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Thymectomy in Children with Juvenile Myasthenia Gravis: Is It Recommended?

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Authors' contributions

This work was carried out in collaboration between all authors. Authors CJ and MM designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors KN and HS managed the literature searches. Author HF performed the anatomo-pathological study. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Objective: Juvenile myasthenia gravis (JMG) is a rare disease with possible severe forms. Thymectomy is supported by many authors particularly in generalised forms with positive AcetylCholine Receptor Antibody (AChR- Ab). The aim of our study was to discuss the indication and the outcome of thymectomy in five children with JMG.
Methods: We performed a retrospective study of the medical files of patients with JMG, who were

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hospitalised in our pediatric surgery department for thymectomy. For all the children we performed Acetylcholine Receptor Autoantibody (ACHRAB) test-system producer, a chest x-ray, a chest Computed Tomography Scan (CT-scan) and a Magnetic Resonance Imaging (MRI).
Thymectomy was indicated on the presence of anomalies on CT-Scan or MRI and realised via either thoracotomy or video-assisted thoracoscopy.
The study was conducted with the approval of the ethics committee at our institution.
Results: Based on our findings, thymectomy in JMG with imaging anomalies seems to be associated with clinical improvement. In our patients complete remission after surgery was seen in one case, a clinical improvement with a decrease of the medical therapeutic dosage was noted in three other cases. One patient could not be evaluated because of non adherence to medical treatment.
Surgery by thoracotomy or video assisted thoracoscopy (VAT) was also well tolerated by all the patients.
Conclusion: The benefits of thymectomy in children with JMG are still controversial. However, many researchers have reported a sustained improvement of symptoms in the majority of patients after thymectomy. Our findings seem to encourage thymectomy in cases of JMG and particularly when imaging anomalies are found. VAT thymectomy was well tolerated and it is considered by many researchers to be the standard method for thymectomy in children.

Keywords: Juvenile myasthenia gravis; thymectomy; children; thoracoscopy.

ABBREVIATIONS AND ACRONYMS

JMG: Juvenile myasthenia gravis; AChR-Ab: Acetylcholine receptor autoantibody; CT-Scan: Computed tomography scan; MRI: Magnetic resonance imaging; VAT: Video assisted thoracoscopy; OMG: Ocular myasthenia gravis.

1. INTRODUCTION

Juvenile myasthenia gravis (JMG) is a rare auto-immune disorder of neuromuscular transmission caused by the production of antibodies against components of postsynaptic membrane of the neuro-muscular junction [1]. Young patients may present severe forms with generalised muscle weakness with or without respiratory insufficiency. Specific treatment is needed including immunosuppressive therapy and thymectomy particularly in presence of thymus abnormalities [1-3]. The aim of our study is to discuss indication and outcome of thymectomy in children with JMG.

2. PATIENTS AND METHODS

We performed a retrospective study of the medical files of patients with JMG hospitalised in our pediatric surgery department for thymectomy.

Diagnosis of JMG was established in pediatric departments based on a combination of clinical symptoms and positive pyridostigmine test. Disease severity was evaluated according to Osserman Classification. For all patients, we performed Acetylcholine Receptor Autoantibody (ACHRAB) test-system producer, a chest x-ray, a chest Computed Tomography Scan (CT-scan) and a Magnetic Resonance Imaging (MRI).

All patients received a medical treatment which consisted of pyridostigmine and corticotherapy.

Thymectomy was indicated in case of thymic anomalies on CT-Scan or MRI. It was realized either via thoracotomy or with video-assisted thoracoscopy (VAT). VAT was introduced in our department in 2009.

3. RESULTS

Five patients (Table 1) were included, 1 male and 4 females with sex ratio of 0.25. Mean age was 7.7 years (2.5 to 14 years old). Four patients had a generalised JMG and one had an ocular myasthenia gravis (OMG). Only one patient was AChR-Ab positive. Prior to thymectomy, disease severity was graded as I for one patient, IIa for two patients and IIb for two other patients.

Mediastinal enlargement was noticed on the chest x-ray of two patients (Fig. 1). The CT-scan showed the presence of an eventual thymoma in three cases (Fig. 2) and a thymus hypertrophy in the two other cases.

