ANAESTHETIC ASPECT OF THYMECTOMY FOR MYASTHENIA GRAVIS

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SINCE 1936 when Blalock performed the first successful thymectomy for myasthenia gravis, there has been much dispute about the value of this procedure as a therapeutic measure. Consideration of the usefulness of this operation is outside the scope of the anaesthesiologist, but readers interested in the pros and cons of this subject may refer to articles by Keynes (1, 2, 3), Eaton and Claggett (4, 5), and Ferguson (6), where varying opinions are set forth.

Although the condition was described by Thomas Willis in 1672, the classical description was made by Jolly in 1895. He made suggestions as to its physiopathology and its treatment with physostigmine, and gave it the name "Myasthenia Gravis Pseudo-paralytica."

CLINICAL PICTURE

Essentially the disease is characterized by muscle weakness, especially of the small muscles of the hand, the extra-ocular muscles and the muscles of the pharyngeal and laryngeal region. All or any of the skeletal muscles may be involved in a completely irregular pattern. It is characterized also by spontaneous remission and exacerbation. The disease can be divided into a localized ocular group, and a generalized group which is usually progressive.

PHYSIO-PATHOLOGY

Although the process of myasthenia gravis is localized anatomically to the myoneural junction, the exact cause of the disease is not known. The reaction of the end-plate in a myasthenic differs from that in the normal person as shown by action-potential recording from the end-plate when acetylcholine is injected intra-arterially followed by the injection of neostigmine (7). Normally there is an early prompt depression of action-potential followed by a late phase of depression, both these phases being enhanced by neostigmine. In the myasthenics, the prompt phase was enhanced and the late phase reversed by neostigmine, indicating a competitive type of block as compared to the normal depolarizing block.

Many theories have been advocated to explain the nature of this disease, such as.

- (1) Increased concentration of cholinesterase.
- (2) Decreased amounts of acetylcholine liberated at the end-plate.
- (3) Decreased susceptibility of the receptors to normal acetylcholine concentration, because of locally produced curare-like toxin or systemically produced toxins. The last hypothesis has attracted much attention since it is postulated that the thymus is the site of production of this curare-like toxin.

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Weigert suggested in 1901 that a curare-like metabolite elaborated by the thymus is the cause of the disease. In 1952 Wilson (8) demonstrated that an extract from operative specimens contains curare-like substance. Further support of the curare-like toxin was forthcoming in 1953, when Schwarz demonstrated that the serum of myasthenic patients contained a factor capable of producing muscular weakness on administration to normal individuals.

DIAGNOSIS

Drugs used in the diagnosis of myasthenia gravis are (1) neostigmine; (2) edrophonium (Tensilon); (3) d-tubocurarine; (4) quinine.

The first two drugs are usually used as the diagnostic agent as they cause temporary improvement of the muscle strength, while the latter drugs are seldom used because the increase in the weakness of the muscles produced by them may lead to respiratory difficulty. "Tensilon" may be more useful in that its onset of action is brief, whereas neostigmine has a longer onset and duration of action. "Tensilon" is a poor therapeutic agent because of its short duration. If curare or quinine are used as diagnostic agents, neostigmine must be available to counteract severe muscular weakness.

TREATMENT

Drugs are one method of treatment. The first group is that of the *anticholinesterases*: (a) physostigmine, (b) neostigmine; (c) pyridostigmine (Mestinon); (d) Mysuran (WIN 8077). Until recently neostigmine has been the drug of choice in the treatment of myasthenia gravis. Neostigmine has two modes of action, primarily it is an anticholinesterase and, in addition, it has a direct depolarizing action at the end-plate. It inactivates not only the true but also the pseudo-cholinesterase of the plasma. Despite the preference for neostigmine for many years, more satisfactory agents are now being used. Both pyridostigmine and "Mysuran" produce similar clinical results with less side reaction and longer duration of action. These side effects are due to the muscarinic action which is responsible for excessive cholinergic stimulation such as discomfort, salivation, bronchorrhea, nausea, urgency, etc. These muscarinic effects may be blocked by atropine.

The second group is that of the *adjuvant drugs*: (a) Atropine, (b) Ephedrine and Amphetamine.

