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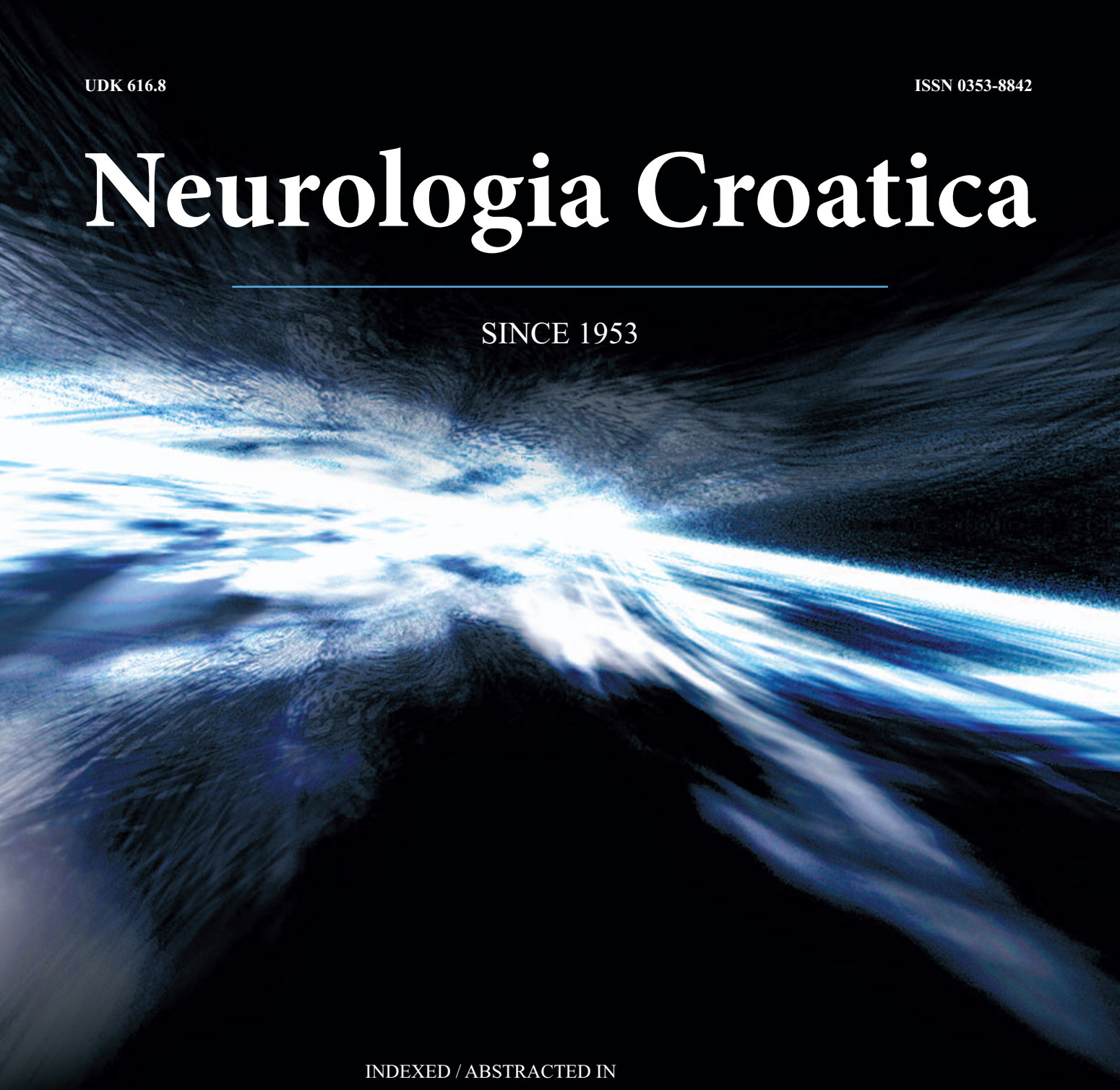

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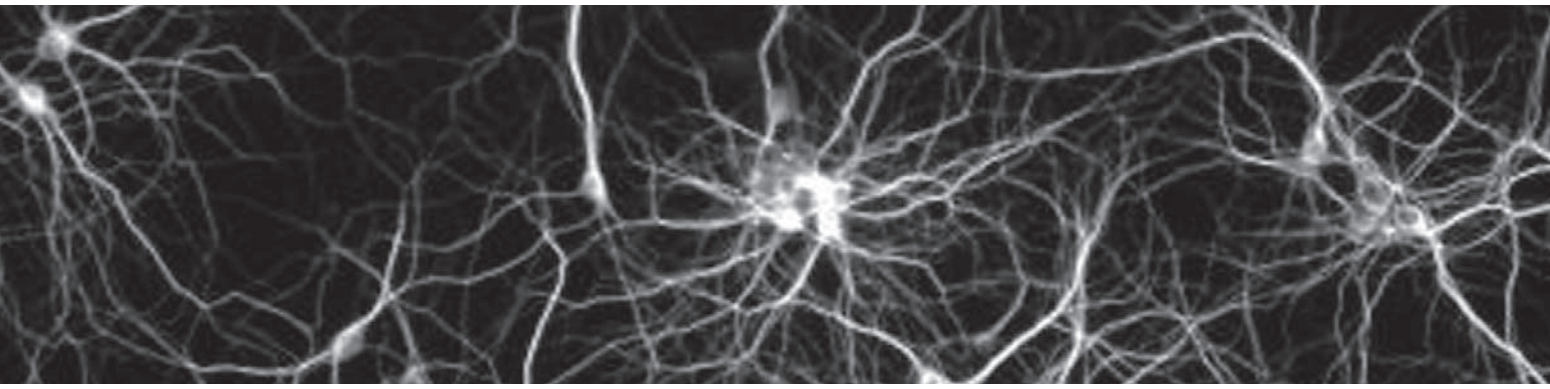


Editorial

Dear Readers and Colleagues,

Welcome to the second issue of Neurologia Croatica 2013. As mentioned previously, we continue to publish articles only in English, hoping this would increase the international visibility of our journal. In addition, we have introduced online submissions and review of all submitted manuscripts in order to make the review process easier for the authors, reviewers and editors. Since the introduction of online submission of the manuscripts, we have significantly shortened the time to the first decision, with average time of 37 days.

Another aspect of the online submission is a significant increase in the number of international reviewers. The quality of the journal's review process is extremely important for the success of Neurologia Croatica and so the contribution of scientific expertise of our reviewers to this process is highly appreciated. A list of all reviewers who completed their reviews in 2013 is given at the end of this issue.

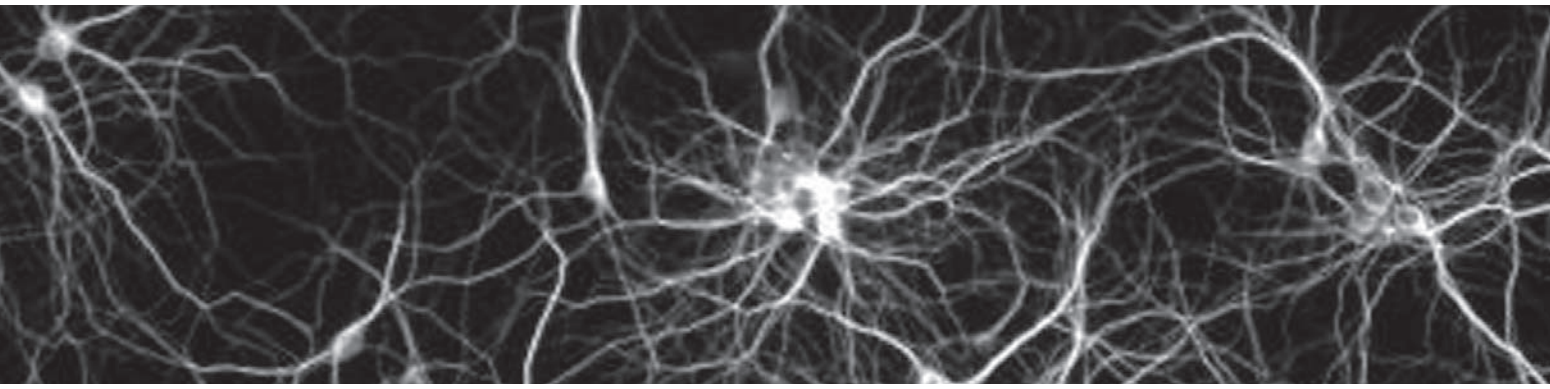
This issue of Neurologia Croatica brings an interesting original article, the aim of which was to measure functional outcomes of stroke patients undergoing rehabilitation in a Croatian rehabilitation center. Dr. Moslavac and colleagues have shown that rehabilitation efforts were started on time and to the extent of the individual rehabilitation needs of the patient, and as such proved useful in all patients irrespective of their age, comorbidity, type and severity of stroke.

Another interesting topic is presented in the review article entitled *Pulse glucocorticoid therapy in neuroimmune disorders*. Dr. Baraba Vurdelja and Dr. Friedrich discuss in depth the use of pulse corticosteroid therapy in different neurologic diseases such as multiple sclerosis or myasthenia gravis. They conclude that the treatment with corticosteroids remains an art, balancing the severity of the individual patient's disease, concurrent medical issues, and clinical experience.

We also bring another interesting case presented in the Case reports of University Department of Neurology, Zagreb University Hospital Center section and unusual Image in neurology presented by our neurosurgery colleagues.

At the end, I hope you will enjoy reading this issue and invite you to submit your next article to Neurologia Croatica.

Mario Habek
Assistant Editor



Stroke outcomes in Croatian patients measured by modified Rankin scale

S. Moslavac, I. Džidić

ABSTRACT - The objective of this study was to measure functional outcomes in stroke patients undergoing rehabilitation at a Croatian rehabilitation center using modified Rankin scale (mRS). Data on 90 stroke patients treated in 2010 and 2011 were analyzed according to gender, age at stroke, days from stroke to the initiation of rehabilitation, type, side and severity of stroke, length of stay, comorbidity and program of rehabilitation. Initial and final mRS scores and change (progress) in the patients' functional abilities were recorded and compared. Patients presented with mRS scores at rehabilitation initiation (4.07±1.00) indicative of high dependence, and it was higher in patients aged >65 (4.21±0.97), hemiplegic patients (4.94±0.25) and those with two or more comorbidities (4.27±0.79). The length of stay was longer than 21 days in patients with higher initial mRS scores (4.61±0.64). The mRS score at the end of rehabilitation was 3.10±1.18, with significant functional improvement of 0.97±0.66 in mRS score. All subgroups of patients improved in mRS score, too. The length of stay of hemiplegic patients (44±11 days) was appropriately longer than in hemiparetic patients (29±12 days) ($p<0.001$) achieving similar mRS improvement as in hemiparetic patients ($p=0.06$), although slightly more in favor of hemiparetic patients (1.03±0.66 *vs.* 0.69±0.60). In conclusion, rehabilitation efforts were indicated on time and to the extent of the individual rehabilitation needs, and were useful in all patients regardless of age, comorbidity, type and severity of stroke.

Key words: outcome, modified Rankin scale, stroke

INTRODUCTION

Functional outcome in stroke patients depends of the treatment provided by an interdisciplinary team of experienced professionals (1,2). The aim of rehabilitation is not only to teach patients to take care of themselves, but to integrate them back into society. In that crucial part of their lives, rehabilitation plays a major role (3). The modified Rankin scale (mRS) is a clinician-reported measure of global disability and has been widely applied for evaluating stroke patient outcomes (4-6). This scale measures independence rather than performance

Special Medical Rehabilitation Hospital, Varaždinske Toplice, Croatia

of specific tasks (Appendix 1). It consists of six grades from 0 to 5 and additional category '6', which means death. According to them, score ≤2 corresponds to independence. Limitations in the use of mRS include lack of consensus on the impact of change in mRS rating to the actual performance of the patient (7-9), or patient's comorbidities (diabetes or cardiovascular diseases) (10) that can influence physical functioning and cognitive abilities. The aim of the study was to assess initial and final mRS scores and improvement in patients' status during inpatient rehabilitation, and to evaluate differences in improvement according to time from stroke to rehabilitation initiation, length of stay, side involved, type of stroke (ischemic or hemmorhagic), severity of stroke (plegia or paresis), gender, age, comorbidity (none or only one *versus* more than one comorbidity) and program of rehabilitation (full or partial).

Provided by the Internet Stroke Center – www.strokecenter.org

MODIFIED RANKIN SCALE (MRS)

Patient Name: _____

Rater Name: _____

Date: _____

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Total (0-6): _____

Appendix 1

PATIENTS AND METHODS

Data on 90 stroke patients were analyzed. Data were collected at a tertiary care unit in a specialized rehabilitation hospital, in accordance with ethical standards of the institution. We recorded data on gender, age at stroke, time from stroke to the initiation of rehabilitation, length of stay at rehabilitation, severity of stroke (plegia or paresis), side of stroke (left or right), type of stroke (ischemic or hemorrhagic), mRS scores at the initiation and at the end of inpatient rehabilitation, difference (change) in mRS scores, type of program (full, including hydrokinesitherapy, or partial, without hydrokinesitherapy but comprising of kinesitherapy, occupational therapy, speech therapy, massage and various forms of electrotherapy, if indicated) and comorbidity (hypertension, diabetes, hyperlipidemia, atrial fibrillation, etc.). Paired t-test for equality of means was used to determine if differences existed before-after study, while independent t-test was used to determine if difference existed between groups of patients. For all analyses, the level of significance was set at $p<0.05$. Descriptive statistics was used and data were presented as mean ± standard deviation (SD). Distribution was tested with Kolmogorov-Smirnov test. Statistical analysis was performed using the SPSS for Windows, version 13.0.

RESULTS

The study included 90 stroke patients undergoing inpatient rehabilitation in 2010 and 2011 (Table 1), 41 male and 49 female patients, 46 with left-side and 44 with right-side involvement.