Table 1. Data about the five patients with JMG

Case	Age (year)	Sex	Osserman classificattion	AchR-Ab	Imaging CT-Scan+/- MRI	Medical treatment Tablets/day	Surgery	Histology	Evolution/ Medical treatment Tablets/day
1	14	M	IIb	Positive	Thymoma	Pyridostigmine 6	Thoracotomy	Hyperplasia	Remission/No
2	2.5	F	Iia	Negative	Hypertrophy	Pyridostigmine 6	Thoracotomy	Hyperplasia	Improvement /yes 3
3	9	F	Iia	Negative	Thymoma	Pyridostigmine 3	Thoracotomy	Hyperplasia	Improvement/yes 2
4	10	F	IIb	Negative	Thymoma	Pyridostigmine 4	VAT	Normal	No improvement+ Non adherence to medical treatment
5	3	F	I	Negative	Hypertrophy	Pyridostigmine 3	VAT	Hyperplasia	Improvement/yes 2

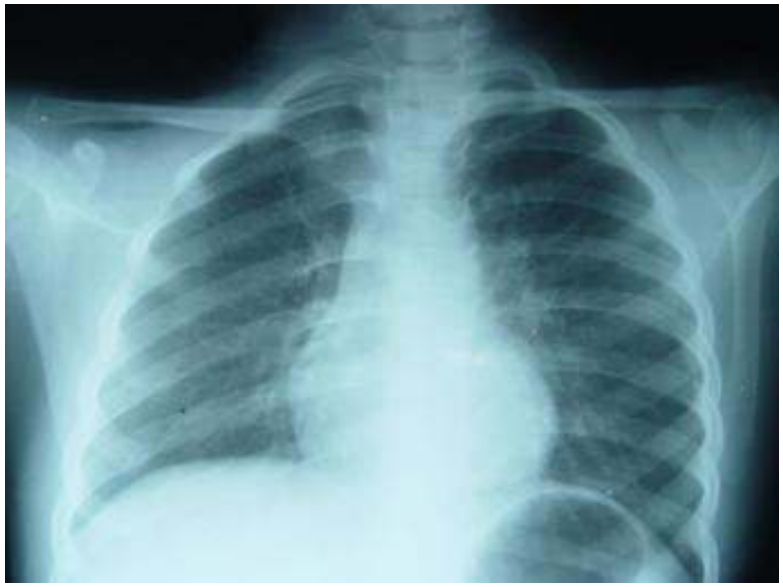

Fig. 1. Chest x-ray: Mediastinal enlargement

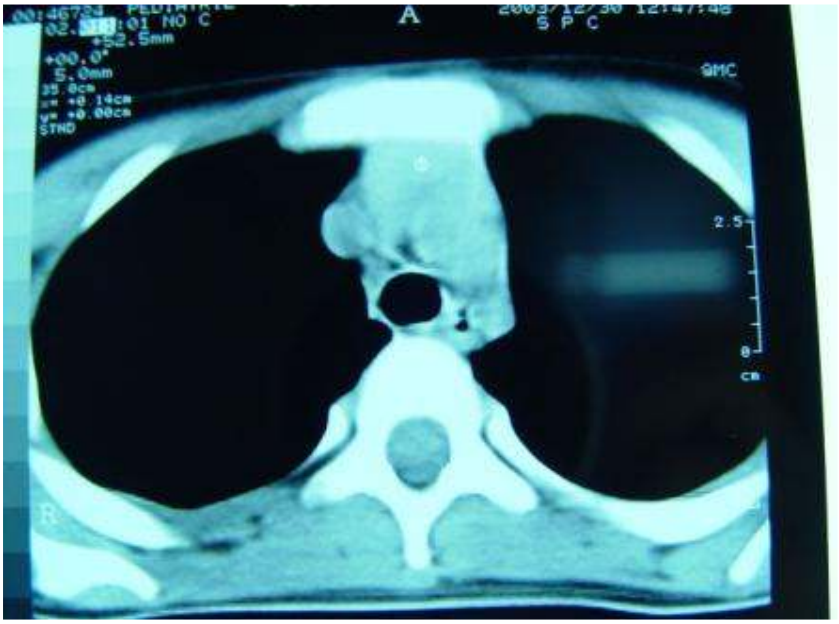

Fig. 2. Mediastinal CT-scan: Shows the presence of a thymoma

An extended thymectomy (Fig. 3) was indicated for all the patients. It was realised via antero-lateral thoracotomy in three cases and via VAT in two cases.

