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RESEARCH REPORT

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Clinical implications of de Barsy syndrome

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Summary

Background: De Barsy syndrome is a rare, autosomal recessive syndrome characterized by cutis laxa, progeroid appearance, ophthalmic opacification, skeletal malformations, growth delays, and intellectual disability.

Aims: The aim of this case series is to identify the anesthetic considerations in the clinical management of patients with de Barsy syndrome.

Methods: A retrospective case review from 1968 to 2016 was performed at a single tertiary medical center to identify patients with de Barsy syndrome who underwent anesthesia for diagnostic and surgical procedures. We collected and analyzed the perioperative records and following data: age, sex, American Society of Anesthesiologists physical status, relevant comorbidities, surgical procedures, anesthesia management, and observed complications.

Results: Three patients underwent 64 unique anesthetics for a diverse collection of diagnostic and surgical procedures. An array of anesthetics and techniques were successfully used. Observations of the perioperative period found 7 episodes of intraoperative hyperthermia (>38.3°), a single difficult airway requiring fiberoptic bronchoscopic-guided intubation, and repeatedly difficult intravenous access.

Conclusion: This expanded case series suggests that providers caring for patients with de Barsy syndrome should be aware of potential challenges with airway management, vascular access, and temperature monitoring.

KEYWORDS
cutis laxa, fever, genetic diseases, rare diseases, syndrome

1 | INTRODUCTION

De Barsy syndrome is a rare genetic syndrome characterized by cutis laxa III (ARCL3 OMIM# 219150, 614438), progeroid appearance, ophthalmic opacification, skeletal malformations, growth delays, and intellectual disability.[1-7] Given the diverse array of ophthalmic and skeletal malformations, de Barsy patients require frequent surgical interventions.[8] First described by de Barsy in 1967,[1] only 100 cases of the syndrome have been documented in the medical literature. Several cases of de Barsy syndrome have been linked to mutations of the PYCR1 or ALDH18A1 genes.[9] The syndrome is inherited in an autosomal recessive pattern.

The constellation of clinical manifestations of de Barsy syndrome include intrauterine growth retardation, postnatal growth delay, motor delay, cognitive impairment, hypotonia, athetoid movements, microcephaly, wormian bones, large fontanelles, facial dysmorphism, cataracts, corneal clouding, thin/wrinkled skin, easy bruising, sparse hair, joint laxity, osteopenia, and inguinal hernias.[1-14] A number of de Barsy syndrome manifestations are directly relevant to perioperative patient management.[3] Craniofacial abnormalities, cognitive delays, and skin fragility (ie, "paper thin") are all issues requiring specific perioperative patient care consideration.

A single investigation relating to anesthetic management of de Barsy syndrome patients was published in 2010 by authors of the

present study.[3] This article reported on 2 patients and 35 anesthetics associated with surgical and diagnostic procedures between 1968 and 2007. The present study identifies another patient with de Barsy syndrome and 29 additional anesthetics performed between 2007 and 2016. Given the rarity of this condition, and limited published data, this case series provides important information to providers encountering de Barsy syndrome patients for the first time or during emergent situations.

What is known

- In a previously published article on anesthetic management of patients with de Barsy syndrome, no major perioperative adverse events were found in 35 separate anesthetic cases.

What this article adds

- This article expands upon the previous series with 29 additional anesthetic cases, and offers management considerations with respect to airway management, vascular access, temperature monitoring and other issues unique to de Barsy syndrome.

2 | MATERIALS AND METHODS

After receiving Institutional Review Board (Rochester, MN, USA) study approval, medical records prior to September 2016 were searched to identify patients with de Barsy syndrome. As no single longitudinal comprehensive medical index at our institution spans this time frame, several medical databases were queried including the Berkson Medical and Surgical Indexing System[a] [1968-1975], the Mayo Clinic Life Science System database [1996-2007] and the Mayo Clinic Medical Index [1995-2016]. No exclusionary criteria were applied. All available anesthetic and surgical records of de Barsy syndrome patients were analyzed. Data collected included age, gender, ASA physical status, relevant comorbid conditions, surgical procedure, airway management, vascular access, monitoring, anesthetic induction and maintenance, intravenous and oral analgesics, muscle relaxants, antibiotics, and blood product transfusions, PACU information, and postoperative complications. Clinical observations made by anesthesia providers were also recorded.

