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EVALUATION OF THE RESPIRATORY FUNCTION IN MYASTHENIA GRAVIS

AN IMPORTANT TOOL FOR CLINICAL FEATURE AND DIAGNOSIS OF THE DISEASE

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ABSTRACT - Myasthenic gravis may affect both inspiratory and expiratory muscles. Respiratory involvement occurred in almost all patients with myasthenia gravis in all clinical forms of the disease: 332 lung function tests done in 324 myasthenic patients without respiratory symptoms (age 34.6 ± 18.3 years) were examined. Lung volumes analysis showed that all the patients of both sexes with generalized or ocular myasthenia gravis showed "myasthenic pattern". Male patients with "ocular" form only presented the "myasthenic pattern"with lung impairment and had, from the lung function point of view, a more benign behaviour. Female patients with the "ocular"form exhibited a behaviour of respiratory variables similar to that of the generalized form. It was not observed modification of the variables that suggested obstruction of the higher airways. The "myasthenic pattern" was rarely observed in other neuromuscular diseases, except in patients with laryngeal stenosis.

KEY WORDS: myasthenia gravis, lung function tests, myasthenic pattern.

Avaliação da função respiratória na miastenia gravis: importância na caracterização clínica e no diagnóstico da doença

RESUMO - O comprometimento respiratório é fator limitante na evolução clinica da miastenia gravis (MG) e as formas clínicas mais graves apresentavam acometimento bulbar e respiratório. Para avaliar a reserva respiratória foram examinados em 324 pacientes com MG (forma ocular 62, generalizada 246 e timomatosa 16) as seguintes variáveis da prova de função pulmonar (PFP): capacidade vital forçada (FVC); volume onde o fluxo expiratório é igual a 1 litro por segundo (VF=1); volume expiratório forçado no primeiro segundo (FEV1); fluxo expiratório forçado medido entre 0,2 e 1,2 litros (FEF); fluxo médio expiratório forçado, medido entre 25 e 75% da FVC (FMF); intervalo de tempo entre 25 e 75% da FVC (FMFT); tempo médio de trânsito na expiração forçada (MTT); capacidade pulmonar total (TLC); volume residual (RV); curva fluxo-volume para pesquisa do "padrão miastênico". A análise estatística realizada foi: "t pareado" entre paciente e seu padrão e "t não pareado" entre grupos. Conclusões: Todos os pacientes apresentaram o padrão miastênico e esta alteração da curva fluxo-volume sugeriu disfunção dos músculos da laringe. Nos pacientes com formas clinicamente localizadas as PFP também se mostraram alteradas revelando a generalização da sintomatologia mais frequentemente no sexo feminino. Não foi observada modificação das variáveis que indicam obstrução das vias aéreas decorrente do uso de anticolinesterásicos no tratamento da MG nem aumento de incidência de asma brônquica com o uso de drogas anticolinesterásicas.

PALAVRAS-CHAVE: miastenia grave, provas funcionais respiratórias, padrão miastênico.

Acquired myasthenia gravis (MG) is a disease of neuromuscular transmission in which antibodies to the nicotinic acetylcholine receptor (AAChR) play an important role in the

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pathogenesis[1,4,8]. The clinical forms are: severe, which patients have respiratory involvement; accentuated, patients with bulbar symptoms without respiratory involvement; moderate, with only a motor dysfunction. Further, there are systemic or localized (ocular) forms[4,11,15]. Diagnosis is based upon the clinical findings, the electromyography (EMG) and on the serum levels of AAChR[9,10,14,19]. The seric levels of AAChR detectable in 68% of our myasthenic patients are important for diagnosis and responsible for the loss of the endplate acetylcholine receptor[6,12]. Unusually low levels of false positive serum concentration of AAChR were also found in other diseases. Furthermore, there is no specific , definitive and consensual diagnostic test for MG. Myasthenia gravis may affect both inspiratory and expiratory muscles[20].

Aiming to study the impairement of other muscles in the localized or systemic forms of myasthenic patients lacking respiratory symptoms, an evaluation of lung functions was undertaken. Lung function tests (LFT) assure the concrete determination of the respiratory functional reserve through the analysis of different respiratory variables[2,3,7].

