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COMPARISON OF CT AND PATHOLOGIC FINDINGS & CLINICAL OUTCOME AFTER THYMECTOMY WITH OR WITHOUT PLASMAPHERESIS IN PATIENTS WITH MYASTHENIA GRAVIS

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ABSTRACT

Objective: To compare computed tomographic (CT) appearance of the thymus with results from histologic examination of thymic tissue and clinical outcome in patients with myasthenia gravis who underwent thymectomy with or without plasmapheresis.

Method and Materials: This study comprised of 47 patients, who were operated on in the period from January 2002 to December 2009 for myasthenia gravis. Computed tomography was done in all cases .Of these 47 patients, preoperative plasmapheresis was performed in 20 patients (group B) and the remaining 27 patients (group A) had no preoperative plasmapheresis based on non availability of plasmapheresis kit. Outcome in the form of requirement of ventilation, symptomatic improvement, hospital stay and requirement of drugs were assessed at the end of one year and compared between the two groups. Specimens sent for histopathology were analyzed. Follow up was done in all cases.

Results: Eighteen out of twenty seven patients (66%) in group A required ventilatory support in the immediate postoperative period, whereas four out of twenty patients (20%) in group B required it. Significant and sustained symptomatic improvement was noted in group B as compared with group A (P-0.01). Twenty-eight patients had normal CT findings, seven had a diffusely enlarged thymus, and 12 had a focal mass. The results of histologic examination showed that 16 of 28 patients with normal CT findings had normal thymic tissue and 12 had lymphoid follicular hyperplasia; all seven patients with an enlarged thymus had lymphoid hyperplasia. Five of 12 patients with a focal mass at CT had lymphoid hyperplasia, and seven had thymoma.

Conclusion: CT is of limited value in distinguishing lymphoid follicular hyperplasia from a normal thymus or thymoma and in predicting clinical outcome. Preoperative plasmapheresis in the patients of myasthenia gravis is beneficial and can cause a significant difference in the postoperative outcome.

Key Words: CT, Thymectomy, Plasmapheresis, Myasthenia Gravis.

INTRODUCTION

Myasthenia gravis is a rare autoimmune disorder, which is characterized by easy fatiguability and muscular weakness with preferential involvement of ocular and facial muscles[1,2]. Muscular fatigue is worsened by exercise and alleviated by rest. Clinical symptoms can vary from isolated ptosis, diplopia or mild proximal muscle weakness to severe degree of generalized weakness, bulbar and respiratory muscle weakness which may ultimately result in ventilator dependency. The basic pathogenesis of the disease so far understood is the production of autoantibody against the acetylcholine receptors of the endplate[1,3], and thereby immunologic destruction and reduction of the number of the receptors. The miniature endplate potential amplitude is decreased, and the endplate potentials are largely subthreshold[1,3] leading to easy fatigability and weakness. The thymus is believed to play an integral role in pathogenesis of myasthenia. The role of the thymus in the development of antibodies against the acetylcholine receptors has been clearly established and therefore the relationship between myasthenia and thymic abnormalities has been suggested[4]. Thymomas and glandular hyperplasia are the commonest underlying pathologic findings seen in many of these patients. Currently, the detection of 'thymoma-specific' striational antibodies in the peripheral blood and mediastinal imaging by computed tomography (CT) are the most specific diagnostic procedures for the detection of thymoma[4-7]. Considering the management issues, patients with minimal symptoms are usually treated with

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anticholinesterase drugs and non-responders require treatment with steroids, immunoglobulins, and immunosuppressants. Plasmapheresis that can rapidly deplete the disease-related plasma factors has been found to be very effective in immune modulation by decreasing the circulating antibodies. It reduces anti Acetylcholine receptor antibody titer in myasthenia gravis and alleviates symptoms. However, its effects are short lasting as it cannot prevent their re-synthesis. Considering the role of the thymus in the pathogenesis, complete removal of the thymus has become a standard procedure for the management of myasthenia gravis with remarkable and sustained improvement in many cases[5,6]. However, most patients require management in the intensive care units and prolonged ventilatory support in the postoperative periods due to respiratory insufficiency with an accompanying complication like pulmonary infection[7,8]. These patients often require a high dose of anticholinesterase drugs, steroids, immunosuppressants, even postoperative plasmapheresis, irrespective of preoperative clinical status[9,10,11]. In our study, we compare computed tomographic (CT) appearance of the thymus with results from histologic examination of thymic tissue and clinical outcome in patients with myasthenia gravis who underwent thymectomy with or without plasmapheresis.

