

Myasthenia gravis története

(Dr. John Keeseey 2002, at the Xth International Conference on Myasthenia Gravis and Related Disorders)

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A betegség első leírója :Thomas Willis 1672

- he wrote about "a woman **who temporarily lost her power of speech and became 'mute as a fish.'**"(1) This has been interpreted as being the first written description of myasthenia gravis
- "**Chief Opechancanough**, a warrior chief, was responsible for several massacres in the (American) colonies **his eyelids were too heavy that he could not see unless they were lifted up by his attendants.** Further, he was unable to walk
- Newsom-Davis szerint Sámsonnak is myastheniája volt...

Erb – a példakép (?)

- **Heinrich Erb** (1840-1921), German neurologist, was responsible (in part) for the delineation of myasthenia gravis: He "described **myasthenia gravis pseudoparalytica** in 1878
- called Erb-**Goldflam**-Oppenheim disease at the time."(3) „
- For a half a century Wilhelm Heinrich Erb ruled over German Neurology with an **imperial hand**

Thymus hypertrophia és myasthenia (1901)

- **Carl Weigert**, German pathologist and histologist, 1845-1904, is credited with drawing attention to the **relation between hypertrophy of the thymus and myasthenia gravis**. Recorded in 1901."(3) Published in *Neurologisches Zentralblatt*, 20:597. (5) "

Thymectomy (1912)

- **Ernst Ferdinand Sauerbruch**, German surgeon, 1875-1951, performed thymectomy for the relief of myasthenia gravis. Recorded by Schumacher and Roth in 1912.(3)

1934

Myasthenia tüneti kezelésének felfedezése

- **Mary Broadfoot Walker (1896-1974),**
- She introduced the use of **physostigmine** in the treatment of myasthenia gravis.
Recorded in 1934

Mi adta az ötletet?

- "Surmising that, since **MG had symptoms like curare poisoning**: the curare antidote physostigmine might help it, she injected physostigmine into her very droopy patients (*OGYI engedély?.... GCP...?*)
- Then, with utter drama, **like Lazarus rising from the grave**, they rose and walked across the room.

Pont egy nő, a Britt Birodalom nagy bánatára

- "In an era when women were not admitted to the University of Edinburgh and when England's first female physician (Elizabeth Garrett Anderson, 1836-1917) had to venture to Paris, France, to earn her M.D. in 1870, She is credited with **making the most significant discovery in medical therapeutic** within the British empire.



A **terápia mechanizmusa**: az acetylcholin lebontásának a gátlása: Nobel díj

- **Sir Henry Dale** (1875-1968) came in the recognition of drugs such as physostigmine, drugs that **block the enzymatic destruction of acetylcholine**, and so allow this substance to accumulate in cases of deficiency, as in myasthenia gravis.,,
- Dale shared in the Nobel Prize in 1936 for developing the theory of neurohumoral transmission.

„azok a hatvanas évek...”

- It was only in the 1960s that Drs Jacques Miller (London and Australia) and Bob Good (USA) finally showed that the **thymus was a key ‘immune organ’**.
- At the same time, it had become clear that several other disorders were caused by an ***immune attack on the patients’ own tissues***, for example thyroid disease. In 1959, another beloved former Vice-President, Prof Iain Simpson, was reviewing all the thymectomies he could trace in Glasgow and London (404 in all).
- He noticed that such ‘autoimmune’ diseases are specially common in relatives of myasthenics.
- He remembered that short-term MG could also be transferred from mother to newborn baby, just like protective antibodies are passed across.
- So ***Simpson he proposed, in 1960, that MG was autoimmune too. He was 12 years ahead of his time.***

1973

elektrofiziológusok: az achetylcholin
receptorhoz kötődik

- These two tracks finally came together in 1973. By then, physiologists realised that the ACh, the **ignition keys**, must somehow latch into specialised ACh receptors (AChRs) – the **ignition locks**.

1975

Myasthenia szérummal átvihető

Science. 1975 Oct 24;190(4212):397-9

- Myasthenia gravis: passive transfer from man to mouse. Toyka KV, Brachman DB, Pestronk A, Kao I.