Other methods of treatment are as follows: (1) Irradiation of the thymus, (2) Surgical removal of the thymus; (3) Combination of the above

ANAESTHETIC CONSIDERATIONS

Preoperative Management

Ideally surgery should be performed during a remission, as patients with severe cases are poor surgical risks. The nutritional state of the patient should be improved, since poor nutrition may be present as the result of weakness of the muscles of swallowing.

Although Keynes is very emphatic that these patients should not be given a

preoperative enema, as it may result in collapse, we have found no adverse effects.

Opiates are not directly harmful but should be prescribed in minimal doses before operation, as anything diminishing the ability to cough should be avoided. Moreover, large doses may depress the respiration sufficiently to cause anoxia. Belladonna drugs are essential since the anticholinesterases stimulate excess secretion.

Anticholinesterase drugs are required before operation in doses equal to or larger than regular amounts (e.g., neostigmine 1 to 2.5 mg. parenterally).

Management during Anaesthesia

Technique. Endotracheal anaesthesia is the method of choice for thymectomy, since it not only provides an unobstructed airway at all times, but also affords an easy means for tracheo-bronchial toilet when excessive secretion is present. Finally, control of respiration is simple if the pleura is accidentally opened. It is worth noting that Keynes, whose personal experience is unequalled, opposed intubation on the grounds that it might contribute to postoperative respiratory infection and atelectasis.

Relaxant drugs. In severe cases with muscle weakness no relaxant will be required, but in the milder cases relaxants may facilitate intubation and control of respiration. Any relaxant drugs that are used should be given judiciously and with care.

Curare and other competitive blockers are contraindicated since they interfere with the action of acetylcholine at the end-plate, thereby increasing and prolonging the muscular weakness. Therefore, prolonged muscular relaxation may result with the use of tubocurarine.

Theoretically, the myasthenic patient should be resistant to the depolarizing group of relaxants such as decamethonium and succinylcholine, because of their depolarizing action at the end-plate. The work of Churchill-Davidson and others has shown that in the myasthenic patients decamethonium and succinylcholine act as a competitive type of blocker, and that their effects are reversed and not potentiated by neostigmine (9, 10). Both agents have been used in our hospital without producing prolonged relaxation.

Anaesthetic agents. A wide choice of anaesthetic agents has been advocated for this procedure. Any gaseous or volatile anaesthetic agent would be satisfactory. Cyclopropane is probably the agent of choice since it is easily administered, causes little irritation of the respiratory tree, and less depression of the muscles. The combination of cyclopropane and neostigmine may theoretically be incompatible because of neostigmine's stimulation of the sympathetic ganglia with resulting epinephrine discharge into the circulation. Clinically, the amount of neostigmine used preoperatively does not produce any appreciable sympathetic reaction. Ether tends to increase secretion in the respiratory tract and to depress the muscles more than cyclopropane. The combination of nitrous oxide and supplementary agents is satisfactory provided excessive amounts of the latter (Pentothal or Demerol, etc.) are not used. These non-volatile agents are metabolized slowly and will depress respiration centrally.

Postoperative Management

(1) Respiratory infection and atelectasis are potential complications after surgery. Good respiratory movement and adequate nursing care will help to prevent them.

(2) Excessive secretions are likely to be troublesome because of: (a) impaired ability to cough, (b) the use of neostigmine, which produces profuse salivation and bronchorrhea. Atropine and tracheo-bronchial toilet will prevent accumulation of secretion.

(3) The possibility of postoperative pneumothorax from surgery must be borne in mind.

(4) Opiates should be used sparingly to allay restlessness, as other causes such as anoxia may be the cause of it. Large doses of opiates will further aggravate anoxia.

(5) Neostigmine or some other anticholinesterase drug must be administered regularly postoperatively to maintain good muscular tone and adequate respiration. Neostigmine in doses of 1.0 to 1.5 mg. may be given every two hours in the immediate postoperative period. The danger of overdosage with anticholinesterase drugs must always be kept in mind.

In the event of inadequate response to neostigmine and other drugs and the patient's inability to maintain adequate respiration, Jorgenson and Therkelson (11) have advocated that all drugs be discontinued and that the patient be treated as one would treat a bulbar poliomyelitis, by placing the patient in a respirator, adequate tracheo-bronchial toilet, and tracheotomy.

