

Myasthenia Gravis and thymectomy : an anaesthetic approach

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Abstract : In this paper, we discuss the case of a 48 year old patient with newly diagnosed myasthenia gravis, who is scheduled for a thymectomy. The patient's history showed an undocumented difficult intubation, which led to the approach of an awake intubation after sevoflurane induction. We used a slightly modified non-muscle relaxant technique, allowing induction and maintenance of anesthesia under safe and excellent conditions.

INTRODUCTION

A 48-year-old man with recently diagnosed myasthenia gravis is scheduled for transsternal thymectomy. The perioperative management of this particular patient introduced several problems and topics for discussion : (1) the preoperative approach and the premedication to be used, (2) the anesthetic drugs and more in particular the use of neuromuscular blocking agents and (3) the postoperative prevention of complications.

CASE REPORT

The 48-year-old patient recently developed an acute ptosis of the left eye, progressing to bulbar symptoms with articulation and chewing disability. The diagnosis of myasthenia gravis was suspected after a prostigmine test, and electromyography. The presence of acetylcholine receptor antibodies in the serum, detected by radioimmunoassay, was diagnostic for myasthenia gravis. According the Myasthenia Gravis Foundation of America Clinical Classification, the patient was staged Class IIIb (disease predominantly affecting oropharyngeal or respiratory muscles, or both) (1). Subsequent CT scan showed a mass in the anterior mediastinum, most likely a thymoma.

Preoperative evaluation revealed a patient in a good condition, with no cardiovascular or pulmonary contraindications to surgery. The patient's medical history included asthma, for which he sporadically used corticosteroids, and morbid obesity (BMI = 48 kg/m²). There was a positive history of a difficult intubation (the patient was intubated for

middle ear surgery 25 years ago, and was told there had been 'problems' with controlling the airway). Clinical examination of the upper airway showed no abnormalities, with a Mallampati class II, thyromental distance less than 3 cm and normal neck length and thickness. His neurological condition was stable with only significant electromyographic changes in the facial area. His regular medications included pyridostigmine and corticosteroids. Although some controversy remains about whether or not to continue anti-cholinesterases on the day of the surgery, we chose to continue them. His further premedication consisted of atropine 0,5 mg IM, but no anxiolytics, sedatives or opioids.

Prior to induction, an 18 gauge i.v. cannula was inserted and a radial artery catheter was placed under local anesthesia. Considering the patient's morbid obesity and history, we preferred intubation of a spontaneously breathing, sedated patient. Method of choice was the single-breath vital capacity rapid induction with sevoflurane 4% and nitrous oxide. Patient was induced under continuous monitoring of oxygen saturation, ECG, end-tidal carbon dioxide, spirometry, invasive blood pressure and accelerograph, but without the use of muscle relaxants. Loss of eyelash reflex occurred after 55s. Laryngoscopy was possible after 60 seconds, with excellent intubation conditions and cord abduction, and an endotracheal tube was placed without difficulty.

Anesthesia was maintained with oxygen, nitrous oxide and sevoflurane 2.5%. Further analgesia was provided with sufentanil. Thoracic epidural anesthesia was impossible in this case due to patient refusal. The 2.5 h lasting operation was uneventful,

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apart from unexpected fixation of the thymoma to the pericardium. Patient was ventilated with $FiO_2 = 0.5$, with end-tidal carbon dioxide ranging between 27 and 32 mm Hg throughout the procedure, and blood gases remained satisfactory. The pulse rate and blood pressure did not vary from the baseline value. Patient received 700 ml of lactated Ringer's solution. Urine output was 300 mL and estimated blood loss was 300 mL. Close to the end of the surgery, the hematocrit was 30%. Postoperatively, the patient was transferred to the ICU, where he was extubated within the hour, after opening his eyes, responding to verbal commands and TOF ratio of 0.7. Special care was provided to optimise pulmonary function, through adequate analgesia and physical therapy. Postoperative analgesia was provided with intravenous paracetamol, diclofenac and piritramide, with excellent result. Transfusion was not required. Oral medications (including pyridostigmine) were restarted on the second postoperative day. Patient remained at the Intensive Care Unit until the third postoperative day and was discharged to the ward in good condition.

