

## MEMORIES BY A MYOLOGIST

# Introducing corticosteroids therapy from 1969 to 1990 at the Centre/Institute for Neuromuscular Diseases, KBC Rebro, Zagreb, Croatia

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The author presents the chronological development of therapy by corticosteroids in myasthenia gravis (MG), as well as dilemmas connected to this kind of treatment at the Centre/Institute Zagreb, she founded. The improvement of postoperative prognosis of thymectomy with corticosteroids is described and transfer of positive experiences to other neurological diseases. The side effects can be reduced significantly by respecting the basic rules: the choice of corticosteroids (fluocortolone, methylprednisolone, no dexamethasone), single dose administered in the morning, not later than 8 a.m. (respecting the circadian rhythm of concentration of cortisol in blood). Initially, the high dose is administered daily, until the stabilisation of signs and symptoms improvement. Then, in my early modification, the initial dose, administered every other day, becomes gradually lowered. The diet is similar to diabetic, with the potassium added. In the period from 1973 to 1990, 212 myasthenia gravis and 37 polymyositis patients were treated that way.

We recommend to continue endocrinological research, on which we already reported, now with contemporary methods. The value of the "pulse therapy" should be analysed in more details, with peroral corticosteroids added afterwards.

**Key words:** Myasthenia gravis, corticosteroids

## Introduction

In the 60's of the last century, myasthenia indeed was a "gravis" disease. It used to be treated with anticholinesterase drugs and thymectomy, the kinds of therapy, that used to raise numerous controversies. Thymectomy was at that time an operation with a high degree of probability for a postoperative deterioration. Myasthenic crises were very frequent and tracheotomies repeatedly indicated.

## *ACTH therapy*

Thanks to Professor Albrecht Struppler, my teacher of electromyography from München, I met K. Osserman, during the World Congress of Neurology, New York, 1969. At that time he was regarded as top MG expert, active at the Mount Sinai Hospital, New York.

He was the first to start treating MG with a series of ACTH injections. At first, the course would cause deterioration, followed by a significant and long-lasting improvement. Upon my return to Zagreb, I tried to introduce that kind of therapy at my unit. The deterioration would sometimes reach to the respiratory crisis, so there was no way of treatment on a "regular" neurological department. I started to allocate the patients on the Intensive Care of the Department for Infectious Diseases chaired by J. Rulnjević, where we usually sent the patients during myasthenic crises. Upon the constitution of the Thoracic Surgery, Jordanovac, Zagreb, with LJ. Topalović, the head, I would transfer them there.

Our ACTH course was followed by azathioprin (Imuran), introduced into therapy of myasthenia gravis in 1969 at the Neurological Department, Hamburg, Germany. Applied as first and only therapy no convincing positive effects were found. However, after ACTH series, it prolonged the remission. The ACTH therapy was a complicated one, risky, and in the end, the results were not as desired.

## *HSDAD therapy*

In 1973 I visited the Bethesda hospital, where I met W. King Engel. He gave me a very useful information about HSDAD (High Single Dose Alternate Day) predni-

sone therapy (1). Prednisone was administered in a single high dose, in the morning, every other day. I introduced that scheme upon my return to Croatia, and very soon we got to modify it.

A corticosteroid with the highest concentration in one pill, and with a long enough half-time was looked for. It was fluocortolon (Ultralan oral), 20 mg a pill, with 24 hours decomposition half-time. However, on the day without corticosteroid, in serious cases, the significant deterioration appeared. The smaller dose of fluocortolon was necessary on the second day, too.

In more difficult cases, we would treat with unchanged high doses of fluocortolon, every day, until the stabilization of the clinical signs and symptoms. Then we would gradually decrease dosage of the second day, decrescendo, into the every other day administration. The phase like this one, would last for several weeks, exceptionally for months. The single morning (until 8 o'clock) dose proved to be crucial, because, within the circadian rhythm of concentration of cortisol in blood, the physiological level of cortisol in blood is the highest at that time. Lack of respect for the physiological rhythms, and for natural laws in general, has bad consequences. The evening dose, so frequently used, had insomnia as the smallest of side effects.