CASE 1. Miss A. J., age 15

Patient gave a history of progressive difficulty in swallowing for one year prior to surgery. She had not taken any medication before admission to hospital. In hospital she was taking 5 mg of prostigmine every three hours. For preoperative preparation, prostigmine 10 mg was injected one hour before surgery along with Morphine gr 1/12 and Hyoscine 1/200. She was anaesthetized with cyclopropane by endotracheal technique. After operation, patient was carried on prostigmine 10 mg q3h I.M. On the second postoperative day X-ray of the chest showed a pneumothorax on both sides with 20 per cent collapse. The pneumothorax absorbed spontaneously without treatment.

CASE 2. Miss D. W., age 22

Patient gave a history of weakness for three years. She had no medication prior to admission to hospital. While in hospital patient took prostigmine 15 mg. twice daily with atropine. Preoperative medication was Seconal grs. 150 90 minutes preoperatively, Demerol 100 mg, plus Hyoscine gr 1/150, one hour preoperatively. Patient was anaesthetized with cyclopropane and ether with endotracheal technique. Postoperatively, prostigmine 10 mg and atropine gr. 1/150 were administered q3h. On the first postoperative day the patient developed a sudden attack of cyanosis and difficulty in respiration. Examination indicated atelectasis which was confirmed by X-ray. Tracheo-bronchial toilet immediately rectified the condition. The patient recovered uneventfully after this episode.

CASE 3 Miss S. A., age 19

Patient gave a history of weakness since childhood. At age eleven she was so weak that she could not dress herself. Prostigmine was started at age fourteen with 8 to 14 tablets daily. The usual dose of prostigmine was administered prior to operation. Pre-

operative sedation included Seconal grs. $\frac{1}{100}$, Morphine gr. $\frac{1}{8}$ and Hyoscine gr. $\frac{1}{150}$. Patient was induced with pentothal 500 mg. and syncurine 3 mg. She was maintained with endotracheal nitrous oxide and ether. Postoperative medication was prostigmine 0.5 mg. q2h. On the first postoperative day, partial pneumothorax was shown by X-rays. The patient had no distress with the pneumothorax. The pneumothorax was reduced by removal of 700 cc. of air. The subsequent course was uneventful.

CASE 4. Mrs. E. W., age 30

Mrs. E. W. gave a history of weakness for one year. She had been on prostigmine and later "Mestinon," which partially controlled her weakness. Before operation she had Mestinon 60 mg., Pantapone gr. $\frac{1}{6}$ and Hyoscine gr. $\frac{1}{150}$. Patient was induced with pentothal 500 mg. and carried on with endotracheal cyclopropane and ether. Prostigmine 0.5 mg. was given intravenously to the patient q2h postoperatively. On the second day, prostigmine was increased to 0.5 mg. q1h because of dyspnoea during that period. Twice, 500 cc. of air were aspirated from the chest. The patient had nine doses of prostigmine over a period of less than eight hours during the night, so that when morning came she was in a state of collapse with gasping respiration, cardiovascular collapse, and disorientation. A bronchoscopy was performed to remove secretion and establish a clear airway, and the patient was then placed in a respirator. After several hours in the respirator her condition became worse, with signs of hypoxia. An endotracheal tube was inserted, large amounts of thick secretion were removed from the trachea, and her condition improved immediately. During the next 24 hours the endotracheal tube was removed and inserted several times. A tracheotomy was performed about 36 hours after the surgery. The patient remained in the respirator for 10 days. During the first few days in the respirator, anticholinesterase drug was given in a slow intravenous drip. Later the drug was given by Levine tube. The patient made a slow recovery and was discharged after a two-month stay in hospital.

DISCUSSION

Although myasthenia gravis is a medical disease of unknown etiology, its great interest to the anaesthesiologist lies in the site of its pathology, the myoneural junction. Myasthenia gravis in some way affects the transmission of the normal neuro-muscular impulses through the end-plate: in anaesthesia we very commonly alter the transmission at this site, in order to produce muscle relaxation. Like myasthenia gravis, the curariform agents mimic the disease by affecting the small muscles of the eyes and pharynx first. Similarly, drugs which are useful in the treatment of myasthenia gravis are antagonistic to the curariform agents. Prostigmine has been the drug of choice in the treatment of myasthenia gravis, but recently newer drugs which are more efficacious in relieving the symptoms have become available. Mestinon and Mysuran produce the same therapeutic effects as prostigmine with the advantage of fewer and less severe side effects and longer duration of action.