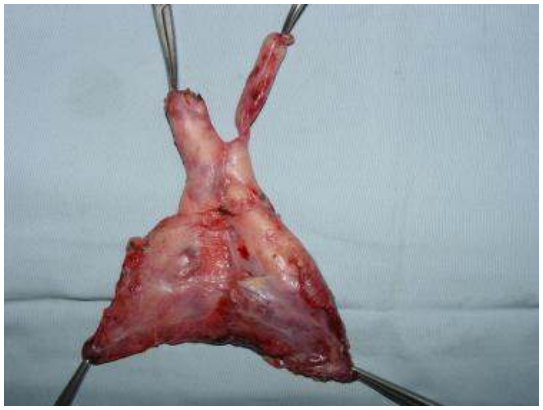

Fig. 3. Complete thymectomy

The initial post operative course was complicated by a pneumothorax in case 2, related to a pleural breach, successfully managed by assisted mechanical ventilation and pleural drainage. Microscopic examination found a follicular hyperplasia in four cases (Figs. 4-5) and was normal for the remaining case.

Four patients experienced a clinical improvement within the first year after thymectomy. A complete remission and a tolerated medical wean occurred two years after thymectomy in case1 which was AchR-Ab positive.

A clinical improvement with medical treatment decrease was obtained in the three other patients. Unfortunately one patient could not be evaluated because of non adherence to medical treatment.

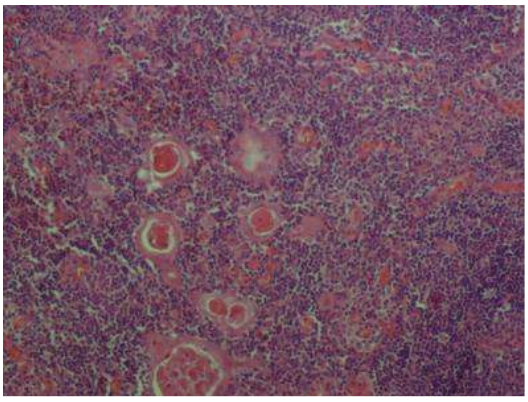

Fig. 4. Thymic hyperplasia (H&E, original magnification x 200)

4. DISCUSSION

Management of JMG was initially adopted from adult patients, whereas recent studies have showed that JMG is different in presentation and

in the course of the disease, particularly the group of prepubertal children [3-5].

Actually, children with JMG exhibit higher rates of remission than adults. This includes spontaneous remission and remission following a period of drug therapy. Prepubertal children have the highest rates of spontaneous remission [2,6].

Therapeutic strategies for JMG have been established. Medical treatment as first line therapy consists of pyridostigmine associated to steroids and long term immunosuppression in generalised muscular weakness and moderat e to severe bulbar symptoms or respiration insufficiency. Plasmapheresis can be indicated in severe forms [1].

All of our patients received pyridostigmine, associated to steroids in two cases and steroids with immunosuppression in one case.

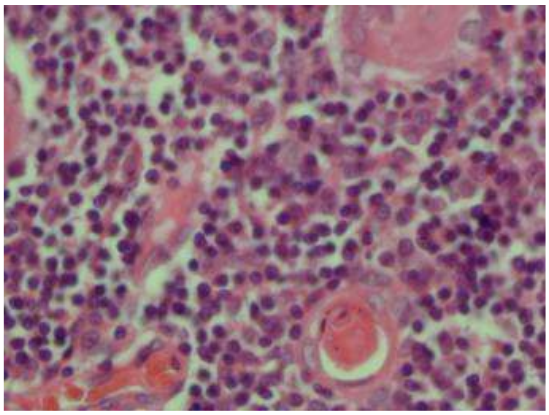

Fig. 5. Thymic hyperplasia (H&E, original magnification x 400)

Because of the presumed role of the thymus in the pathogenesis of myasthenia gravis, thymectomy is a recognised aspect of management [2,7].

Although, the fact of existing of immunological side effects after thymectomy during early childhood is still to be discussed [1], many researchers have argued against the surgical intervention in prepubertal patients [8].

We compared our findings with other series of thymectomised JMG (Table 2).

More patients with thymic hyperplasia achieved remission compared to patients with normal thymus [2]. In our series, four patients had thymic hyperplasia, one of them showed a complete remission after surgery.

In JMG thymic hyperplasia is evident in 83% of patients and in 3.8% thymoma could be detected [1,9].

Although the outcome of thymectomy has not been evaluated with randomised controlled trials in children, some case series have suggested that remission rate following thymectomy in JMG is higher than the remission rate with or without medical treatment [3,10,11].

Thymectomy is followed by improvement in most cases: remission rate was higher in children after thymectomy than in the group of spontaneous evolution [1,7,9,11-13].

Chao Cheng et al. [11] made a comparison of major series of patients with JMG who underwent thymectomy from different areas of the world with his own study (135 patients). He noted a comparable complete remission rate after surgery across the different series, which varied between 37.5 - 60%.