The mean age at stroke was 69±11 (median=71, range=31-85) years, with 29 (32%) patients aged ≤65 and 61 (68%) patients aged >65. Patients presented to rehabilitation ward at 31±25 (median 23, range 7-164) days following stroke; 59 (66%) at ≤30 days and 31 (34%) at >30 days following stroke. The overall length of stay at rehabilitation ward was 31±13 (median=28, range=17-81) days, with 39 (43%) patients staying at the ward for ≤21 days and 51 (57%) patients for >21 days. Sixteen (18%) patients presented with paralysis and 74 (82%) with paresis of the affected side. Seventy (78%) patients suffered from ischemic stroke and 20 (22%) from hemorrhagic incidents. Full rehabilitation program modalities including hydrokinesitherapy were used in 77 (86%) patients, while comorbidities and overall poor health prevented 13 (14%) patients to be fully involved. Comorbidity was present in 85

Table 1. *General data (number and percentage of patients within subgroups)*

General data	*Subgroup*	*n*	*%*	*Subgroup*	*n*	*%*
Gender	Male	41	46	Female	49	54
Age (yrs)	≤65	29	32	>65	61	68
Days of stroke	≤30	59	66	>30	31	34
Length of stay (days)	≤21	39	43	>21	51	57
Severity	Hemiplegia	16	18	Hemiparesis	74	82
Side	Left	46	51	Right	44	49
Type	Ischemic	70	78	Hemorrhagic	20	22
Program	Full	77	86	Partial	13	14
Comorbidity	0-1	35	39	2 or more	55	61

Table 2. *Comorbidities in patients with stroke (number and percentage of patients with comorbidities)*

Hypertension	76	84
Diabetes	25	28
Hyperlipidemia	25	28
Atrial fibrillation	21	23
Alcohol abuse	4	4

(94%) patients; 35 (39%) patients were without any or with one comorbidity, while 55 (61%) patients had two or more comorbidities (Table 1). The most frequent comorbid condition (or risk factor) was hypertension in 76 (84%) patients, followed by diabetes and hyperlipidemia in 25 (28%) patients and atrial fibrillation in 21 (23%) patients (Table 2).

Initial mRS score at rehabilitation initiation

The mean mRS score at rehabilitation initiation in all patients was 4.07±1.00 (median=4, range=1-5) and by subgroups it is presented in Table 3.

It was higher in patients aged >65 (4.21±0.97) than in younger patients (3.76±1.02; p=0.04) (Fig. 1), in hemiplegic patients (4.94±0.25) than in hemiparetic patients (3.88±1.01; p<0.001) (Fig. 2), and in patients with two or more comorbidities (4.27±0.79) than in those with none or one comorbid condition (3.71±1.15; p=0.007) (Fig. 3).

As expected, the length of stay was longer than 21 days in patients with higher initial mRS scores (4.61±0.64), and 21 days or less in patients with lower initial mRS scores (3.36±0.96; p<0.001) (Fig. 4).

There were no differences in initial mRS scores between genders (p=0.43) or between patients with

Table 3. *Initial mRS score at initiation of rehabilitation (mean ± standard deviation)*

Initial mRS score	*Subgroup*	*Initial mRS score (mean±SD)*	*Subgroup*	*Initial mRS score (mean±SD)*	*p*
Gender	Male	3.98±1.01	Female	4.14±1.00	0.43
Age (yrs)	≤65	3.76±1.02	>65	4.21±0.97	0.04
Days of stroke	≤30	4.20±0.91	>30	3.81±1.14	0.07
Length of stay (days)	≤21	3.36±0.96	>21	4.61±0.64	<0.001
Severity	Hemiplegia	4.94±0.25	Hemiparesis	3.88±1.01	<0.001
Side	Left	3.87±1.11	Right	4.27±0.85	0.06
Type	Ischemic	4.11±0.96	Hemorrhagic	3.90±1.17	0.40
Comorbidity	0-1	3.71±1.15	2 or more	4.27±0.79	0.007

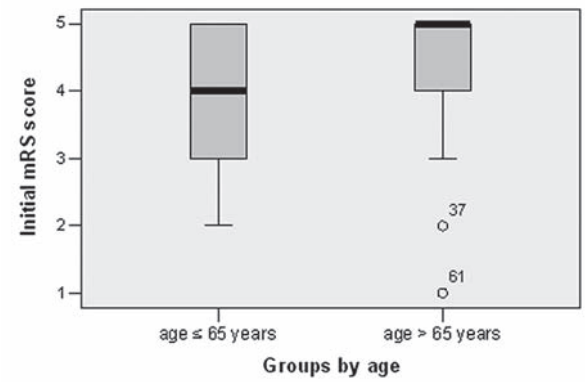


Fig. 1. *Initial mRS score in patients aged ≤65 and >65 years.*

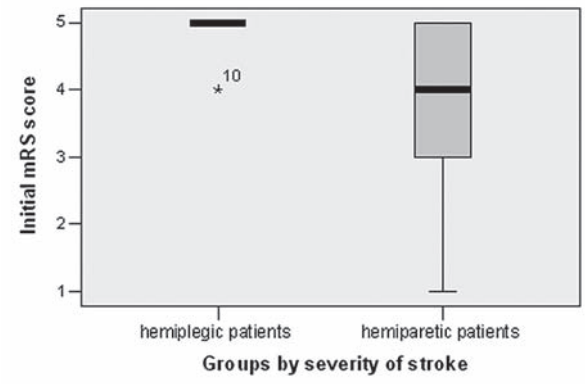


Fig. 2. *Initial mRS score according to the severity of stroke: hemiplegia and hemiparesis.*

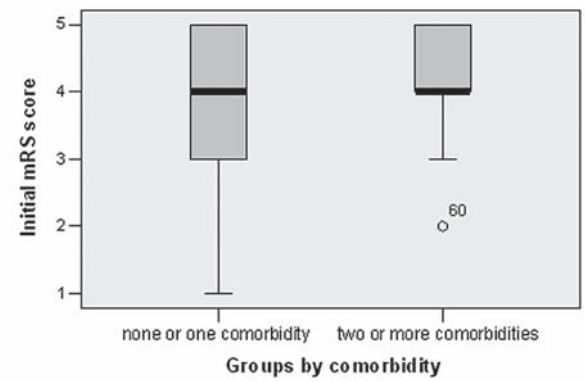


Fig. 3. *Initial mRS score in patients with none or one, and with two or more comorbidities.*

left-side and right-side affection (p=0.06), although being slightly in favor of left-side affection (3.87±1.11) compared to right-side affection (4.27±0.85), or between ischemic or hemorrhagic etiology of stroke (p=0.40). Initial mRS scores were similar in patients admitted to rehabilitation before or after post-stroke day 30 (p=0.07).

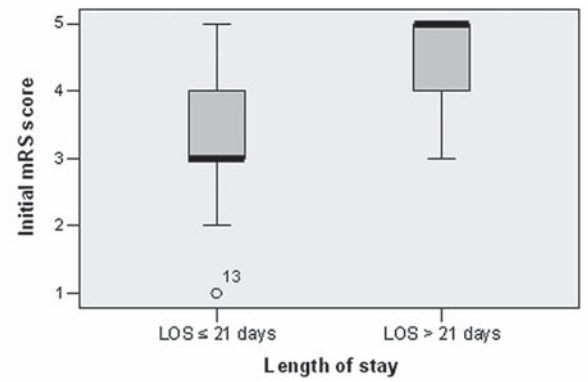


Fig. 4. *Initial mRS score in patients with the length of stay of up to 21 days and more than 21 days.*

Improvement in mRS score

The mRS score at rehabilitation initiation was 4.07±1.00 (median=4, range=1-5), and at the end of rehabilitation it was 3.10±1.18 (median=3, range=1-5) (Fig. 5).

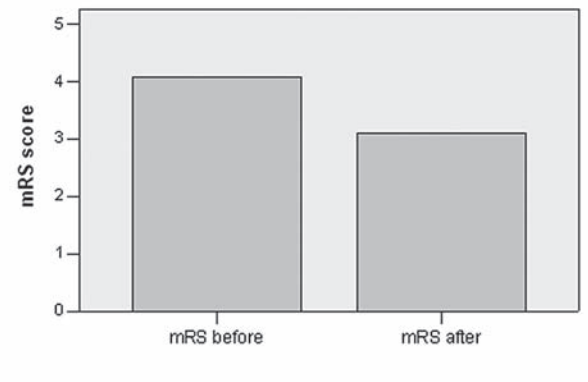


Fig. 5. *mRS score of all patients at rehabilitation initiation (before) and completion of inpatient rehabilitation (after).*

There were significant improvements in mRS scores between initiation and end of rehabilitation (p<0.001), with a mean score of 0.97±0.66. All patient subgroups (by gender, age, days from stroke, length of stay, severity of dysfunction, side involved, type of stroke, type of program, and comorbidity) showed significant improvement in mRS scores (Table 4).

Differences in mRS progress between subgroups of patients are shown in Table 5.

There was no difference in mRS score improvement between patients arriving to rehabilitation before or after post-stroke day 30 (p=0.32) or between patients with the length of stay up to 21 days

Table 4. *Initial mRS score, final mRS score and progress in mRS score on inpatient rehabilitation (mean ± standard deviation)*

mRS score before-after study		*Initial mRS score (mean±SD)*	*Final mRS score (mean±SD)*	*mRS score progress (mean±SD)*	*p*
All		4.07±1.00	3.10±1.18	0.97±0.66	<0.001
Gender	Male	3.98±1.01	2.93±1.13	1.05±0.59	<0.001
	Female	4.14±1.00	3.24±1.21	0.90±0.71	<0.001
Age (yrs)	≤65	3.76±1.02	2.86±1.25	0.90±0.62	<0.001
	>65	4.21±0.97	3.21±1.14	1.00±0.68	<0.001
Days from stroke	≤30	4.20±0.91	3.19±1.17	1.02±0.71	<0.001
	>30	3.81±1.14	2.94±1.21	0.87±0.56	<0.001
Length of stay (days)	≤21	3.36±0.96	2.26±0.97	1.10±0.64	<0.001
	>21	4.61±0.64	3.75±0.89	0.86±0.66	<0.001
Severity	Hemiplegia	4.94±0.25	4.25±0.58	0.69±0.60	<0.001
	Hemiparesis	3.88±1.00	2.85±1.13	1.03±0.66	<0.001
Side	Left	3.87±1.11	2.96±1.33	0.91±0.69	<0.001
	Right	4.27±0.85	3.25±0.99	1.02±0.63	<0.001
Type	Ischemic	4.11±0.96	3.16±1.14	0.96±0.71	<0.001
	Hemorrhagic	3.90±1.17	2.90±1.33	1.00±0.46	<0.001
Program	Full	4.06±1.02	3.09±1.21	0.97±0.69	<0.001
	partial	4.08±0.95	3.15±1.07	0.92±0.64	<0.001
Comorbidity	0-1	3.71±1.15	2.74±1.27	0.97±0.66	<0.001
	2 and more	4.27±0.79	3.35±1.08	0.92±0.68	<0.001

Table 5. *Differences in mRS score progress between subgroups of patients (mean ± standard deviation)*

mRS score progress	Subgroup	mRS score progress (mean±SD)	Subgroup	mRS score progress (mean±SD)	*p*
Gender	Male	1.05±0.59	Female	0.90±0.71	0.28
Age (yrs)	≤65	0.90±0.62	>65	1.00±0.68	0.49
Days of stroke	≤30	1.02±0.71	>30	0.87±0.56	0.32
Length of stay (days)	≤21	1.10±0.64	>21	0.86±0.67	0.09
Severity	Hemiplegia	0.69±0.60	Hemiparesis	1.03±0.66	0.06
Side	Left	0.91±0.69	Right	1.02±0.63	0.44
Type	Ischemic	0.96±0.71	Hemorrhagic	1.00±0.46	0.80
Program	Full	0.97±0.67	Partial	0.92±0.64	0.80
Comorbidity	0-1	0.97±0.66	2 and more	0.96±0.67	0.96

or longer (p=0.09). Similarly, there were no differences according to the right and left side involvement (p=0.44), ischemic and hemorrhagic stroke (p=0.80), gender (p=0.28), age at the time of stroke ≤65 and ≥65 (p=0.49), none or one *versus* two or more comorbidities (p=0.96), and full and partial rehabilitation program (p=0.80). Difference was not found in mRS score progress according to the

severity of the affected side paralysis, i.e. hemiplegia or hemiparesis (p=0.06), although the improvement was more in favor of hemiparetic patients (1.03±0.66) than hemiplegic patients (0.69±0.60). The length of stay of hemiplegic patients (44±11 days) was appropriately longer than in hemiparetic patients (29±12 days; p<0.001).

DISCUSSION

Results of the study demonstrated significant functional gains in rehabilitation process of stroke patients as assessed by mRS. Although admission to rehabilitation after stroke was in most patients appropriate (31±25 days), there were some too early (e.g., 7-9 days) or too late admissions (e.g., 120 or 164 days from stroke). Patients presented with higher mRS scores at rehabilitation initiation (4.07±1.00) indicating high dependence and need of thorough approach and commitment of the whole rehabilitation team, including occupational and speech therapy as well as basic kinesitherapy (2). Moreover, the presence of comorbidities and risk factors in the majority of patients contributed to the complexity of rehabilitation process (10). Some patients were restricted from full program because of contraindications (e.g., the program did not include hydrokinesitherapy). Patients made a statistically significant improvement in the course of rehabilitation (mRS score at end was 3.10±1.18, p<0.001) with a mean difference in mRS score of 0.97±0.66. This indicates change in one level of independence and important functional gains, e.g., from: "unable to walk without assistance and unable to attend to own bodily needs without assistance" in score 4 to: "requiring some help, but able to walk without assistance" in score 3; or from score 3 to score ≤2, which corresponds to independence. As expected and more demanding, initial mRS score at rehabilitation initiation was higher in patients aged over 65 (Fig. 1), hemiplegic patients (Fig. 2) and patients with two or more comorbidities (Fig. 3). The need of focused rehabilitation care in hemiplegic patients was confirmed by a significantly longer length of stay (44±11 *vs*. 29±12 days) necessary to achieve similar mRS score improvement as in hemiparetic patients (p=0.06), although still slightly more in favor of hemiparetic patients (1.03±0.66 *vs*. 0.69±0.60). This means that rehabilitation efforts are valuable in all patients and should be indicated according to the actual rehabilitation needs. Similarly, regardless of the severity of paralysis, the length of stay was longer in patients with higher initial mRS score and shorter (up to 21 days) in patients with lower scores (Fig. 4). The mRS score improvement was evident in all groups of patients, but there was no statistical difference between patients arriving to rehabilitation before or after post-stroke day 30 (p=0.32), or between patients with the length of stay up to and more than 21 days (p=0.09) (Table 5), indicating that rehabilitation was initiated timely and prolonged up to the needs of patients. A recent comparison of Bulgarian and Croatian stroke patients showed significantly better results in mRS improvement in Croatian patients (0.96±0.67) compared to Bulgarian patients (0.42±0.50), with appropriately longer length of stay, which was 33±15 days for Croatian patients and 8±2 days in Bulgarian sample (11). There were no differences in mRS progress between patients according to the side involved, type of stroke, gender, age at stroke, comorbidities, or type of program, again proving that rehabilitation interventions may be of help in all groups of patients. Stroke patients require calm environment with structured rehabilitation effort of the multidisciplinary team, and length of stay that allows for the expected variations of their physical, psychological and motivational state, which occur over days and weeks (2,3).