On the fourth postoperative day, the patient deteriorated clinically, and electrocardiography showed severe ST-segment changes in the anterior wall. TTE was non-contributively as a result of the patient's obesity. Subsequent coronarography showed a normal coronary angiogram; CT showed a diagnosis of pericarditis. After treatment with salicylates the ST-elevations disappeared. Typing of the tumour later showed a mixed AB tumour with B2 and possibly B3 components, worsening the prognosis, and a Masaoka type II (i.e. macroscopic invasion into surrounding fatty tissue or mediastinal pleura, or microscopic invasion into capsule), which implied the use of further radiotherapy. There proved to be no lymph-node invasion.

The patient's neurological symptoms had stabilised and diminished at the time of the first follow-up consultation. By that time, he had received 30 courses of radiotherapy. Although the corticosteroids had been reduced at the time of the follow-up, he was still dependent on them.

DISCUSSION

The thymus, derived from the Greek word meaning life-force, is an anterior mediastinal organ that weighs 12 to 15 grams at birth, reaches its maximum weight of 40 grams at puberty and involutes in an atrophic state at older age. The thymus is involved in the processing and maturation of

lymphocytes which become T-lymphocytes upon release into the circulation. A thymoma is a representative tumour derived from the thymic epithelium with heterogeneous oncological behaviour, variability in histological appearance and association with autoimmune diseases (2). Thymomas are the most common neoplasm of the anterior mediastinum with an incidence of 0.15 cases per 100.000 (3). Most patients are between 40 and 60 years of age with a slight male predominance. A WHO-classification is based on the morphology of epithelial cells as well as the lymphocyte-to-epithelial cell ratio. The WHO classification system reflects the invasive nature of the thymoma, with type B2 and B3 having more malignant nature in terms of prognosis and tumour recurrence compared with other types (4). Staging of thymomas is based upon clinicopathological criteria, especially the presence of invasion. The Masaoka system incorporates the presence of invasion and the anatomic extent of involvement, defined both clinically and histopathologically, and correlates well with five year survival rates (5). There is a good correlation between the WHO classification and the Masaoka staging system in terms of long-term outcome (6). Up to one half of thymomas may be found as an incidentally detected radiographic abnormality in an asymptomatic patient. Clinical signs are present in one third of the patients and are related to the size of the tumour and effects on adjacent organs, or less commonly, "B" symptoms (7). Pleural or pericardial effusion represents the most common form of metastatic involvement.

Myasthenia gravis is a chronic autoimmune neuromuscular disorder, involving postsynaptic acetylcholine receptors, which are blocked by specific antibodies binding to proteins that are involved in signalling at the neuromuscular junction (NMJ). This results in striated muscle weakness and fatigue. The incidence is 2-10/100000 cases/year (8).

Myasthenic patients are classified by the Myasthenia Gravis Foundation of America Classification in five distinct categories, depending on the extent of the disease and the primary muscle involvement. Ocular muscles are involved in 40 percent of patients, and in a lesser percentage cranial nerves and limb and/or neck weakness. Characteristic is muscle weakness that worsens after use of affected muscles. In two-thirds of the patients, extrinsic ocular muscles present initial symptoms. With one-tenth of the patients, the disease remains confined to ocular symptoms. Progression of the disease can lead to oropharyngeal weakness and respiratory muscle involvement,

making the myasthenia gravis patient prone to aspiration and respiratory failure, especially during myasthenic crisis (9). Acute components of myasthenia gravis are myasthenic crisis and cholinergic crisis. A myasthenic crisis is an exacerbation of symptoms, leading to respiratory failure requiring intubation, with or without mechanical ventilation. It frequently occurs within 2 years of the disease onset, while a third of the patients who survive a crisis experience a second. In contrast, a cholinergic crisis results from overtreatment of anticholinesterase agents, with an excess of acetylcholine at the nicotinic and muscarinic receptors. Symptoms include involuntary twisting, fasciculations and weakness, resulting from an inability to coordinate muscle relaxation and contraction. Although myasthenia gravis fulfils the strict criteria of an antibody(Ab)-mediated autoimmune disorder, pathogenesis remains unclear and complex. Anti-acetylcholine-receptor-antibodies (Anti-AChR-Abs) affect neuromuscular transmission by at least 3 mechanisms : (a) binding and activation of complement at the NMJ ; (b) accelerated degradation of AChR molecules crosslinked by Ab (antigenic modulation) and (c) functional AChR block (10). Different lines of indirect evidence suggest that complement activation at the NMJ might be the primary cause of AChR loss and failure of neuromuscular transmission. Anti-AChR-Abs are high affinity IgG's, requiring activated CD4⁺T cells to interact with B cells. Myasthenic patients have AChR-specific CD4⁺T cells in the blood and thymus (11). Although the connection between thymoma and myasthenia gravis is unclear, thirty to fifty percent of patients with thymomas have myasthenia gravis, compared to ten to fifteen percent of patients with myasthenia gravis who have a thymoma (12). Clinical diagnosis of myasthenia gravis is not always straightforward and delayed diagnosis occurs frequently. Once suspected, the diagnosis relies on serological tests that detect anti-AChR (detectable in approximately 80-90% of generalised myasthenia gravis patients and 30-50% of ocular myasthenia gravis patients) or anti-muscle-specific tyrosine kinase antibodies and electrodiagnostic tests that detect characteristic defects in neuromuscular transmission (single-fiber electromyography is positive in 95-99% of myasthenia gravis patients). The current management of myasthenia gravis includes the use of anticholinesterase drugs for temporary improvement, immunomodulation through removal of the anti-AChR-Abs by plasma exchange, the use of non-specific immunosuppressants or immunomodulators to curb the anti-AChR