Thymectomy is recommended as early as possible in case of generalised weakness [1]. The duration between disease onset and thymectomy is a significant predictor of the efficacy after surgery in generalised JMG. Remission is higher if thymectomy is performed within the first year after onset [1,6,11,13,15,16].

More recent review of children, including prepubertal patients, also suggested increased remission rates after thymectomy [2,13,15,17].

Chao Cheng et al. [11] suggested an algorithm for treatment of juvenile myasthenia gravis (JMG) patients based on age (>12 years old), Osserman classification (>I), duration of the disease (≥24 months) and medical treatment response.

Current evidence suggests that thymectomy should not be indicated in Musk-positive disease as it is unclear whether it confers any benefit [3, 18,19,20]. In our patients Musk-antibodies were not practiced.

Thymectomy in pure OMG remains controversial. Whereas OMG is not life threatening, patients may be dependent on long term immunosuppressant medications, including corticosteroids with the resultant side effects which can be substantial in children.

Table 2. Comparison of different series of patients with Juvenile myasthenia gravis who underwent thymectomy

Study	Seybold et al. [18]	Rodriguez et al. [10]	Adams C et al. [14]	Lindner et al. [21]	Lakhoo K et al. [22]	Essa M et al. [23]	KanzakiM et al. [24]	Tracy MM et al. [13]	Heckmann et al. [25]	Cheng C et al. [11]	Ware TL et al. [26]	Heng HS et al. [3]	Our series
Year	1971	1983	1990	1997	1997	2003	2008	2009	2012	2012	2012	2014	2015
Nb	49	85	24	65	12	30	3	13	60	135	10	20	5
Sternotomy/ Thoracotomy	49/0	ND	ND	ND	12/0	ND	3/0	ND	ND	ND	1/0	20/0	0/3
Thoracoscopy	0	ND	ND	ND	0	ND	0	ND	ND	ND	9	0	2
Morbidity	0	0	0	0	0	0	0	0	0	0	0	0	1*
Mortality	0	0	0	0	0	0	0	0	0	0	0	0	0
Hyperplasia	ND	ND	ND	89	10	ND	3	ND	ND	99.3	4	9	4
AChR-Ab (+)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	9	ND	1
Outcome of thymecomy (%)													
-GCR	37.5	67	66	60	ND	43.4	1 case	31	55	45.9	50	30	1 case
- Clinically improved	33	ND	29	15	83	46.6	2 cases	61	ND	45.2	40	65	4 cases

*Nb: number, AChR-Ab(+) : Acetylcholine receptor-Autoantibody seropositive, GCR: general complete remission, ND: no data available, *: one case had a pneumothorax.*

Thymectomy has been performed in refractory cases [2].

A variety of surgical methods for thymectomy have been described: full or partial sternotomy, thoracoscopic or transcervical approaches [2,27,28].

Many authors recommend a transsternal approach in children to prevent incomplete removal of all thymic tissue, which may lead to poor outcome [3,23].

Less invasive techniques such as VAT thymectomy are now resulting in comparable remission rates following thymectomy in adult MG [3,29].

Della Marina et al recommend thoracoscopic techniques but these are restricted to specialised centers [1].

Kolski HK et al. [30] has applied VAT to a group of juvenile patients for thymectomy and compared it to a similar group of six patients (in terms of age and clinical severity) operated via a median transsternal approach. He concluded that VAT thymectomies are comparably effective to transsternal procedures in treating generalised JMG and can be safely performed in children as young as 20 months of age. In addition, VAT surgery is less invasive and significantly shortens the postoperative hospital stay, and has superior cosmetic results.

In our series, thymectomy was performed via antero-lateral thoracotomy in three cases. Thoracotomy was practiced by our surgical team because they mastered it better than sternotomy. VAT was introduced recently and served to treat the two other cases.

A larger series with a randomised controlled study is necessary to elucidate the benefit of thymectomy in JMG and to compare results of different surgical methods.

5. CONCLUSION

The benefit of thymectomy in children with JMG is still controversial. However, many researchers have reported a sustained improvement of symptoms in the majority of patients after thymectomy. Although the number of our patients is too few to indicate any treatment recommendations, our findings seem to encourage thymectomy in case of JMG and particularly when imaging anomalies are found. VAT thymectomy was well tolerated and it is considered by many researchers to be the standard method for thymectomy in children.

Randomised controlled trials are necessary to elucidate the advantages of thymectomy and to establish a clear treatment algorithm for children with JMG.

CONSENT

It is not applicable.

NOTE

Research Laboratory LR12SP13.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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