CONCLUSION

Individually adjusted rehabilitation efforts, if initiated on time and to the extent of the rehabilitation needs of the patients, proved useful in all stroke patients regardless of their age, comorbidity and type and severity of stroke, with the judicious use of available resources.

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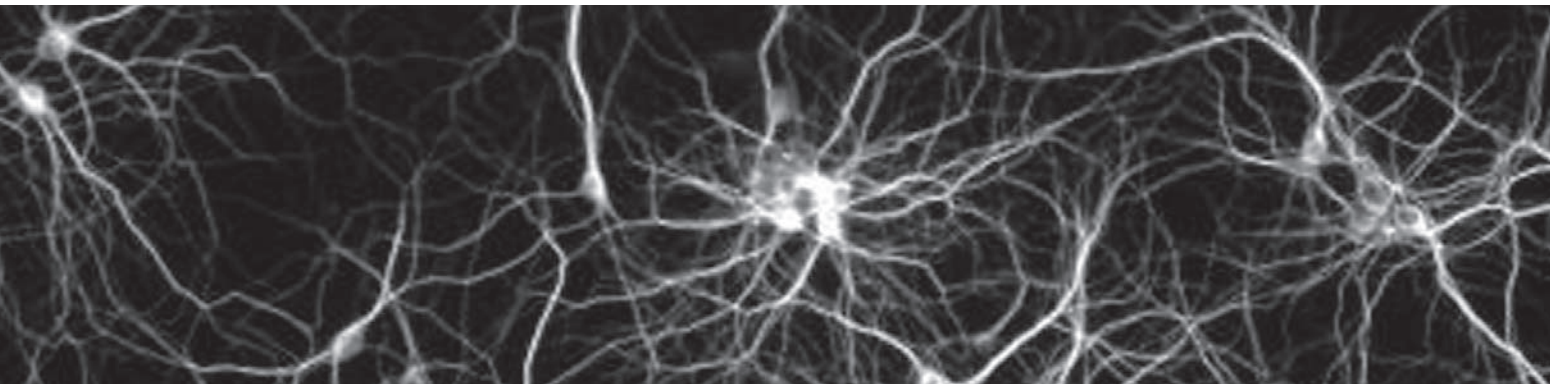
Ishod moždanog udara pacijenata u Hrvatskoj mjeren modificiranom Rankinovom ljestvicom

SAŽETAK - Cilj ovoga istraživanja bio je mjerenje funkcijskih ishoda bolesnika nakon moždanog udara tijekom rehabilitacije u hrvatskom centru za rehabilitaciju uz primjenu modificirane Rankinove ljestvice (mRS). Analizirani su podaci 90 bolesnika s moždanim udarom u 2010. i 2011. godini prema spolu, dobi u vrijeme moždanog udara, danima od udara do početka rehabilitacije, tipu, lateralizaciji i težini udara, duljini boravka na rehabilitaciji, komorbiditetu i programu rehabilitacije. Bilježeni su početni i završni rezultati mRS te promjene (napredak) u bolesnikovim funkcijskim sposobnostima. Bolesnici su na početku rehabilitacije imali rezultat mRS (4,07±1,00) koji je ukazivao na veću ovisnost, a bio je veći u bolesnika starijih od 65 godina (4,21±0,97), u hemiplegičnih bolesnika (4,94±0,25) i u bolesnika s dva ili više komorbiditeta (4,27±0,79). Duljina boravka je bila duža od 21 dana kod bolesnika s većim početnim rezultatom mRS (4,61±0,64). Rezultat mRS nakon rehabilitacije bio je 3,10±1,18 sa značajnim funkcijskim oporavkom od 0.97±0,66. Također, kod svih podskupina bolesnika zabilježen je značajan funkcijski napredak mjeren pomoću mRS. Duljina boravka hemiplegičnih bolesnika (44±11 dana) bila je primjereno veća no u hemiparetičnih bolesnika (29±12 dana) (p<0,001) uz postizanje sličnog napretka u rezultatu mRS (p=0,06), premda malo u korist hemiparetičnih bolesnika (1,03±0,66 prema 0,69±0,60). Zaključuje se da su rehabilitacijski postupci bili vremenski i opsegom sukladni individualnim potrebama bolesnika te se pokazali korisnima u svih bolesnika bez obzira na njihovu dob, komorbiditet, tip ili težinu moždanog udara.

Ključne riječi: ishodi, modificirana Rankinova ljestvica, moždani udar



Pulse glucocorticoid therapy in neuroimmune disorders

R. Baraba Vurdelja, L. Friedrich

ABSTRACT - The goals of this review were to examine published data concerning glucocorticoid pulse therapy in general, as well as evidence-based treatment regimens in several neurological disorders. The aim of pulse therapy is achieving a stronger and more rapid therapeutic effect, and decreasing the need for long-term use of steroids. It is supposed that the action of supra pharmacological doses of glucocorticoids is mediated through nongenomic actions within the cell. Only in multiple sclerosis there is enough evidence from relatively large randomized controlled trials (class I evidence) for the efficacy of pulse therapy, so that it can be recommended as first-line therapy (recommendation level A). More information is needed to define the specific diseases to be treated and the optimal timing of pulses to obtain maximal benefit.

Key words: pulse glucocorticoid therapy, nongenomic glucocorticoid effects, multiple sclerosis, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, diabetic proximal neuropathy

INTRODUCTION

Due to their anti-inflammatory and immunosuppressive action, glucocorticoids are among most frequently used medications. They have been in clinical practice for more than 55 years, and today oral route of administration of small but efficient doses is preferred, usually with a maximal dose of 1 mg of prednisone *per* kg of body weight, or 100 mg of prednisone daily. Very high doses of methylprednisolone administered intravenously were for the first time used in order to prevent renal transplant rejection. Afterwards, a series of reports on successful usage of glucocorticoid mega doses in autoimmune diseases followed. However, there is evident discrepancy between long-standing and frequent usage of glucocorticoids and a shortage of quality evidence about their action, together with precise instructions concerning dosing regimen, duration of treatment, choice of medication and administration route. Frequently, the method of their utilization is based on empirical evidence; so it is not surprising that both oral and intravenous regimens often vary from one affiliation to another.

In this article, the most important information from the available scientific papers about the

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mechanisms of action of pulse glucocorticoid therapy and its application in neuroimmune disorders has been summarized.

GENOMIC AND NONGENOMIC ACTION OF GLUCOCORTICOIDS

Glucocorticoids exhibit their pharmacological effects in two ways. Classic genomic mechanisms are well known – as lipophilic substances, they easily pass through the cell membrane and bind to cytoplasmic glucocorticoid receptors, then migrate to nucleus, and through binding with DNA initiate or inhibit transcription of certain genes and consequently influence synthesis of different proteins, such as cytokines and inflammatory mediators. These processes take a relatively long time; the genomic effect develops after at least 30 minutes, often even after several hours. However, glucocorticoids can exhibit immediate action in terms of seconds to minutes *via* nongenomic mechanisms of action. Nongenomic actions are not related to gene transcription *via* receptor binding – they are the result of binding to specific cell membrane receptors or direct interactions with biologic membranes (1,2). The mechanisms of nonspecific nongenomic effects were explained by Buttgereit *et al*. in a series of studies exploring direct effects of glucocorticoids on the energy metabolism of rat thymocytes that were stimulated with concanavalin-A. It was shown that high concentrations of methylprednisolone changed the physical and chemical qualities of cell membrane by intercalating in it, which caused inhibition of Na and Ca transport through the membrane with a subsequent decrease of free calcium ion concentration in the cytoplasm and decline in the production of ATP (3). Direct effect on the membrane of mitochondria is exhibited through increased proton transport and a disturbance in oxidative phosphorylation (4,5). Due to these prompt effects on immune cells, their activation is obstructed, which leads to rapid immunosuppression. Most likely, there is also a rapid induction of apoptosis of immune cells (6). The genomic mechanisms are developed with low doses of glucocorticoids – it was found that with a 100-200 mg of prednisone dose, all of the glucocorticoid receptors were occupied and an increase in the genomic effect could not be caused by further dose increase. Nongenomic effect is developed with high concentrations and it is an important mechanism of the therapeutic effect of pulse glucocorticoid therapy (Fig. 1).

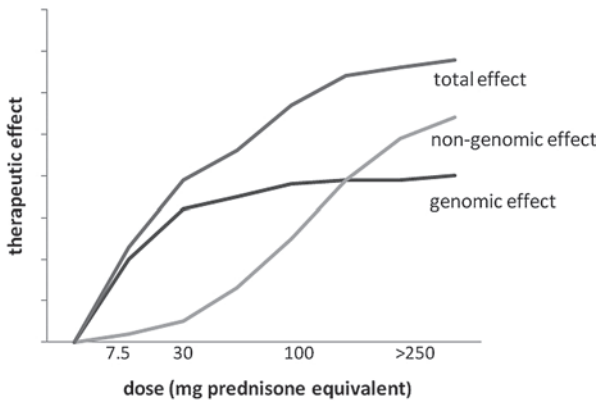

Fig. 1. *Therapeutic effect of pulse glucocorticoid therapy.*

GLUCOCORTICOID PULSE THERAPY

Pulse therapy is defined as the application of suprapharmacological doses intermittently over a short time period. Pulse glucocorticoid therapy is defined as therapy with 250 mg or more of prednisone or its equivalent in one pulse. The increased clinical effect of pulse therapy compared to the usual doses of glucocorticoids is explained by nongenomic mechanisms; when high doses are used, alongside with genomic, the nongenomic effects occur, which leads to a faster and more pronounced therapy response. These findings encourage the use of pulse glucocorticoid therapy in acute exacerbations of immune diseases, but it is also successfully used in chronic autoimmune disorders. The goal of pulse therapy is to achieve a more rapid and efficient therapeutic effect together with a reduced need for long-term administration of high glucocorticoid doses, which results in a lower frequency of unwanted effects. The relative potencies of nongenomic and classic genomic effects are very different. For pulse therapy, a strong nongenomic effect is desired, with a balance between genomic and nongenomic potency, so methylprednisolone (MP) and dexamethasone are preferred (7,8). The dosage regimen is not standardized. A dosage of 500-1000 mg MP (10-20 mg/kg) or 50-200 mg of dexamethasone (2-5 mg/kg) is commonly used. Furthermore, the length of treatment and the frequency of pulses for different disorders have not been defined. Pulse therapy is generally well tolerated. The classic side effects of long-term therapy are typically not expected (9). Most often, redness of the face, metallic taste in mouth, insomnia, mild edema and mood changes are experienced. Although it is believed that pulse therapy with MP does not lead to a change in bone density, Hauge-

berg *et al*. report that pulse therapy in patients with different rheumatologic disorders leads to a notable loss of bone mass. Interestingly, the loss was most profound during the first 6-12 months of therapy, and parallel administration of bisphosphonates had a favorable effect (10). In a study on 539 subjects with systemic lupus erythematosus, Zonana-Nacach *et al*. did not find relationship between intravenous MP therapy and avascular hip necrosis; the only statistically significant association was established between pulse therapy and cognitive dysfunction (11). Although pulse therapy is generally safe, cases of sudden death, cardiac arrhythmia and cardiac arrest have been described; most often when the infusion was administered very rapidly (9,12). Therefore, short infusions are not recommended; slow infusion (2 hours) is safer because a sudden electrolyte imbalance is avoided. The first pulse therapy ought to be under close medical supervision due to the possibility of anaphylaxis, psychosis, pancreatitis, hepatitis, seizures and blood pressure changes. During and after therapy, monitoring of cardiac rhythm, blood pressure, blood glucose and electrolytes is required. Contraindications for pulse glucocorticoid therapy include systemic infection, unregulated arterial hypertension, psychosis, drug hypersensitivity, and active peptic ulcer.

PULSE THERAPY IN MULTIPLE SCLEROSIS

Numerous studies have proved the efficacy of MP intravenous pulse therapy in the management of acute multiple sclerosis relapse (level A recommendation). A significant reduction of contrast enhancing lesions on MR images has been demonstrated, although this effect is transient, i.e. prevention of new active lesions is not possible. The occurrence of new inflammatory activity is probably dependent on the dose and length of treatment (13,14). However, optimal dosing regimen (considering clinical efficacy and unwanted effects) has not yet been fully established. Great variability exists in terms of doses, duration of treatment and ways of its termination. Applied doses of MP in different studies vary from 500 mg (15), 15 mg/kg (16), 1000 mg (17,18) up to 2000 mg in a single pulse. Today, a generally accepted treatment is 500 to 1000 mg daily over 3-5 days (19). Occasional studies that compared the efficacy of different doses of MP provide evidence in favor of larger doses. Oliveri *et al*. compared the efficacy of 500 mg and 2000 mg of IV MP over the course of five days. Larger dose was significantly more efficient in reducing the number of contrast enhancing lesions 30 and 60 days after therapy, i.e. it showed a stronger and longer effect on maintaining the integrity of blood-brain barrier after clinical relapse (20). Animal studies also showed results that were in favor of ultrahigh doses. It was proved that high doses of MP induced apoptosis of T cells in serum and *in situ* in experimental autoimmune encephalomyelitis. This effect was directly proportional to the dose (10 and 50 mg/kg MP) and severity of the disease, i.e. in a severe disease due to a more pronounced damage of the blood-brain barrier, the same dose caused a stronger effect than in a mild form of the disease. A dose of 1 mg/kg was ineffective in all disease forms (6). These data justify the use of higher doses of MP (2 g) or duration of treatment longer than 3 days with 1 g MP in cases of insufficient therapy response to lower doses.