Surgical treatment of myasthenia gravis is carried out in many cases, although there are diversified opinions as to its effectiveness in controlling the disease and as to the indications for surgery. The results of thymectomy vary in different centres because of the different criteria for operation. In the early benign ocular cases, the results of thymectomy were good, while in the progressive severe generalized cases, the results were poor. Cases undergoing surgery of the thymus are of great interest to the anaesthesiologist because they present problems with many facets. In the benign early cases the anaesthetic management and post-

operative care are no real problem, while in the progressive severe cases with generalized weakness the management is a great challenge to the anaesthesiologist.

Preoperative preparation of these patients is important. Prostigmine or similar drugs should be given immediately prior to surgery. Light pre-anaesthetic sedation is preferable, with special attention being paid to the belladonna drugs, because the anticholinesterase drugs increase the secretion of the salivary and bronchial glands. The choice of anaesthetic agents is of great importance. The volatile or gaseous anaesthetics are agents of choice because non-volatile drugs may give prolonged depression. Relaxant drugs should be avoided. If given, they should be administered with great care, as they directly affect the diseased myoneural junction. The competitive curare group will potentiate the disease, and thus may lead to prolonged muscle relaxation. Similarly, with altered response of the end-plate, the depolarizing agents may give a competitive type of reaction, again leading to prolonged relaxation.

The immediate postoperative period is the most serious stage of the anaesthetic management and requires strict vigilance. Prolonged relaxation may be present if relaxant drugs were used. In severe cases of myasthenia gravis the disease itself, plus depression by the anaesthetic agents may be enough to produce poor muscular tone. Prostigmine at the end of the operation will usually provide sufficient control of the disease to maintain adequate respiration. Dyspnoea, causes of which may not be immediately evident, must be recognized and treated. Of the many aetiologies, pain from the surgical insult is commonly the cause of dyspnoea. Judicious use of analgesics will eliminate this discomfort. Pneumothorax may give rise to the sensation of dyspnoea along with the symptoms of inadequate ventilation such as cyanosis, tachycardia, sweating and vasomotor collapse. Weakness of the muscles of respiration, from the lack of anticholinesterase drugs, will cause dyspnoea with associated symptoms of anoxia. Excessive secretion from the stimulation of the bronchial glands by the anticholinesterases may cause obstruction, dyspnoea and atelectasis. Finally, over-medication with the anticholinesterase drugs gives a picture similar to under-medication; that is, weakness of the muscles and difficulty in respiration. Recognition of these causes of respiratory difficulty is essential because the treatment of each is specific. Pneumothorax can be found by physical examination and confirmed by X-ray of the chest. Withdrawal of air from the chest gives dramatic recovery. Similarly a tracheo-bronchial toilet will dramatically relieve the symptoms of excessive secretion and will cure atelectasis. In severe cases, bronchoscopy may be required to remove the secretions. The recognition of the state of the anticholinesterases is a more difficult problem, since the signs and symptoms of too much drug and too little drug are similar. Over-medication with anticholinesterase drugs is known as "Cholinergic Crisis," and has the following manifestations. muscle weakness; gastrointestinal stimulation; salivation; excessive bronchial secretion; pallor; cold sweat; urgency; fasciculation of voluntary muscles; constriction of the pupils; increased blood pressure with or without bradycardia; faintness and collapse; subjective symptoms such as anxiety and internal trembling. "Tensilon" has been advocated for the diagnosis of

cholinergic crisis because of its brief duration of action. In crisis, weakness would be potentiated, whereas the strength is increased if too little drug was given. The treatment of crisis consists of: stopping all anticholinesterase drugs; administration of atropine to block the muscarinic effects; artificial ventilation until adequate respiration is restored; tracheotomy to provide for proper tracheo-bronchial toilet. The problem of tracheotomy must be considered seriously. Although it is a life saving procedure, tracheotomy in the early post-thymectomy period may predispose the patient to mediastinitis.

SUMMARY

The authors have presented from their experience some of the difficulties encountered in the anaesthetic management of myasthenic patients for thymectomy. The hypotheses concerning the nature of the disorder and the pathophysiology have been outlined briefly to provide a better understanding of the problem. Methods of treatment and anaesthetic management of these patients have been outlined, and complications discussed.

