




Neurosurgical Management of Patients with Alpha-Gal Syndrome

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Abstract

Alpha-gal syndrome (AGS) is an immunoglobulin E–mediated hypersensitivity to galatose-alpha-1,3-galactose (alpha-gal), a carbohydrate compound present in non-primate mammalian products. Initial exposure to alpha-gal most often occurs through a tick bite, most commonly the lone star tick in the United States. Repeated exposure to alpha-gal may elicit severe allergic reactions, including anaphylaxis. The allergy restricts dietary intake and may significantly impact perioperative risk, as many medications, anesthetics, and intraoperative surgical products utilize bovine or porcine-derived agents, including those containing magnesium stearate, glycerol, and gelatin. Here, we review the perineurosurgical care of two individuals with AGS and highlight pertinent clinical practices and perioperative management of these patients.

Keywords

- ▶ alpha-gal syndrome
- ▶ hemostasis
- ▶ mammalian products
- ▶ neurosurgery
- ▶ anesthesia
- ▶ gelatin allergy

Introduction

Alpha-gal syndrome (AGS) is an immunoglobulin E (IgE)-mediated hypersensitivity response to galatose-alpha-1,3-galactose (alpha-gal), an oligosaccharide found in the cell membrane of nonprimate mammals, such as cattle, pigs, and sheep. Immune response is facilitated by exposure to tick saliva. In the United States, *Amblyomma americanum*, commonly known as the lone star tick, is the primary cause, while other tick species have been implicated worldwide. Nearly 34,000 suspected AGS cases were reported in the

United States from 2010 to 2018, primarily in the mid-Atlantic and midwestern states.^{1,2}

Patients with AGS may suffer from an allergic reaction following exposure to mammalian-derived products, ranging in severity from mild to life-threatening anaphylaxis, and the allergy may develop at any age.^{1–4} Highlighting the sensitivity in some patients, 10 to 20% also do not tolerate bovine milk products due to a small amount of alpha-gal present in milk.^{1,3,5} In addition, patients may experience variable allergic reactions over time to the same allergen, and they may start to not tolerate some mammalian products

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they previously tolerated due to a decreasing threshold dose for an allergic reaction.^{3,5}

These allergies are most notable during food consumption; however, many pharmaceuticals and surgical products utilize animal byproducts and may be hazardous to patients before, during, and after surgery—creating unique considerations for the management of these patients.^{2,4,6–10} For example, for neurosurgical patients, many of the typical hemostatic and dural reconstructive agents may cause severe reactions, and thus, special care should be taken. Notably, chicken, turkey, fish, and shellfish—as well as human-derived clinical and pharmaceutical products—do not contain this carbohydrate; therefore, patients are not impacted by the consumption of these products. Herein, we review the perioperative management of two patients with AGS who recently underwent neurosurgical care, and we highlight the main relevant medications and surgical products at risk and discuss safe alternatives.

Diagnosis and Preoperative Management

For patients with confirmed or suspected AGS undergoing elective procedures, specific preoperative testing of individual medications and animal byproducts may be prudent. Testing performed by a trained allergy specialist should be considered to identify individual allergic reactions. This should also be considered even if previous testing was performed, as the severity and allergy profile may evolve over time, and, indeed, even AGS itself may be transient. However, despite rigorous preoperative testing, many pharmaceuticals may not test for or highlight the presence of possible alpha-gal moieties and such notations may be absent from the package inserts—even among the inactive agents lists. Considering this risk, discretion should be considered even with proper perioperative evaluations, and it is essential to review specific products and formulations with your institutional pharmacy. Notable medication and product ingredients to be critical of include gelatin,

glycerin, magnesium stearate, bovine extract, and many additives, stabilizers, and pill coatings.^{2,3,5,11}