MATERIAL AND METHODS

This study was conducted in the Department of Cardio Thoracic Surgery, Post Graduate Medical Institute, Lady Reading Hospital, Peshawar and Department of Radiology, Hayatabad Medical Complex, Peshawar in 47 patients who had undergone trans-sternal thymectomy from January 2002 to December 2009.These patients had a clinical diagnosis of myasthenia gravis with high anti Ach receptor antibody titer and myasthenic symptoms controlled with medication. They were classified into five classes (grades), according to the classification by Osserman and Genkins[9] (1, ocular signs only; 2A, generalized mild muscle weakness; 2B, generalized moderate weakness and/or bulbar dysfunction; 3, acute fulminating presentation and/ or respiratory dysfunction; 4, late generalized weakness). Patients with class 2B, 3 or 4symptoms are included for the study. Patients with the following preoperative risk factors for postoperative ventilation are considered for preoperative plasmapheresis: 1. Duration of disease > 6 years 2. History of COPD 3. Dose requirement of Pyridostigmine >750 mg besides routine examinations, all patients had preoperative chest X-ray, computed tomography scan and detection of circulating autoantibody titer (anti-acetylcholine receptor). Contiguous 0.5–1.0 cm collimation slides were obtained from Th1 to the diaphragm. Imaging parameters were 120–150 kV, 125–280 mA and slice thickness was 5–10 mm. Intravenously administered contrast medium was used in all patients. All scans were interpreted by one radiologist. Out of 47 patients, in 20 patients (group B) plasmapheresis (membrane plasma separation using Plasma Separation Filter; rate of plasma removal (40 ml/kg of body weight daily) was performed preoperatively. In the remaining 27 patients (group A), thymectomy was done without preoperative plasmapheresis. The statistical analysis was done by using standard statistical software, SPSS software for statistical calculation) (Version-16) for Windows. The values were expressed as mean standard deviation wherever applicable. X2-test was used for non-parametric data. A *P*-value -0.05 was considered as statistically significant.

RESULTS

We analyzed the results of thymectomies in group A (no preoperative plasmapheresis) and group

Table 1: Demographic characteristics of patients in group A and group B

Character	Group A (n=27) age in yrs	Group B (n=20) age in yrs
Age (mean)	Male=54.5 Female=38.6	Male=62.3 Female=40.5
Sex	Male (*n*=12) Female(*n*=15)	Male (*n*=8) Female (*n*=12)
Time interval between diagnosis and surgery (years)	Range=2 to 5.5 mean=2.9	Range=2.5 to 8.5 mean= 4.5
Osserman grade	2B (*n*=17) 3(n=5) 4(n=5)	2B (*n*=8) 3(n=8) 4(n=4)
Anticholine-sterase therapy	Yes	Yes
Preoperative plasmaphere-sis	No	Yes
No. of patients having COPD	Nil	08
No. of patients requiring pyri-dostigmine 750 mg	Nil	20
Duration of disease >6 years	Nil	15

B (with preoperative plasmapheresis) patients. The demographic characteristics and post operative results in Group A and B are shown in Table 1 and 2. Twenty-eight patients had normal CT findings, seven had a diffusely enlarged thymus, and 12 had a focal mass. The results of histologic examination showed that 16 of 28 patients with normal CT findings had normal thymic tissue and 12 had lymphoid follicular hyperplasia; all seven patients with an enlarged thymus had lymphoid hyperplasia. Five of 12 patients with a focal mass at CT had lymphoid hyperplasia, and seven had thymoma. (Table 3).

Table 2: Postoperative results in group A and group B

	Group A (n=27)	Group B (n=20)	P-value
Hospital stay in days	9.0	4.7	0.035
No. of patients requiring ventilation	18 (66.6%)	04 (20%)	
Postoperative ventilation requirement in days	4.7	1.3	0.003
Myasthenic crisis Postoperative infection	09 (33.3%) 18 (66.7%)	Nil 04 (20%)	
Wound infection	15 (55.5%)	04(20%)	
Pneumonia	09 (33.3%)	02 (10%)	
Improvement in Osserman grade	1.7	2.7	0.005
Drug dosage reduction	15 (55.6%)	16 (80%)	

Table 3: Preoperative Computed tomography findings /postoperative histology of thymic tissue

Computed tomography n=47	Histopathology n=47	CT Sensitivity 53.84%
Normal = 28	Normal = 16	CT specificity 76.19%
Diffusely enlarged thymus = 07	Lymphoid hyperplasia = 07	CT positive predictive value 73.68%
Focal mass = 12	Thymoma = 07 Lymphoid hyperplasia = 05	CT negative predictive value 57.14%