Frequently, once the pulse therapy has been finished, oral corticosteroid therapy is initiated for a shorter period of time in smaller, gradually decreasing doses. It was used differently by different authors. This method of treatment was not proven to be effective (21).

Since 1990, oral administration of high doses of MP has been analyzed and in most studies it proved to be as efficient as intravenous application (22,23). Pulse therapy in multiple sclerosis is well tolerated and usually accompanied by transient side effects. There is no evidence for osteoporosis development in repeated pulse therapy in multiple sclerosis (24).

PULSE THERAPY IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Chronic inflammatory demyelinating polyneuropathy (CIDP) is historically described as a polyneuropathy that responds to corticosteroids. In CIDP, according to EFNS guidelines, intravenous immunoglobulins are indicated (level A recommendation) or glucocorticoids (level C recommendation – no large controlled studies were performed) (25). In an attempt to achieve a faster therapeutic effect and lessen the side effects of long-term corticosteroid therapy, pulse therapy was analyzed in both smaller and larger controlled studies. So far, there is no solid evidence in favor of pulse therapy, but the conclusion of existing studies is that it is as effective as immunoglobulins, but cheaper, and that

it has less unwanted side effects compared to classic glucocorticoid therapy (26,27). However, unlike pulse therapy in a multiple sclerosis relapse, here the pulse therapy is applied long-term, repeatedly. For this reason, side effects are more pronounced than in MS treatment. In long-term use, osteoporosis is possible and prevention is needed.

Dosing regimen of pulse therapy differs from author to author. Lopate *et al.* in a retrospective study found the recovery of patients to be the same when treated with pulse intravenous MP, oral prednisone or immunoglobulins. Treatment was started with 1000 mg MP for 3-5 consecutive days, followed by 1000 mg once a week for 4 weeks and then a gradual decrease in the frequency of pulses and doses was carried out, depending on the patient clinical state (26). Muley *et al.* in an open prospective study successfully applied pulse oral MP 500 mg a week for 3 months, followed by a decrease of pulse dose by 50-100 mg every three months, depending on the patient clinical state (27). When pulses of high doses of dexamethasone were applied (40 mg orally on 4 consecutive days of every month for 6 months), remission was achieved as with oral prednisone therapy (28). The same group of patients were followed long-term in a prospective cohort study. The results suggest advantages of pulse dexamethasone therapy due to faster recovery, somewhat longer remission and fewer unwanted side effects when compared with oral prednisolone treatment (29). Nobile-Orazio *et al.* compared the efficacy and tolerability of six-month therapy with IV immunoglobulins and IV MP (500 mg daily for 4 consecutive days each month). In the MP group, a more frequent discontinuation of therapy was noted due to intolerability and weak efficacy, but on the other hand, MP caused longer remission compared to immunoglobulin (30).

PULSE THERAPY IN MYASTHENIA GRAVIS

Glucocorticoid therapy of myasthenia gravis has some peculiarities compared to other conditions. Namely, when initiating therapy, a transient deterioration in about 50% of myasthenia patients is noted, and among those, 6%-10% can have serious deterioration, which can lead to a myasthenic crisis (31,32). Current view is that initiating therapy with low doses and with a gradual increase reduces the risk of deterioration, and in an outpatient setting mild forms of the disease are preferably initially treated with a low dose of prednisolone (33). If immunosuppression is needed, glucocorticoids are the first therapeutic choice in this condition (level of evidence IV – efficacy has not been proved in case control studies) (34). There are ever more scientific reports on the advantages of pulse therapy with MP in myasthenia gravis – fewer side effects, faster recovery and even less pronounced disease deterioration on therapy initiation have been reported. It is somewhat paradoxical that mega doses are used in order to have less side effects, but this proved to be true according to many papers on this topic. Namely, with this type of treatment, a lower long-term maintenance dose is required, which reduces the frequency of unwanted side effects. Better results are notably achieved in older patients, who due to their age and comorbidities often do not tolerate long-term corticosteroid therapy well (35). Still, a lack of highly rated studies prevents reaching evidence-based recommendations. Also, there are no recommendations on the dose of a single pulse or dosage regimen. Pulse therapy with MP was applied in different ways by different authors: intermittently 20-30 mg/kg without a maintenance dose in pediatric patients with myasthenia whose condition was not sufficiently controlled by oral prednisone therapy (36); 2000 mg every five days day until improvement, followed by 30 mg oral prednisone with gradual dose decrease (37); 2000 mg on two consecutive days, with the duration of improvement of 4-14 weeks (38); and plasmapheresis with 1000 mg IV MP administered after plasmapheresis and for the next two days in the morning, long term maintenance dose 5-15 mg prednisone (35). We successfully applied pulse therapy with IV MP as initial therapy in four female patients (1000 mg MP for three consecutive days or 500 mg MP for four to five consecutive days), and also on four occasions in patients who were on smaller doses of glucocorticoids, but experienced exacerbation of the disease. No deterioration of the disease after therapy initiation was observed. Nevertheless, additional studies are required to evaluate long-term efficacy and safety of this type of therapy in myasthenia gravis.

PULSE THERAPY IN PROXIMAL DIABETIC NEUROPATHY

Clinical and histopathological studies appearing in the 1990s pointed to the immune mechanisms in the etiopathogenesis of this condition (microvasculitis of vasa nervorum) and justified the use of immunosuppressive and immunomodulatory therapy in this disease. Still, an optimal therapy for these patients has not yet been established, partly

so because this condition tends to resolve spontaneously. There are numerous reports on a beneficial action of immunomodulatory and corticosteroid therapy on positive sensory symptoms and faster recovery (39). In a retrospective study with 500 mg IV MP on two consecutive days every two weeks during three months, Kilfoyle *et al*. report a prompt effect on pain reduction and slower effect on motor deficit recovery (40). In an abstract from 2006, Dyck *et al*. report results from a double-blind placebo controlled study on 75 patients with IV MP (significant pain reduction was noted, but without a statistically significant difference in final recovery) (41). Nevertheless, a Cochrane meta-analysis from 2009 does not find evidence in randomized controlled trials that would support immunotherapy application in this condition (42). An updated Cochrane review from 2012 still does not report any new evidence that could contribute to a recommendation for corticosteroid use in this condition (43).

CONCLUSION

Administration of very high doses of glucocorticoids (above 250 mg MP) exhibits, apart from genomic action, an additional nongenomic action, which results in a faster and stronger therapy response. In multiple sclerosis relapse, pulse therapy alone is sufficient to achieve remission, but in the majority of patients with a chronic autoimmune disease such as CIDP or myasthenia gravis, due to transience of the initial positive effect of pulse therapy, pulse therapy alone is not enough to achieve remission. For this reason, initial pulse therapy is usually followed by long-term application of smaller glucocorticoid doses or pulse therapy is repeated long-term. Apart from multiple sclerosis relapse, so far there is no evidence from highly ranked studies, which would enable making recommendations for this therapy in neuroimmune conditions. All studies on this topic agree that pulse therapy results in fewer unwanted side effects compared to classic glucocorticoid therapy, although this is not yet supported by prospective randomized controlled studies. The treatment with corticosteroids remains an art, balancing the severity of the individual patient's disease, concurrent medical issues, and clinical experience.

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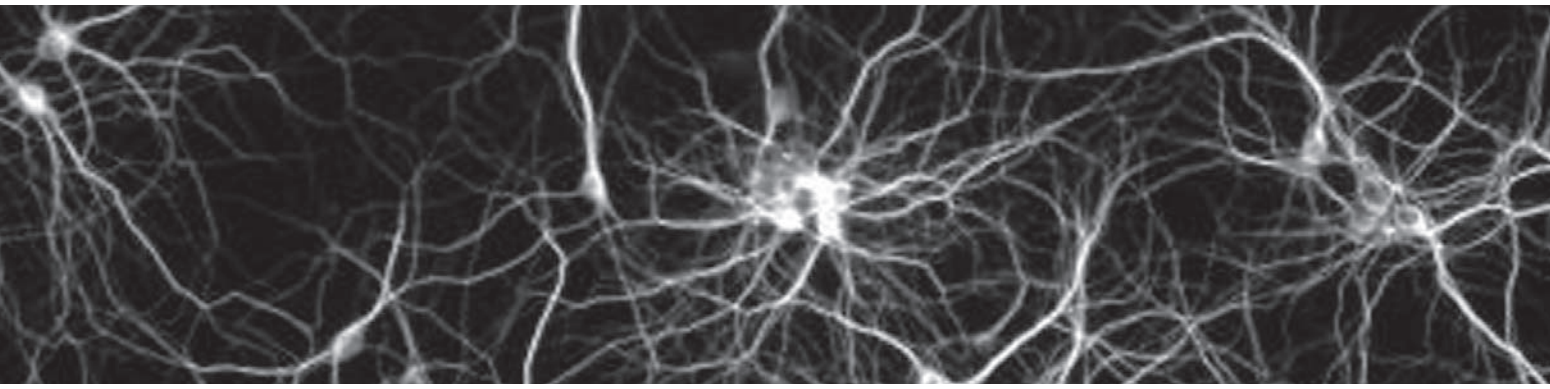
Pulsna glukokortikoidna terapija kod neuroimunoloških poremećaja

SAŽETAK - Cilj ovoga pregleda je bio je istražiti objavljene podatke koji se odnose općenito na pulsnu glukokortikoidnu terapiju, kao i režim liječenja utemeljen na dokazima u različitim neurološkim bolestima. Pulsnom terapijom postiže se brži i snažniji terapijski učinak uz smanjenje potrebe za dugoročnom steroidnom terapijom. Pretpostavlja se da se djelovanje suprafarmakoloških doza glukokortikoida razvija putem negenomskih mehanizama u stanici. Jedino u multiploj sklerozi postoji dovoljno dokaza na temelju relativno velikih randomiziranih kontroliranih studija o učinkovitosti pulsne terapije (klasa dokaza I.), tako da se može preporučiti kao prva linija terapije (preporuka razine A). Potrebni su dodatni podaci da bi se definirao način liječenja u pojedinim bolestima i optimalna primjena pulseva za postizanje maksimalnog učinka.

Ključne riječi: pulsna glukokortikoidna terapija, negenomsko glukokortikoidno djelovanje, multipla skleroza, miastenija gravis, CIDP, proksimalna dijabetična neuropatija



Carnitine palmitoyl transferase type 2 deficiency - case report and review of the literature

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ABSTRACT - Carnitine palmitoyl transferase (CPT) deficiency is a relatively rare disease of fatty acid oxidation inherited autosomal recessively. CPT2 deficiency presents frequently in adults with rhabdomyolysis and myoglobinuria triggered most often by prolonged exercise. Carnitine is required for the transfer of long-chain fatty acids from the cytoplasm to the mitochondrial matrix for their oxidation. Strenuous exercise is known to increase serum creatine kinase (CK) in nearly all healthy people and can be elevated often over ten times the upper limit of normal. Rhabdomyolysis can be of inherited etiology (disorders of glycogenolysis, fatty acid oxidation, mitochondrial respiratory chain pathways) or acquired (trauma, compartment syndrome, drugs, caffeine, toxins, infections, inflammatory muscle diseases, and exertion). Here we present a female patient with CPT2 deficiency diagnosed after recurrent rhabdomyolysis upon physical exertion and carbohydrate-restrictive diet. With the implementation of dietary measures and lifestyle changes that included more frequent but shorter interval exercise and avoidance of inappropriate physical exertion, the patient had a normal neurological status with only slightly elevated CK levels. This example illustrates the importance of careful monitoring of patients with increased levels of CK, even when there are no evident clinical, histopathologic or electromyoneurography (EMNG) indicators of myopathy.

Key words: palmitoyl transferase, rhabdomyolysis, carnitine

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INTRODUCTION

Carnitine palmitoyl transferase (CPT) deficiency is a relatively rare disease of fatty acid oxidation inherited autosomal recessively. CPT1 deficiency presents with recurrent attacks of fasting hypoketotic hypoglycemia but not affecting the heart and the muscle. The more common of the two, CPT2, presents frequently in adults with rhabdomyolysis and myoglobinuria triggered most often by prolonged exercise. More severe forms will present during the neonatal period. This report will review the features of CPT2 deficiency caused by exertional rhabdomyolysis in a genotype-verified adult patient.

Carnitine is required for the transfer of long-chain fatty acids from the cytoplasm to the mitochondrial matrix for their oxidation (1). For fatty acids to enter the mitochondria, they must undergo conjugation to carnitine, which will then accumulate inside the cell by the action of organic cation transporter type 2 (OCTN2) carnitine transporter in the heart, muscle, and kidney. CPT, located in the inner part of the outer mitochondrial membrane, will induce the formation of a high-energy ester bond with long chain carboxylic acids. Acylcarnitine is translocated across the inner mitochondrial membrane *via* carnitine acylcarnitine translocase and cleaved by CPT2 in the inner aspect of the inner mitochondrial membrane. Carnitine is then released to the mitochondrial matrix for the cycle to repeat itself. Consequently, fatty acids are conjugated back to coenzyme A (CoA) in order to enter beta-oxidation with the production of acetyl-CoA for oxidative phosphorylation or production of ketone bodies in the liver (2). Deficiencies can also arise in OCTN2 carnitine transporters and carnitine-acylcarnitine translocase, however, these will not be discussed here.

CPT 1 deficiency

Three different isoforms exist including the liver, muscle and brain, with only the liver-type showing deficiency in humans. It usually presents itself in infancy with altered mental status, hepatomegaly, nonketotic hypoglycemia, elevated free fatty acids, elevated heart function tests, increased plasma carnitine levels, and mild hyperammonemia triggered by fasting or viral illness (2). Diagnosis is based on the elevation of free and short-chain acylcarnitine, with low levels of long-chain acylcarnitine, and confirmed by the assay of CPT1 in fibroblasts whose activity is reduced to 5%-20% (2).