PATIENTS AND METHODS

Three-hundred-thirty-two LFT of MG patients, confirmed by EMG and serum concentration of AAChR measuring the flow-volume curve were analysed and 324 of these patients were chosen as considered clinically stable, from a ventilatory point of view. Of those, 62 patients had a predominantly ocular form (POF), 27 were male (age 39±19 years) and 35 female (age 33±18 years); 246 had the generalized form, 68 were male (age 38±17 years) and 178 female (age 32±14 years); 16 had the thymomatous form, 8 male (age 38±26 years) and 8 female (age 44±21 years) (Table 1). Three patients with oculopharyngeal dystrophy, 2 with inflammatory myositis, 2 with chronic demyelinating polyneuropathy, one with pseudomyasthenic syndrome, and one with upper stenosis of trachea were also evaluated.

To plot the curves a vitalograph spyrometer was used and to analyse the shape of the curves the Hewlett Packard electronic Vertek spyrograph was used.

Respiratory muscle function can be evaluated with several different maners. So, in this investigation, the variable of the LFT studied were: 1. Forced vital capacity (FVC); 2. Volume where the expiratory flow equals one liter per second (VF=1); 3. Forced expiratory volume in the first second (FEV1); 4. Forced expiratory flow measured between 0.2 and 1.2 liters (FEF); 5. Median forced expiratory flow measured between 25 and

Table 1. General characteristics of patients.

Form	Sex	N	Age (y)	Height (cm)	Weight (Kg)
Ocular*	M	27	39.0±19.0	166.7±15.2	67.8±18.0
	F	35	33.0±18.0	155.7±10.6	54.4±12.2
Gener*	M	68	38.0±17.0	168.6±11.1	68.4±18.8
	F	178	32.0±14.0	157.9±14.1	57.5±13.8
Thym*	M	8	38.0±26.0	171.8±7.8	69.4±13.5
	F	8	44.0±21.3	153.6±7.4	60.3±14.4
Others**	M	1			
	F	17			
Total	M	104			
	F	228			

±, average and standard deviation; gener, generalized; thym, thymomatous; *, myasthenic patients without respiratory clinical findings; **, myasthenic patients with respiratory clinical findings; M, masculin; F, feminin.

Table 2. Lung function: number of cases and RSD

	Ocular		Generalized		Thymomatous	
	M	F	M	F	M	F
FVC	27	35*	67*	179*	8*	8
VF1	17	34*	29*	142*	4	7
FEV1	27	35	67	179*	8*	8
FEF	27	35	67	179	8	8
FMF	27	35	67	179	8	8
FMFT	27	35	67*	179	8	8
MTT	22	26	39*	99	5	3
TLC	11	14	20	58	3	3
RV	11	14*	20*	58*	3	3

M, male; F, female; *, significant difference.

Table 3. Comparison between ocular and systemic clinical form.

	Females			Males		
	O	S	O-S	O	S	O-S
FVC	35	179	0.136	27	67	0.016
VF1	34	142	0.140	17	29	0.649*
FEV1	35	179	0.121	27	67	0.084
FEF	35	179	0.370	27	67	2.154*
FMF	35	179	0.124	27	67	0.136
FMFT	35	179	0.025	27	67	0.078
MTT	26	99	-0.044	22	39	0.098
TLC	14	58	-0.003	11	20	0.932*
RV	14	58	-0.012	11	20	0.256

O, Ocular form; S, systemic form; * significant ($p < 0.05$).

75% of FVC (FMF); 6. Time lapse between 25 and 75% of FVC (FMFT); 7. Average transit time of expiration (MTT); 8. Total lung capacity (TLC); 9. Residual volume (RV); 10. "Myasthenic pattern".

The airways closure volume (CIV) has been used for many years - demanding expensive and specialized equipment and also a major participation of the patients, not guaranteed in many instances. It was observed that airway closure capacity was more reliable, although patient and equipment requirements were the same. We noted that they might undergo a different reference: instead of the end of FVC, not always stable, the beginning of the forced expiratory curve, and thus define a point called "J"-where the expiratory flow is equal to one which presents a close correlation to function of total lung capacity (TLC) and airways closure capacity (CIC). The volume corresponding to point "J" was designated VF=1 with the same defining strenght of CIC, however much easier to measure and not requiring sophisticated and expensive equipment.

All variables of the myasthenic patients were compared with the standard variables of the normal lung functional test.