Due to such administration, especially in combination with azathioprin I changed the prognosis of myasthenia gravis in Croatia significantly. The patient's mobility would quickly improve and the hospitalization would shorten. Myasthenic crises, especially tracheotomies, became rare. The possibility of plasmapheresis was the further significant step towards better prognosis of MG.

By the way, I also used the ACTH therapy to try to cure a young woman with a verified Porphyria Acuta Intermittens, in a very bad condition. The result was exceptional and remission complete. After the series of injections, fluocortolon was administered. The remission with fluocortolon was achieved even with the patient's sister who became ill several years later. The result was published in *European Neurology* (2). The administration of fluocortolon also in patients with Sclerosis Multiplex started. We reported the first results in polymyositis 1978 (3) and in myasthenia gravis 1979 (4).

Many specialists persisted to refuse the corticosteroid therapy, considering it very dangerous. Their choice was the dexamethason, eventually pronison several times a day. Its side effects were really significant, from pronounced Cushing Syndrome to isolated arterial hypertension, hyperglycemia, osteoporosis etc.

#### *Endocrinological research for side-effects*

Very early we started looking for the side effects with prof. Vanja Mikuličić and Danilo Tepavčević and later on

with prof. Mirko Koršić. (Department of Endocrinology, KBC, Zagreb) At the same time we started analyzing the bone system with ing. Magda Harmut, Institute for Medical Research and Work Medicine of JAZU (Yugoslav Academy of Sciences and Arts). The preliminary results were reported at the First Symposium on Neuromuscular Diseases, Zagreb, 1977, and The Second Symposium on Neuromuscular Diseases, Dubrovnik, 1979 and printed (5-7).

In the article from 1978, entitled *Studying the Influence of Corticosteroids Therapy of HSDAD Type on Daily Rhythm of 11-OHCS Secretion, the Metabolites of Cortisol and Calciuria in Patients with Myasthenia Gravis*, in the Summary, there is the following statement: "The first results of our research show that the corticosteroids therapy administered according to HSDAD scheme is less dangerous than it is generally thought, especially if the rare side effects are compared to the positive effects of this form of therapy. The values of 11-OHCS, 17-OH, secretion of cortisol, calciuria, OGTT do not differ from the normal significantly. As an exception, the type IV of differential lipidogramme according to Friedrichson can develop, as well as hypertension and facies lunata, but they disappear after the end of therapy. Lower calciuria was sometimes found before starting the therapy."

### **General survey of results**

In 1990 on the Fourth Yugoslav Symposium on Neuromuscular Diseases there were five round tables. The fourth was entitled *Problems of Using Corticosteroids in Neuromuscular Diseases* (8). In the English summary entitled: *Fluocortolon Long-term Therapy of Myasthenia Gravis and Polymyositis*, it says:

"Fluocortolon was introduced in Croatia, into therapy of two especially important autoimmune neuromuscular diseases by Anica Jušić as early as 1973. It was administered according to the following scheme: a single high dose, administered every morning after breakfast, before 8 a.m., during 3 to 6 weeks, depending on the clinical test results. Later, fluocortolon was administered one day the initial dose, the next day an increasingly smaller dose. Between 1973 and 1990, 212 myasthenia gravis and 37 polymyositis patients were treated that way".

The youngest patient was a three years old girl with fulminant form of MG. The oldest patient was 76 years old. The MG patients were recovering more quickly than those with polymyositis. In MG patients, 2 to 4 weeks of administration of fluocortolon resulted in first signs of recovery. In polymyositis patients improvement was achieved after one to three months of treatment. The dosage of fluocortolon was then gradually decreased – sudden decrease was not recommended for possible deterioration.

The unwanted side effects were rare. An increase in body mass could be avoided with a diet. The patients would sometimes have irregular menstruations, without the necessity for a corrective therapy. Retention of water was corrected with diuretics, the low values of potassium by substitution. Cataract developed in 16 cases, and only in 4 of them an operation was necessary. In only two cases diabetes mellitus developed. In one of them, the administration of flucortolon was stopped, and in the other a diet helped. Only one patient developed a depressive psychotic reaction, which completely disappeared after the flucortolon was omitted. No significant osteoporosis was found by gamma absorptiometric densitometry. The results of endocrinological testing (cortisol, aldosterone, growth hormone, insulin, insulin hypoglycemic test) showed no significant deviation from normal.