CPT2 deficiency

CPT2 deficiency is seen more frequently, and often presents in adolescents or young adults with evident muscle involvement. Presentation in infancy indicates a more severe form of the disease, usually with respiratory distress, seizures, altered mental status, hepatomegaly, cardiomegaly, arrhythmia, dysmorphic features, renal dysgenesis, and neuronal migration defects (2). The myopathic form can present with or without myoglobinuria and elevated serum CK triggered by exertional exercise, cold, fever, infection, or prolonged fasting. Diagnosis is based on an abnormal acylcarnitine profile obtained from blood spotted on filter paper with increased (C16 + C18:1)/C2 ratio (3). Regarding their genotype, most patients have at least one copy of S113L, P50H, or Q413fs-F448L mutation. This creates an accumulation of fatty acids in fibroblasts (4). However, histologic analysis fails to show any myopathologic hallmarks.

Rhabdomyolysis

Strenuous exercise is known to increase serum CK in nearly all healthy people and can often be elevated often ten times the upper normal limit (5). However, there are differences in baseline between races and genders (6,7). Nevertheless, elevated levels of CK indicate a breakdown of striated muscle, otherwise known as rhabdomyolysis. Clinically, rhabdomyolysis presents with features such as myalgia, tenderness, muscle weakness, swelling of involved muscles and myoglobinuria, manifesting as dark or tea colored urine. It can be of inherited etiology (disorders of glycogenolysis, fatty acid oxidation, mitochondrial respiratory chain pathways) or acquired (trauma, compartment syndrome, drugs, caffeine, toxins, infections, inflammatory muscle diseases, and exertion) (8-10). Consequently, recurrent rhabdomyolysis can lead to acute kidney injury, disseminated intravascular coagulopathy, arrhythmias, hyperkalemia, and other metabolic disorders.

Elevated levels of CK after strenuous exercise typically occur in subjects who, besides the typical soreness after exercise, are otherwise asymptomatic, although there is a wide variation between individuals engaged in the same degree of exertion. CK levels parallel the increase in myoglobin and are used clinically as a surrogate marker of muscle injury to determine whether to administer treatment to prevent renal failure (11). Greater increases also occur after excessive muscle activity.

CASE REPORT

Here we present a female patient with CPT2 deficiency diagnosed after recurrent rhabdomyolysis upon exertion and carbohydrate-restrictive diet. First signs of myalgia due to physical activity occurred at the age of ten and usually subsided within 2-3 days. Upon subsequent recurrences, EMNG and immunologic testing were performed but produced normal results. Muscle biopsy showed inflammatory myopathy. After yet another episode of physical exertion in 2010 (prolonged dancing), the patient described weakness in her legs, nausea, and renal insufficiency was diagnosed with a CK of 11000. Genetic analysis was performed, which demonstrated two gene mutations: c.338 C to C/T; p. S113S/L c.534-558 del 25 bp and ins T {del AACCCTGCAAAAAGTGACACTATC ins T]. Both mutations have been previously described in the literature (4). Our patient is a heterozygote with two recessive mutations, which confirm the diagnosis of muscle CPT2 deficiency. With appropriate dietary measures (frequent smaller meals rich in carbohydrates), hydration, and antipyretics, our patient now shows no signs of the disease, with only slightly elevated CK levels.

DISCUSSION

Leg pains and exercise intolerance are common complaints in children and young adults. In most cases, the cause will be considered benign and idiopathic, especially when symptoms occur at nighttime, after unaccustomed intense exercise, or in the course of a concurrent viral illness (12,13). Myopathic diseases presenting with leg pain and cramps carry a risk of either acute rhabdomyolysis or progressive muscle weakness and can be easily missed. Milder episodes of rhabdomyolysis presenting with myoglobinuria can go unnoticed or be mistaken for hematuria and investigated by nephrologist, leading to a delay in the correct diagnosis (12,13). When a history of dark urine in association with muscle aches is given, biochemical assessment of urine during an episode is essential to confirm myoglobinuria. All neurologists, especially those dealing with neuromuscular diseases, are faced with elevated CK values in patients with an unknown muscle disease origin. Chronically elevated CK of unknown origin is otherwise known as benign hyper-CK-emia. In patients with muscle dystrophies, muscle aches usually occur after, but not during, exercise and myoglobinuria is usually mild with no severe rhabdomyolysis or renal failure (13). In Becker muscle dystrophy, exercise-induced cramps and myoglobinuria may be the only symptoms before muscle weakness develops and the diagnosis is established (14,15). Exertional myalgia and rhabdomyolysis may also be a presenting feature in female carriers of X-linked dystrophinopathies (16). Disorders of glycogen metabolism may also cause muscle pain and elevated CK values caused by exercise. McArdle disease is the most common disorder of glycogen metabolism and is caused by homozygous mutations in the PYGM gene, resulting in complete or almost complete absence of the muscle glycogen phosphorylase enzyme (17). Patients with this disease experience muscle fatigue followed by discomfort in the first few minutes of aerobic activity and they are vulnerable to rhabdomyolysis following isometric muscle activity (weights lifting, squatting) (18). Other, less frequent inherited metabolic diseases, including phosphorylase B kinase deficiency, phosphoglycerate kinase deficiency, phosphoglycerate mutase deficiency, beta enolase deficiency and lactate dehydrogenase deficiency, may also cause rhabdomyolysis after exercise (19). In rare cases, congenital myopathies such as malignant hyperthermia susceptibility, central core disease, centronuclear myopathy or multi-minicore disease may cause rhabdomyolysis after exercise (20-25). Disorders of fatty acid oxidation are rare and often present in infancy with episodes of hypoglycemia and liver and cardiac involvement but milder cases may cause first symptoms (elevated CK values, muscle pain, exercise intolerance or rhabdomyolysis) in adolescent age, usually provoked by exercise, prolonged fever or reduced food intake. CPT2 deficiency presenting in adolescents and young adults is characterized by recurrent myoglobinuria, high CK values, muscle aching, stiffness induced by prolonged aerobic exercise, fasting, infections, emotional stress or cold (13). The condition may appear silent until the first episode of rhabdomyolysis with CK value above 100000 IU/L (26). Very long-chain acyl-CoA deficiency has similar presentation to CPT2 deficiency (27).

The value of CK, like myoglobin, may be elevated in various states and diseases (28) (Tables 1 and 2).

Myopathy, leg pains, exercise intolerance and elevated levels of CK may also be a consequence of certain drug side effects. Statin-induced myopathy is a common side effect of these vastly prescribed drugs. However, it is important to mention that different, often prescribed, drugs, or a combination of drugs (antiarrhythmics, antihypertensives, benzodiazepines), which compete for the same meta-

Table 1. *Differential diagnosis of myoglobinuria*

Differential diagnosis of myoglobinuria	• Prolonged physical exertion • Viral and bacterial infections • Toxins (alcohol) • Neuroleptic malignant syndrome • Heat shock • Trauma • Prolonged febrile state • Inflammatory myopathy • Limb girdle muscular dystrophy • Malignant hyperthermia • Metabolic myopathy

Table 2. *Differential diagnosis of increased CK value*

Myopathies	Muscle dystrophies Congenital myopathy Metabolic myopathy Inflammatory myopathy Drug-induced myopathy Healthy gene carriers for muscular dystrophy
Ion channel disorders	
Motor neuron disorders (in case of muscle mass deterioration due to denervation)	Amyotrophic lateral sclerosis Spinal muscular atrophy Post polio syndrome
Neuropathy	Guillain-Barré syndrome
Viral diseases	Hepatitis C Flu
Drugs	Statins, niacin, gemfibrozil Chloroquine Colchicine Cyclosporine Zidovudine
Hypothyroidism Hypoparathyroidism	
Operative procedures	
Trauma injections, EMNG	
Increase in exercise	
Increase in muscle mass	
Racial differences	
Gender differences	
'Idiopathic hyper-CK-emia'	

bolic processes, may burden or change the way of acquiring metabolic energy in muscle and in this way make the muscle more sensitive to external damage, like strenuous exercise.

In this paper, we present a young woman with a long history of occasional elevations of CK with previously normal neurological and EMNG findings. Our patient suffered a life-threatening condition consisting of renal failure and rhabdomyolysis provoked by exercise and minimal food intake. With further metabolic and molecular genetic analysis, the diagnosis of CPT2 deficiency was made. After the diagnosis, the patient was given dietary recommendations that involved repeated intakes of small meals rich in carbohydrates, followed by clinical recovery. This example illustrates the importance of careful monitoring a patient with increased levels of CK, even when there are no evident clinical, histopathologic or EMNG indicators of myopathy. Every patient with elevated CK levels of unknown origin should obtain neurological monitoring and control when taking into account the different conditions, diseases, or other external factors that could be causing this sign. Recognizing the exact causes of elevated CK may prevent the development of more severe forms of muscle disease, serious drug complications, or related diseases of other organs. Leg pain and elevated CK values are common symptoms with many causes; however, myalgia associated with exercise intolerance may be the presenting feature of underlying metabolic or myopathic disease with potentially serious consequences. Careful history and examination should point to the most appropriate first-line investigations. Elevated CK values may reflect different disorders of energy metabolism in the demanding muscle cell and properly diagnosing the muscle disease can prevent the development of serious complications.

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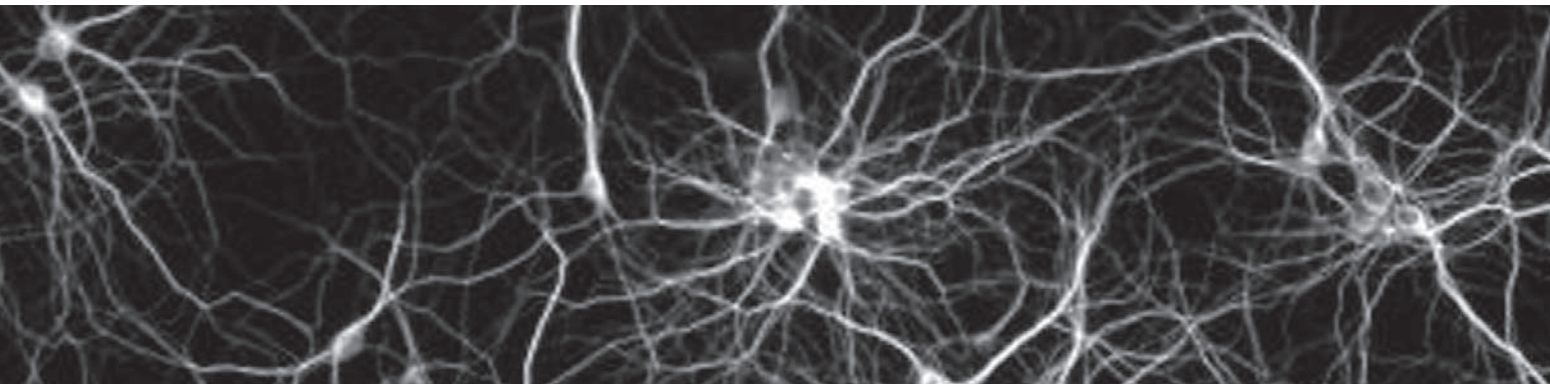
Deficit karnitin palmitoil transferaze tipa 2 – prikaz bolesnice i pregled literature

SAŽETAK - Deficit karnitin palmitoil transferaze (KPT) je rijetka autosomno recesivno nasljedna bolest u osnovi koje je poremećaj oksidacije masnih kiselina i dobivanje energije iz masti. Simptomi deficita KPT tipa 2 obično se javljaju u odrasloj dobi nakon redukcijske dijete, febriliteta ili značajnog fizičkog opterećenja. Karnitin je neophodan za transport dugolančanih masnih kiselina iz citoplazme u mitohondrijski matriks za daljnju oksidaciju i proizvodnju energije. Iznimna fizička aktivnost može dovesti do porasta serumske kreatin kinaze u zdravih osoba, pri čemu ta vrijednost može biti i višestruko veća od normalnih vrijednosti. Rabdomioliza može imati različite uzroke (toksini, lijekovi, infekcije, upalna bolest mišića), a nasljedni poremećaji metabolizma su važna skupina ovoga ponekad životno ugrožavajućeg stanja. U ovom radu prikazujemo bolesnicu u koje je tijekom života u više navrata dokumentirana visoka vrijednost kreatin kinaze pa je zbog tog nalaza neurološki pregledana, a učinjena je i elektromioneurografija koja je bila urednog nalaza. U naše je bolesnice došlo do naglog razvoja životno ugrožavajućeg stanja, odnosno rabdomiolize s akutnom bubrežnom insuficijencijom, nakon redukcijske dijete i pojačanog fizičkog napora. Nakon postavljanja dijagnoze deficita KPT tipa 2 i provođenja odgovarajućih dijetetskih mjera bolesnica je dobro, urednog neurološkog statusa s minimalno povećanom vrijednosti kreatin kinaze. Ovaj primjer ilustrira važnost praćenja i dijagnostičke obrade bolesnika s povišenim vrijednostima kreatin kinaze u kojih u podlozi navedenog laboratorijskog nalaza mogu biti najrazličitiji uzroci pa i nasljedni poremećaj metabolizma.

Ključne riječi: palmitoil transferaza, rabdomioliza, karnitin



Late sequels of Herpes simplex encephalitis

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ABSTRACT - Herpes simplex virus encephalitis (HSVE) is a serious disease associated with high morbidity and mortality. In the last two decades, considerable progress has been made in the diagnosis and treatment of the disease; however, the risk of HSVE and its complications remains high. The predilection sites for the infection are temporal lobes, less frequently frontal lobes. The most common late complications are epilepsy of the complex partial seizure type, behavioral changes, and cognitive impairment. While epilepsy can be successfully treated with good therapeutic outcome, cognitive impairment is permanent in a high proportion of individuals having sustained HSV1 encephalitis. Polymerase chain reaction of viral DNA is a reliable diagnostic assay, while treatment includes acyclovir therapy along with other symptomatic therapeutic procedures. A female patient with late stage HSVE is described in order to illustrate the severe memory and behavioral impairment consequential to HSV infection, to report on diagnostic work-up results, and to point to the role of early diagnosis and treatment of this severe disease.

Key words: herpes virus, encephalitis, cognitive impairment, cognitive function testing, single-photon emission computed tomography

INTRODUCTION

Herpesvirus type 1 (HSV1) belongs to the group of herpesviruses, which also includes varicella-zoster virus and cytomegalovirus (1,2). Animal models used in the studies of the disease pathophysiology suggest that the virus enters the central nervous system *via* peripheral nerves. Temporal lobes are the most common site of infection; extratemporal pathology is found in about 15% of patients, whereas temporal and extratemporal pathology is simultaneously present in about 55% of patients. Herpes simplex virus encephalitis (HSVE) is the most common non-epidemic encephalitis, with the incidence estimated at 2 million *per* year (3).

