orphanaesthesia

Anaesthesia recommendations for

Sheldon-Hall syndrome

Disease name: Sheldon-Hall syndrome

ICD 10: Q74.3

Synonyms: Freeman-Sheldon variant, distal arthrogryposis multiplex congenita, distal arthrogryposis type 2B, distal arthrogryposis multiplex congenita type II with craniofacial abnormalities

Disease summary: Originally described as a skeletal dysplasia and later as a myopathic distal arthrogryposis, Sheldon-Hall syndrome (SHS) involved a congenital non-progressive constellation of craniofacial, hand and feet, and sometimes spinal malformations. The features in patients with SHS were less dramatic but similar to those found in patients with Freeman-Burian syndrome (FBS), with which it was often confused. Relatively little was known about SHS. While treatment for FBS and SHS was similar, distinguishing between SHS and FBS was of great therapeutic importance, with FBS being more severe, less responsive to therapy, and having an overall worse clinical outcome than SHS. The diagnostic criteria for SHS required small mouth (not microstomia), small but prominent chin, prominent nasolabial folds, neck webbing, and deformities of the distal extremities. Previous criteria included: triangular face, micrognathia, highly arched palate, attached ear lobules, down-slanting palpebral fissures, short stature, and deformities of the distal extremities. Limb malformations that were accepted in the diagnostic criteria for both FBS and SHS included two or more of the following: talipes equinovarus, metatarsus varus, vertical talus, talipes equinovalgus, calcaneovalgus, camptodactyly, ulnar deviation of wrists and fingers, overlapping fingers or toes, and hypoplastic or absent interphalangeal creases. Patients with SHS lacked a history of dysphagia and the five craniofacial features pathognomonic for FBS. Most instances of SHS were sporadic, but autosomal dominant inheritance has been established, as well. There was no apparent gender, ethnic, or geographical preference, and environmental and parental factors were not implicated in pathogenesis.

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Perhaps the diagnosis is wrong

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A	**AIRWAY / ANAESTHETIC TECHNIQUE**	Midfacial hypoplasia may prevent mask sealing. Micrognathia, small mouth, class II malocclusion, dental crowding, highly arched hard palate, and limited cervical spine flexibility may make endotracheal intubation and use of airway adjuncts difficult. Tracheotomy may be needed for emergent or unusually challenging intubations. Hypoplastic cartilaginous landmarks may make cricothyroidotomy impossible. Spinal deformities may complicate but are unlikely to preclude epidural or spinal anaesthesia. Extremity contractures may complicate RA. Limited cervical mobility, distal extremity contractures, and small diameter/poor quality of veins complicate vascular access. Due to technical difficulty and possible post-operative pulmonary complications, consider avoiding pre-medication, sedation, and GA. If possible, consider local, RA, spinal, and epidural anaesthesia as alternatives when possible. If GA is needed, use recruitment manoeuvrers and endotracheal suctioning before extubation to maximise lung volume and reduce the risk of atelectasis.
B	**BLOOD PRODUCTS (COAGULATION)**	No coagulation disorder associated; no special considerations necessary.
C	**CIRCULATION**	No cardiopulmonary malformations, pathologies, arrhythmias, congenital heart disease, risk for heart failure, or haemodynamic issues.
D	**DRUGS**	Due to potential intercostal myopathy, avoid opioids and other potential respiratory depressants to reduce risk of apnoea, over-sedation, hypoventilation, and post-operative respiratory distress. There are no typical home medications. No evidence for increased risk of MH/rhabdomyolysis.
E	**EQUIPMENT**	Use of a small gauge vascular catheter (22 or less), paediatric spinal needle and epidural catheter, and 12 French or smaller urinary catheter are often required. Nasopharyngeal, endotracheal tubes, other airway devices, and BP cuffs typically need to be smaller, as well. Nasal and oral intubation require a flexible fibre-optic bronchoscope; if not available, blind nasal intubation may be attempted.