Many patients demonstrate heterogenous severity of this disease, and many of the agents, even those derived from bovine or porcine sources, may in fact be tolerated. To this point, a recent retrospective study identified heparin, which is porcine derived, as being tolerated in 56 of the 57 patients (98.3%), and a documented allergic response to unfractionated heparin and enoxaparin was 2.6% (1/39) and 0% (0/22), respectively.¹¹ However, a study evaluating heparin use during cardiopulmonary bypass in AGS patients identified severe reactions in 50% of the cohort, highlighting the diligence required when managing this condition.¹²

If an allergic reaction to a product essential for surgery or perioperative management is identified, pretreatment regimens to reduce the risk of IgE-mediated hypersensitivity reactions exist. For example, pretreatment with omalizumab (Xolair) for 4 months (600 mg every 28 days), prior to the surgery may reduce the risk of an allergic reaction—particularly for gelatin products. When the surgery has been completed, omalizumab may be discontinued.

Perioperative Management and Case Examples

Mammalian protein-derived products are commonly found in the pre-, intra-, and postoperative setting. They exist in the medications and several valuable surgical adjuncts and implants (►Table 1).^{2,4,7,9,10} Many anesthetic agents, medications, and infusions administered by the anesthesiology team also have variable risk, largely due to glycerol and other preservatives—with a review in ►Table 1.^{4,7,9,10} Surgical products should also be reviewed by the surgical team—particularly dural reconstruction agents and hemostatic products (►Table 1). Thoughtful anesthetic and surgical product use is important for avoiding severe allergic reactions but also in ameliorating clinical problems and delays related to unclear workarounds for common products that may be restricted in patients with AGS.

Table 1 Safe and potentially unsafe medications and surgical products for patients with alpha-gal syndrome

	Safe	Potentially unsafe
Anesthesia	Volatile anesthetics (-fluranes, NO)	Propofol ³ (glycerol)
	Ketamine	Diazepam, clonazepam, lorazepam
	Paralytics (succinylcholine, rocuronium)	Intralipid
	Mannitol	IV colloidal agents
	Albumin (human)	A and O blood types
	Glycopyrrolate/atropine	Haloperidol (animal lactic acid)
	Sugammadex	
Vasoactive agents	Lidocaine (IV)	
	Epinephrine/norepinephrine	Clevidipine (glycerin)
	Phenylephrine	Vasopressin (lactic acid)
		Milrinone (lactic acid)

(Continued)

Table 1 (Continued)

	Safe	Potentially unsafe
Pain	Ketorolac	Oxycodone, hydromorphone (IV, PO), morphine (glycerin, lactose, MS)
	Fentanyl/remifentanyl	Acetaminophen (tabs, liquid, suppository—gelatin, glycerin, MS)
	Acetaminophen (IV)	Gabapentin/pregabalin (some formulations contain gelatin)
		Lidocaine patch (gelatin)
		Naproxen/celecoxib/ibuprofen (lactose or gelatin)
		Methocarbamol
		Exparel (bupivacaine liposomal injection; glycerol)
		Cyclobenzaprine
Antibiotics	Synthetic (ciprofloxacin)	Cephalosporins—some formulations (gelatin and/or MS)
	Vancomycin	
	Cefepime/ceftriaxone/cefazolin	
	Piperacillin/tazobactam (IV)	
	Ampicillin/sulbactam (IV)	
	Metronidazole (IV)	
Suture	Synthetic (Nylon, Prolene, Vicryl)	Catgut
Hemostasis	Surgical	Gelfoam (porcine skin gelatin granules)
	Tranexamic acid (spray and IV)	Thrombin (many formulations—bovine, ovine, porcine)
	Fresh frozen plasma	Floseal/Surgiflo (bovine gelatin matrix)
	Tisseel	Surgifoam (porcine gelatin)
	Vistaseal/human thrombin	Avitene (bovine microfibrillar collagen)
	Evarrest patch	Kcentra (prothrombin complex concentration; porcine heparin)
	Arista AH	TachoSil (equine collagen)
	Surgicel powder AH	
Dural reconstruction	Autograft (pericranium, fascia)	DuraGen (bovine tendon)
	AlloDerm (human dermal matrix)	Dura-Guard (bovine pericardium)
	Gore-Tex	Durepair (bovine dermis)
	Bionext (biocellulose mesh)	Durasis (porcine small intestine ECM)
AED	Levetiracetam (IV)	Lacosamide (glycerin)
		Levetiracetam (some PO formulations contain MS)
VTE prophylaxis	Fondaparinux	Heparin (porcine intestinal or bovine lung extract)
		Enoxaparin (porcine intestinal mucosa extract)
Anticoagulant/platelet	Argatroban	Apixaban (MS and lactose)
	Bivalirudin	Warfarin (MS and lactose)
		Rivaroxaban (lactose)
		Aspirin (MS)—some formulations
		Clopidogrel (lactose)
	Ticagrelor (MS)	
Bowel regimen	Docusate	Bisacodyl
	Polyethylene glycol	Senokot-S tab
		Magnesium hydroxide (glycerin)