DIAGNOSIS

Cerebrospinal fluid polymerase chain reaction for detection of viral DNA (deoxyribonucleic acid).

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Electroencephalogram (EEG) typically shows focal temporal lesions or diffuse slowing down.

Magnetic resonance imaging (MRI) of the brain typically reveals lesions in the region of temporal lobes, occasionally also hemorrhage and early lesions in the cerebral hemispheric white matter (4-9).

CASE REPORT

A female patient born in 1972 was diagnosed with HSVE in January 2009.

Personal history: Mother to two children; completed 12-year education with good results. Before HSVE, treated for depression for 3 years; still on occasional psychiatric follow up.

Current disease: Disease onset characterized by nonspecific signs of viral infection. On the second day of disease, the patient developed confusional state and was hospitalized according to the place of residence. On day 4 of disease, transferred to the University Hospital for Infectious Diseases because of deteriorated state of consciousness. On admission, the patient was soporous, with urinary incontinence and without overt motor events on extremities. Diagnostic work-up indicated HSVE. During 46-day hospital stay, the patient's condition gradually improved and her neurologic status was normal at discharge from the hospital. Memory impairment was noted in her letter of discharge. Brain MRI acquired during her hospital stay showed extensive edema of the left temporal lobe, along with lesions of the gray and subcortical white matter, eradicated border between the gray and white mat-

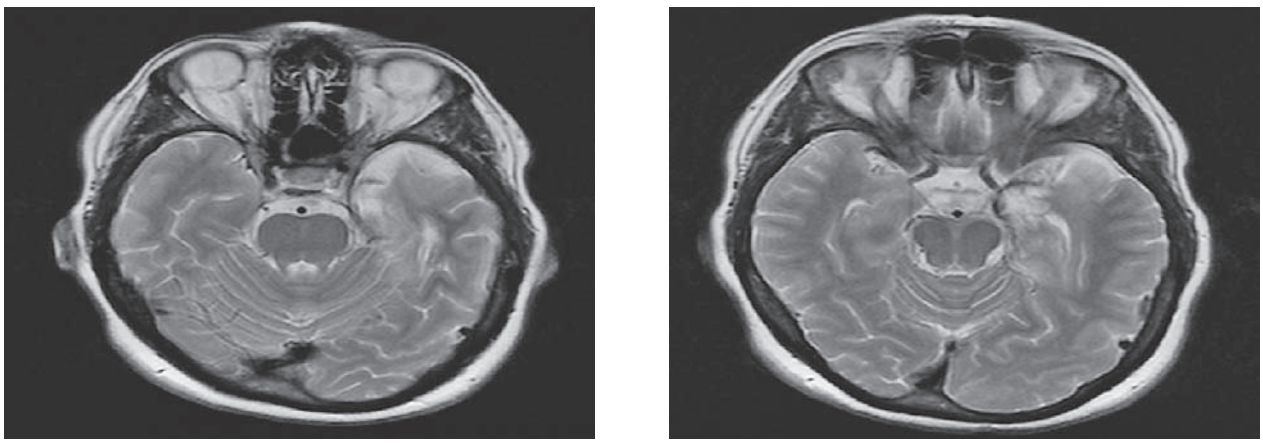

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Fig. 1. *Brain MRI: edema temporobasally on the left (a), with eradicated border between the gray and white matter (b).*

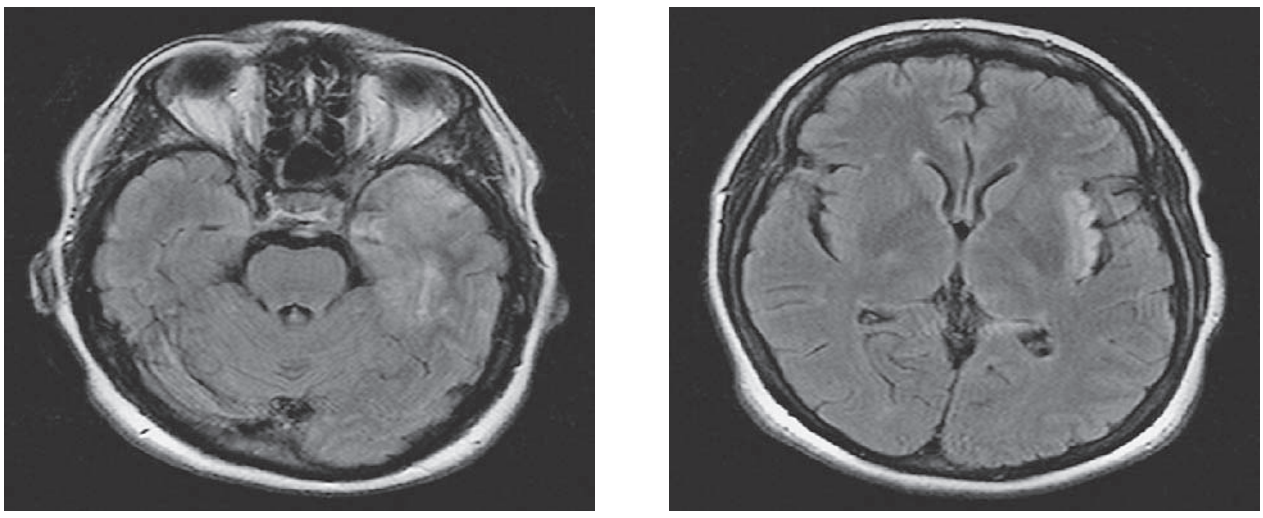

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Fig. 2. *Brain MRI: extensive lesions in the left temporal lobe (a) and insularly on the left (b).*

ter, and identical lesions in the insular region on the left. Upon contrast administration, spotty imbibition of temporal gyrus and insula on the left, with discrete imbibition mediotemporally and leptomeningeal imbibition insularly on the right was observed (Figs. 1 a, b and 2 a, b).

On regular infectological follow up four months later revealed severe memory impairment, therefore the patient was advised to undergo neurological examination. She was examined at general neurology outpatient clinic of the Clinical Department of Neurology, Zagreb University Hospital Center, and scheduled for work-up at Department of Cognitive Function Disorders.

TEST RESULTS:

1) Cognitive function test results:

Mini Mental State Examination (MMSE) 26; corrected for age and education 26 (87%); mMMSE 51 (82%); clock drawing test (CDT) 9; retrograde amnesia for all events occurring in the past 6 years of viral infection; markedly disturbed direct verbal and visual memory; mild disturbance of delayed visual recognition; mood changes.

2) EEG – continuous video-EEG polygraph monitoring: irritative changes temporally on the right.

3) Single-photon emission computed tomography (SPECT) – inhomogeneous and somewhat weaker

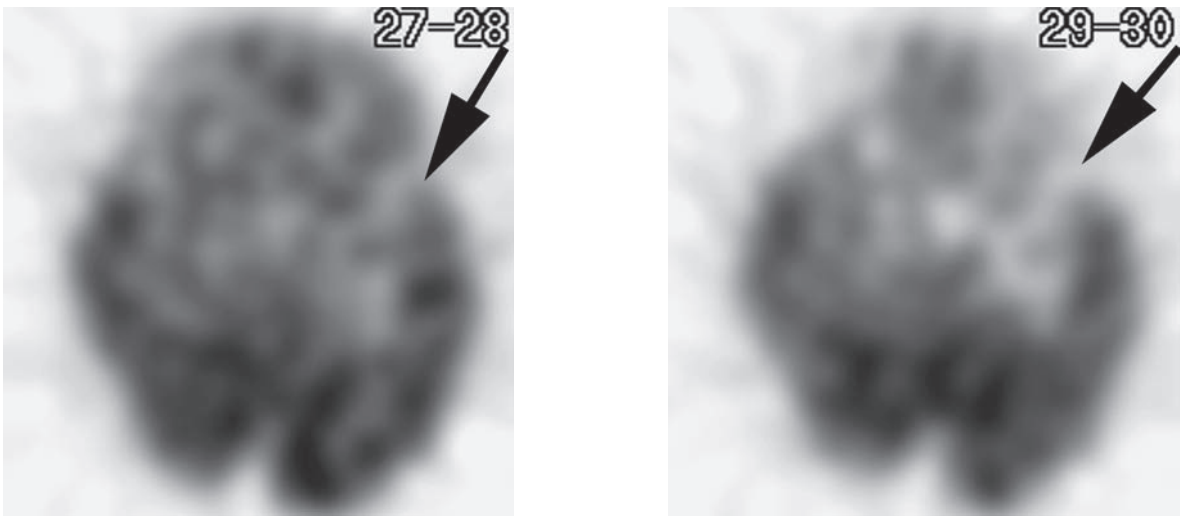

Fig. 3. *Single-photon emission computed tomography (scan 27-28; 29-30): mild diffuse cortical global hypoperfusion, severe hypoperfusion temporobasally on the left and hippocampally on the left (arrows).*

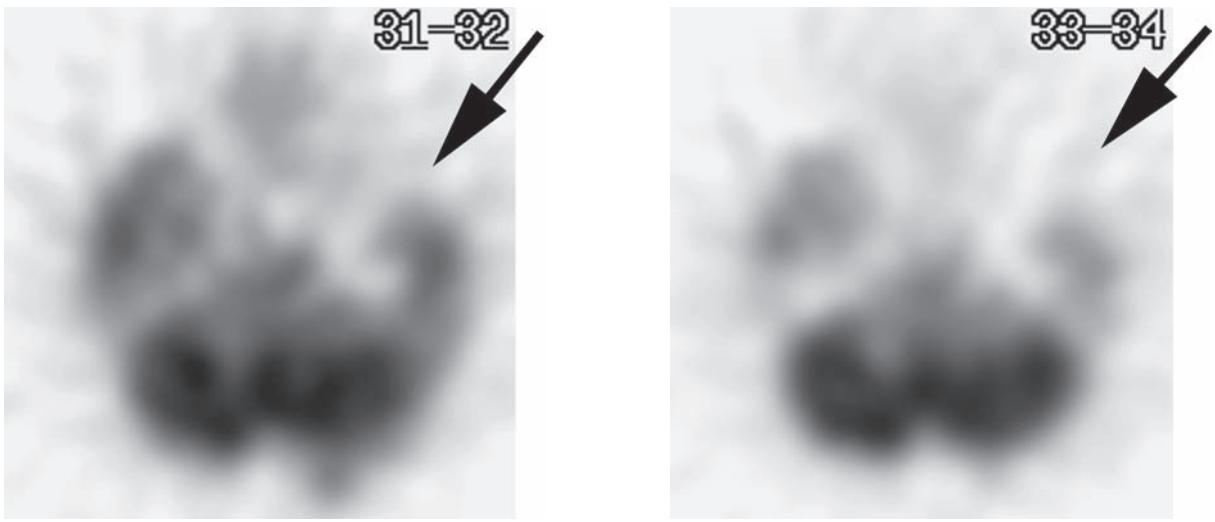

Fig. 4. *Single-photon emission computed tomography (scan 31-32; 33-34): extensive hypoperfusion of the left temporal lobe and left hippocampus.*

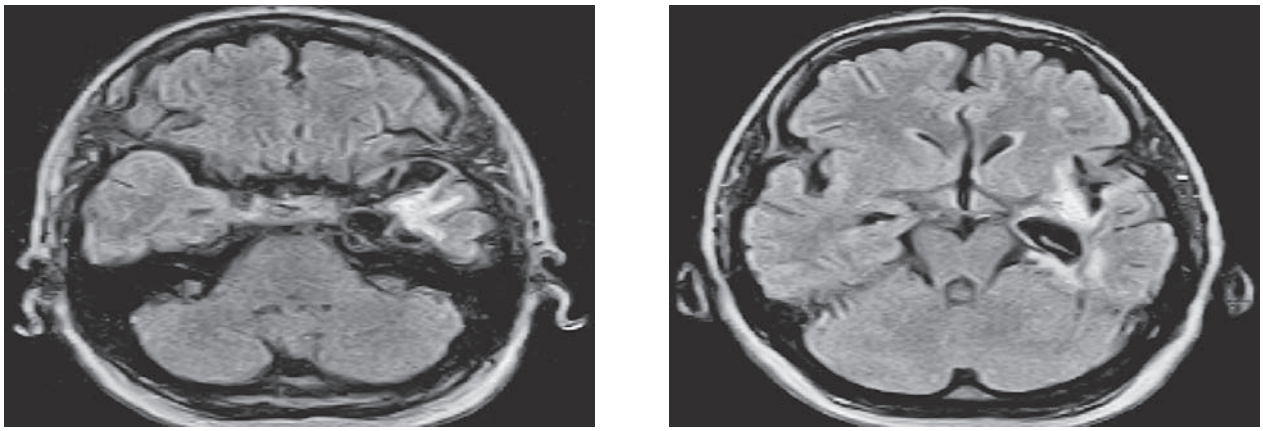

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Fig. 5. *Brain MRI: extensive gliotic lesions in the region of the left temporal lobe (a) and atrophy of the brain parenchyma (b).*

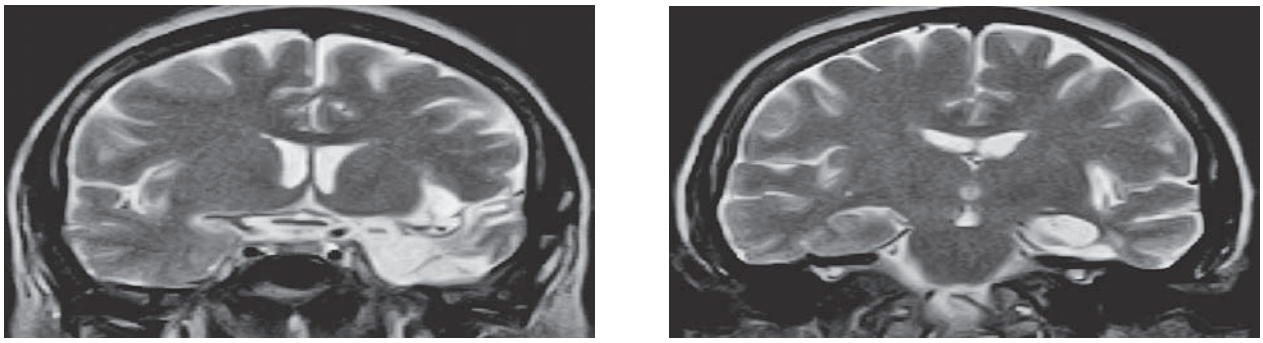

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Fig. 6. *Brain MRI: T2 weighted coronal sections show extensive gliotic lesions of the left temporal lobe (a) and gliotic lesions in the region of the left hippocampus (b).*

radiopharmaceutical accumulation in the cortex; mild, hardly perceivable diffuse cortical hypoperfusion. Areas of severe hypoperfusion pronounced temporobasally on the left, in the hypothalamus projection area in particular (Figs. 3 and 4).