Disease background

Originally described as a skeletal dysplasia by Freeman and Sheldon (1938)[1] and later as a myopathic distal arthrogryposis[2-3], Sheldon-Hall syndrome (SHS; MIM: 601680) involved a congenital non-progressive constellation of craniofacial, hand and feet, and sometimes spinal malformations. Relatively little was known about SHS. The features in patients with SHS were less dramatic but similar to those found in patients with Freeman-Burian syndrome (FBS; MIM 193700). Indeed, experience indicates the features in patients with SHS were so much more moderate than those exhibited in FBS that SHS patients were far less likely to present to a craniofacial surgeon[4]. Beginning with the initial report[1] and continuing for many years, FBS and SHS were considered to represent different severities of a single pathological entity. In a review of published cases with a similar phenotype, Krakowiak et al. (1998)[5] suggested that Sheldon's patient expressed a similar but distinct phenotype from Freeman's patient[1]. The genotypical uniqueness of FBS and SHS was subsequently established[6]. Both were later renamed to reflect their divergent natural histories[4, 7-8]. While treatment for FBS and SHS was similar, distinguishing between SHS and FBS was of great therapeutic importance, with FBS being more severe, less responsive to therapy, and having an overall worse clinical outcome than SHS[7]. Furthermore, FBS was primarily a craniofacial condition, while SHS was primarily limb malformation disorder[8].

The diagnostic criteria for SHS required small mouth (not microstomia), small but prominent chin, prominent nasolabial folds, neck webbing, and deformities of the distal extremities[7]. Another criteria included: triangular face, micrognathia, highly arched palate, attached ear lobules, down-slanting palpebral fissures, short stature, and deformities of the distal extremities[9]. Limb malformations that were accepted in the diagnostic criteria[6-7] included two or more of the following: talipes equinovarus, metatarsus varus, vertical talus, talipes equinovalgus, calcaneovalgus, camptodactyly, ulnar deviation of wrists and fingers, overlapping fingers or toes, and hypoplastic or absent interphalangeal creases. Patients with SHS lacked a history of dysphagia and the five craniofacial features pathognomonic for FBS (microstomia, pursed lips or so-called whistling face, H or V- shaped chin defect, hypoplastic ala nasi, prominent nasolabial folds). Other major differential diagnoses included distal arthrogryposis types 1, 3, 7, and 8; Schwartz-Jampel syndrome; and non-syndromic distal contractures. SHS was distinguished from all other conditions by the presence of pathognomonic head and neck findings.

Most instances of SHS were sporadic, but autosomal dominant inheritance has been established, as well[7]. There was no apparent gender, ethnic, or geographical preference, and environmental and parental factors were not implicated in pathogenesis[10]. Krakowiak et al. (1997) mapped SHS to 11p15.5[11]. Sung et al. (2003) provided evidence that SHS was associated with allelic variations in the fast skeletal muscle troponin T and I (*TNNT3* and *TNNI2*; MIM 600692 and 191043) genes[12]. Tajsharghi et al. (2007) noted heterozygous allelic variation of tropomyosin beta chain (*TPM2*; MIM 190990) gene, at 9p13.2-13.1[13]. Toydemir et al. (2006) showed that allelic variations in the embryonic myosin heavy chain 3 (*MYH3*; MIM 160720) gene, at 17p-13.1, could also cause an SHS phenotype[6]. In *MYH3*, *TNNT3*, and *TMP2* allelic variation screening of patients with heritable equniovarus (N 20), vertical talus (N 5), or distal arthrogryposis type 1 (DA1) (N 6), only one *de novo* allelic variation (R63H) in *TNNT3* was found in a single patient with DA1[14]. This finding highlighted the genotype uniqueness of FBS, SHS, and DA1[14]. In investigating contracture pathogenesis, Robinson et al. (2007) showed that R174Q and R156X allelic variations on *TNNI2* gene and R63H allelic variation on *TNNT3* gene were associated with increased ATPase activity, suggesting increased calcium sensitivity and increased contractility[15].

SHS was considered to be the most common in a group of phenotypically similar entities termed distal arthrogryposes[2-3], which were thought to be the most common form of arthrogryposis syndromes. Arthrogryposis multiplex congenita is unique from the distal arthrogryposes classification of syndromes[2]. Due to the paucity of literature on anaesthesia care for patients with SHS, these clinical recommendations were based on clinical experience and a systematic

review and meta-analysis that included distal arthrogryposis syndromes and FBS[16-17], the protocol for which has been described elsewhere[18-19].

Typical surgeries

Patients with SHS frequently undergo numerous orthopaedic surgeries, because attempts at operative deformity correction may have suboptimal results and require subsequent revision. Due to wide variability of SHS presentation and the lack of research, there are a great diversity of operative approaches employed for the following reasons: ankle-foot complex contracture correction, spinal curvature correction (rod insertion and vertebral fusion), hand contracture correction, and craniofacial reconstruction. Less frequently, involvement of more proximal joints (e. g., recurrent dislocation or dysplasia of shoulders and hips, contracture of elbows, or patellar instability) is the focus of operative interventions.