3 | RESULTS

In 3 different pediatric patients with genetically confirmed de Barsy syndrome, a total of 64 anesthetics were reviewed. One female and 2 male patients had each undergone 14, 11, and 39 anesthetics, respectively. With respect to airway management, 7 oral/nasal airways, 6 laryngeal mask airways, and 48 endotracheal tubes were placed. Of the latter, 23 were placed by direct laryngoscopy, 24 by videolaryngoscopy, and 1 by fiberoptic intubation for unanticipated difficult airway. In this patient, although providers had been able to secure his airway easily by direct laryngoscopy prior to 2012, subsequent airway management required videolaryngoscopy with a maximum of 2 attempts for successful intubation. This same patient, by the age of 15, also began requiring 2-handed mask ventilation. In the other 2 patients, no difficulties were reported with mask ventilation or endotracheal intubation. A single incident of vomiting during preoxygenation was documented which required rapid sequence intubation. The remaining airways were managed with a mask or spontaneous breathing.

A wide range of inhalational agents and intravenous medication were used throughout the 64 anesthetics. For induction, inhalational agents, propofol, or a combined technique were used in 54%, 39%, and 8%, respectively. For analgesia, 2 caudal blocks and 1 peripheral extremity block were performed. Fentanyl was the dominant opioid administered and used in 59% of all anesthetics. No significant medication reactions or complications were observed. A comprehensive list of medications used (number of times) is as follows:

- Induction: Propofol (25), sodium pentothal (2)
- Opioids: Fentanyl (38), oxymorphone (3), morphine (2), oxycodone (2), sufentanil (1)
- Antibiotics: Cefazolin (25), piperacillin sodium/tazobactam sodium (1), gentamicin (1), vancomycin (1)
- Antiemetics: Ondansetron (25), dexamethasone (10), droperidol (3), granisetron (1)
- Vasoactive: Atropine (7), labetalol (1), phenylephrine (1), racemic epinephrine (1)
- Other: Glycopyrolate (14), neostigmine (12), acetaminophen (11), midazolam (6), albuterol (3), lidocaine (3), calcium gluconate (1), clonidine (1), diazepam (1), heparin (1), ibuprofen (1), papaverine (1), tranexamic acid (1)
- Neuraxial: Bupivacaine (2), hydromorphone(1)
- Regional: Bupivacaine(1)

In 7 distinct cases, intraoperative hyperthermia (temperature > 38°C) was noted. This represents 11% of total cases, and occurred in more than 1 child. Difficulty was reported with peripheral venous line placement due to the cutis laxa component of the syndrome. Eleven arterial lines (9 radial, 2 femoral) and 4 central lines (2 right internal jugular, 2 femoral) were placed without difficulty. Blood products, albumin, neuromonitoring, central line placement, and peripheral blocks were all administered without recognized complications.

4 | DISCUSSION

Although basic science has begun to unravel the genetic basis of de Barsy syndrome, the literature describing clinical management of these patients remains exceedingly limited. Several known genetic

[a]An early epidemiologic database established by Dr. Joseph Berkson in 1935. Searchable years: 1968-1975.