1975

Kísérletes autoimmun myasthenia

J Exp Med. 1975 :141:1365-75

- Immunization of animals with acetylcholine receptor (AChR) protein from the electric organs of *Electrophorus electricus* and *Torpedo californica* induces an autoimmune response to the AChR of mammalian skeletal muscle.
- Rats and guinea pigs develop experimental autoimmune myasthenia gravis (EAMG) **after a single inoculation with small quantities of AChR** and adjuvant
- Physostigminre tünetek javultak

2001

muscle-specific receptor tyrosine kinase,

MuSK

Nat Med. 2001;7:365-8



- Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. Hoch W, McConville J, Helms S, Newsom-Davis J, Melms A, **Vincent A.**
- **MuSK ellenanyag pozitív a „szeronegatív” betegek fele (~7%)**
- **AChR ellenanyag pozitív ~ 73%**

Magyarország

- **Szobor Albert:** Myasthenia gravis Akadémiai Könyvkiadó, 1990
- SZA első betege: 1951, akinél az első magyarországi **thymectómia is megtörtént: Sebestyén Gyula,**
- Nyírő Gyula támogatta SZA tevékenységét
- Plasmapheresis bevezetése
- Diagnosztika bevezetése
- Betegek összegyűjtése, gondozása
- Országos központ létrehozása

Myasthenia in a patient with sarcoidosis and schizophrenia.

Ideggyogy Sz. 2004 Jul 20;57(7-8):242-4.

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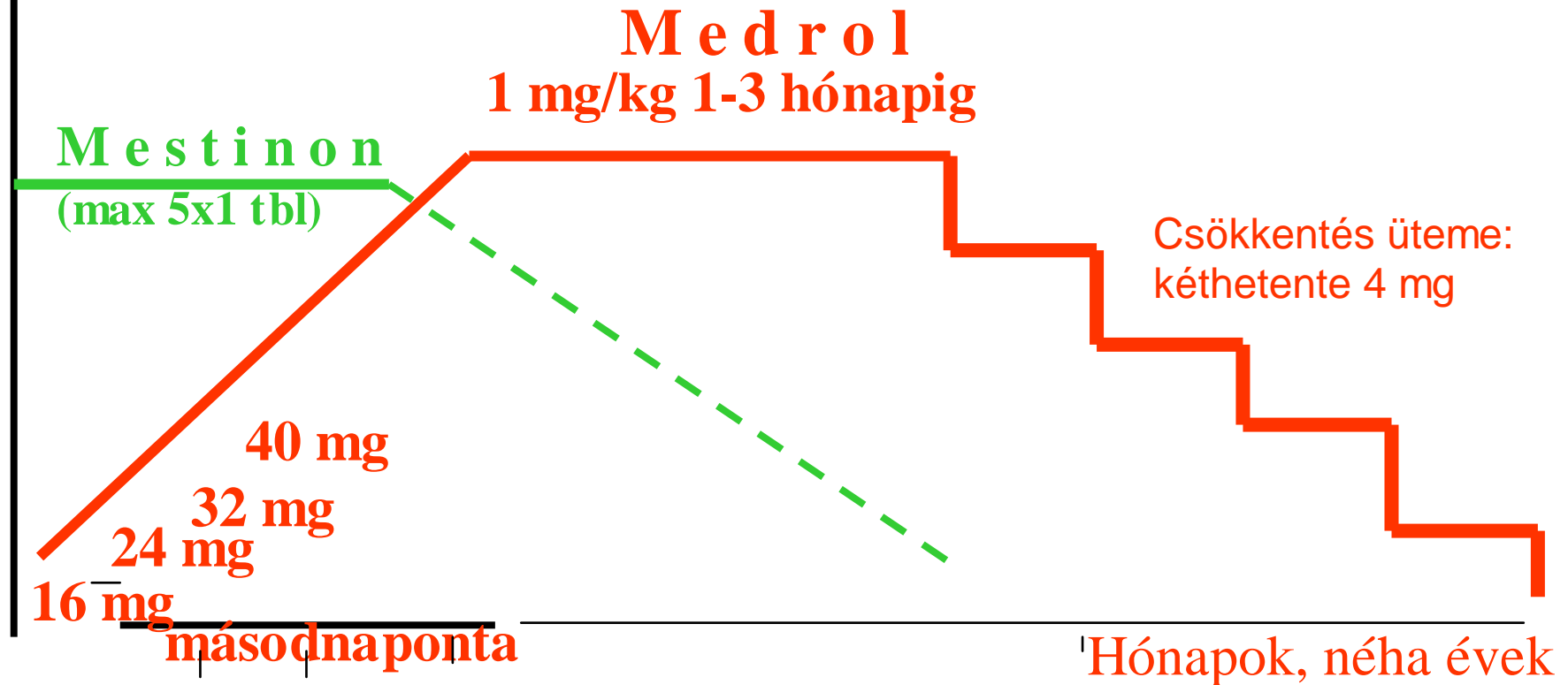
John Newsom-Davis

