"anesthetic depth" or "hypnotic state." Algorithms will have to be developed to avoid misinterpretation of the clinical state of the brain.

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Uneventful Propofol Anesthesia in a Patient with Coexisting Hereditary Coproporphyria and Hereditary Angioneurotic Edema

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HEREDITARY coproporphyria (HC) and hereditary angioneurotic edema (HANE) are rare diseases with significant perianesthetic morbidity and mortality.[1,2] Their prompt recognition and meticulous perioperative management are essential for an uneventful outcome. The authors describe the anesthetic management of a patient with coexisting HC and HANE who underwent arthroscopic temporomandibular joint surgery twice under general anesthesia.

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Case Report

A 35-yr-old woman with HC and HANE underwent temporomandibular joint arthroscopic surgery on two occasions, 9 months apart. She had a history of angioneurotic edema attacks involving the airway, bowel, and extremities, and porphyric crises with urine and fecal porphyrin patterns consistent with HC. Her serum C1-esterase inhibitor level was low and nonfunctional. Family history was positive for both HC and HANE. She reported severe crises after previous surgeries, episodes of severe airway edema after dental procedures and colds, and chronic abdominal and bilateral upper extremity pain. Because of the severity of the airway edema episodes she was prescribed long-term stanozolol treatment. At both of the current admissions the patient was free of any acute symptoms. Her mouth opening was 25 mm and results of her physical examination were unremarkable.

The anesthetic management for both temporomandibular joint procedures was similar. Intravenous dextrose and fresh frozen plasma

Table 1. Plasma and Urine Porphyrin Levels, Qualitative and Quantitative Urine Porphobilinogen Assays, and Serum Complement Levels before and after the Second Operation

	Preoperatively	Postoperatively
Plasma porphyrins, total	<1 μg/ml	<1 μg/ml
Urine porphobilinogen, qualitative	Negative	
Urine porphobilinogen, quantitative	4.0 mg/14 h	<0.1 mg/24 h
Urine uroporphyrins, quantitative	16 μg/14 h	32 μg/24 h
Urine coproporphyrins, quantitative	159 μg/14 h	187 μg/24 h
Serum complement C2		1679 C2 U/ml
Serum complement C3	176 mg/dl	167 mg/dl
Serum complement C4	32 mg/dl	30 mg/dl

(Normal values: plasma porphyrins, total: <1 μg/dl; urine porphobilinogen, qualitative: negative; urine porphobilinogen, quantitative: 0–1.5 mg/24 h; urine uroporphyrins, quantitative: 0–22 μg/24 h; urine coproporphyrins, quantitative: 0–60 μg/24 h; serum complement C2: 986–1931 C2 U/ml; serum complement C3: 73–156 mg/dl; serum complement C4: 16–50 mg/dl).

were given preoperatively. Standard monitors were used. Premedication included glycopyrrolate, midazolam, and fentanyl. The airway was anesthetized locally with a solution of procaine and epinephrine for the first procedure and with bupivacaine and epinephrine and inhaled bupivacaine in albuterol for the second surgery. Nasotracheal fiberoptic intubation, with a No. 6.5 reinforced tube, was then performed uneventfully during propofol sedation (75–100 mg · kg^{-1} · min^{-1}). Anesthesia was induced with 2 mg/kg and maintained with 140–180 mg · kg^{-1} · min^{-1} propofol. Vecuronium was used for paralysis, and the lungs were ventilated with 35–40% O_2 in N_2O. Dextrose was continued intraoperatively, and normothermia was maintained. Clindamycin was also given intravenously, and bupivacaine and betamethasone were injected into the joint by the surgeon. After completion of surgery, neostigmine and glycopyrrolate were given and the trachea was extubated. The postoperative course and follow-up was unremarkable on both occasions. Plasma porphyrins at admission before the first operation and on the next day were less than 1 μg/dl. Porphyrin and complement assays before and after the second operation are shown in table 1.

Discussion

Hereditary coproporphyria may coexist with other types of porphyria, and hereditary angioedema with connective tissue disorders and polycystic ovary disease, but no other case of HC coexisting with HANE, has been reported.