4) Brain MRI – extensive gliotic retraction lesions temporobasally and insularly on the left (Figs. 5 a, b and 6 a, b).

In the first 3-4 months of discharge from the University Hospital for Infectious Diseases, the patient had increased appetite with episodes of binge eating, especially sweet, which resulted in 7 kg weight gain. She exhibited pronounced behavioral and mood changes without any obvious reason, along with verbal and physical aggressiveness and uncontrolled outbursts of rage. She also had increased libido with exaggerated declarations of love toward her husband. Her mood changes and aggressiveness have diminished with time, but abrupt mood changes and intolerance, even occasional aggressiveness, have persisted.

The patient has severely impaired short-term memory, i.e. forgetting what she started doing 3-4 minutes before. She is cooking using recipes, however, unsuccessfully, so other family members had to take over all the housework. She writes messages and notes to herself but regularly forgets them too.

Her retrograde amnesia covers the previous 6 years, since the onset of the disease. She can recollect her attending high school (science school) and working as chemical technician for some time but cannot recollect when she ceased working (after her first childbirth) nor can say anything about her past job. She got married in 2004 but now she does not remember it. She is very close to her husband but she thinks he is her boyfriend. He is the only person she shows emotions to, frequently beyond control, without considering the current environment and situation. She cannot recollect when she gave birth to her children, does not remember their birthdays and other important life events of her children and other family members. She is mother to two children but she is emotionally cold toward

them, almost quite disinterested. She does recognize her children but does not know when they were born nor can remember their major life events. Her husband has noticed that she does not recognize persons from her close environment if she has not met them for a while. She recollects with difficulty the names of famous persons. Clinical examination revealed nominal dysphasia and visual agnosia (inability to recognize familiar objects by sight).

Her family has denied epileptic seizures. During the patient's stay at our Department, no impairments corresponding to complex partial seizures were observed.

In daily life, the patient is heavily dependent on her family's help and surveillance, her husband in particular.

DISCUSSION

The risk of permanent impairment of cognitive functions is 2-4 times greater in HSVE than in encephalitides caused by other neurotrophic viruses. More than half of the individuals having sustained encephalitis can function normally in their environment and resume working after appropriate treatment, whereas others suffer permanent and severe cognitive impairments (10).

This case report is presented to describe late HSVE sequels, since neurological work-up was made one year after the disease, i.e. a period long enough for the patient's condition to be considered definitive. Neurological work-up revealed diffuse cortical hypoperfusion, severe damage to the left temporal lobe, and near-destruction of the left hippocampus.

Brain MRI (SPECT): As the left lobe is dominant in the patient, this destruction has resulted in severe memory loss (retrograde and anterograde amnesia) and behavioral changes with development of visual agnosia and nominal dysphasia (11). Hippocampal destruction has prevented information transfer and short-term to long-term memory transition, with uncontrolled, frequently quite embarrassing emotional reactions (12).

Therapy with acyclovir has proved efficacious in a number of studies; however, treatment should be initiated as early as possible (13). Early treatment is also associated with better recovery of cognitive functions (14). Anticonvulsant therapy is recommended due to the frequent occurrence of symptomatic epileptic seizures, mostly of the complex partial type. Carbamazepine is the drug of choice (15).

Unfortunately, there are no pathognomonic symptoms of HSVE. On the differential diagnosis of confusional states, headaches and subfebrile states with epileptic seizures, HSVE should be taken in consideration because severe and permanent lesions of the brain parenchyma can only be prevented by early therapy introduction. Early diagnosis and therapy means intervention within the first few hours of the onset of infection symptoms.

Bearing in mind that PCR remains positive for 5 days of therapy initiation, there is no fear from false-negative results due to therapy introduction before completion of diagnostic work-up.

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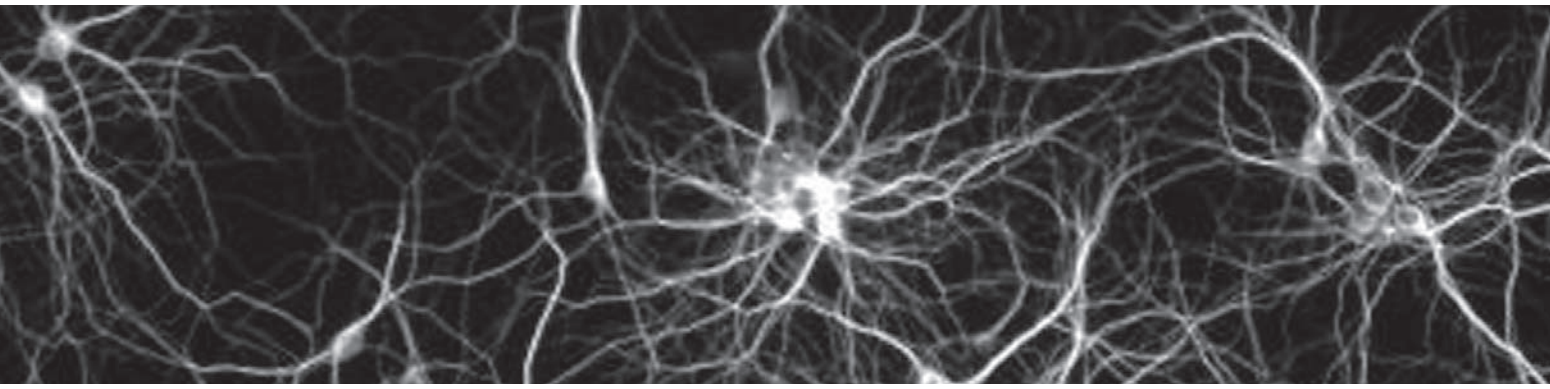
Kasne posljedice encefalitisa uzrokovanog virusom *Herpes simplex*

SAŽETAK - Encefalitis uzrokovan virusom *Herpes simplex* (HSVE) je teška bolest povezana s visokim morbiditetom i mortalitetom. Posljednjih dvaju desetljeća dijagnostika i liječenje te bolesti znatno su napredovale, ali su još uvijek i rizik i komplikacije encefalitisa uzrokovanog herpesom simpleks vrlo visoki. Predilekcijska mjesta infekcije su temporalni, rjeđe frontalni režnjevi. Najčešće kasne komplikacije su epilepsija tipa kompleksnog parcijalnog tipa, promjene ponašanja i oštećenje spoznaje. Dok se epilepsiju može uspješno liječiti s dobrim terapijskim ishodom, u pojedinaca koji su preboljeli takav virusni encefalitis oštećenje spoznaje je trajno. Pouzdani dijagnostički test je polimerazna lančana reakcija virusnog DNA, a liječenje uključuje terapiju aciklovirom uz druge simptomatske terapijske postupke.

Opisana je bolesnica s HSVE u cilju prikazivanja teškog oštećenja spoznaje i ponašanja kao posljedice infekcije virusom herpesa simpleksa, ukazivanja na dijagnostičke rezultate te naglaska na ulogu rane dijagnostike i liječenja te teške bolesti.

Ključne riječi: herpes virus, encefalitis, oštećenje spoznaje, testovi spoznajne funkcije, single-photon emission kompjutorizirana tomografija



Thrombolytic treatment of intraventricular hemorrhage

Z. Poljaković, J. Ljevak, S. Šupe, V. Matijević, D. Alvir, A. Bazina, A. Mišmaš, V. Peterković[1], B. Malojčić, I. Antončić[2]

SUMMARY - Standard approach in the treatment of intraventricular hemorrhage (IVH) with developing hydrocephalus is external ventricular drainage combined with conservative symptomatic therapy. Intraventricular thrombolysis with recombinant tissue plasminogen activator (rt-PA) was for the first time introduced for treating this condition about ten years ago. Since then, many clinical studies with different treatment protocols of intraventricular thrombolysis have been reported, all presenting similar results of faster intraventricular clot resolution and improved outcome. We present our first experience with intraventricular thrombolysis in a young male patient with IVH who was treated in the early stage of his illness and finally had an excellent outcome. We also present the accepted Croatian protocol of intraventricular thrombolysis, approved by the ethics committees of two university hospitals in Croatia.

Key words: intraventricular thrombolysis, intraventricular hemorrhage, external ventricular drainage

INTRODUCTION

Intraventricular hemorrhage (IVH) is a frequent life threatening complication of intracerebral hematoma, independently associated with a worse outcome. Routine treatment of IVH is external ventricular drainage (EVD) aiming to treat obstructive hydrocephalus followed by raised intracranial pressure. However, blood clot, formed inside the ventricles, slows clearance of the ventricles and very often leads to obstruction of drainage catheter compromising therapeutic effects of EVD (1,2).

The possibility of intraventricular thrombolysis of blood clot has been introduced for more than 10 years now and the results of several clinical studies show promising results. In all series, patients in the treatment group with thrombolytic agent achieved more rapid clearance of IVH as well as improved outcome compared with controls. In this article,

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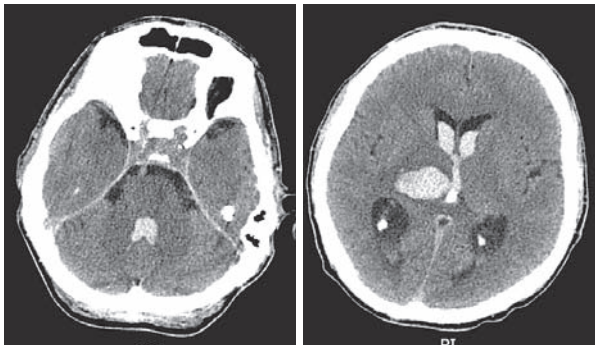
we present our first patient with IVH treated with thrombolytic agent (1-3).

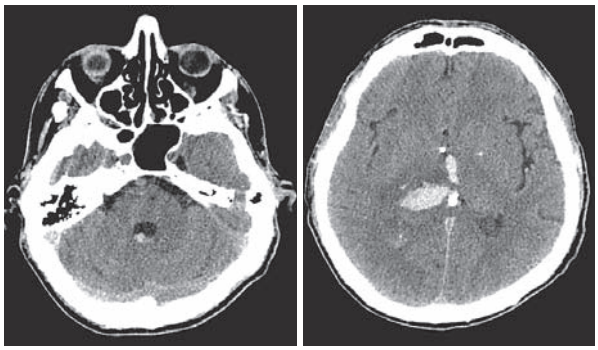
CASE REPORT

Our 52-year-old hypertensive patient presented himself to emergency ward with left-sided hemiparesis, mild headache, and dysarthria. Computed tomography (CT) scan revealed a middle-sized typical intracerebral hematoma located in the right thalamic region with clear intraventricular hemorrhage as well, being most prominent in the fourth ventricle. The fourth ventricle appeared already on the first scan larger and rounder than normally expected, and lateral ventricles showed some early signs of hydrocephalus (Fig. 1). Based on the initial diagnosis, age of the patient and neuroradiological characteristics, EVD was considered. Our decision at this time was to treat the developing hydrocephalus. However, being aware of a large amount of blood in the fourth ventricle, we also considered intraventricular thrombolytic therapy after the position of the drainage catheter had been checked by follow up CT scan. As all inclusion criteria were met, without any of exclusion criteria according to our protocol, the patient received 1 mg of Actylise in the left lateral ventricle, followed by another 1 mg after 12 hours. Follow up CT scan performed immediately after the second dosage of recombinant tissue plasminogen activator (rtPA) showed remarkable clot resolution in the fourth ventricle without any radiological or clinical signs of therapy complications (Fig. 2). EVD was removed on the third day of the illness, and the patient was referred to rehabilitation institution 8 days after the treatment without any neurological complications and with clear improvement of neurological deficit, as well as marked radiological improvement of intracranial status (Fig. 3).



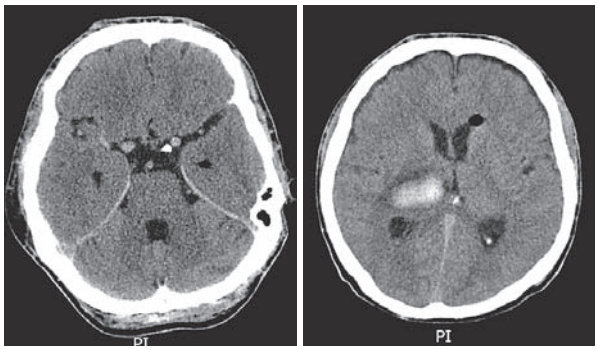
A B

Fig. 1. *Initial multislice computerized tomography (MSCT) showing intracerebral haemorrhage (ICH) with blood in ventricular system including lateral ventricles (B) as well as fourth ventricle, which is fulfilled with blood (A)*



A B

Fig. 2. *Follow up MSCT performed after second dosage of rt-PA (14 hours after the initial MSCT scan) showing nearly a complete clot resolution from fourth ventricle (A) and significant reduction of blood in other ventricles (B). Note lack of perifocal edema around ICH as well.*



A B

Fig. 3. *MSCT on eight day of illness (patients referral to rehabilitation institution). Note complete resolution of blood in ventricular system (A & B) as well as just a mild perifocal oedema around ICH which is partly resolved. A small amount of air still remaining on the top of left lateral ventricle after removing the external ventricular drainage (B)*

DISCUSSION

Thrombolytic therapy for IVH has evolved in response to the problems of catheter obstruction and slow IVH clearance, and has been shown to be safe and effective in animal studies and in small clinical case series. A systematic review of published retrospective case series comparing the outcome of conservative treatment, EVD and EVD combined with fibrinolysis in the setting of severe IVH due to subarachnoid hemorrhage or intracerebral hematoma showed that the fatality rate was 78% for conserva-

tive treatment, 58% for extraventricular drainage, and 6% for EVD with fibrinolytic agents. The poor outcome rate was 90% for conservative treatment, 89% for EVD, and 34% for EVD with fibrinolytic agents (1-3).