- *Plasmapheresis bevezetése*
- *'60-as években a szteroid kezelés bevezetése*
- *Szteroid-Imran kombinált kezelés bevezetése, evidenciákra helyezése*

Áttörés a myasthenia kezelésében (John Newsom-Davis)

Medrol - Imuran kombinációs kezelés

Imuran 2.5 mg/tkg – 3- 5(?) évig



Safety of long-term combined immunosuppressive treatment in myasthenia gravis – analysis of adverse effects of 163 patients

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Table 2 Frequency of different AEs in different patient groups

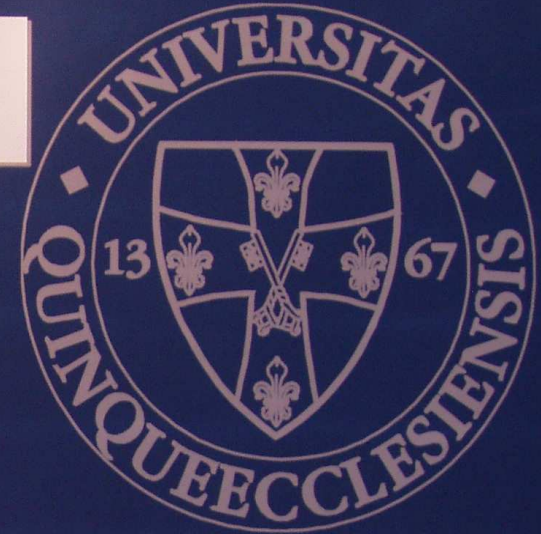
| | Number of AEs in the group of patients who had exclusively steroid AEs | Number of AEs in the group of patients who had exclusively AZA AEs | Number of AEs in the group of patients had both AZA and steroid AEs |
|-----------------------------------|--|--|---|
| Adverse effect – gastrointestinal | | | |
| Nausea | 0 | 2 | 0 |
| Vomiting | 0 | 1 | 1 |
| Gastric discomfort – pain | 5 | 1 | 0 |
| Ulcer | 1 | 0 | 0 |
| Diabetes mellitus | 8 | 0 | 3 |
| Hypertension | 7 | 0 | 2 |
| Hair loss | 12 | 0 | 4 |
| Symptomatic osteoporosis | 3 | 0 | 3 |
| Weight gain | 41 | 0 | 13 |
| Cushingoid features | 49 | 0 | 9 |
| Severe infection | 0 | 1 | 2 |
| Allergy | 0 | 0 | 1 |
| Chills and fever | 0 | 1 | 1 |
| Polyneuropathy | 0 | 1 | 0 |
| Hepatotoxicity | 0 | 2 | 3 |
| Joint pain | 0 | 2 | 6 |
| Hematologic AEs (total) | 0 | 8 | 7 |
| Leukopenia (neutropenia) | 0 | 7 | 4 |
| Neutropenia + anemia | 0 | 1 | 1 |
| Thrombocytopenia | 0 | 0 | 1 |
| Pancytopenia | 0 | 0 | 1 |



Combined immunosuppressive treatment after myasthenic crisis – effects on the long-term outcome

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Abstract

Objective: Myasthenic "crisis" (MC), the most severe complication of myasthenia gravis (MG) is defined by respiratory failure requiring intubation and ventilatory assistance. Crisis occurs in approximately 12 to 20% of patients, with a mortality rate of 4%. The accepted treatment of the MC is plasmapheresis/intravenous immunoglobulin (IVIg), steroids, and supportive treatment in the intensive care unit (ICU), however, the long-term survival and outcome depends on the long-term treatment. The efficacy of the combined azathioprine and prednisolone treatment was proven in a double-blind placebo-controlled study. In our former study we have analysed the safety and adverse effects of long-term combined azathioprine and prednisolone treatment in 163 myasthenic patients (6). The goal of the present study was to analyse the frequency of recurrent MCs in a patient population on azathioprine and prednisolone treatment, which was introduced during the first MC. Patients and methods: In this study we analysed retrospectively 36 MCs of 30 MG patients (mean age 61y, range 27-91 y, 15 male and 15 female) treated in our hospital from January 1997 until December 2000. A prospective post-crisis follow-up was conducted until December 2005. All patients were treated by plasmapheresis during the crisis as well as combined treatment with azathioprine and prednisolone was initiated during the crisis. Results: A second MC developed in 6 pts (20%). All of the recurrent MC-s happened within the first 3 months of treatment (within 4.3 weeks in average). None of the patients who remained continuously on treatment developed any other MC during the follow-up (mean: 6 years). The decrease of the incidence of MC at 3 months and at 1 year of treatment was highly significant (p<0.001).