DISCUSSION

Immunologic attack on synaptic receptors in the muscle causes receptor deficiency. In myasthenic muscles, the miniature endplate potential amplitude is decreased, and the endplate potentials are largely sub-threshold[14]. There is a decremental response in the action potentials evoked from muscles on repetitive stimulation of peripheral nerves. These patients are usually treated with anticholinesterase drugs. Non-responders require treatment with steroids, immunoglobulins, immunosuppressants, plasmapheresis and surgical removal of the thymus[1,2,11]. However, controlled trials have not been done to evaluate therapies. The role of the thymus in the development of antibodies against the acetylcholine receptors has been clearly established and therefore the relationships between myasthenia and thymic abnormalities have been suggested[15]. Since the reports by Schumacher 1912 and Blalock et al, in 1941, many series have shown the beneficial effects of thymectomy. Currently, thymectomy is considered a safe and effective procedure in myasthenic patients with or without thymoma, even in the elderly[16]. However, the morbidity and mortality of the procedure still remains the concern among surgeons. Routine postoperative ventilatory support and planned extubation in the ICU have been recommended considering the risk of postoperative respiratory failure and other complications that may result from operative stress[8,9,11]. Those patients who require prolonged ventilatory support often fare less favorably so far as the myasthenic symptoms are concerned and require high doses of medications, even periods of plasmapheresis irrespective of preoperative clinical status[8,10,11].

Nowadays, in many institutions the surgical strategy in patients with myastehnia Gravis is influenced by the suspicion of thymoma based on mediastinal imaging. Currently, CT is thought to be the best imaging technique in detecting mediastinal abnormalities, but one must be familiar with potential pitfalls and controversies[6]. It is difficult to distinguish lymphoid follicular hyperplasia from thymoma. To obtain the most accurate preoperative diagnosis, a CT scan with contrast should be made and all patient characteristics, especially, age, stage of MG and the presence of striational-antibodies should be assessed[4,17-19]. In our study twenty-eight patients had normal CT findings, seven had a diffusely enlarged thymus, and 12 had a focal mass. The results of histologic examination showed that 16 of 28 patients with normal CT findings had normal thymic tissue and 12 had lymphoid follicular hyperplasia; all seven patients with an enlarged thymus had lymphoid hyperplasia. Five of 12 patients with a focal mass at CT had lymphoid hyperplasia, and seven had thymoma,this gives the sensitivity of 53.84%,

specificity 76.19%, positive predictive value 73.68% and negative predictive value 57.14% respectively.

Plasmapheresis can improve the overall neuromuscular function by decreasing the circulating antibodies and may reverse the pathologic process related to these antibodies.Unfortunately, the beneficial results are only transient and periodic plasmapheresis treatments are often necessary[20].

Preoperative plasmapheresis in group B has resulted in remarkable improvement in the postoperative morbidity profile in comparison to group A, with less ventilatory requirement and prompt postoperative recovery, thereby reducing the length of hospital stay, particularly in ICUs.The rate of remission was high in group B in follow-up. But the rate of persistence of remission did not differ between the two groups. The mean Osserman grade of patients in group B improved by 2.7 after surgery; where as in group A the improvement was 1.7 after surgery. The change in Osserman grade from before surgery to recent follow-up when compared is highly significant (-0.05).

In the present series, the remission rate at the end of one year after surgery in group B is 80%; whereas in group A (without plasmapheresis), it is 44.4%. Cooper and associates[21] in their series of thymectomy,reported an early complete remission rate of 35% and44.2%, respectively, which is comparable to the result in group A patients (without plasmapheresis) in our series. Some authors[22] in their series of thymectomy used high doses of steroid perioperatively to improve postoperative outcome; but the results are conflicting. The fewer requirements of medication and overall improvement in physical status and social function in follow-up could be related to beneficial effects of plasmapheresis and surgery on the overall neuromuscular function in myasthenic patients by modifying the abnormalities of the immune system. However, it needs to be seen whether this short-term improvement remains sustained over a prolonged period of time and, therefore, further long-term study is required to substantiate the beneficial effect of the combination of plasmapheresis and surgery.

CONCLUSION

CT is of limited value in distinguishing lymphoid follicular hyperplasia from a normal thymus or thymoma and in predicting clinical outcome. Preoperative plasmapheresis in the patients of myasthenia gravis is beneficial and can cause a significant difference in the postoperative outcome.

