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ONLINE CASE REPORT

Anaesthesia Management of a Patient with Hereditary Angioedema with Prophylactic Administration of C1 Esterase Inhibitor

Case report and literature review

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إدارة التخدير لمريض الوذمة الوعائية الوراثية مع إعطاء الجرعة الوقائية من مثبط C1 استريز

تقرير حالة ومراجعة الأدبيات

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الملخص: الوذمة الوعائية الوراثية هو اضطراب نادر ناجم عن عوز في مثبط C1 استريز. الصدمات الطفيفة والضغط النفسي هي الأسباب الأكثر شيوعا التي تؤدي للشروع في الاتصال لتفعيل النظام والإفراز للبراديكينين المفرط غير المنضبط. هذا مما يؤدي لظهور وذمة وعائية، وهو رد فعل الأوعية الدموية في الطبقات العميقة من الجلد والأغشية المخاطية، مع توسع الأوعية وزيادة النفاذية مما يؤدى إلى تورم الأنسجة. يمكن أن تحدث الوذمة الوعائية الحادة في الفترة المحيطة بالجراحة، مما قد يؤدى إلى انسداد مجرى الهواء مسببا الوفاة. في هذه التادة تأهيل الأسنان لحالة طفل مصاب بالوذمة الوعائية الوراثية، مع مراجعة الأدبيات ذات الصلة.

مفتاح الكلمات: التخدير، وذمة وعائية وراثية، عوز مثبط C1 استريز، تقرير حالة ،عمان.

ABSTRACT: Hereditary angioedema (HAE) is a rare disorder caused by a deficiency of C1 esterase inhibitor. Minor trauma and emotional stress are the most common initiating events leading to contact system activation and excessive uncontrolled bradykinin release. This manifests as angioedema, a vascular reaction of the deeper layers of the skin and mucous membranes, with vasodilatation and increased permeability resulting in tissue swelling. Severe angioedema can occur in the perioperative period, leading to fatal airway obstruction. We describe the anaesthetic management of a child with HAE for dental rehabilitation and provide an review of the relevant literature.

Keywords: Anesthesia; Hereditary angioedema; C1 esterase inhibitor deficiency; Case Report; Oman.

Hereditary angioedema (HAE) is caused by a deficiency of C1 esterase inhibitor (C1-INH). C1-INH is a serine protease which inhibits "Activated Factor XIIa" and "Kallikrein". Deficiency of this key inhibitor leads to uncontrolled activation of the Contact System thereby generating profuse amounts of Bradykinin; which is a potent local vasodilator. Trivial stressors can then lead to uncontrolled bradykinin production, with increased vascular permeability of deeper tissues. Airway oedema and hypovolemic shock due to the tissue leak of fluids are especially significant in the perioperative period, challenging even the most experienced anaesthesiologist.

Case Report

A 6-year-old girl weighing 15 Kg who had been diagnosed with C1-INH deficiency was admitted to Sultan Qaboos University Hospital (SQUH), Oman, for dental rehabilitation from multiple dental caries. From two years of age, there had been episodes of abdominal pain and facial swelling, which were self-limiting within 2 to 3 days. Subsequently, there were more aggressive attacks with acute dyspnoea, dysphagia and diarrhoea combined with the progressive swelling of the right side of the neck for which she required admission to the intensive care unit (ICU) for observation; however, no endotracheal intubation was required.

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At 3 years old, she was diagnosed by the SQUH Immunology Team with HAE type II and received 500 units of plasma-derived C1-INH concentrate (pdC1INH) (Berinert P®, CSL Behring, Marburg, Germany) for the successful management of severe periorbital swelling and subacute intestinal obstruction. Laboratory investigations revealed low complement 4 (C4) levels of 0.06 g/L (reference value: 0.16–0.38 g/L) and high C1-INH antigenic levels of 694 mg/L (reference value: 210–345 mg/L). However, the functional activity of C1-INH was only 22% at 4.9 U/ml (reference value: 17.2–27.4) and C1 INH-specific activity was 7.0 U/mg (reference value: 67.4–93.6).

Her pre-anaesthetic evaluation was otherwise unremarkable. The plasma-derived C1-INH (pdC1-INH) concentrate was administered prophylactically, one hour preoperatively. Two additional doses of pdC1-INH and fresh frozen plasma (FFP) were kept ready.

With difficult airway equipment, an emergency tracheostomy kit and an experienced otorhinolaryngologist present, the anaesthesia was induced with propofol with 2.5 mg/Kg and fentanyl at 2 µg/Kg. Under neuromuscular blockade, cisatracurium 0.1 mg/Kg, the airway was secured via the nasal route using a cuffed Ring-Adair-Elwyn (RAE) endotracheal tube, and a throat pack was inserted using minimal manipulation of the oropharyngeal airway. A paracetamol (375mg) suppository was placed rectally. Her intraoperative course was uneventful. Residual muscle paralysis was reversed using neostigmine (0.05 mg/Kg) and glycopyrolate (0.01 mg/Kg). After ensuring a positive audible air leak with cuff deflation, the trachea was extubated when she became fully awake so as to rule out any airway oedema. She was transferred to the Pediatric Intensive Care Unit for further observation. Apart from a mild lip swelling which persisted for a few hours post-operatively, there was no other complication. She was discharged after two days.