The longest period of administration of flucortolon in the study group was 12 years. The largest dose administered was 120 mg/day, every day during three months. The reduction of the dose on the second day would, namely, each time again, result in increased myasthenic symptoms. Now, two years later (1990), the patient, a teacher, still receives 30 mg every day without significant side effects. In spite of his disease, he is able to do his work, with occasional sick leaves. He still has no unwanted side effects”.

The described results were reported in 1990 at the World Neuromuscular Congress in München (9) too. The results of treating myasthenia gravis at the Centre/Institute for Neuromuscular Diseases were also reported at the International symposium in Pula 1993 (10), where authors referred to 410 patients with diagnosed myasthenia gravis over fifteen years (1978-1993), treated at the KBC Rebro, Institute for Neuromuscular Diseases in various modifications.

## Other indications for corticosteroids

### *Thymectomy*

The results of thymectomy were significantly better, if the patients took flucortolon during 2 to 3 months preoperative, without interruptions perioperative and later after the operation. Some of those, not subjected to preoperative treatment, at least in a shortened form, even died (a female patient from Croatia, with ocular myasthenia, who went for her operation to Hamburg without corticosteroids). In Croatia, only few, due to surgeons ignoring our recommendations, continued to have serious postoperative crises.

### *“Pulse therapy”*

Some additional controversies should be pointed out. It is obvious that high dosages administered over shorter

periods have fewer side effects than small dosages administered for a long time. The “pulse therapy” is becoming more and more established. It simply suddenly interrupts the course of development of an immunological process. With small initial dosages we can lose the time race. Of course, the pulse therapy comes into consideration only in stationary conditions with possibility of intervention in case of unwanted deteriorations.

The pulse therapy of MG, with iv corticosteroids is gradually becoming established in the world (11-13). The first pulse therapy of MG in Croatia, the one with methylprednisolone, 1000 mg iv, combined with plasmapheresis, was administered by Ranka Baraba (City Hospital – “Dr. Josip Kajfeš”, Department of Neurology, Zagreb) as early as 1985. The patient was a 31 years old woman with MG, hyperthyroidism and secondary hypothyroidism and extremely malignant exophthalmos. Orbitotomy or enucleation were considered. The result was a very quick and extensive withdrawal of extreme symptoms. Later on, with oral corticosteroids – a full remission was reached.

### *Multiple sclerosis*

In the therapy of Multiple Sclerosis, the pulse therapy proved to be repeatedly more successful if it was extended by oral corticosteroid. In a case, described extensively, I started already with high oral doses of flucortolon, administered according to the modified HSDAD scheme.

Tanja, born 1971. First attack, when she was 16 years old (1988), withdraw spontaneously. In 1989, the second attack was treated according to the modified HSDAD scheme with flucortolon. Despite full remission, the plan was to continue therapy. It was stopped by the mother, following a suggestion of specialist-friend from Switzerland. In not more than 3 weeks, there was a severe relapse again. The same interruption after the flucortolon course was repeated two more times. In 1993 mother finally accepts continuous therapy during an especially severe relapse, and since then to 2008 Tanja was treated with “up and down” flucortolon titration. In 1999 she changed to methylprednisolone (Medrol). Any significant lowering of dosage resulted in obvious deterioration. A significant worsening happened after she broke her hip during therapeutic riding and after an especially severe psychological trauma. The residual symptoms of spasticity, ataxia and dysarthria increased. Despite that, the dosage increase displays improvement of recent symptoms again. The clinical signs and symptoms were stabilized only in 2008. The corticosteroid therapy was now stopped, after 15 years of continuous administration, without significant clinical signs or symptoms of adrenal cortex failure. There were only a few side effects, like moon face, which disappeared very soon afterwards. She never had arterial hypertension, hyperglycemia, changes

in blood test results, lipidograms, significant swelling or significant lowering of potassium in blood. There was a cataract of a low intensity. She had irregular menstruations and some *striae*. After 21 years of disease, with extremely hard periods, she can sit, communicate or eat a sandwich all by herself etc.