Table 1 (Continued)

	Safe	Potentially unsafe
Other	Dexamethasone (IV)	Diphenhydramine PO (may contain lactose, MS, or glycerol)
	Ondansetron (IV)	Furosemide ^a
	Famotidine	Zofran (PO)
	Diphenhydramine (IV)	Levothroid
	Calcium chloride/gluconate	Nitroglycerin
		Oxybutynin
		lisinopril (MS)
		Insulin ^a
Vaccines	Recommendations on a case-by-case basis	Herpes zoster and varicella
Diet	Chicken	Red meats
	Seafood and fish	Dairy
	Turkey	Gelatin (gummy bears, Jell-O, fruit snacks, etc.)
	Duck	
	Plant-based sources	
	Eggs	

Abbreviations: AED, antiepileptic drug; AH, absorbable hemostat; ECM, extracellular matrix; IV, intravenous; MS, magnesium stearate; NO, nitric oxide; PO, per os; VTE, venous thromboembolism.

^aReports or concerns for being potentially unsafe, but were used in our patients safely or identified from isolated reports of being safely used.

Unfortunately, the exclusion list also includes many patient-favorite perioperative snacks such as Jell-O, fruit snacks, and gummy bears. Fortunately, there seems to be considerable reactivity of various agents among patients, and it is likely that not all the listed “unsafe” animal-derived products will be problematic in various patients. Indeed, many of these same agents were used safely in our two example patients. A thoughtful and tailored approach to medication and surgical product selection is critical to ensure optimal patient outcomes. To highlight these considerations, we review our clinical management of two surgical cases of patients with AGS.

Patient 1

A 59-year-old man presented with worsening vision and was found to have a giant nonfunctioning pituitary adenoma. He had a 10-year history of alpha-gal allergy, which was first diagnosed after suffering an anaphylactic reaction from ingestion of a hamburger. He had multiple known tick exposures around that time. He underwent limited testing at an outside facility that noted he had strong reactivity to all bovine and porcine-derived products; however, the specific testing details are unknown. Due to his significant progressive vision loss, it was not thought appropriate to delay surgery for pretreatment of his AGS. He was taken for a staged endoscopic endonasal approach to debulk the vast majority of tumor, but a considerable residual of tumor was noted on immediate postoperative MRI that was at risk for apoplectic hemorrhage. He thus underwent a same-day subsequent pterional craniotomy, translamina terminalis approach, to remove residual tumor within the third ventricle. He was anesthetized using remi-

