Freeman-Sheldon syndrome: report of three cases and the anaesthetic implications

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The Freeman-Sheldon syndrome is a rare congenital myopathy and dysplasia. Fibrotic contractures of the facial muscles result in the characteristic "whistling face." Difficulties with intubation may be attributed in part to microstomia and micrognathia. In addition to other deformities, limb myopathy results in ulnar flexion contractures of the hand and equinovarus/valgus deformities of the feet. Intravenous access may be difficult because of limb deformities and thickened subcutaneous tissues. Limbs may be encased in plaster casts or splints limiting the available sites for venepuncture. Three case reports of children with Freeman-Sheldon syndrome are presented. The pathophysiology and anaesthetic problems encountered are discussed.

The Freeman-Sheldon syndrome[1] is a rare congenital dysplasia principally characterised by facial and skeletal abnormalities secondary to a generalised myopathy. Although more than 50 cases have now been described this syndrome has received little attention in the anaesthetic literature. Patients with the syndrome may present anaesthetic problems involving difficulties with both intubation and intravenous access. Therefore we describe three children with the Freeman-Sheldon syndrome who presented for elective surgery and discuss the features of significance to the anaesthetist.

Key words
GENETIC FACTORS: Freeman-Sheldon syndrome, craniofacial dysostosis; ANAESTHESIA: complications.

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The syndrome may be diagnosed by the clinical examination of an affected newborn infant. Not all of the features described are necessarily present in a single patient. The increased tone and fibrosis of the facial muscles gives rise to an immobile mask-like facial expression. In addition to hypertelorism, the eyes are deeply set below a supraorbital ridge with blepharophimosis and ptosis. Other eye features which may be present are epicanthic folds and strabismus. The nose is small and the alae nasi are hypoplastic. The myopathic fibrotic circumoral musculature results in microstomia with the characteristic protruding pursed "whistling" lips and a prominent long philtrum. The contracted facial musculature and soft tissues produce a lingually directed force on the lower teeth. This in turn pushes the lower incisors lingually and leads to an unusual modelling of the chin. Externally there is a mound of subcutaneous tissue inferior to the lower lip and demarcated by vertical furrows on either side. Mandibular development may also be abnormal with small mandibular bodies of the rami. The high arched palate, small tongue and limited palatal movement eventually results in a nasal quality of speech. The overall appearance of the skull is often dolichocephalic. Muscle contractures result in the development of a relatively short neck and high (cephalad) positioning of the larynx.

The generalised myopathy is associated with the later development of kyphoscoliosis. In addition to intercostal myopathy, this can lead to restrictive lung disease. By affecting the oro- and nasopharyngeal muscles, the myopathy may produce chronic upper airway obstruction, most notably

observed in infants. Secondary to this, pulmonary hypertension may develop and should be sought specifically when evaluating these patients. There is an increased incidence of pectus excavatum and spina bifida occulta in this syndrome. Other associated truncal abnormalities include inguinal herniae and incomplete descent of the testes. The limbs are commonly involved by the myopathy and contracture deformities develop. In the upper limb, ulnar deviation of the wrist and flexion contractures of the fingers occur. In the lower limb, talipes equinovarus, vertical talus and contracted toes may be present. Difficulty with swallowing may lead to malnourishment and failure to thrive. Although overall growth may be retarded, eventual intelligence is usually in the normal range. The incidence of congenital heart disease is not increased in this syndrome. The results of electromyography and muscle biopsy may support the diagnosis.[2]

Most of the features of this syndrome remain into adulthood. Treatment consists of correcting malnutrition in the infant combined with corrective surgery in the child and adult for the wide range of musculoskeletal deformities. Formerly it was observed that improvement of the manifestations occurred on reaching adult age.[3] More recently Malkawi *et al.*[4] have suggested that early surgery, especially of the hand of the affected child, may improve the outcome of the deformities. Kyphoscoliosis, as in idiopathic scoliosis, develops with growth of the child and commonly presents in the teenager when it may require surgical treatment. Microstomia remains into adulthood and, by reducing the oral aperture, presents difficulties to both the dentist and the anaesthetist. In most cases, early corrective surgery of the deformities can result in the patient leading a normal life with normal expectancy.