Type of anaesthesia

Although most case reports describe general anaesthesia, this is not meant to imply general anaesthesia is always needed in SHS. While the anaesthetic approach is ultimately dictated by patient safety, the patient's understanding and affect regarding surgery, and technical feasibility, it may be desirable to avoid pre-medication, sedation, and general anaesthesia for appropriately selected patients with SHS[20]. Though spinal deformities occur in SHS, this typically does not preclude epidural or spinal anaesthesia, which may have far fewer syndromic-associated challenges and complications and a more favourable safety profile over sedation and general anaesthesia. Whenever possible, consider and explore local, regional, spinal, and epidural anaesthesia with patients during the pre-anaesthetic consultation. Age is not necessarily a contraindication to any particular anaesthesia modality[20]. Many adults are poor candidates for local or regional anaesthesia, and many children handle the experience very well[20]. Proper psychological preparation for patients undergoing surgery exclusively under local or regional anaesthesia does not differ substantively from any other pre-operative consent and preparation process[20].

Pre-operative testing

Anaesthetic care for patients with SHS often presents a challenge and requires considerable pre-operative planning. Patients should be evaluated well in advance of proposed procedures, if possible. The anaesthesiologist performing the evaluation should also be the anaesthesiologist assigned for the procedure. A thorough and complete history should include questions about: current medications and allergies, reactive airways disease, gastro-oesophageal reflux disease (GERD), previous acute and chronic respiratory problems, prior anaesthesia and surgeries, seizures, and any symptoms of possible central nervous system dysfunction, especially increased intracranial pressure[21]. Examination includes: vital signs, mental status, airway, spinal, neurological, and cardiopulmonary assessments[21]. It is important to explain to the patient and family possible risks and ensure questions are answered and concerns fully addressed[20-21]. Findings, concerns, and management plans must be discussed with participating surgeons[21]. The preceding pre-operative consultation and planning process may seem obvious, but unfortunately, this process does not represent a universal standard for the care of potentially high-risk patients undergoing surgery.

Some suggest that malignant hyperthermia (MH) does not have an association[22-23], with most myopathies in which anaesthetically-related hypermetabolic states resembling MH have been reported. Unless there is specific concern, an anaesthetic technique considered MH-safe

is not required for patients with SHS, but this should not preclude the use of a such a technique, if desired. An expanded metabolic panel and 12-lead electrocardiogram are appropriately included in pre-operative screening for many patients who carry a potentially higher risk for anaesthesia or sedation and prevent misinterpretation of the pre-existing status as being associated with intra-operative changes. As arterial puncture for blood gases may be infeasible, point-of-care capillary blood testing can be helpful for baseline and subsequent assessment, when available. Alternatively, pulse oxymetry on room air is a valuable non-invasive modality for assessing pulmonary gas exchange, and venous serum bicarbonate is reflective of the state of carbon dioxide exchange. Though muscle biopsy for determination of MH susceptibility can be a worthwhile assessment to make if there is some index of concern, it is not advised, due to the large muscle sample required for the *in vitro* caffeine-halothane contraction test. Genomic testing for the *RYR1* mutation is feasible, but the mutation is not associated with SHS. Notably, SHS is not associated with any cardiac muscle pathology.

Airway management

In patients with SHS, some degree of micrognathia, small mouth, class II malocclusion, dental crowding, highly arched hard palate, and limited cervical spine flexibility may make endotracheal intubation and use of airway adjuncts difficult. Although there are reports of successful direct laryngoscopy, it is likely to be difficult, if not impossible. While some providers may elect to attempt use of a Laryngeal Mask Airway (LMA) to avoid a difficult intubation, successful introduction and seating of an LMA is likely to be quite difficult or infeasible in SHS patients. A smaller LMA device than typically used for the patient's age may be necessary. LMA devices are not judged to be a reasonable airway management method for patients presenting with more severe features. The possibility for GERD in this population may also modify intubation options[21], but appropriate fasting times and commonly prescribed GERD medical prophylaxis may reduce the risk.

