orphanaesthesia

Anaesthesia recommendations for

distal arthrogryposis type 3

Disease name: Distal arthrogryposis type 3

ICD 10: Q74.3

Synonyms: Gordon syndrome; distal arthrogryposis multiplex congenita type IIA; camptodactyly, cleft palate, and clubfoot

Disease summary: Distal arthrogryposis type 3 (DA3) was a congenital non-progressive myopathy and included contractures of the hands and ankle-foot complex plus cleft palate, blepharoptosis, and abnormal spinal curvatures. DA3 lacked specific craniofacial findings required for either Freeman-Burian or Sheldon-Hall syndromes. Limb malformations accepted in the diagnostic criteria 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. Most instances of DA3 were sporadic, but autosomal dominant inheritance was 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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A	**AIRWAY / ANAESTHETIC TECHNIQUE**	Midfacial hypoplasia may prevent mask sealing. Cleft palate, some degree of micrognathia, class II malocclusion, dental crowding, highly arched hard palate, stiffness of the orofacial musculature, and limited cervical spine flexibility may make endotracheal intubation and use of airway adjuncts difficult. 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.
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**	Consider avoiding opioids and other potential respiratory depressants to reduce risk of apnoea, over-sedation, hypoventilation, and post-operative pneumonia. There are no typical home medications. No evidence for increased risk of MH/rhabdomyolysis exists.
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

First described by Gordon (1969)[1], distal arthrogryposis type 3 (DA3; MIM 114300) was a congenital non-progressive myopathy and included contractures of the hands and ankle-foot complex, cleft palate, blepharoptosis, and abnormal spinal curvatures[2]. DA3 lacked specific craniofacial findings required for either Freeman-Burian[3-4] or Sheldon-Hall syndromes (FBS or SHS)[5], but included findings not present in distal arthrogryposis type 1, which essentially manifested only distal extremity contractures. Limb malformations that were common to FBS, SHS, and DA3 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. Major differential diagnoses included distal arthrogryposis types 1A, 1B, 2B, 7, and 8; Marden-Walker syndrome; Schwartz-Jampel syndrome; and non-syndromic distal contractures. DA3 was distinguished from other conditions with apparent distal extremity contractures by presence of cleft palate, blepharoptosis, and abnormal spinal curvatures, and absence of additional features, especially ocular pathology and mental retardation[2].

Most instances of DA3 were sporadic, but autosomal dominant inheritance was established, as well[2]. There was no apparent gender, ethnic, or geographical preference, and environmental and parental factors were not implicated in pathogenesis[2]. DA3 was associated with allelic variation on the piezo type mechanosensitive ion channel component 2 (*PIEZO2*; MIM 613629) gene, at 18p11.22-p11.21[6]. DA3 was considered to belong to the group of phenotypically similar entities termed distal arthrogryposes[7-8]. Arthrogryposis multiplex congenita was a distinct entity from the distal arthrogryposes[2]. Due to the paucity of literature on anaesthesia care for patients with DA3, these clinical recommendations were based on clinical experience and a systematic review and meta-analysis that included distal arthrogryposis syndromes and FBS[9-10], the protocol for which has been described elsewhere[11-12].

Typical surgeries

Though not as severe as FBS or SHS, patients with DA3 still frequently undergo many orthopaedic surgeries, because many of the attempts at operative deformity correction may have suboptimal results and require subsequent revision. Several craniofacial manifestations of the syndrome also typically require operative treatment. Due to the wide variability of DA3 presentation and the paucity of research, there are a great diversity of operative approaches employed for the following reasons: ankle-foot complex contracture correction, spinal curvature correction, hand contracture correction, cleft palate and blepharoptosis repair, and possibly additional 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) or spine (rod insertion and vertebral fusion for abnormal curvatures) are 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 DA3. 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 DA3[13]. Though mild spinal deformities may be seen in

DA3, this typically does not preclude epidural or spinal anaesthesia, which may have far fewer the 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[13]. Many adults are poor candidates for local or regional anaesthesia, and many children handle the experience very well[13]. 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[13].