Discussion

HAE is an uncommon hereditary disorder (1:10,000–150,000) caused by the congenital deficiency of C1-INH, which inhibits function in three different pathways: the complement system, the fibrinolytic system and the contact activation system, in which C1-INH inhibits both activated factor XIIa and kallikrein in the ultimate cascade to the production of bradykinin.[1,2] The uncontrolled release of bradykinin (a vasoactive peptide) is central to the pathophysiology of HAE.[3,4] Excessive bradykinin eventually leads to vasodilatation and microvascular fluid leakage with subcutaneous and mucosal oedema.

HAE has autosomal dominant inheritance with mutations of the HAE-*C1-INH* gene on chromosome 11q12-q13.1.5 Three forms of HAE have been described: type I with low C1-INH antigenic protein and functional activity (85% of cases), type II with normal or elevated protein but low C1-INH function (15% of cases), and type III HAE with normal C1-INH. Type III is further classified into two types: HAE-XII, a familial oestrogen-dependent variety, described only in females and thought to be due to the mutation of coagulation factor XII, and HAE-unknown, with an as yet unidentified genetic defect.[5–7]

Most HAE patients have a positive family history. The age of onset is variable with laryngeal attacks uncommon before the age of 3 and tending to occur later than other symptoms.[8] HAE can be precipitated or exacerbated by minor trauma (50% of cases), emotional upset (30–40% of cases), infection, menstruation, pregnancy, cold exposure, certain foods or drugs (angiotensin-converting-enzyme inhibitors or oestrogen oral contraceptives) or sometimes without any obvious trigger.[9] Surgical trauma and stress can be a potent trigger of HAE and fatal attacks have been reported after dental surgeries.[10,11]

Angioedema attacks typically involve the extremities, genitourinary tract, bowel, face, oropharynx or larynx. Attacks may last for 72 to 96 hours, and are often severe and disabling. Extremity and/or abdominal attacks account for almost 50% of all attacks, and more than 50% of patients experience at least one upper airway attack during their lifetime, which carries a risk of asphyxiation.[10,12,13] Prodromal symptoms such as fatigue, irritability, weakness, nausea and *erythema marginatum* precede an angioedema attack by several hours or even a whole day in up to 50% of HAE patients.[4] A prodromal serpiginous erythematous rash is sometimes seen, but pruritic urticaria usually makes the diagnosis of HAE unlikely.[14] Airway obstruction can be fatal if left

untreated.[13] Unexplained episodic mucocutaneous oedema in a patient with recurrent abdominal pain, cramps, vomiting and a lack of fever should raise suspicion of HAE.

A diagnosis of C1-INH deficiency requires laboratory confirmation with measurement of the C4 level, C1-INH antigenic level and C1-INH functional level. C4 level assessment allows excellent rapid screening, with nearly 100% of patients having a reduced C4 level during attacks. A normal C4 level during an attack of angioedema strongly supports an alternative diagnosis, whereas decreased levels (less than 30% of normal levels) warrants an assay of C1-INH. Childhood presentation, strong family history and a low serum level of antigenic C1-INH (<30% of normal levels) are diagnostic. If a patient's C1-INH level is normal, or raised along with a low C4 level, a functional assay of C1-INH should be done to detect the possibility of the type II defect.[4] Diagnostic uncertainty is higher in the paediatric age group because of age-related variations in the normal level of C1-INH.[8]

HAE is especially important to anaesthesiologists because these patients are prone to develop massive upper aerodigestive tract swelling and life-threatening airway obstruction.[15] Airway trauma during intubation may rapidly progress to laryngotracheal oedema leading to a fatal airway obstruction, and is more prevalent in children who have narrow airways—a 1-mm thick oedema causes a 44% airway diameter reduction in children *versus* 27% in adults.[16] The initial facial or labial oedema seen in 15–30% cases may mask the early indicators of airway oedema such as hoarseness, voice change, stridor and dyspnoea.[16] Mortality from acute laryngeal oedema is as high as 15–33% in undiagnosed *versus* 4–6% in diagnosed HAE patients.[13] Considering the risk of airway compromise, all patients with HAE should be carefully observed for at least 36 hours postoperatively as the onset time can vary between 60 minutes to 36 hours.[10,17]

Management of HAE consists of long-term prophylaxis, short-term prophylaxis and treatment of established acute attack. Pharmacologic agents are considered in patients who experience more than one attack per month with recurrent abdominal symptoms or life-threatening laryngotracheal symptoms.[18] In addition to being efficacious as an on-demand treatment of attacks, pdC1-INH is also effective for long-term prophylaxis.[16] Treatment with oral 17a-alkylated androgens like methyltestosterone, danazol and stanozolol may be useful in long-term therapy as they stimulate the hepatic synthesis of C1-INH. However, their long-term use may produce serious steroid-related adverse events and hepatocellular tumours; hence, they should be avoided in children. Antifibrinolytics like epsilon-aminocaproic acid and tranexamic acid are no longer employed because of their poor efficacy.[16,4]