*Table 4. Results of respiratory functional test and a characteristic myasthenic pattern in flow-volume-plot.**

Test	Standard	Patient	%	Comment
FVC (1)	3.313	2.908	88	normal
VF=1 (1)	2.820	2.243	80	normal
FEV1 (1)	2.659	2.523	95	normal
FEV 1%	80.300	86.700	108	normal
MVV (1/s)	99.700	94.600	95	normal
FEF (1/s)	5.080	7.411	146	normal
FMF (1/s)	3.278	2.727	83	normal
FMFT (s)	0.510	0.530	106	normal
TLC (1)	4.372	4.204	96	normal
MTT (s)	0.620	0.700	113	normal

*AHGL, 28 years old, female, height 151cm , weight 48,5 Kg.

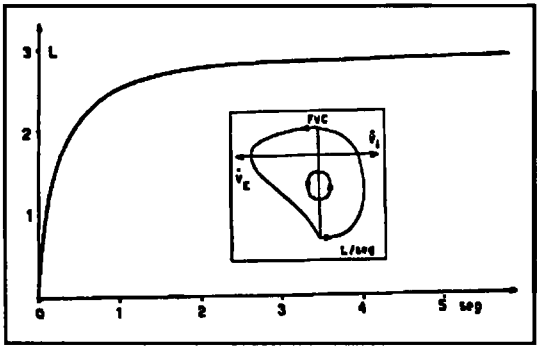

Fig 1. Results of respiratory functional test and a characteristic myasthenic pattern in flow-volume-plot.
Patient AHGL, 28 years old, female, height 151 cm; weight 48.5 Kg

Statistical analysis used was: a) descriptive statistics; b) paired Student t test between the values of each different variable and its standard; c) unpaired Student t test between the different clinical forms. The number Cruncher Statistical System was used.

RESULTS

Table 1 shows the distribution of the patients. Table 2 shows the distribution of the diverse clinical forms according to sex, number of studied cases and presence or absence of really significant differences (RSD). Table 3 shows the results of the studied variables. Table 4 shows the results of the lung test of MG patients. Table 5 shows a respiratory functional proof in a chronic demyelinating polyneuropathy (CIDP). Figure 1 shows the characteristic flow-volume loop in this patient with MG. Figure 2 shows the flow-volume in a patient with CIDP.

DISCUSSION

From the respiratory involvement depend on severity of MG[5]. To evaluate the respiratory function to prevent respiratory complication in thymectomy is very important for a good prognosis

*Table 5. Results of respiratory functional test and a plot of flow-volume in a patient with chronic demyelinating polyneuropathy**

Test	Standard	Patient	%	Comment
FVC (1)	4.964	4.822	97	normal
VF=1 (1)	4.059	3.747	**92**	normal
FEV1 (1)	3.886	3.868	**100**	normal
FEV 1%	78.300	80.200	**102**	normal
MVV (1/s)	145.700	145.100	**100**	normal
FEF (1/s)	7.789	6.603	**85**	normal
FMF (1/s)	4.139	14.466	**349**	normal
FMFT (s)	0.060	0.170	**28**	normal
TLC (1)	6.533	72.098	**110**	normal
MTT (s)	0.660	0.980	148	normal

*NEL 35 years old, male, height 173 cm, weight 66 Kg.

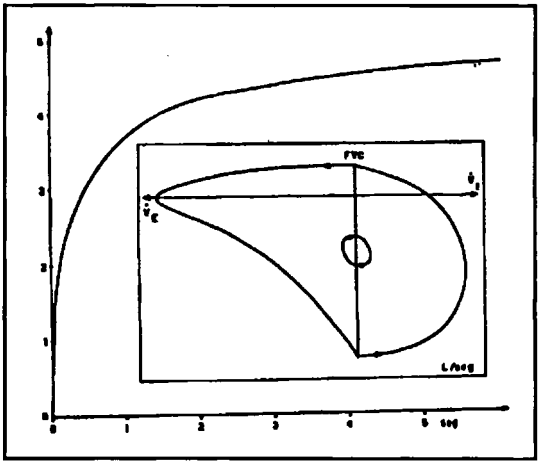

Fig 2. Results of respiratory functional test and a plot of flow-volume in a patient with chronic demyelinating polyneuropathy*