Case history 1

A female infant, aged 11 weeks, with failure to thrive was scheduled for gastrostomy under general anaesthesia.

This infant was born to a 26-year-old healthy primigravid mother. The mother had suffered a salmonella infection at 19 weeks gestation. An ultrasound examination was performed and confirmed polyhydramnios with a deformity of the right foot of the fetus. The infant was born at term, with a birth weight of 3.38 kg, after the onset of spontaneous labour and a normal vaginal delivery. The dysmorphic features of the infant suggested a diagnosis of the Freeman-Sheldon syndrome. The infant did not require neonatal intensive care. Chromosomal analysis was normal and there was no family history of congenital disease.

At nine weeks of age, the infant was admitted to hospital for evaluation of her feeding difficulties and failure to thrive. Physical examination revealed a 3.88 kg infant with dysmorphic features affecting the face and all four limbs. The eyes were deeply set below a broad ridge of supraorbital soft tissue with hypertelorism, blepharophimosis and epicanthic folds. A high arched palate and a small tongue were observed. The combination of microstomia, micrognathia and a fixed facial expression (see Figures 1 and 2) presented the characteristic "whistling face." The pathognomonic chin mound was present and the neck was short. Intermittent partial upper airway obstruction was characterised by noisy breathing, tracheal tugging, intercostal recession and pectus excavatum. Although there was a history of difficulty with swallowing and intermittent choking, the chest was clear to auscultation. Tongue movement and the sucking reflex were poor with vocalisation absent. Cardiovascular examination was normal. Bilateral inguinal herniae were present and the genitalia were normal. All four limbs were hyperreflexic, without evidence of weakness. Distal limb abnormalities were present with fixed ulnar deviation and dorsi-flexion of both wrists, fixed flexion of the third and fourth digits on both hands at the proximal interphalangeal joints, left foot calcaneovalgus and severe rigid equinovarus of the right foot. Results of the preoperative laboratory investigations were unremarkable. Echocardiography was also normal. Radiology of the skull demonstrated craniofacial disproportion.

On arrival in the operating room, precordial stethoscope, blood pressure cuff, electrocardiography and doppler pulse monitors were applied to the unpremedicated infant. Atropine (0.02 $mg \cdot kg^{-1}$) was administered intramuscularly in view of difficult venous access. In the presence of partial upper airway obstruction and anticipated intubation difficulties, the infant was preoxygenated and an awake intubation was attempted. Using a Miller size 1 laryngoscope blade, only the posterior parts of the arytenoid cartilages were visible. With difficulty and after repeated attempts at intubation,

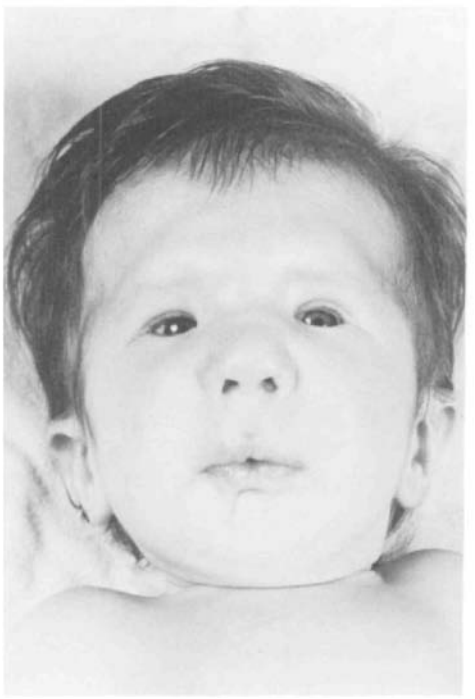

FIGURE 1 Frontal photograph of patient 1, showing the characteristic facies of Freeman-Sheldon syndrome including microstomia and hypertelorism.