mutations are thought to explain the physical manifestations of de Barsy syndrome. These include a mutation in the pyrroline-5-carboxylate reductase gene (PYCR-1, known as type B) and the ALDH18A1 gene (type A).[13,15] Malfunctioning of these genes leads to mitochondrial fragmentation with high apoptosis rates during oxidative stress.[4] A third mutation, ATP6V0A2-CDG, is also thought to be possibly related to de Barsy syndrome.[16] Two recent publications have described additional clinical features in de Barsy syndrome patients. In 2016, Dutta et al reported slowly progressive dilatation of the aortic root, suggesting the need for cardiac evaluation and longitudinal monitoring.[4] Lin et al described glaucoma and idiopathic hypertrophic pyloric stenosis in patients with de Barsy syndrome.[15]

With regard to perioperative management, little is known about Barsy syndrome patients. Extrapolating from known physical abnormalities, features such as joint hyperlaxity may pose positioning issues, while pectus excavatum could present difficulty with ventilation.[15] Other features, such as developmental delay, present universal concern with regard to patient coping and cooperation during the delivery of anesthesia. Given the rarity of this condition, and limited published data, making available institutional experience pertaining to clinical management offers providers of de Barsy syndrome patients a basis of care. This study extends the published anesthesia experience with de Barsy syndrome, including various anesthetic techniques and pharmacologic agents safely utilized. Moreover, we have highlighted clinical considerations and management concerns associated with de Barsy syndrome including airway management, vascular access, and monitoring for hyperpyrexia.

In this case series, 3 major concerns for de Barsy patients were identified, ie, difficult vascular access, hyperthermia, and potential for difficult airway. With cutis laxa, thin skin and minimal subcutaneous tissue contribute not only to challenging intravenous access but also concerns for skin fragility and breakdown.[7,10] Ultrasound or other advanced imaging techniques may be useful in facilitating vascular access in these patients.

In 11% of our cases, intraoperative hyperthermia occurred. A review of these cases did not identify any direct etiology for hyperthermia from such causes as infection, neuroendocrine disorder, anti-cholinergic use, or neuroleptic medication. Moreover, dantrolene administration was not required in any case and no additional metabolic derangements were reported. Previously published reports of nonmalignant hyperthermia in such conditions as Costello syndrome, Osteogenesis Imperfecta, and Arthrogryposis, have speculated that central temperature control dysregulation occurs during general anesthesia.[16-18] To date, however, no defect has been identified and no direct evidence supports such a mechanism. In fact, a recent investigation at our institution specifically examined intraoperative hyperthermia in 369 discrete anesthetic cases involving patients with arthrogryposis multiplex congenital and distal arthrogryposis syndrome.[19] In contrast to prior studies, this investigation found no increased risk of intraoperative hyperthermia or hypermetabolic events compared to control subjects without arthrogryposis. Similar to our intraoperative hyperthermia rate of 11%, Gleich et al reported 10.3% of cases were associated with hyperthermia, all of which responded to active cooling alone. Iatrogenic intraoperative overwarming remains the most likely explanation of hyperthermia in our case series. This explanation may be seen in the context of limited subcutaneous insulation due to cutis laxa, and relatively low body mass indexes (range: 11-19), both of which would increase susceptibility to room warming, heating lamps, or forced air blankets. Accordingly, close attention to temperature monitoring and the use of warming devices constitutes prudent clinical care of de Barsy syndrome patients.

Providers should also consider having advanced airway management equipment readily available. Although craniofacial abnormalities are present in this syndrome, they did not present severe airway management challenges in the overwhelming majority of anesthetics. Difficulty with both mask ventilation and endotracheal intubation were observed in our series but limited to clinical experience with 1 patient. In the era of videolaryngoscopy, safe airway management would be anticipated.

While patient safety cannot be definitively established by any case series, given the extreme rarity of the syndrome, this report attempts to provide successful management options to potential anesthesia providers of patients with de Barsy syndrome. And as widespread genetic testing is capable of confirming new cases, further research will enhance our understanding of the risks surgery and anesthesia pose to these unique patients.

ETHICAL APPROVAL

This study was approved by Mayo Clinic IRB (16-007092).

CONFLICT OF INTEREST

Nothing to disclose.