fentanyl and sevoflurane, and paralyzed using rocuronium. Throughout the case, he did receive sugammadex, etomidate, propofol, norepinephrine, phenylephrine, vasopressin, albumin (human), cefepime/vancomycin/metronidazole, dexamethasone, and mannitol—all of which he tolerated without incident. Propofol, vasopressin, and etomidate were given in small test doses to ensure tolerability at the case onset. Hemostatic agents used in both the endonasal and open approaches included Surgicel/Surgicel powder, and tranexamic acid spray; during the craniotomy approach, he was also given fresh frozen plasma, and Surgicel Fibrillar was used to aid in hemostasis. During both stages, it was challenging to obtain hemostasis at times, and the surgery was notably slowed to ensure the bleeding was controlled at every phase. The endonasal repair was completed using Surgicel, abdominal fat, and a middle turbinate graft. Nasopore and merocele agents were employed to help bolster the reconstruction. During the craniotomy, the dura was closed primarily with numerous dural tack-ups. The tissue was closed using polyglactin (Vicryl) sutures and staples for skin. Postoperatively, he was managed with acetaminophen, fentanyl, and dexmedetomidine hydrochloride for pain, as well as levetiracetam, dexamethasone, hydrocortisone, and desmopressin for transient diabetes insipidus, and docusate and polyethylene glycol for his bowel regimen. Fondaparinux was used for pharmacologic deep vein thrombosis prophylaxis out of an abundance of caution, which was started on postoperative day 2. Small dose testing was performed early during his hospitalization, and he was cleared to take medications coated with magnesium stearate. He was ultimately discharged home on postoperative day 12.

Patient 2

A 56-year-old man who presented with meningitis was found to have a spontaneous cerebrospinal fluid (CSF) leak with numerous corresponding areas of tegmen dehiscence on CT of the head. He previously had been diagnosed with AGS 5 years prior to presentation after developing nausea, bloating, and dyspnea over several episodes of consuming beef and pork products. He does not recall a specific tick bite event during that time. He received formal allergy testing where he had elevated alpha-gal IgE, elevated alpha-gal:total IgE ratio, elevated beef IgE, and elevated pork IgE, and no adverse reactions to dairy. His meningitis was treated safely with vancomycin and ceftriaxone. Once his infection resolved, he underwent a middle fossa craniotomy approach and repair of numerous CSF leaks and tegmen dehiscence. Anesthesia was performed using succinylcholine, propofol (after a small test dose), remifentanyl, and sevoflurane. Mannitol was given at the start of the case to reduce need for temporal lobe retraction. Levetiracetam (after a small test dose) and vancomycin/cefepime were also given prior to surgical incision. The main hemostatic agents used for the approach were Surgicel/Surgicel powder/Surgicel Fibrillar. The subtemporal dura was found to have numerous holes, many >5 mm, and could not be repaired primarily; therefore, an AlloDerm inlay was performed. Autograft temporalis fascia and a split-thickness calvarial bone were used to reconstruct the temporal floor. His temporalis muscle and soft tissues were closed using Vicryl sutures and staples for skin. Postoperatively, he was managed pharmacologically with acetaminophen, oxycodone, docusate/polyethylene glycol as needed, famotidine, levetiracetam for 7 days, and vancomycin/cefepime. He had no noted allergic or anaphylactic reactions during his hospitalization and was discharged on hospital day 3. We are monitoring his contralateral tegmen dehiscence, without active CSF leak, identified during his initial evaluation to determine whether surgical repair is necessary. Additional outpatient alpha-gal-related allergy testing is scheduled.

Conclusion

AGS is a tick-borne disorder encountered throughout the United States that may cause severe allergy to a nonprimate mammalian carbohydrate found not only in meat products but also in many pharmaceuticals and surgical products. AGS can cause heterogenous allergic reactions in patients, and the symptomatology may evolve or even resolve overtime. For elective

surgical cases, review of pertinent medicines and surgical products preoperatively for potential allergens may be useful. Additionally, pretreatment with omalizumab may even allow use of certain agents if deemed essential. However, avoidance may be necessary when AGS is suspected in emergent cases or after equivocal testing. To minimize AGS-associated morbidity and mortality, the associated risks and alternative management options should be reviewed and discussed with patients, institutional pharmacists, and allergists.

Conflict of Interest

None declared.

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