

## Modern Experience of Pharmacotherapeutic Use and Effectiveness of Endolumbal Administration of Glucocorticoids in Progressive Types of Course for Multiple Sclerosis

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Received: July 29, 2024

Published: August 31, 2024

**Abstract.** Effective pharmacotherapy of low-bondly progredient forms of the multiple sclerosis is a difficult task that requires the search for new and improving existing methods of treatment. The author set the task to the optimize the treatment of progredient forms of multiple sclerosis using the method of endolumbal introduction of glucocorticoids and to evaluate its efficiency. The results of treatment of 76 patients with poor curable progresses of multiple sclerosis by intrathecal introduction of glucocorticoids (dexamethasone) are presented in the study. The advantages of method, methodic of introduction, the patient's selection parameters were given. The efficiency criterions of intration of glucocorticoids were defined, including the neurological deficiency regress, stabilization and the delay of multiple sclerosis progressing. Integral assessment of efficiency was made as 4 gradations: “good

rate”, “low” and “absence of effect”. The positive dynamics of neurological state was registered predominantly on spastic-paretic syndrome with presence of several active foci with contrast enhancement. The sphincter infringements and brain stem symptomatic were observed as rarely reversible, extremely rarely - cerebellar symptom complex. As the results of the treatment (the term of the observation – 6 months and more) 80.2% of multiple sclerosis patrols marked the efficiency as "good" and "moderate". The obtained data indicated the reasonability of the proposed method of treatment for patrols with saversive courses of multiple sclerosis, occurring inly with spinal symptomatic.

**Keywords:** multiple sclerosis, progressive courses, intrathecal introduction of glucocorticoids, efficiency.

**Introduction.** The World Health Assembly (May 2022) approved the intersector of global action for epilepsy and other neurological disorders for the period 2022-2031. The plan is aimed at solving problems and gaps in providing assistance and services to citizens with neurological disorders (Multiple sclerosis, epilepsy, etc.) that exist in all countries of the world [1]. Health care is aimed at increasing the priority of policy to strengthen management, ensuring effective, timely and

surgical diagnosis, treatment with modern medicines and care, implementation of strategies for promotion and prevention, stimulation of research and innovation and strengthening of information systems.

WHO experts support countries in timely treatment of multiple sclerosis, with more than 1.8 million people around the world. WHO is recommended the following algorithm:

- ✓ work on the inclusion of drugs from multiple sclerosis to the lists of the main drugs of WHO (EML);
- ✓ cooperation with civil society, such as the Multiple Sclerosis International Federation (MSIF), on broad issues and propaganda, in particular through World Multiple Sclerosis Day (May 30);
- ✓ creation of multiple sclerosis atlas for use by citizens suffering from multiple sclerosis, medical and pharmaceutical workers, charitable organizations to stimulate and inform campaigns to improve patients for quality and life expectancy;
- ✓ support to implement management principles to promote health care, improve rehabilitation services for patients suffering from neurological health disorders.

It is important to note that it was Professor Voloshyn P.V. initiated the publication of the monograph "Medicines in Neurology, Psychiatry and Drugs" [2]. He initiated multidisciplinary studies in neurology, psychiatry and narcology in Ukraine against the background of evidence-based pharmacy to include modern, safe, effective and accessible drugs from multiple sclerosis in accordance with ICD-11 [3, 4].

Today, medical professionals are waiting for the latest updates in research and continue to improve therapeutic options for patients with multiple sclerosis, including recurrent and progressive multiple sclerosis and related disorders. Over the past few decades, significant positive achievements have been achieved in this area in understanding the fundamental factors of the disease, identification of risk genes; more accurate accounting of epidemiology and developing effective treatments. Currently, multiple sclerosis recurrence can be safely eliminated in most patients with the latest treatments, and the progressive symptoms are partially slowed [5-7].

Modern data, obtained by the results of the wedge and epidemiological relevance of the relevant to the reconstruction of the impact of the fierce vicious forms of multiple sclerosis with the progressive. Identify the early loss of work and insecurity of the citizen of young labor exponent (20-40 years) [8-12].

Clinical symptoms with progredient types of the flow of the multiple sclerosis flow are distinguished by stability, severity, high frequency of damage to pyramidal, cerebellar and stem systems, decompensation of the functions of the pelvic organs, the absence or extreme rarity of the dissection syndrome, resistance to adequately conducted pathogenetic therapy [13-15].