Where available, a flexible fibre-optic bronchoscope guided technique is advised for non-emergent nasal or oral intubation. In institutions with limited facilities, blind nasal intubation may be attempted but risks airway trauma. These patients are most safely cared for in hospitals with the full range of airway equipment that may needed. Patients can spontaneously ventilate with positive airway pressure support delivered through a soft nasopharyngeal airway in one nare, while fibre-optically guided intubation is performed through the other nare or the mouth. Mask ventilation may be possible, as well, but patients must be evaluated for adequate sealing pre-operatively, given the anatomical challenges involved. If an LMA can be introduced, fibre-optic intubation can be performed through the LMA. Tracheotomy may be needed for emergent or unusually challenging intubations but may be technically challenging. Surgical back up should be arranged for the most difficult airways. Airway management can be performed by spontaneous breathing of an inhaled agent or with intravenous infusion of propofol or dexmedetomidine, alone or in combination.

Transfusion or administration of blood products

No reports in the literature or known clinical experience indicate any unusual problems or needed precaution for patients with SHS needing transfusion or administration of any blood components. Distal extremity contractures and the consequent poor quality of veins may make establishing peripheral intravenous access challenging in many patients with SHS, and limited cervical mobility complicates neck vein access. Use of a small gauge catheter, 22 or less is often required. Need for the use of a small gauge vascular catheter may impair transfusion, intravenous hydration, medication administration, and blood draw efforts. With increased use of ultrasound assisted peripheral vein cannulation, central line placement has a diminished role in providing vascular access for these patients but still may be necessary more frequently.

Anticoagulation

While many patients have reduced pre-operative mobility and, therefore, are at a somewhat higher pre-operative thrombogenic risk, no reports in the literature or known clinical experience indicate any disorder of coagulation associated with SHS.

Patient transportation and positioning

Carefully evaluate patients pre-operatively to assess the extent of contractures. Any range of motion limitations found should be discussed with surgeons to plan the best positioning for the patient during surgery. If possible, positioning before induction of anaesthesia is recommended but may not be feasible. Patients should always be placed in a position of respiratory comfort, with avoidance of unnatural mobilisation under anaesthesia, kept warm, and provided with generous padding to avoid pressure points. Use of padded dressings is recommended for areas at risk for pressure injury (sacrum if supine; breasts and iliac crests if prone). Thin patients and those with extended inpatient confinement are at higher risk for loss of skin integrity. Patients with skin complications should be seen by a plastic surgeon. Active forced air heating systems should be used to maintain patient normothermia during anaesthesia and surgery, as many of these patients have reduced adipose tissue and are at increased risk of hypothermia.

Interactions of chronic disease and anaesthesia medications

There are no syndrome-specific chronic medications for patients with SHS, and there is no syndrome-specific treatment. Therapeutic interventions focus on improving functional outcomes. There is no cure, though SHS is believed to be non-progressive.

Anaesthetic procedure

The evidence base does not support an association between MH and SHS[22-23]. Nonetheless, in some clinical situations it may be desirable to avoid MH-triggering agents, any of which are safely used in patients with SHS, though some are used more extensively. Oral midazolam is routinely used for pre-medication, and intravenous midazolam is often used for mild procedural sedation. If an MH-safe technique is preferred, induction of general anaesthesia is safely achieved with nitrous oxide, which is not a volatile MH-triggering gas. If maintenance of spontaneous respiration is essential, nitrous oxide is used in conjunction with ketamine to achieve and maintain surgical anaesthesia. If vascular access is established before induction, propofol is frequently used for induction and maintenance of surgical anaesthesia. Intravenous infusion of either propofol or dexmedetomidine or both can be used to establish moderate sedation, with preservation of spontaneous ventilation for airway management and surgical anaesthesia. Spontaneous ventilation also can be maintained with nitrous oxide, ketamine, propofol, dexmedetomidine, or low-dose infusion of short-acting opioids, such as remifentanil.

Lidocaine with or without epinephrine for local anaesthesia or bupivacaine (0.25 – 0.5%) or ropivicaine for local anaesthesia, spinal, or epidural anaesthesia may be used. If performing spinal or epidural anaesthesia, a paediatric size needle and catheter is used, even for adults, as most patients with SHS are small. When using lidocaine or bupivacaine for anaesthesia without adjuvants, no special precautions are required, except for precautions related to the actual operative intervention, itself. Peripheral nerve blocks, either single bolus injection or with catheter placement, may be used for extremity surgery and post-operatively for analgesia.