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REFERENCES

1. De Barsy AM, Moens E, Dierckx L. Nanism, oligophrenia, and hypoplasia of the elastic tissue in the skin and the cornea. *Arch Belg Dermatol Syphiligr*. 1967;23:411-412.
2. Aldave AJ, Eagle Jr RC, Streeten BW, Qi J, Raber IM. Congenital corneal opacification in de Barsy syndrome. *Arch Ophthalmol*. 2001;119:285-288.
3. Aponte EP, Smith HM, Wanek BJ, Rettke SR. Anesthesia considerations for patients with de Barsy syndrome. *J Clin Anesth*. 2010;22:499-504.
4. Dutta AK, Ekbote AV, Thomas N, Omprakash S, Danda S. De Barsy syndrome type B presenting with cardiac and genitourinary abnormalities. *Clin Dysmorphol*. 2016;25:190-191.
5. Dutta A, Ghosh SK, Ghosh A, Roy S. A 5-year journey with cutis laxa in an Indian child: the de Barsy syndrome revisited. *Indian J Dermatol*. 2016;61:81-84.

6. Bartsocas CS, Dimitriou J, Kavadias A, Kyrzopoulos D. De Barsy syndrome. *Progress Clin Biological Res*. 1982;104:157-160.
7. Arazi M, Kapicioglu MI, Mutlu M. The de Barsy syndrome. *Turkish J Pediatrics*. 2001;43:79-84.
8. Al-Owain M, Alanazi S, Khalifa O, et al. A case of de Barsy syndrome with a severe eye phenotype. *Am J Med Genet*. 2012;158:2364-2366.
9. Bicknell LS, Pitt J, Aftimos S, Ramadas R, Maw MA, Robertson SP. A missense mutation in ALDH18A1, encoding delta 1-pyrroline-5-carboxylate synthase (P5CS), causes an autosomal recessive neurocutaneous syndrome. *Eur J Hum Genet*. 2008;16:1176-1186.
10. Hoekx J, Smeitink J, Brunner H, Monnens L. The de Barsy syndrome. *Tijdschrift Voor Kindergeneeskunde*. 1989;57:53-57.
11. Pontz BF, Zepp F, Stoss H. Biochemical, morphological and immunological findings in a patient with a cutis laxa-associated inborn disorder (de Barsy syndrome). *Eur J Pediatrics*. 1986;145:428-434.
12. Karnes PS, Shamban AT, Olsen DR, Fazio MJ, Falk RE. De Barsy syndrome: report of a case, literature review, and elastin gene expression studies of the skin. *Am J Med Genet*. 1992;42:29-34.
13. Zampatti S, Castori M, Fischer B, et al. De Barsy syndrome: a genetically heterogeneous autosomal recessive cutis laxa syndrome related to P5CS and PYCR1 dysfunction. *Am J Med Genet*. 2012;158:927-931.
14. Guerra D, Fornieri C, Bacchelli B, et al. The de Barsy syndrome. *J Cutaneous Path*. 2004;31:616-624.
15. Lin DS, Chang JH, Liu HL, et al. Compound heterozygous mutations in PYCR1 further expand the phenotypic spectrum of De Barsy syndrome. *Am J Med Genet A*. 2011;155A:3095-3099.
16. Leao-Teles E, Quelhas D, Vilarinho L, Jaeken J. De Barsy syndrome and ATP6V0A2-CDG. *Eur J Hum Genet*. 2010;18:526.
17. Stanton RP, Rao N, Scott Jr CI. Orthopaedic manifestations in de Barsy syndrome. *J Pediatr Orthop*. 1994;14:60-62.
18. Benni F, Leoni T, Iacobucci T, D'Avolio S, de Francisci G. Anaesthesiological considerations in Costello Syndrome. *Paediatr Anaesth*. 2002;12:376-378.
19. Dearlove O, Harper N. Costello syndrome. *Paediatr Anaesth*. 1997;7:476-477.

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