To relieve exacerbations of the disease, Glucocorticoids is traditionally used as the first line medicines, which have a wide range of pharmacotherapeutic action. Affect immune reactions in various ways:

- using lymphocytolysis;
- acceleration of catabolism of immunoglobulins;
- reducing the products of pro-inflammatory cytokines;
- suppression of transcription and increased degradation of genes;
- interleukin-2 controlling synthesis;
- occupying a central place in the development of an immune response;
- improvement of axonal conduct;
- reducing permeability of the hematoencephalic barrier.

It is necessary to indicate that the mechanism of anti-inflammatory and decongestant effects of Glucocorticoids consists in the inhibitory effect on macrophages and polymorphine leukocytes (on their mobilization, migration to the focus of inflammation, phagocytosis), narrowing of blood vessels and decreasing their permeability by inhibition of prostaglandins synthesis. Due to the decrease in the permeability of the capillary endothelium, microcirculation improves and the

exudation of leukocytes and mast cells decreases, conductivity improves by increasing the efficiency of suction mechanisms in demyelinated fibers [16].

Note that hormonal pharmacotherapy for multiple sclerosis is important as a factor that suppresses the autoimmune process. And also, as a type of replacement pharmacotherapy in connection with the development of glucocorticoid deficiency in this disease, which changes immunological reactivity towards increased allergic manifestations and contributes to the demyelination process.

At the same time, Glucocorticoids is used for multiple sclerosis for several decades. The problems associated with their appointment with different types of the Multiple Sclerosis current are still not resolved. There is no consensus regarding adequate dosages, schemes, methods and duration of hormone administration with the recurrent course of the disease, taking into account the frequency and severity of relapse, the appropriateness of appointment in the debut, assessing their effect on the reaccines during isolated use and in combination with alternative treatment methods [17].

The treatment strategy for the progredient types of the multiple sclerosis course, taking into account the significant predominance of degenerative-aconal lesions over the inflammatory, traditionally limits indications for Glucocorticoids. Therapeutic measures with these forms are reduced to taking cytostatics, with prolonged admission of a significant number of complications [18].

It should be noted that there is no need to revise the unreasonably skeptical attitude to the purpose of Glucocorticoids in progressive types of the multiple sclerosis. In favor of this statement, studies of recent years testify to the ability of Glucocorticoids to slow down the formation of “black holes” (places of neurons) and prevent the development of brain atrophy [19].

These processes prevent the early formation of persistent disability due to slowing down the rate of accumulation of residual neurological deficiency. It is also important to take into account that degenerative-aconal lesions at the rapid rates of progression, characteristic of the steady and recurrent variants of the progredient types of the multiple sclerosis, are usually combined with autoimmune changes in varying degrees of severity, especially in secondary-transgredient course [10, 11].

The activity of the demyelinating process with a rapid progressive type of Multiple Sclerosis course is comparable to relapse with a recurrent course. Another temporary algorithm for the development of the inflammatory process is manifested by clinical-immunological and clinical and morphological dissociations. These provisions are the basis for the use of active immunosuppressive pharmacotherapy Glucocorticoids at the stages of rapid progression in progressive types of multiple sclerosis, primarily the second -hand type of current.

The main goal of the Glucocorticoids immunosuppressive therapy in such cases is not so much to reduce the neurological deficit as in slowing down the rate of progression and the formation of the stabilization stage. The duration of this stage serves as the main criterion for the effectiveness of pharmacotherapy Glucocorticoids in progredient types of the multiple sclerosis.

Thus, the effective pharmacotherapy of low -bonded progressive forms of the multiple sclerosis is a difficult task that requires the search for new and improving existing methods of treatment.

**The purpose of the study** was to optimize the treatment of predictive forms of multiple sclerosis using the method of endolumbal introduction of glucocorticoids and evaluate its effectiveness.

Research tasks:

- to study the clinical characteristics and features of the course of progredient forms of the multiple sclerosis;
- to develop indications for the use of glucocorticoids by endolumbal administration in patients with a progredient type of multiple sclerosis course;

- to evaluate the clinical efficiency and substantiate the advantages of the Glucocorticoids endolombal introduction method compared to other treatment methods in patients with multiple sclerosis.

**Materials and methods.** Endolombally, by cerebrospinal puncture, the dexamethasone of potassium salt was introduced – 40 mg. The course of treatment consisted of 6 endolombal administrations every other day. Premopting skin anesthesia was carried out with a 2% solution of lidocaine (after a negative test) in compliance with all precautions in order to avoid an anesthetic entering the cavity of the spinal canal, which could cause the development of hemorrhagic spinal stroke.

Before course treatment, a study of cerebrospinal fluid for sterility and the absence of neurotropic viruses were conducted. All patients gave a written informed consent to conduct endolombal administration of hormones.