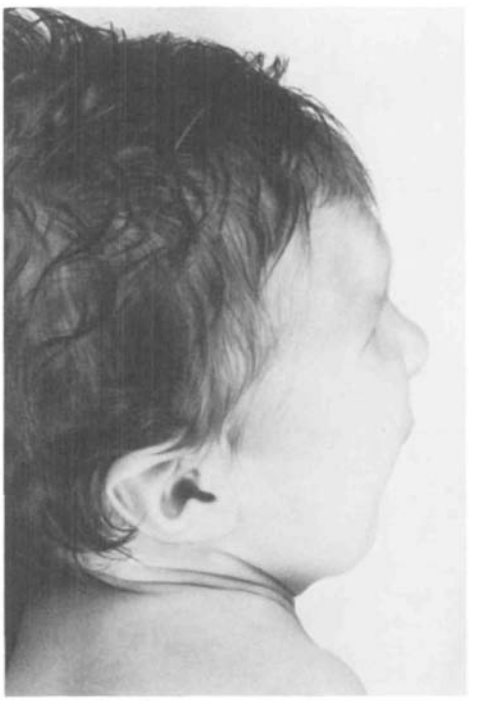

FIGURE 2 Lateral photograph of patient 1 showing micrognathia.

the airway was secured with a 3.0 mm orotracheal tube, utilizing a stylette. Anaesthesia was then induced and maintained with halothane and 50 per cent nitrous oxide in oxygen. Percutaneous venous cannulation proved to be impossible and venous access was achieved by direct surgical cut down. The use of muscle relaxants and opiates was avoided. Intraoperatively, anaesthesia was complicated by tachycardia (heart rate 200/minute) and hyperpyrexia (38.7° C) as measured by rectal thermistor probe. Suspecting the onset of malignant hyperpyrexia, arterial blood gas analysis was performed and found to be normal. Both complications resolved spontaneously during the course of anaesthesia without specific treatment, except for cooling of the operating room. Therefore it was interpreted that these events were produced by the combination of atropine, poor infantile temperature regulation, and a difficult intubation in the awake vigorous infant. On recovery from anaesthesia and when fully responsive, the infant was extubated in the operating room without complication. Postoperative recovery was uneventful.

Case history 2

A five-year-old male, weighing 14.6 kg, was scheduled for surgical release of oral contractures under general anaesthesia. The presence of a supraorbital ridge, hypertelorism, epicanthic folds, microstomia, micrognathia, characteristic chin mound and a short neck confirmed the diagnosis of Freeman-Sheldon syndrome (Figures 3 and 4). There were no other abnormalities except for a contracture of the first interosseous space of the right hand. Chromosomal analysis was normal and family history of congenital disease was negative. General anaesthesia had been administered to the child on four previous occasions during the preced-

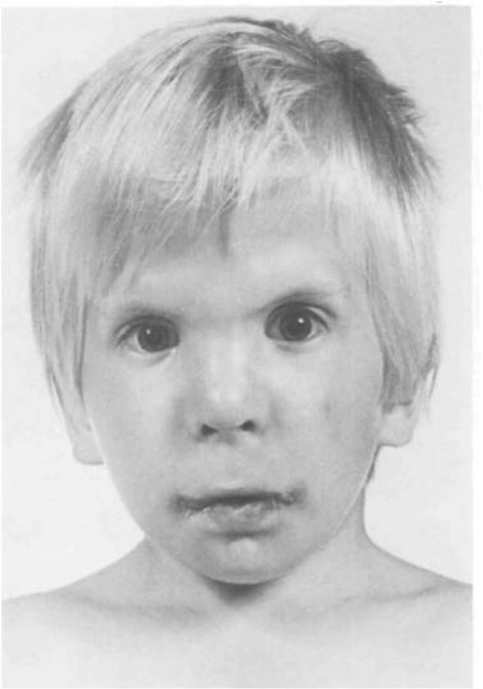

FIGURE 3 Frontal photograph of patient 2 showing the characteristic facies including microstomia.