Pre-operative testing

Anaesthetic care for patients with DA3 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[14]. Examination includes: vial signs, mental status, airway, spinal, neurological, and cardiopulmonary assessments[14]. It is important to explain to the patient and family possible risks and ensure questions are answered and concerns fully addressed[13-14]. Findings, concerns, and management plans must be discussed with participating surgeons[14]. 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[15-16], 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 DA3, 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 DA3. Notably, DA3 is not associated with any cardiac muscle pathology.

Airway management

In patients with DA3, cleft palate, some degree of micrognathia, class II malocclusion, dental crowding, highly arched hard palate, and limited cervical spine flexibility may make endotracheal intubation and use of airway adjuncts difficult. 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 may be difficult or infeasible in DA3 patients. A smaller LMA device than typically used for the patient's age may be necessary.

Other techniques of oral or nasal intubation include: indirect video intubation (Blide scope, C-Mac, etc.) or a flexible fibre-optic bronchoscope guided technique. 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. Care must be taken to avoid the palatal cleft. Similarly, prior operative repair of a cleft palate may have resulted in unknown nasal narrowing or obstruction, making a nasal intubation difficult or impossible. 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 but technically challenging in emergent or unusually challenging intubations. Surgical back up should be arranged for the most difficult airways. There are multiple anaesthetic techniques available for airway management, including spontaneous breathing of inhalational agents or intravenous infusion of propofol, dexmedetomidine, or both.

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 DA3 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 DA3, and if present, limited cervical mobility complicates neck vein access. Use of a small gauge catheter, 22 or less is generally 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 in a greater frequency than the general population.

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 DA3.

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 may have reduced adipose tissue and be at increased risk of hypothermia.

Interactions of chronic disease and anaesthesia medications

There are no syndrome-specific chronic medications for patients with DA3, and there is no syndrome-specific treatment. Therapeutic interventions focus on improving functional outcomes. There is no cure, though DA3 is believed to be non-progressive.

Anaesthetic procedure

The evidence base does not support an association between MH and DA3[15-16]. Nonetheless, in some clinical situations it may be desirable to avoid MH-triggering agents, any of which are safely used in patients with DA3, 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 DA3 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 continued 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 DA3. 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 DA3 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 DA3 may not have an association with MH[15-16]; however, the following have traditionally been considered potential complications of general anaesthesia or sedation in patients with DA3: 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). Meticulous anaesthetic care usually prevents aspiration, but opioids should be avoided to prevent respiratory depression and post-operative airway complications, especially in patients with unrepaired cleft palate. If present, spinal deformities may complicate epidural and spinal anaesthesia but rarely preclude it.

Post-operative care

The potential for excessive analgesia with opioids and other potential respiratory depressants in DA3 must be considered. These agents potentiate the risk for apnoea, over-sedation, and hypoventilation and may lead to post-operative respiratory distress. Non-steroidal anti-inflammatory medications and continuation of regional or epidural catheter techniques for post-operative analgesia probably provide the best pain control modalities for patients with DA3. 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

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, such as in empiric treatment failure, consider if bronchoscopy is necessary to obtain a clean specimen, such as patients with poor tussive ability. 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 DA3 previously described apply with proper balancing of risks and benefits, to all types and settings of anaesthesia, including obstetric, ambulatory, or emergent.