Patient monitoring

While standard modern anaesthesia monitoring modalities (e.g., heart rate, oxygen saturation, blood pressure, end tidal carbon dioxide ($ETCO_2$), respiratory rate and depth, and temperature) are sufficient, vigilance is needed for monitoring in patients with SHS. Muscle rigidity or relaxation is not a reliable indicator of anaesthesia depth or neuromuscular blockade effectiveness, as syndromically affected muscles, especially those exhibiting overt contracture, are unaffected by anaesthesia and muscle relaxants. Oxygen saturation and $ETCO_2$ must be closely observed, especially if obstructive sleep apnoea or intercostal muscle pathology causing restrictive pulmonary disease is suspected. As clip sensors may not fit well, flexible adhesive oxygen saturation sensors are preferred and readily available in all institutions. They are applied circumferentially and fit any digit in the largest or smallest of patients. If a urinary catheter is used for monitoring, during a long surgery, or when epidural anaesthesia-analgesia is used, a paediatric size is typically chosen, even for adults, as most patients with SHS are small. If present, the character of dysphasia caused by orofacial anatomical abnormalities and muscle contractures should be documented before administration of any medication is noted to reduce potential mischaracterisation of dysphasia during pre-medication, sedation, or monitored anaesthesia when spoken patient responses are required.

Complications

As noted previously, evidence suggests SHS may not have an association with MH[22-23]; however, the following have traditionally been considered potential complications of general anaesthesia or sedation in patients with SHS: hyperpyrexia without the malignant hyperthermia triad, malignant hyperthermia, and neuroleptic malignant syndrome (hypermetabolic syndrome similar to malignant hyperthermia). Other complications that are more likely to present include, rhabdomyolysis without hyperpyrexia, challenging peripheral vascular access, impaired operative access due to ineffectiveness of neuromuscular blockade, and oro-tracheal intubation difficulty due to anatomic abnormalities. Airway abnormalities leading to difficult intubation includes: small mouth, cervical spine immobility, and stiffness of the orofacial musculature. While primarily reported in FBS, post-operative or post-sedation pneumonia may be caused by hypoventilation (atelectasis). In contrast to FBS, dysphagia, with an attendant elevated aspiration risk, is not a finding in SHS, and meticulous anaesthetic care usually prevents aspiration. If present, spinal deformities complicate epidural and spinal anaesthesia but rarely preclude it.

Post-operative care

In some patients, intercostal muscles are unable to provide adequate changes in intrathoracic pressure due to fibrous replacement. If intercostal myopathy is present, opioids and other potential respiratory depressants potentiate the risk for apnoea, over-sedation, and hypoventilation and may lead to post-operative respiratory distress. Non-steroidal anti-inflammatory medications, enhanced recovery after anaesthesia and surgery protocols, and continuation of regional or epidural catheter techniques for post-operative analgesia provide the best pain control modalities for patients with SHS. Most patients are observed in the intensive or intermediate care unit for at least some time, especially after major surgery.

Disease-related acute problems and effect on anaesthesia and recovery

Although primarily reported in FBS, the possibility for acute consequences of potential decreased thoracic cage compliance from non-functioning intercostal muscles in patients with SHS must be considered. If intercostal muscle pathology is suspected, it predisposes the patient to lower respiratory infections, with prolonged recovery. Aggressive antibiotic use and guaifenesin are warranted in the presence of positive physical examination findings of râles, rhonchi, wheezes, and pyrexia. In patients with intercostal muscle pathology, chest radiographs often are uninterpretable, with poor lung inflation due to decreased forced vital capacity and poor cough. In the advent of lower respiratory infection, sputum culture often is non-diagnostic, as many of these patients do not have adequate ability to cough. These patients require meticulous respiratory therapy in the post-operative period, which may include incentive spirometry, chest physiotherapy, with or without the use of a cough assist machine, and implementation of BiLevel Positive Airway Pressure, if airway obstruction or hypoventilation occur. If a culture is required, consider bronchoscopy to obtain a clean specimen. If general anaesthesia with intubation is necessary, the anaesthesiologist should use recruitment manoeuvrers and endotracheal suctioning prior to exubation to maximise lung volume and reduce the risk of atelectasis.

Special settings or types of anaesthesia

The general principles for the anaesthetic care of patients with SHS previously described apply with proper balancing of risks and benefits, to all types and settings of anaesthesia, including obstetric, ambulatory, or emergent.

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