% |
| Short palpebral fissures | 77% |
| Bitemporal narrowing | 65% |
| Long ears | 61% |
| Macrocephaly | 58% |
| Downturned mouth | 58% |
| Thin upper lip | 54% |
| Small mouth | 38% |
| Shallow philtrum | 35% |
| Long philtrum | 35% |
| Ptosis | 27% |

Characteristic facies:15,25 retrognathia/micrognathia, wide forehead, downward palpebral fissure, malar hypoplasia, low nasal bridge, large nose, small mouth, thin upper lip and slightly everted lower lip

Modified from Moore et al.9

Table 4: Grading of anterior laryngeal webs and subglottic stenosis

| Condition | Grade I | Grade II | Grade III | Grade IV |
|-----------|---------|----------|-----------|----------|
| Anterior laryngeal webs | 0–35% | 35–50% | 50–75% | 75–90% |
| Subglottic stenosis | 0–50% | 51–70% | 71–99% | Absent lumen |

Cohen grading

Meyer–Cotton grading
Differentiating voice disorders from stridor and laryngospasm

Stridor is an obvious sign of pathological narrowing or obstruction of the airway resulting in turbulent airflow and is exacerbated by crying, feeding or the supine position. Acute or worsening stridor may indicate an impending airway emergency. Laryngospasm (LS) is an exaggerated response of the laryngeal closure reflex to a stimulus, causing sustained glottic closure with partial or total cessation of airflow. (See Table 5 for voice descriptions and grading of stridor and LS.)

An abnormal voice has been described in BBS and is thought to be due to a combination of neurological and anatomical dysfunction with uncoordinated movement of palate, tongue and lips. Dysphonia is a disorder of voice and the commonest cause in older children is overuse of the voice rather than laryngeal pathology. Subtle or persistent dysphonia in neonates and infants should always raise the suspicion of an underlying laryngeal anomaly, even in the absence of stridor or respiratory distress.

Discussion

UAO and stridor under anaesthesia

Even normal infants and neonates are at greater risk of airway events, including UAO and laryngospasm, which may result in significant morbidity. UAO occurs due to an imbalance of anatomical structures and neural mechanisms under anaesthesia, favouring airway collapse and increasing turbulent airflow. Children with abnormal craniofacial or airway anatomy are critically reliant on intact neural mechanisms and protective reflexes to maintain airway patency, making UAO and stridor common under anaesthesia.

The work of breathing and airway resistance in spontaneously breathing children under anaesthesia is greatest with mask anaesthesia but improved by SGAD or tracheal tube. Management of UAO and stridor (including LS) is beyond the scope of the review, but correct mask technique, adequate depth of anaesthesia, correct head and neck position and sequential manoeuvres, including (in increasing order of effectiveness) chin lift, jaw thrust, or either of these with CPAP, are essential to maintain airway patency.

| Condition | Quality |
|-----------|---------|
| Bardet–Biedl syndrome | Breathy, high-pitched and hypernasal speech is slow with misarticulation |
| Congenital laryngeal abnormalities | High-pitched, soft, weak cry, but may be hoarse or aphonc |
| Stridor | High-pitched or harsh, often exaggerated during crying or feeding |
| Grading: | Inspiratory |
| Grade I | Inspiratory and expiratory |
| Grade II | Inspiratory and expiratory plus pulsus paradoxus |
| Grade III | Silent, respiratory arrest |
| Phase: | Anatomic position: |
| Muffled | Upper airway obstruction |
| Inspiratory | Pharynx, supraglottic, extrathoracic |
| Expiratory | Trachea, lower airways, intrathoracic |
| Biphasic | Glottic or infraglottic |
| Laryngospasm | High-pitched, initially grade I stridor, which progresses to silent with complete obstruction |
Airway management in BBS, and laryngeal anomalies

Intubation by DL has been reported as successful in all paediatric patients with BBS, albeit occasionally difficult (CL Grade 3).\textsuperscript{74,14,22,24,45,55,56} In contrast, 67% of adults required an awake FOB or videolaryngoscopy-aided intubation (VL).\textsuperscript{17} The difference may be partly due to lack of paediatric videolaryngoscopes in the earlier cases described; intubation trends may change with currently available equipment.\textsuperscript{13,14,82–84}

Intubation in patients with BBS and with a BE may be difficult but has been described as ‘unexpectedly easy … through the separate leaflets’.\textsuperscript{56} Airway management in symptomatic laryngeal anomalies may be extremely challenging, and may require a tracheostomy.\textsuperscript{83,86} Asymptomatic webs may also cause unexpected difficulty at intubation,\textsuperscript{77,87} or may be confused with other symptoms such as airway obstruction, stridor or bronchospasm if a mask or SGAD is used.\textsuperscript{88}

The expected versus the unexpected difficult airway in children

The expected difficult airway is infrequently encountered in paediatric anaesthesia, and recommendations regarding management are based primarily on case reports/series rather than large trials.\textsuperscript{74,75,89} Such cases must be referred to specialist centres with requisite expertise and equipment.\textsuperscript{74,85} The current gold standard for elective intubation remains the FOB; however, VL is expected to impact on these recommendations as evidence for their use is increasing in children, including those with a predicted difficult airway.\textsuperscript{13,82–84,89–94} VL may not always be successful, either because of restricted mouth opening or inability to pass the tube in a very anterior larynx,\textsuperscript{75,95} thus FOB skills still need to be maintained.