Short-term prophylaxis can be achieved with the administration of 10–25 U/Kg of pdC1-INH (Berinert P®) given one hour before the procedure. Alternatively, an infusion of 10 mL/Kg of solvent-treated plasma or FFP can be administered up to 6 hours before a scheduled procedure. Although FFP is a good source of C1-INH, it also contains kinins and uncleaved C2 and C4 which may exacerbate acute attacks, apart from its transfusion-related hazards.[19] FFP is less effective, having a shorter duration of action and requiring a longer time for administration. Therefore, pdC1-INH concentrate has emerged as the most favoured option for prophylaxis before any provocative surgical procedure.[20] High-dose androgens (danazol 6–10 mg/Kg/day in 3 divided doses) taken for 5–7 days before and two days after the procedure is an alternative strategy. For emergency procedures and in pregnant patients, the administration of pdC1-INH is preferred.[14,4]

For acute attacks, standard angioedema treatment modalities, such as epinephrine, corticosteroids or antihistamines, do not have a salutary effect and are not recommended.[5] On- demand treatment modalities include the replacement of C1-inhibitor with filtered pdC1-INH (Berinert P®), bradykinin-2-receptor inhibitor (icatibant: subcutaneous self-administration possible; 10% recurrence after 16–24 hours), kallikrein antagonists (ecallantide: 4–6% anaphylaxis chance) and a recombinant C1-INH, conestat alfa (Rhucin®, Pharming Group NV, Leiden, Netherlands) with a half-life of 3 hours.[18,14,21,22] After administration, most patients experience relief after 15–120 minutes but a major swelling might take up to 24 hours to resolve completely. Swellings respond more quickly when treated early in the course of the attack.

The pdC1-INH concentrate is preferred for acute attacks because of evidence of higher efficacy

and safety.[4,14,23] It has minimal to no transfusion hazards and can be safely used in paediatric as well as pregnant patients. It causes a partial resolution of symptoms within 30 minutes, and a complete resolution in 4–24 hours.[21] The normalisation of laryngeal oedema occurs faster than any other manifestations. The pdC1-INH increases C1-INH levels by more than 50% within 30 minutes and the level remains above the baseline for 3–4 days. Thus, it can be used to treat acute attacks as well as short- and long-term prophylaxis when other drugs are not effective. When injected slowly, pdC1-INH is free from any major adverse effects. Its main disadvantages are the high cost, limited duration of activity, necessity of parenteral administration and the possible transmission of blood-borne infections.[4]

Because of the rarity of occurrence, reports of perioperative management of HAE are very limited in the literature.[1,15,10] This makes it difficult to formulate any specific guidelines for anaesthetic or perioperative management. However International Consensus Guidelines have emerged in the last two years elucidating an algorithmic approach to the management of HAE.[4,5] The precipitating triggers mentioned earlier should be avoided. Regional or general anaesthesia can be safely performed in such patients. Regional anaesthesia is preferred wherever possible because of the better suppression of the stress response and the avoidance of airway manipulation.[2,24] There is no known contraindication related to the use of any of the available intravenous or volatile anaesthetics and neuromuscular blocking agents, including succinylcholine. Although tracheal intubation is not contraindicated, it is important to reduce airway manipulation to the minimum. The role of the laryngeal mask airway in HAE patients is not completely clear, but it is reasonable to believe that the larger contact area may aggravate airway oedema. A dose of an on-demand short-term treatment drug (pdC1-INH, ecallantide or icatibant) or FFP should be held ready, particularly for dental procedures or surgical procedures that require intubation.[11,17]

Upper airway oedema is the most dangerous presentation of HAE and is associated with high mortality.[4,13,17] Fatalities are most commonly seen after dental surgeries.[11] Intubation is always the first choice in the case of acute airway compromise and should be done as early as possible. While performing laryngoscopy and intubation, the presence of difficult airway equipment and a provision for urgent tracheostomy or cricothyroidotomy is mandatory. Airway swelling may become so severe at times that even a tracheostomy may be ineffective in maintaining a patent airway.[2] The presence of severe airway oedema, swelling and the demand for immediate intervention can greatly limit the usefulness of fiberoptic intubation.[24]

This patient had already been diagnosed with HAE with a positive history of successful management with pdC1-INH concentrate. The case was managed successfully with a multidisciplinary team, using pdC1-INH prophylaxis as recommended and extubating the patient in a fully-awake condition in order to avoid any airway complications or subsequent precipitation of an acute attack. The absence of any airway oedema was confirmed by a cuff-leak test before the extubation and the patient was observed strictly for the recommended period for the development of any postoperative events.[25] Although the immediate postoperative period was uneventful, she developed an acute attack after two weeks. The acute relapse occurring two weeks after the operation is unlikely to have been related to perioperative events.

Conclusion

A high index of suspicion for the early diagnosis and active management with pdC1-INH forms the cornerstone of the successful management of HAE cases. Successful perioperative management requires prophylactic pdC1-INH, diligent monitoring and measures to avoid airway oedema triggers.

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