References

1. Gordon H, Davies D, Berman MM. Camptodactyly, cleft palate and club foot: syndrome showing the autosomal-dominant pattern of inheritance. *J Med Genet*. 1969;6:266-274. PMID: 5345097
2. McKusick VA. *Online mendelian inheritance in man, OMIM*™. Johns Hopkins University, Baltimore, MD. MIM Number: 114300. Retrieved: 30 April 2017. URL: http://omim.org
3. Poling MI, Dufresne CR. Revisiting the many names of Freeman-Sheldon syndrome. *J Craniofac Surg*. In Press. DOI: 10.1097/SCS.0000000000004802
4. Poling MI, Dufresne CR. Head first, not feet first: Freeman-Sheldon syndrome as primarily a craniofacial condition. *Cleft Palate-Craniofac J*. 2018;55(5):787-788. doi: 10.1177/1055665617753482
5. Stevenson DA, Carey JC, Palumbos J, Rutherford A, Dolcourt J, and Bamshad MJ. Clinical characteristics and natural history of Freeman-Sheldon syndrome. *Pediatrics*. 2006;117(3):754-762. DOI: 10.1542/peds.2005-1219
6. McMillin MJ, Beck AE, Chong JX, Shively KM, Buckingham KJ, Gildersleeve HIS, Aracena MI, Aylsworth AS, Bitoun P, Carey JC, Clericuzio CL, Crow YJ, et al. Mutations in PIEZO2 cause Gordon syndrome, Marden-Walker syndrome, and distal arthrogryposis type 5. *Am J Hum Genet*. 2014;94:734-744. DOI: 10.1016/j.ajhg.2014.03.015
7. Hall JG, Reed SD, Greene G. The distal arthrogryposes: delineation of new entities—review and nosologic discussion. *Am J Med Genet*. 1982;11(2):185-239. DOI: 10.1002/ajmg.1320110208
8. Bamshad M, Jorde LB, Carey JC. A revised and extended classification of the distal arthrogryposes. *Am J Med Genet*. 1996;65(4):277-81. DOI: 10.1002/(SICI)1096-8628(19961111)65:4<277::AID-AJMG6>3.0.CO;2-M
9. Poling MI, Dufresne CR, Chamberlain RL. Findings, Phenotypes, Diagnostic Accuracy, and Treatment in Freeman-Burian Syndrome. J Craniofac Surg. 2020;31(4):1063-1069. DOI: 10.1097/SCS.0000000000006299
10. Poling MI, Dufresne CR, Portillo AL. Identification and Recent Approaches for Evaluation, Operative Counseling, and Management in Patients With Freeman-Burian Syndrome: Principles for Global Treatment. J Craniofac Surg. 2019;30(8):2502-2508. DOI: 10.1097/SCS.0000000000005968
11. Poling MI, Morales Corado JA, Chamberlain RL. Findings, phenotypes, and outcomes in Freeman-Sheldon and Sheldon-Hall syndromes, and distal arthrogryposis types 1 and 3: protocol for systematic review and patient-level data meta-analysis. *Syst Rev*. 2017;6:46. DOI: 10.1186/s13643-017-0444-4
12. Poling MI, Morales Corado JA, Chamberlain RL. Findings, Phenotypes, and Outcomes in Freeman-Sheldon and Sheldon-Hall syndromes, and Distal Arthrogryposis Types 1 and 3: Protocol for Systematic Review and Patient-Level Data Meta-Analysis. PROSPERO. 2015. Accession number: CRD42015024740. Available from: http://www.crd.york.ac.uk/PROSPERO_REBRANDING/display_record.asp?ID=CRD42015024740
13. Portillo AL, Poling MI, McCormick RJ. Surgical approach, findings, and 8-year follow-up in a 21-year-old woman with Freeman-Sheldon syndrome presenting with blepharophimosis causing near-complete visual obstruction. *J Craniofac Surg*. 2016;27(5):1273-1276. DOI: 10.1097/SCS.0000000000002781
14. Deshpande J, Maxwell LG. Chapter 9: Anesthetic management. In: Dufesne CR, Carson BS, Zinreich SJ, eds. *Complex craniofacial problems: a guide to analysis and treatment*. New York: Churchill Livingstone, 1992.

15. Benca J, Hogan K. Malignant hyperthermia, coexisting disorders, and enzymopathies: risks and management options. *Anesth Analg*. 2009;109:1049-1053. DOI: 10.1213/ane.0b013e3181adca28
16. Gleich SJ, Tien M, Schroeder DR, Hanson AC, Flick R, Nemergut ME. Anesthetic outcomes of children with arthrogryposis syndromes: no evidence of hyperthermia *Anesth Analg.* 2017;124:908-914. DOI: 10.1213/ANE.0000000000001822

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This recommendation was authored by:

Authors
Mikaela I Poling, Research Assistant, Office of Craig R Dufresne, MD, PC, Fairfax, VA, USA

Craig R Dufresne, Plastic Surgeon, Private Practice, Fairfax, VA, USA

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This recommendation was reviewed by:

Reviewers
Lynne G Maxwell, Emeritus Professor CE of Anesthesiology and Critical Care; Diversity Search Advisor, Department of Anesthesiology and Critical Care, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

Robert B Mesrobian, Pediatric Anesthesiologist, Department of Anesthesiology, Inova Fairfax Hospital, Falls Church, VA, USA

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