SGADs have an established role in emergency airway rescue or as a conduit for intubation.\textsuperscript{75} Elective use of an SGAD as the primary airway in an expected difficult airway may be more controversial, although the literature supports its use.\textsuperscript{96–98} Provisos would include availability of alternative rescue devices or intubating strategies, low risk of aspiration, adequate oral access and practitioner experience.\textsuperscript{89,98} As all these criteria were met, primary use of an SGAD in the case presented was considered justified.

Airway management in the case presented

All patients with craniofacial abnormalities should be considered potentially difficult. Our patient was otherwise well; his soft cry and subtle dysmorphism did not raise significant concerns about airway management. His voice was in keeping with that described in BBS, which masked the dysphonia associated with the web. A combination of obesity, craniofacial pathology and malacic BE led to UAO and airflow turbulence, causing grade 1 stridor through the laryngeal web. Difficult PSV was due to the combination of laryngeal anomalies. Signs were initially mistaken for common paediatric airway problems but failure to resolve after following the recommended steps mandated direct laryngoscopy. Curved and straight blades have been shown to be equivalent in attaining an optimal laryngeal view in children <2 years;\textsuperscript{99} however, the curved blade achieved a better POGO score in this case. Difficult DL demonstrated the impact even mild retrognathia has on obtaining the full glottic view essential to identify all possible lesions. Clinical recommendations and insights gained from this case and review are presented in Table 6.

| Table 6: Clinical insights and recommendations |
|-----------------------------------------------|
| **Factor** | **Considerations** |
| Obesity | • Risk for co-morbidities, airway events and syndrome |
| Polydactyly/brachydactyly/syndactyly | • Suspect craniofacial syndromes and CLA |
| Craniofacial patterns | • Sydrome examples: Trisomies 13, 18, 21; Apert Carpenter, Pffeifer, Saethre–Chotzen, Muenke, BBS |
| Congenital laryngeal anomalies (BE, ALW) | • Recognise subtle craniofacial patterns to anticipate difficult airway |
| Obstructive sleep apnoea | • May be asymptomatic |
| Voice/dysphonia | • Increases perioperative risk |
| UAO and stridor under anaesthesia | • Exclude in obesity, craniofacial syndromes and CLA |
| Glottic view: | • Voice in BBS may mask laryngeal pathology |
| POGO score | • View larynx |
| Blade shape | • POGO score describes views better than CL, aiding communication between physicians/researchers |
| Expected difficult airway | • 100% POGO required view to identify all lesions |
| | • Curved or straight blades are effective in infants |
| | • FOB remains the ‘gold standard’ |
| | • VL has an increasing role in paediatric difficult airway management but is not fail-safe |
| | • SGAD may be used as the primary airway in expected difficult airway with strict provisos |

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| Craniofacial patterns | • Sydrome examples: Trisomies 13, 18, 21; Apert Carpenter, Pffeifer, Saethre–Chotzen, Muenke, BBS |
| Congenital laryngeal anomalies (BE, ALW) | • May be asymptomatic |
| Obstructive sleep apnoea | • Associated with craniofacial syndromes and organ (cardiac) abnormalities e.g. 22q11.2 deletion syndrome |
| Voice/dysphonia | • BE associated syndromes: Pallister–Hall, Joubert, BBS |
| UAO and stridor under anaesthesia | • Increases perioperative risk |
| Glottic view: | • Exclude in obesity, craniofacial syndromes and CLA |
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Conclusion
This is the first description of a case of Bardet–Biedl syndrome with the combination of a malacic bifid epiglottis and anterior laryngeal web. Few anaesthetists will encounter a patient with BBS or the even rarer associated anomalies discussed. However, as a ‘model’ craniofacial ciliopathy, BBS provides insights into a range of syndromes and the case and review has highlighted several important lessons that are applicable to the paediatric anaesthetist, especially those anaesthetising syndromic children. Unexpected difficulties with airway management should always be anticipated, and unsuspected lesions should always be considered.

Consent
Signed consent was obtained from the mother for publication of this case.

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