#### *Neuromyotonia*

Ivan, 48 years old. His illness had started three years earlier, with progressive hands and feet paresis and generalized fasciculations. The clinical and electromyographic analysis confirmed the diagnosis of neuromyotonia. The pathology was reduced by carbamazepine application. The result of liquor tests: total proteins (Rieder) and the percentage of gamma globulin were increased. IgG increased too. Phosphates in urine were quadrupled, with normal calcium, phosphates and alkaline phosphatase in the serum. Methylprednisolone was introduced and carbamazepine omitted with significant further improvement. The improvement was recorded in all control tests too. The hypothesis of autoimmune disease, was based on the liquor results and the positive effect of methylprednisolone treatment (14).

#### *PER syndrome*

Vlado, 52 years old. I met him during my hospice house calls. He had been lying in bed immobile for more than five days. Attacks occurred during day or night on every attempt of drinking or eating or just simply moving the arm. They appeared, on sudden sound or a slightly stronger touch. Attacks consisted of very sudden anteflexion of the arm at the shoulder, extension at the elbow and volar flexion in the hand joint. At the same time, the feet would extend maximally, with plantar flexion of the sole. Attacks lasted 1-2 minutes. After they stopped, the extremities were immobile and probably of a heightened tonus. A more accurate examination was impossible because it would provoke a new attack. During attacks the patient was fully conscious, with dreadful screams because of the extremely painful contractions. He was dehydrated, with a huge sacral decubitus (15:10 cm) and urinal catheter because of urine retention.

Before the described culmination, the other neurologists prescribed diazepam, baclofen, gabapentin, with no effect. Because of anamnestic and MRI similarities with Multiple Sclerosis, I introduced Medrol at a dosage of 64 mg/every day. After six days attacks became less frequent. Thirteen days later active feet movements appeared, and they did not provoke attacks. In arms, the

movement could be continued in spite of spasms. Twenty days later, there were no more night attacks. After thirty days, he started walking using the walker. Doses were decreased every second day, every 2-3 weeks (64/32, 64/16, 64/8, 64/0). Upon the last decrease, the old attacks came back, but they were stopped by going back to 64/64, with slower "*decrescendo*". As a result, he could walk on his own again and regained partial control of his sphincters. Due to strong water retention I switched to Decortin 60/60. The change soon provoked attacks. During one of this attacks he fell and broke his hip. It was treated only by immobilization. Medrol 96/96 was reintroduced, with very slow decrease of dosage. After a year, the condition, without relapses was reached. The dose was decreased to 4/0 and finally to 0/0. In 2009 the patient reported 90% remission for three years already, being able for gardening, 8-12 hours a day (15).

## Conclusion

In the 1960s, as a young specialist of Neurological Department, Rebro, Zagreb, I met a very skeptical attitude regarding corticosteroids. Among internists and rheumatologists, the dominant attitude was that the use of corticosteroids could expose the patient to high danger. Dexamethason two times a day was the most frequently drug used, sometimes prnison. The side effects were obvious.

After my contacts in New York and Bethesda, I dared to define therapy on the "cost-benefit" principle. My question to myself was: what is better to let the severe quadriplegia or dysarthria develop, decreasing significantly the quality of life, or to risk the side effects?

To me, a significant motivation was the possibility to decrease side effects by changing the "rules of the game". I started asking myself: which are, those side effects for sure, for which such a powerful remedy, was often being avoided. The question was also, how far they can be avoided, by the right choice of the drug type, by appropriate diet or medical substitution. Anyhow the treatment should be tried, it should be followed up, and critically correlated the investment with results. It should be chosen "the lesser evil, of the two", or followed "cost/benefit" strategy.

The contemporary medicine promotes more and more the basic principles of palliative care, the holistic approach to the patient and the increase in the quality of life in disease. The most pleasant situation for the physician is to make a diagnosis of the almost complete recovery, instead of an approaching death. I am lucky that something like that, happened to me, many times. I dared!

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