REFERENCES

1. Calhoun RF, Ritter JH, Guthrie TJ, Pestronk A, Meyers BF, Patterson GA, Pohl MS, Cooper JD. Results of transcervical thymectomy for myastheniagravis in 100 consecutive patients. Ann Surg 1999 Oct; 230: 555-59.
2. Olanow CW, Roses AD. The pathogenesis of myasthenia gravis – ahypothesis. Med Hypotheses 1981 Jul; 7: 957-68.
3. Moulian N, Wakkach A, Guyon T, Poe¨a S, Ai¨ssaoui A, Levasseur P, Cohen-Kaminsky S, Berrih-Aknin S. Respective role of thymus and muscle inauto-immune myasthenia gravis. Ann NY Acad Sci 1998; 841: 397-06.
4. Nicolau S, Muller SL, Li DKB, Oger JJF. Thymus in myasthenia gravis: comparison of CT and pathological findings and clinical outcome after thymectomy. Radiology 1996; 201: 471-74.
5. Pirronti T, Rinaldi P, Batocchi AP, Evoli A, Di Schino C, Marano P. Thymic lesions and myasthenia gravis. Diagnosis based on mediastinal imaging and pathological findings. Acta Radiol 2002; 43: 380-84.
6. Brown LR, Muhm JR, Sheedy PF, Unni KK, Bernatz PE, Hermann RC jr. The value of computed tomography. AJR 1983; 140: 31-35.
7. Camera L, Brunetti A, Romano M, Larobina M, Marano I, Salvatore M. Morphological imaging of thymic disorders. Ann Med 1999; 31: 57-62.
8. Gracey DR, Divertie MB, Howard FM Jr, Payne WS. Postoperativerespiratory care after transsternal thymectomy in myasthenia gravis. A 3-year experience in 53 patients. Chest 1984 Jul; 86: 67-71.
9. Baraka A. Anaesthesia and myasthenia gravis. Can J Anaesth 1992; 39: 476-86.
10. Leventhal SR, Orkin FK, Hirsh RA. Prediction of the need for postoperativemechanical ventilation in myasthenia gravis. Anesthesiology 1980; 53: 26-30.
11. Chevalley C, Spiliopoulos A, de Perrot M, Tschopp JM, Licker M.Perioperative medical management and outcome following Thymectomy for myasthenia gravis. Can J Anaesth 2001 May; 48: 446-51.
12. Dau PC, Lindstrom JM, Cassel CK, Denys EH, Shev EE, Spitler LE. Plasmapheresis and immunosuppressive drug therapy in myasthenia gravis. N Engl J Med 1977 Nov; 297: 1134-40.
13. Osserman KE, Genkins G. Studies in myasthenia gravis: review of a twenty-year experience in over 1200 patients. Mt Sinai J Med 1971; 38: 497-537.
14. Pollard JD, Basten A, Hassall JE, Kronenberg H, Cobcroft R, Dawkins R. Current trends in the management of myasthenia gravis: Plasmapheresis and immunosuppressive therapy. Aust N Z J Med 1980 Apr; 10: 212-17.
15. Drachman DB. Myasthenia gravis. N Engl J Med 1978; 298: 136-42.
16. Busch C, Machens A, Pichlmeier U, Emskotter T, Izbicki JR. Long-term outcome and quality of life

after thymectomy for myasthenia gravis. Ann Surg 1998 Apr; 227: 604-05.

17. Fletcher BD, Glicksman AS, Gieser P. Interobserver variability in the detection of cervical-thoracic Hodgkin's disease by computed tomography. J Clin Oncol 1999; 17: 2153-59.

18. Thorvinger B, Lyttkens K, Samuelsson L. Computed tomography of the thymusgland in myasthenia gravis. Acta Radiol 1987; 28: 399-401.

19. Cascade PN, Gross BH, Kazerooni EA, Quint LE, Francis IR, Strawderman M, Korobkin M. Variability in the detection of enlarged mediastinal lymph nodes in staging lung cancer: a comparison of contrast-enhanced and unenhanced CT. AJR 1998; 170: 927-31.

20. Kernstine KH. Preoperative preparation of the patient with myasthenia gravis. Thorac Surg Clin 2005 May; 15: 287-95.

21. Cooper JD, Al-Jilaihawa A, Pearson FG, Humphrey J, Humphrey H. Animproved technique to facilitate transcervical thymectomy for myasthenia gravis. Ann Thorac Surg 1988; 45: 242-47.

22. Masaoka A, Yamakawa Y, Niwa H, Fukai I, Kondo S, Kobayashi M, Fujii Y, Monden Y. Extended thymectomy for myasthenia gravis patients: A 20-year review. Ann Thorac Surg 1996; 67: 853-59.