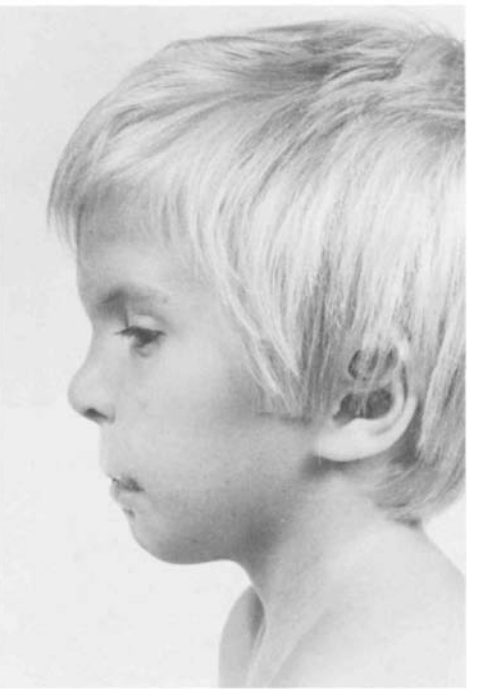

FIGURE 4 Lateral photograph of patient 2 showing micrognathia.

ing two years for release of oral contractures, hand surgery and restorative dental work. For three of these anaesthetics, an intravenous induction had been used, with thiopentone ($5\ mg \cdot kg^{-1}$), atropine ($0.02\ mg \cdot kg^{-1}$) and succinylcholine ($2\ mg \cdot kg^{-1}$). Induction of the fourth anaesthetic had been by inhalation of halothane with nitrous oxide and oxygen. At each laryngoscopy the larynx was visualised and only the presence of a small mouth impeded an otherwise straightforward intubation. There were no other previously documented complications of anaesthesia.

On this occasion the child was brought to the operating room and the routine monitors were applied. Intravenous access was secured with difficulty and prior to induction of anaesthesia intravenous atropine ($0.02\ mg \cdot kg^{-1}$) was administered. In view of the microstomia and the possibility of a difficult intubation, anaesthesia was induced by inhalation of halothane with 66 per cent nitrous oxide in oxygen. Despite deep halothane anaesthesia, only the arytenoid cartilages could be visualized at laryngoscopy. Intubation was achieved with difficulty using a 5 mm orotracheal tube. Anaesthesia was maintained by 66 per cent nitrous oxide in oxygen and halothane with positive pressure ventilation. The remainder of the anaesthetic and recovery was uneventful.

Case history 3

A seven-year-old female, weighing 25 kg, presented with residual features of the Freeman-Sheldon syndrome, as she had undergone previous cranio-facial surgery and correction of club feet at another hospital. In addition to bilateral ptosis, the other facial signs observed were the supraorbital ridge, hypertelorism, microstomia and the chin mound. There were no other abnormalities present.

Family history of congenital disease was negative. One previous anaesthetic had been administered to the patient at this hospital for surgical release of oral contractures. An inhalational induction had been used with halothane and methoxyflurane in 66 per cent nitrous oxide in oxygen. Oral intubation had been achieved with considerable difficulty in view of the microstomia and high larynx. There had been no further complications.

On this admission, the child was scheduled for bilateral ptosis repair and myringotomies under general anaesthesia. The unpremedicted child arrived in the operating room and the routine monitors were applied. Following the administration of intravenous atropine ($0.02\ mg \cdot kg^{-1}$) induction of anaesthesia was achieved using an inhalational technique with halothane and methoxyflurane in 66 per cent nitrous oxide and oxygen. At laryngoscopy, under deep anaesthesia, there was considerable difficulty visualising the larynx even with the application of anterior neck pressure. The airway was eventually secured with a 5 mm orotracheal tube and the use of a stillette. Anaesthesia was maintained by halothane with 66 per cent nitrous oxide in oxygen and spontaneous respiration. There were no further anaesthetic complications and the child was extubated uneventfully at the end of the surgical procedure.