By now, there is strong evidence suggesting that thrombolytics used for the lysis of blood in the setting of IVH in humans may improve outcomes. The potential clinical benefits include faster reduction of IVH clot size, faster removal of blood from the ventricular system, reduction in the incidence of hydrocephalus, reduced time in coma, and improved outcome (significantly lower mortality rates). This may result in improved patient survival, reduction in the number of patients requiring long term shunting and reduced length of stay at intensive care unit. At this time, there is a clinical consensus that rt-PA is the most commonly used thrombolytic and studies are testing rt-PA in this setting. Future clinical trials using this drug are under way and rt-PA appears to be the drug for which the most accurate information about safety and efficacy will exist (1-3).

According to the protocol which was for the first time used in the Croatian setting (approved by local ethics committees), patients suitable for intraventricular thrombolysis should: 1) have diagnosis of IVH with no angiographic signs of intracranial aneurysm or arteriovenous malformation confirmed on multislice computerized tomography scan (MSCT) and MSCT angiography or magnetic resonance imaging (MRI) and MR angiography; 2) be younger than 65 years; and 3) be free from clinical or laboratory signs of coagulopathy.

There are a number of issues that must be resolved about the use of rt-PA in the setting of IVH, e.g., what dose and period of dosing is safest, when to stop treatment, and in which ventricle should the catheters be placed in order to achieve maximum clot reduction (4). The CLEAR-IVH program is assessing the efficacy of intraventricular rtPA for spontaneous intraventricular hemorrhage (4). This subanalysis assesses the effect of rtPA dose by region on clearance of IVH. Sixty-four patients within 12-24 hours of spontaneous IVH were randomized to placebo, 0.3 mg, 1 mg or 3 mg of rtPA twice daily *via* an extraventricular drain. Twelve subregions of the ventricles were scored 0-4. The effect of dose on IVH clearance to 50% (t50) of baseline score was compared by survival analysis for all regions combined and by subregions. The models including ventricular region, dose and baseline score were compared by Cox-Proportional Hazards. IVH score reduced faster across all regions with increasing rtPA dose (t50: log-rank $p<0.0001$; placebo 11.43 days, 95%CI 5.68-17.18; 0.3 mg 3.19 days, 1.00-5.38; 1 mg 3.54 days, 0.45-6.64; and 3 mg 2.59 days, 1.72-3.46). In combined models, the dose and baseline score were independently associated with reduction in IVH score, which was most rapid in midline ventricles, then the anterior half of lateral ventricles, and slowest in the posterior half of lateral ventricles (t50: $p<0.0001$; rtPA dose: HR=1.47, 1.30-1.67; midline *vs*. anterior-lateral HR=1.71, 1.08-2.71; midline *vs*. posterior-lateral HR=4.05, 2.46-6.65; baseline score HR=0.96, 0.91-1.01), with a significant interaction between dose and ventricular region ($p=0.005$). According to these results, a conclusion based on the study subanalysis was that rtPA clearly accelerated resolution of intraventricular hemorrhage. This effect is dose-dependent, and greatest in midline ventricles and least in posterior-lateral ventricles (4,5).

In our patient, we followed the Croatian model of treatment protocol (for the first time introduced at Rijeka University Hospital Center), which uses a relatively lower dosage of rt-PA (1 mg) each 12 hours routinely twice, exceptionally 3 times (6). Our patient showed a surprisingly fast and complete clot resolution of IVH, especially considering localization of blood clot (fourth ventricle). This result poses even more questions about correct dosing and timing of drug application (in most studies, the best results were achieved with 3 mg of rtPa every 8-12 hours) as well as about the dynamics of intraventricular fluid (excellent clot resolution in the fourth ventricle with drainage catheter placed in the lateral one). One explanation of our good result of intraventricular thrombolysis might be a very early treatment (less than 6 hours after illness onset), when definite clinical and radiological signs of hydrocephalus had not yet been present. However, in order to be able to make a definite conclusion, much more data in a larger group of patients should be collected.

CONCLUSION

In our report, we witnessed an excellent outcome of a patient with hypertensive intracerebral and intraventricular hematoma after intraventricular thrombolysis. Further investigations in a larger number of patients with similar diagnosis have to be conducted in order to conclude about the efficacy and safety of this therapeutic method.

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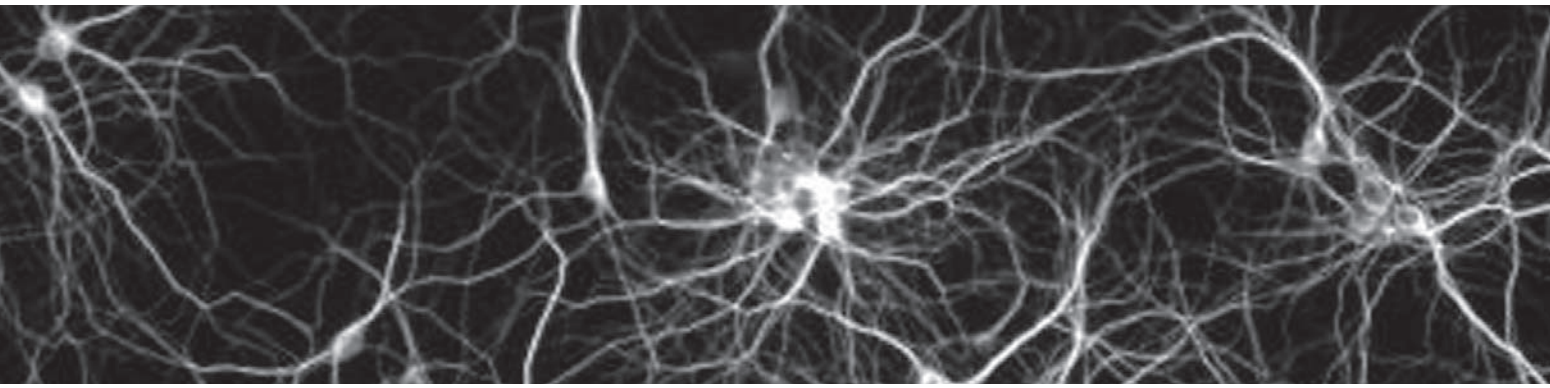
Trombolitičko liječenje intraventrikulske hemoragije

SAŽETAK – Standardni pristup liječenju intraventrikulske hemoragije (IVH) i posljedičnog hidrocefalusa je vanjska drenaža ventrikula kombinirana s konzervativnom simptomatskom terapijom. Intraventrikulska tromboliza s rekombinantnim aktivatorom tkivnog plazminogena (rt-PA) je prvi puta uvedena u liječenje toga stanja prije oko deset godina. Od tada je prikazano mnogo kliničkih studija s različitim terapijskim protokolima intraventrikulske trombolize, koji su svi imali slične rezultate brzog otapanja intraventrikulskog ugruška i poboljšanja ishoda.

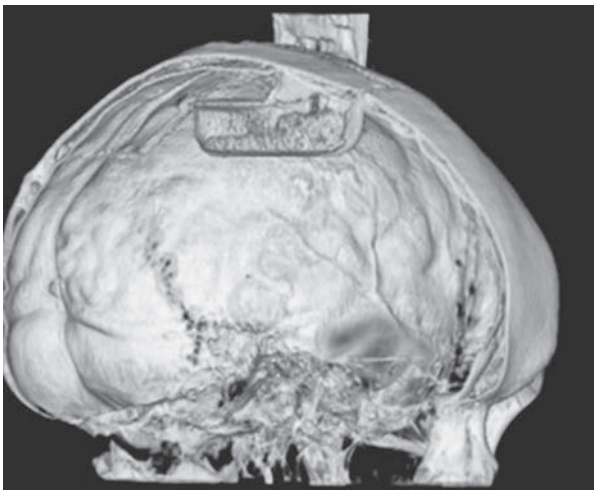
Prikazujemo naše prvo iskustvo s intraventrikulskom trombolizom kod mladog muškarca s IVH, koji je bio liječen u ranom stadiju bolesti i ishod bolesti bio je odličan. Osim toga prikazujemo prijedlog hrvatskog protokola intraventrikulske trombolize koji su odobrila etička povjerenstva dviju hrvatskih kliničkih bolničkih centara.

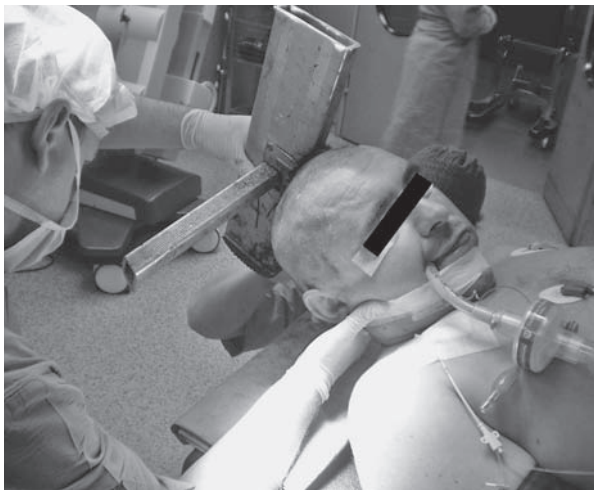
Ključne riječi: intraventrikulska tromboliza, intraventrikulska hemoragija, vanjska ventrikulska drenaža



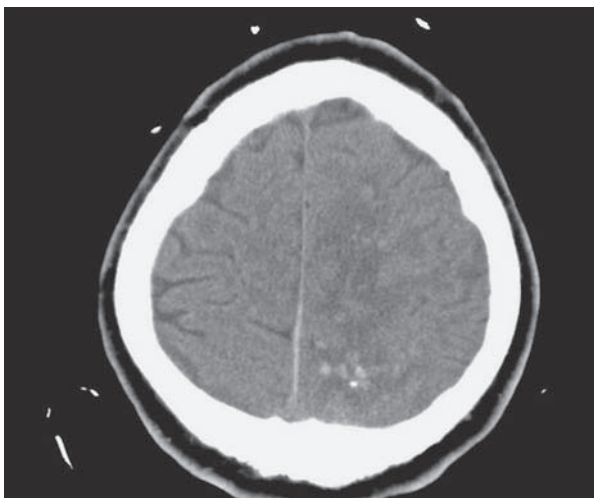
Penetrating skull injury with the ladder

G. Grahovac, D. Romić, D. Dlaka, I. Francisković, F. Almahariq, M. Vilendečić





A 37-year-old male patient had sustained penetrant head injury with the ladder hook after falling five meters from a roof. The ladder fell down on the patient's head and the ladder hook penetrated the left parietal bone. The ladder was sawed at the scene and the patient was transferred to our hospital. Computed tomography scan was obtained to visualize the trajectory and the exact position of the hook (Fig. 1). The exact localization of the brain lesion is shown in Fig. 2. The ladder hook was removed in the operating room. We enlarged the scalp incision and bone hole. The foreign object was removed in one piece. The patient recovered with mild spastic right hemiplegia. High-energy non-missile head penetrating injuries account for a



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small percentage of penetrating head injuries and they present a series of special features for the neurosurgeon (1). Proper preoperative planning and team approach is required for safe surgical removal of the penetrating object.

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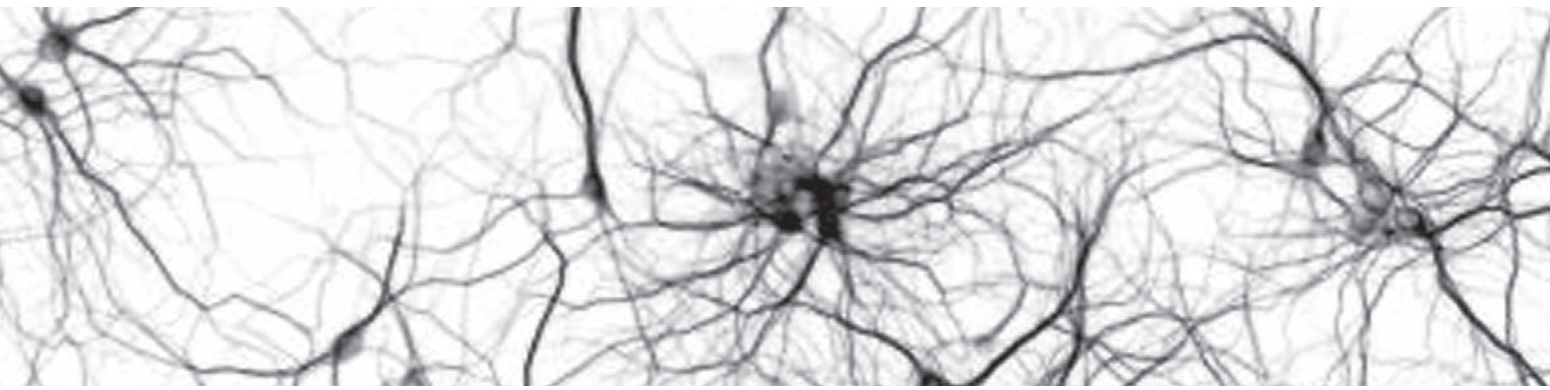

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If the article is written by seven or more authors, only names of the first three authors should be listed, followed by *"et al"*.:

Baršić B, Lisić M, Himbele J *et al*. Pneumoccocal meningitis in the elderly. Neurol Croat 1992; 41: 131 - 140.

Books

Critchley M. The ventricle of memory. New York: Raven Press, 1990.

Chapter in a book

Geschwind N. The borderland of neurology and psychiatry: some common misconceptions. In: Bensom DF, Blumer D, eds. Psychiatric aspects of neurologic disease. New York: Grune and Stratton, 1975; 1 - 9.

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Upute autorima

NEUROLOGIA CROATICA, službeno glasilo Hrvatskoga neurološkog društva i Hrvatskoga neurokirurškog društva, izdaje Klinika za neurologiju, Klinički bolnički centar Zagreb, dva puta na godinu. Neurologia Croatica objavljuje radove iz područja kliničke neurologije, temeljnih neuroznanosti i drugih pridruženih područja.

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