response, and thymectomy. Anticholinesterase drugs (e.g. oral pyridostigmine) improve symptoms in nearly all patients but they fully relieve the symptoms in only a few so most need additional treatment. Corticosteroids are frequently used despite the lack of large controlled trials and have high rate of complications. Azathioprine has been utilised and has a proven steroid-sparing effect (13). Cyclophosphamide is effective but limited to non-responders to more conventional therapy due to its side effects (hair loss, nausea, vomiting). Plasma exchange or intravenous immunoglobulin therapy are used for management of acute muscular weakness.

The clinical efficacy of thymectomy has been questioned due to lack of solid evidence (14). Usually, thymectomy is performed on patients early in the course of their disease and restricted to patients younger than 60. Various surgical approaches to thymic resection exist, with minimally invasive techniques becoming increasingly popular due to their low procedural morbidity and mortality, improved cosmesis, and lesser access trauma.

Only contradicting evidence is available about premedication and the myasthenic patients. Reports indicate that the administration of pyridostigmine, and especially the dose taken, was a predictor of the risk of reintubation (15). According to one study, patients who receive at least or more than 240 mg of pyridostigmine are at risk for reintubation. Anticholinesterase agents complicate the anaesthetic management, as they potentiate vagal responses (making atropinization necessary) and decrease the metabolism of ester local anaesthetics (through inhibition of plasma cholinesterases). Relaxation may be more difficult to produce. No effect has been shown on potency of sevoflurane (16). Although oral pyridostigmine is well tolerated, it can be given intramuscularly or intravenously with a dose of 30 mg being equivalent to 1 mg IV or IM. Patients with little respiratory reserve tolerate any depressant and sedative premedication poorly. Only in patients with primarily ocular symptoms, a small dose of anxiolytics is acceptable. There have been reports that alternate-day administration of high-dose prednisolone reduces the risk of post-thymectomy myasthenic crisis (17) and the overall complication rate, without negative impact on morbidity or mortality (18). In patients with generalised myasthenia, where plasmapheresis is indicated, intravenous immunoglobulin may offer a safe and effective alternative.

We preferred to use sevoflurane as a sole anaesthetic, since sevoflurane provides good

muscle relaxation, although some variation of relaxation exists. Sevoflurane has a low blood gas solubility coefficient, constant uptake and elimination kinetics in all age groups (it has been successfully used for this indication in paediatric subgroups), good muscle relaxant properties (at 2.5% it depresses EMG responses with T1/TC at 47% and T4/T1 at 57% (19)), and rapid adjustment of anaesthetic depth. All this makes sevoflurane suitable as a sole induction and maintenance agent in cases where muscle relaxants are best avoided (20). Although the single-breath technique has been used and published extensively in both children and adults, data concerning the use with adults with myasthenia gravis is limited (21). There is evidence that sevoflurane might potentiate the neuromuscular block of some neuromuscular blockers, but since we chose not to use any this was of lesser importance (22). There are insufficient data to evaluate desflurane in myasthenic patients. Experience and data of the use of propofol induction and maintenance is limited, although some authors do suggest it as an alternative for sevoflurane (23). LORIMER and HALL (1998) used total i.v. general anesthesia with propofol and remifentanyl, a combination that allowed excellent control of heart rate and pressor response and early return to spontaneous ventilation (24). Remifentanyl is hydrolysed by non-specific tissue and plasma esterases, and its duration of action is not prolonged in patients with cholinesterase deficiency. However, there have been reports of delayed arousal for 12 h following a sevoflurane and remifentanyl anesthesia. In this case, awake intubation was possible after propofol infusion but is considered less safe. In the absence of neuromuscular blockade, propofol – not thiopental or etomidate – with remifentanyl does provide adequate intubating conditions (25).