Discussion

Since its original description in 1938,[1] Freeman-Sheldon syndrome has also been variously described as the Windmill-Vane-Hand syndrome,[5] cranio-carpo-tarsal dysplasia and the whistling face syndrome.[6] Although most cases occur sporadically it is thought to be transmitted by autosomal dominant inheritance[2] and there are at least two case reports of first degree transmission.[3,4] Not all cases are equally affected and there exists a spectrum of deformity and disability. The precise mechanism of this combined skeletal and muscular dysplasia is unclear, although Sauk *et al.*[2] suggest that hypoplasia of muscle bundles supplied by the motor branch of major nerves may cause these abnormalities. Biopsy of the affected muscles reveals fibrosis which may contribute to the contractures.

With the presence of facial and orthopaedic abnormalities, inguinal herniae and feeding difficulties, patients with this syndrome may be frequently scheduled for anaesthesia and surgery. Only one previous report has mentioned anaesthetic difficulties.[4] In this report intubation was described as impossible in the child and achieved only with difficulty in the father. Although true micrognathia may not be confirmed radiologically, we believe that intubation difficulties are compounded by the contracture of facial and anterior neck muscles. Contracture of the pharyngeal muscles may also contribute to partial upper airway obstruction. Intravenous access may prove difficult since the deformed hands and feet may be encased in plaster casts. Difficulty with intravenous access may also be caused by thickening of subcutaneous tissues.[3]

The three cases reported illustrate the spectrum of the deformities as observed in this syndrome. In all cases the features of the "whistling face" were present. In the infant (Case 1), the relatively small oral cavity increased the difficulties of intubation caused by the combination of microstomia, micrognathia and neck shortening. It is interesting to note that in the older children (cases 2 and 3) previous surgery to increase the oral aperture did not necessarily improve subsequent intubation conditions. Moreover in case 2 intubation difficulties were encountered even though previous intubation had been straightforward. This emphasizes that fibrotic oral contractures may recur and become more pronounced with age. Provided that the airway can be maintained, the use of succinylcholine may theoretically facilitate intubation by maximizing muscle relaxation. However, where the muscle contractures are caused by muscle hypoplasia and fibrosis, a muscle relaxant may not produce this effect reliably on dysplastic muscle.

The increased temperature of the first patient alerted the possibility of malignant hyperpyrexia (MH). Although not previously reported with Freeman-Sheldon syndrome, it is known that MH is associated with other myopathies and dystrophies (e.g., Duchenne and osteogrenesis imperfecta). In the case reported, with normal blood gas analysis and spontaneously correcting temperature, we concluded that there were other reasons for the temperature rise. Halothane was used in cases 2 and 3, and succinylcholine was used in case 2. In neither of these cases was there a temperature rise. In the absence of the recognised association between Freeman-Sheldon syndrome and MH, we would therefore support the use of halothane in these cases. In a patient with an anticipated difficult

intubation, halothane is often the safest induction agent.

In conclusion, difficulties with the airway, intubation and intravenous access may complicate the course of anaesthesia in patients with the Freeman-Sheldon syndrome. The anaesthetist should therefore be aware of the problems associated with this syndrome.

Acknowledgements

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Résumé

Le syndrome de Freeman-Sheldon est une myopathie congénitale rare associé à une dysplasie. Les contractures fibrotiques des muscles faciaux aboutissent aux signes caractéristiques de la "face de siffleur" (whistling face). Les difficultés d'intubation seront attribuées en partie à la microstomie et la micrognatie. En plus d'autres déformités, la myopathie des membres provoque une contracture en flexion de la main et une déformité des pieds en equinovarus/valgus. L'accès intraveineux peut être difficile à cause des déformités des membres et de l'épaisseur des tissus sous-cutanés. Les membres peuvent être plâtrés imitant ainsi l'accès aux veines. On présente trois cas de patients atteint de ce syndrome. La pathophysiologie et les problèmes anesthésiques encourus sont discutés.