**NEL, 35 years old, male, height 173 cm; weight 66 Kg.*

of MG and safety of surgery. It is also feasible to assess the respiratory function involvement in all clinical forms of MG without respiratory symptoms. In a patients with MG, vital capacity VC is usually low, total lung capacity (TLC) tends to be normal, and residual volume (RV) is normal or elevated. VC is reduced because of both inspiratory and expiratory muscle weakness. The former reduces inspiratory capacity, and the latter eliminates expiratory reserve volume. In patients with neuromuscular diseases, the increase in RV and the reduction in expiratory muscle strenght as assessed by PEmax correlate well. The reduction in PImax do not correlate weakly with changes in TLC and VC.

Myasthenic Pattern

The typical spirometric pattern in patients with respiratory muscles weakness is a restrictive ventilatory defect with fairly well-preserved forced expiratory flow-rates[16]. Among all variables of respiratory function evaluated we observed that the myasthenic pattern is characterized by the modification of the flow-volume curve which appears flattened, both at inspiration, resembling, at calm breathing, more to a rectangle than to a lozenge, and even more evident at forced movements. These modifications were also observed in some cases of neurologic disease where the motricity of the pharynx and of the larynx is impaired. This pattern is similar to the changes found in patients with larynx, trachea and/or large bronchi stenosis. Its finding in MG suggested an eventual fatigue of the laryngeal muscles, with reduction of its useful gauge at the vocal chords level.

Differences between clinical forms and sex

The ocular form of MG has peculiar clinical, antigenic and therapeutic characteristics different from those of the systemic form[2,3,17,18]. Although frequently reported the authors of this paper question this characterization, as RSD were found: in myasthenic pattern and, in females, also of the FVC, VF=1 and RV, thus suggesting that in the ocular form other muscle groups also undergo changes.

Male patients with "ocular" form only presented the "myasthenic pattern" with lung impairment and had, from functional respiratory test (FRT) point view, a more benign clinical finding. Female patients with the "ocular" form exhibit a behaviour of the respiratory variables similar to that of the systemic form. Male patients with "ocular" exhibit a different behaviour pattern form that of female patients.

The bronchoconstriction effect of anticholinesterasic agent

The anticholinesterasic agent was associated with an increase in airway resistance by muscarinic stimulation of bronchial smooth muscle by acetylcholine.

The acute changes after anticholinesterasic therapy are: improved global respiratory muscle function (increased PImax and PEmax), increased FRC because of greater respiratory muscle tone, increased static compliance, increased maximal transdiaphragmatic pressure, minimal changes in lung volume, and improved ventilatory response to hypercapnia

It is known that anticholinesterase agents may trigger by their vagal action a greater resistance of the airways to the gas flow, particularly in asthmatic subjects. It should be expected that in MG this would be more frequent with a more evident modification of the VF=1, FEV1, FEF, FMF, FMFT, MTT variables. However, there is no such evidence. The incidence of asthma was not higher than that found in the overall population cared for at the LFL-IOT.

CONCLUSION

All clinically stable myasthenic patients, without clear respiratory symptoms presented the so called "myasthenic pattern". A change in the flow-volume curve which characterizes "myasthenic pattern", observed in the generalized forms as well as in the localized (ocular) form, suggests malfunction of other muscle groups. The observed modifications reveal persistent and early impairment of the laryngeal muscles.

A flow-volume curve of myasthenic patients disclosed a pattern resembling that of upper airways obstruction, thus suggesting that there is at least some impairment of laryngeal and tracheal muscles.

Male patients with the "ocular" form only presented the "myasthenic pattern" with lung impairment.

Female patients with the "ocular"form exhibit a behaviour of the respiratory variables similar to that of the systemic form.

Male patients with the ocular form exhibited a different behaviour pattern from that of female patients.

Findings of the lung function tests did not reveal really significant differences between the generalized and the "ocular" form.

No change of the variables that indicate obstruction of the airways due to use of acetylcholinesterase agents employed in the treatment of MG was found.

The involvement of the muscle of vocal chord evaluated by FRT, the dysfunction of the stapedius muscle and dysfunction of some type of the muscle fiber of the ocular motor system can reveal a wide dysfunction of the polysynaptic neuromuscular junction of MG[5,13].

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