Neuromuscular blocking drugs act by interrupting neuromuscular transmission at the level of the nicotinic acetylcholine receptors at the motor end plate and can be classified as antagonist (non-depolarising) or agonist (polarizing). In myasthenia gravis, antibodies against the acetylcholine receptors of the motor endplate reduce the number of active receptors, implying that the correct use of muscle relaxants in myasthenia patients can only happen if full neuromuscular monitoring is provided and only after careful consideration of the necessity and indication of its use. One ought to remember that sensitivity to the muscle relaxants varies and that the response to stimulating the ulnar nerve may not predict the degree of weakness of the accessory muscles of respiration. Myasthenic

patients may be extremely sensitive to nondepolarizing relaxants but intermediate-acting nondepolarizing relaxants such as atracurium and vecuronium are eliminated rapidly, and can be titrated to achieve the required neuromuscular block that can be completely reversed at the end of the surgery. It is important however to consider numerous pharmacological interactions, such as the continued use of pyridostigmine preoperatively which can influence sensitivity to vecuronium, and sevoflurane which can potentiate the neuromuscular block of neuromuscular relaxants. Drugs as aminoglycoside antibiotics depress neuromuscular transmission and corticosteroids can greatly influence sensitivity to neuromuscular blocking agents. Long-acting drugs as d-tubocurarine or pancuronium should be avoided. Some authors will suggest induction and intubation without muscle relaxants, only to use judiciously titrated NMB drugs as vecuronium or atracurium if intubation is unsuccessful. A pre-anaesthetic train-of-four ratio < 0.9 in myasthenics can predict a higher sensitivity to nondepolarising neuromuscular blocking agents (26). In myasthenic patients, the ED₉₅ for vecuronium ranges from 40% to 55% of that in normal controls. For atracurium, the ED₉₅ was 58% of the value of normal patients. As expected, the pharmacokinetics remain normal, so the dose needed per hour is related to the original sensitivity. Larger doses of succinylcholine are needed to produce adequate block in myasthenics (ED₉₅ 2.6 times that of non-myasthenic patients). Some authors have pointed out the risk of a Phase II block, even at 0.5 mg/kg, with slow recovery. Since mivacurium is metabolized by pseudocholinesterase, patients taking anticholinesterase agents may recover slowly. One study revealed a depolarising effect that was twice as great in myasthenic patients (27). Patients not taking these agents may benefit from the short duration of action.

Regional and local anesthesia should be performed using amide local anaesthetics at lower doses. The combination of high thoracic epidural analgesia (TEA) and general anesthesia is recommended by some authors (28). This technique assures a better postoperative analgesia and this leads to a higher incidence of early extubation, due to minimal interaction with opiates (29). Inherent sedative properties of neuraxial blockade have been shown to reduce requirements for general anaesthetic agents by 50% and the addition of opiates to epidural bupivacaine further enhances such effect (30). Patient refusal made such an approach impossible in this case.

The postoperative care confronts the clinician with the issue of postoperative ventilation. At present, no criteria have been developed that uniformly distinguish patients who require long-term ventilation from those who do not. In a retrospective study published in 1980, LEVENTHAL *et al.* tried to identify preoperative factors which would predict the need of postoperative ventilation (duration of myasthenia gravis > 6 y, history of chronic respiratory disease, pyridostigmine dosage > 750 mg/d, and vital capacity < 2.9 L) but later proved to be of rather limited value. Other variables such as glucocorticoids dosage, the presence of bulbar symptoms, previous history of respiratory failure, arterial blood gas values, the titre of acetylcholine receptor binding antibodies, type of anaesthetic, the use of neuromuscular blocking drugs, or duration of anaesthesia all failed to add a statistically significant increment to this model.

In 1996 a model was presented based on seven variables (functional vital capacity, forced midexpiratory flow rate, maximum expiratory flow and their percentages of the predicted values along with sex) (31). It correctly predicted the actual ventilatory outcome in 88.2% of the patients.

CONCLUSION

In this paper, we present a 48 year old, morbidly obese patient with a history of difficult intubation. We discuss a slightly modified non-muscle relaxant technique based on sevoflurane induction, allowing intubation of a sedated and spontaneously breathing patient, under safe and excellent conditions.

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