Patients and methods:

We analyzed retrospectively 36 MCs of 30 MG patients treated in our hospital from January 1997 until December 2000. The clinical data of the patients are given in table 1. 17 MC episodes of 10 patients occurred before the initiation of the combined IM treatment - before 1997. (Figure1). All patients were initially treated by plasmapheresis (five exchanges of 2-3L every other day), together with methylprednisolone (1mg/kg/od), Azathioprine treatment (2-2.5mg/kg qd) was added immediately after the crisis. As the patient needed no ventilation support the dose of methylprednisolone was gradually tapered and switched to alternate day treatment (1-1,5mg/kg qod).

| | |
|---|----------------------|
| Women/men | 15/15 |
| Number of myasthenic crisis episodes | 36 + 17 previous MCs |
| Median age at onset of MG (range) | 53 (17-83) |
| Median age at first crisis (range) | 61 (27-91) |
| Median interval (in months) from MG onset to first crisis (range) | 7 (1-150) |
| Thymoma | 4 |
| Thymectomy | 16 |
| AchR AB positive/negative | 26/4 |
| Time of follow-up in years (mean, range) | 6,1 (1-9) |

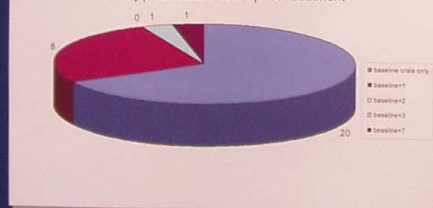
Results:

A second MC developed in 6 patients (figure 2). All the recurrent MC-s happened within the first 3 months of treatment (within 4.3 weeks in average). None of the patients who remained continuously on treatment developed any other MC during the follow-up (mean 6 years). The decrease of the incidence of MC at 3 months and at 1 year of treatment was highly significant (p<0.001). The MGFA Post intervention status7 of the patients at the end of the follow-up is shown in figure 3.

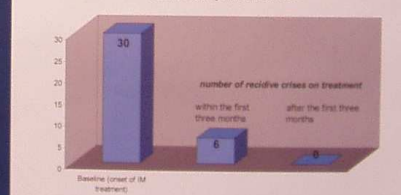
Introduction and Purpose:

Myasthenic crisis (MC), defined as respiratory failure requiring mechanical ventilation is the most severe, potentially life-threatening complication of MG. MC occurs in approximately 12-20% of patients, the mortality rate of the first crisis is 4-5%. The accepted treatment of the MC in addition to supportive care in the ICU is plasma exchange (PE)/IVIg2 Steroids are usually also given, especially in prolonged MCs (1,2,4) Repeated crises are not rare, approximately one-third of the patients experience a second episode of crisis (1,2) Most of the recurrent attacks occur within one year of the first (3) The overall mortality rate of the second crisis is much higher (29%) (1), i.e. the prevention of a second crisis is essential. The efficacy of the long-term combined azathioprine and prednisolone treatment was proven in a double-blind placebo-controlled study (5). The goal of the present study was to analyse the recurrence of MCs in a patient population on continuous azathioprine and prednisolone treatment which was introduced during the first MC.

Number of myasthenic crises before combined methylprednisolone-azathioprine treatment

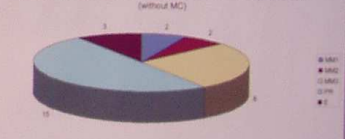


Number of myasthenic crises



MGFA postintervention status at the end of follow-up

MM: minimal manifestation PR: Pharmacological remission E: Exacerbation (without MC)



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Conclusion:

In our patient cohort combined azathioprine and prednisolone treatment introduced during the first myasthenic crises prevented any recidive myasthenic crisis on the long term

European Journal of Neurology 2006, 13: 691–699

doi:10.1111/j.1468-1331.2006.01476.x

EFNS TASK FORCE ARTICLE

Guidelines for the treatment of autoimmune neuromuscular transmission disorders