RÉSUMÉ

La myasthénie gravis est caractérisée essentiellement par de la faiblesse musculaire, faiblesse localisée plus spécialement aux petits muscles de la main, aux muscles extra-oculaires et aux muscles du larynx et du pharynx. Indistinctement, tous les muscles du squelette peuvent être affectés et de façon tout-à-fait irrégulière. Bien que la pathologie soit localisée anatomiquement à la jonction myo-neurale, la nature exacte des troubles demeure inconnue. Plusieurs théories ont été émises pour expliquer la nature de cette maladie. Parmi ces théories, l'une a prétendu que le thymus sécrétait une substance curariforme qui diminuait, à la jonction myo-neurale, la susceptibilité aux concentrations normales d'acétylcholine d'où est né le traitement chirurgical de ces malades par la thymectomie.

La néostigmine et l'édrophonium (tensilon) améliorent temporairement la force musculaire dans la myasthénie gravis et on les emploie pour préciser le diagnostic de la maladie. La d-tubocurarine et la quinine augmentent la faiblesse musculaire, on peut également les employer pour préciser le diagnostic, mais plus rarement.

Jusqu'à ces derniers temps, la néostigmine était le médicament de choix pour traiter la myasthénie, maintenant de nouveaux médicaments tels que la Pyridostigmine (Mestinon) et le Mysuran (Win 8077) donnent plus de satisfaction parce que leur action est plus prolongée et ils n'ont pas d'action muscarinique comme la néostigmine.

Le moment idéal d'appliquer le traitement chirurgical, c'est au cours d'une rémission de la maladie. Avant d'opérer, il s'impose d'améliorer l'état de nutrition du malade qui peut laisser à désirer à cause de la faiblesse des muscles de la déglutition. Avant l'opération, il est suggéré de réduire au minimum les opiacés pour ne pas déprimer les réflexes à la toux. Les médicaments du type belladone

sont à conseiller car les médicaments anticholinestérasiques favorisent l'accumulation de l'acétylcholine. Ces médicaments, avant l'opération, sont prescrits à doses égales et même à doses supérieures à celles données ordinairement (e.g., Néostigmine 1 à 2.5 mgm en injection).

Pour la thymectomie, l'anesthésie endotrachéale est la technique de choix: elle permet de maintenir libres les voies respiratoires, d'enlever les sécrétions s'il y a lieu et aussi de maintenir une pression positive si, accidentellement, la plèvre est ouverte.

Ce n'est qu'avec de grandes précautions qu'il faut recourir à l'usage des agents curarisants. Le curare et les autres bloqueurs à compétition sont contrindiqués. Dans la myasthénie, le décaméthonium et la succinylcholine agissent comme des bloqueurs à compétition et leurs effets sont détruits et non potentialisés par la néostigmine (9, 10). Les auteurs ont fait l'usage de ces deux médicaments chez des myasthéniques sans observer d'atonie prolongée.

Le cyclopropane est probablement l'agent de choix. L'éther tend à augmenter les sécrétions dans les voies respiratoires et il déprime les muscles plus que le cyclopropane. Les agents non volatils sont métabolisés lentement, ils auront tendance à déprimer les centres respiratoires et leur emploi doit s'accompagner d'une grande prudence.

Parmi les complications post-opératoires possibles, citons les infections respiratoires et l'atélectasie. Il peut exister des sécrétions abondantes et ennuyeuses résultant de salivation et de bronchorrhée favorisées par la néostigmine en même temps qu'une incapacité de tousser. Il y a également possibilité de pneumothorax post-opératoire résultant de la chirurgie.

Il faut faire usage des opiacés avec discrétion pour calmer l'agitation, car cette agitation peut être causée par un manque d'oxygène qui ne pourrait être accentué par les opiacés. Dans les suites opératoires, il est conseillé de donner de la néostigmine ou un autre médicament anticholinestérasique régulièrement pour maintenir un bon tonus musculaire et une respiration adéquate. Toutefois, il ne faut pas oublier la possibilité de surdosage de ces médicaments.

Un malade qui ne répondrait pas de façon satisfaisante aux médicaments anticholinestérasiques devrait être placé dans un respirateur. Il peut devenir nécessaire de pratiquer une trachéotomie pour aspirer adéquatement les sécrétions bronchiques excessives, particulièrement au moment des crises cholinergiques.

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