Porphyrias are diseases that arise from enzymatic defects in the biosynthetic pathway of heme. Depending on the site of the defect in the metabolic pathway, different precursors may accumulate and lead to the manifestations of each specific type of porphyria. Hereditary coproporphyria is the least common of the acute hepatic porphyrias, which can present with inducible attacks of neurologic, psychiatric, and gastrointestinal manifestations. Crises of porphyria, with significant morbidity and mortality, can be precipitated by perioperative events, such as fasting, dehydration, hypothermia, surgical stress, and many anesthetic or nonanesthetic drugs.[1,3] Prevention depends on avoidance of precipitating factors and drugs in susceptible individuals. Data regarding the capacity of drugs to induce porphyric crises are based on experimental studies, case reports, and clinical studies[1] and show that many commonly used drugs have been implicated as potential triggering agents.[3]

In our perioperative management, we tried meticulously to avoid or treat perioperative factors that might precipitate an attack by providing adequate sedation, fluids, and carbohydrates, in addition to preventing hypothermia. The drugs selected were those for which there was ample evidence or convergence of data to support their safety. Most intravenous anesthetics and volatile agents either have been shown to be porphyrinogenic or have not been definitely cleared as "safe," according to previously published reports.[1,3] We decided to use a propofol-nitrous oxide-oxygen-opioid relaxant technique for both procedures. Propofol is nonporphyrinogenic in animals[4] and has been reported to be safe for induction.[5,6] Nevertheless, Kasraie and Cousins[7] reported an HC attack occurrence after induction and maintenance with propofol, but four other potentially porphyrinogenic drugs were concomitantly used (erythromycin, metoclopramide, cocaine, and lidocaine). Bichel *et al.*[8] also noticed increased urine porphyrins in an asymptomatic patient with variegate porphyria after propofol anesthesia. In our patient at the time of the second operation, elevated porphyrins already were seen initially in the preoperative, and also in the postoperative, urine sample. The postoperative levels were higher, but we cannot know if this is a result of random variation or porphyrinogenic activity secondary to drugs, or related to the fact that the preoperative measurement was based on a 14-h urine collection *versus* a 24-h collection postoperatively. It is possible that the postoperative values would not differ significantly from the preoperative ones, if the latter were extrapolated for a 24-h collection. Thus, we can speculate that our negative clinical and most laboratory findings are consistent with the safety of propofol for induction and maintenance and are in agreement with most other reports.[9,10]

All other anesthetic drugs we used did not appear to

be porphyrinogenic.[3] Lidocaine, which has not been reported as safe,[3,11] was avoided. For the first procedure, procaine was selected because of its documented safety,[3,11] but it had an incomplete local anesthetic effect on the mucosa; therefore, bupivacaine, for which there is no evidence of porphyrinogenicity,[3,11] was used for the second procedure. We also selected epinephrine for mucosal vasoconstriction because of the potential porphyrinogenicity of other vasoconstrictors.

Nonanesthetic porphyrinogenic drugs include anabolic steroids, such as the stanozolol,[12] which the patient was receiving as prophylaxis against the severe HANE occurrences, but this did not seem to have any adverse consequences, consistent with the finding that porphyrinogenic drugs do not always precipitate occurrences, especially in the latent stages of the disease.[1] A possible dose-dependent drug-effect relation may be another explanation.[5]

Hereditary angioneurotic edema results from decreased C1-esterase inhibitor activity.[2] Affected patients experience episodic edema involving the face, upper airway, gastrointestinal tract, and extremities. These attacks can be precipitated by stress, anxiety, inflammation, and trauma, even of minor degree. Airway obstruction from HANE is associated with a 15–30% mortality[2] and can result from even minimally invasive procedures conducted in or near the airway.[2,13,14] Thus, tracheal intubation is contraindicated, but, if unavoidable, pharmacologic and replacement prophylaxis should be used.[2,13] Anabolic steroids (stanozolol) and plasmin inhibitors decrease the incidence or reduce the severity of the attacks. Plasma levels of C1-esterase inhibitor can be raised by fresh frozen plasma (2–4 U), given within up to 24 h before surgery, or purified C1-esterase inhibitor concentrate.[2,13]

In our patient, pretreatment included stanozolol and fresh frozen plasma. The airway had to be protected with an endotracheal tube because of the proximity of the surgical procedures, and nasal fiberoptic intubation was indicated because of the poor mouth opening. Nasotracheal intubation is more traumatic than the orotracheal, and more dangerous for patients with HANE,[13] but, in our case, it did not precipitate any attack. The appropriate pretreatment and the significant variability regarding the angioedema attack threshold[14] may be the explanations.

The documentation of the perianesthetic course as uneventful is based on negative clinical and laboratory data. Plasma porphyrins follow a characteristic pattern in HC and can be used for assessment of the activity of the disease.[15] Levels were low preoperatively and remained low after both procedures. We do not have an explanation for the elevated urine porphyrins we noted the second time in the preoperative and postoperative samples: Whether stanozolol or other exposures produced this elevation is difficult to know. Complement factors were not measured in the first anesthetic, and in the second the preoperative C_2 measurement failed, but no suspicious clinical or biochemical evidence was found.

Acute porphyrias and HANE may be frequently underdiagnosed because many patients are asymptomatic in the latent phases.[14,15] Nevertheless, proper identification is of primary importance for an uneventful outcome after surgery and should be considered with a higher index of suspicion preoperatively in patients with suggestive presentation and family history.

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