The study was open, placebo-unconnected prospective nature. Conducted, studied and described in the period 2005-2023. On the basis of the clinical department of neuroinfections and multiple sclerosis of the State Institution “Institute of neurology, psychiatry and narcology of the National Academy of Medical Sciences of Ukraine”.

Patient selection criteria:

- age of patients was from 18 to 55 years;
- diagnosis of multiple sclerosis, confirmed clinically and laboratory (according to the criteria McDonald, 2005);
- duration of the disease is at least 3 years;
- primary and secondary-transgressive types of the flow of the Multiple Sclerosis;
- quick rates of progression with the formation of gross neurological deficiency for 3 years;
- disability on the Expanded Disability Status Scale (EDSS) scale of 5.0 points and more with a predominance of spastic-paretical syndrome;
- low effectiveness of pathogenetic therapy in the previous stages of the disease;
- presence of active foci in the spinal cord or brain that accumulate contrast, according to Magnetic and Resonance Imaging;
- presence of written informed consent to conduct an endolombal introduction of Glucocorticoids.

It is important that the following groups of patients were not included in the study:

- ❖ during pregnancy and breastfeeding;
- ❖ with the presence of active neurotropic viruses and other pathogenic organisms in accordance with blood tests and cerebrospinal fluid;
- ❖ secondary ascending urological infection with persistent subfebrilet, underflow, severe chronic somatic pathology, a predominance of cerebellar symptom complex in the clinical picture of the disease.

Medical personnel inspection of patients with an evaluation on the EDSS scale was carried out before treatment, immediately after the end of treatment and after 6 months. For all patients for a number of years, catamnestic observation was carried out. Research results were processed by mathematical statistics using the Vilcoxon criterion.

The research of the article is a fragment of research works of State Institution “Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine” on the topic of "To study mechanisms of inheritance of multiple sclerosis in persons born from parents with this disease (state registration number 0121U111900, implementation period 2022-2024).

**Results and discussion.** To solve the task, we developed the method of endolombal administration of glucocorticoids by spinal puncture, carried out according to the generally accepted methodology in compliance with all the rules of aseptic and antiseptics [16].

It is necessary to indicate that the advantage of the method of endolombal administration of glucocorticoids we have developed is to create high hormone concentrations directly in the cerebrospinal fluid, bypassing the hematoencephalic barrier. This method allows not only to

enhance the anti-inflammatory effect, but also to avoid side effects that often occur with oral or intravenous use glucocorticoids.

Endolombal administration of Glucocorticoids was made in 76 patients (52 women and 24 men) aged 23 to 55 years (average age –  $33.4 \pm 7.2$  years). The secondary-transmitted type of course was diagnosed in 42 patients. The progredient type of the multiple sclerosis current in 34 patients.

The duration of the disease in the secondary-transcious course was from 6 to 32 years (on average  $22.5 \pm 6.8$ ).

In case of progressive types of multiple sclerosis, from 3 to 12 years (on average  $7.9 \pm 5.7$  years).

The age of the debut in the secondary-transient type of current is from 18 to 38 years (the average age of the debut was  $24.8 \pm 6.7$  years).

In case of progressive types of multiple sclerosis, from 24 to 49 years (average age  $35.4 \pm 7.7$  years).

The duration of the progression stage in the secondary transmission course on average was  $14.5 \pm 6.1$  years.

Switching to secondary progression after a recurrent stage of different durations was noted in 23 of 42 patients.

The formation of secondary progression after remission after the debut, bypassing the recurrence stage in 19 patients.

The progression stage in the progressive types of the multiple sclerosis course began immediately after the debut in 21 patients. In 13 patients, the progression of the disease was noted after the stage of stabilization that came after the debut [20].

In all patients, regardless of the type of progressive course, the disease proceeded rapidly in the form of a steady progression variant (43 cases). It was characterized by an increase in neurological deficit without stabilization, and a recurrent progression variant (33 cases). It flowed in the form of sharp, periodically repeated spasmodic deteriorations of the state resembling relapses [21-24].

Before starting treatment, clinical symptoms with the indicated variants of the progredient course were characterized by the predominance of persistent and pronounced cerebrospinal or local spinal symptoms with deep disability, resistance to the therapy or its insufficient efficiency.

In the structure of pyramidal symptoms, coarse lower spastic parapares prevailed. Less commonly – tetra and tripareses, combined with high tendon and periostal reflexes, stop clonuses, pathological stop signs of extensor (more often) and flexion (less often) types, lack of abdominal reflexes.

The syndrome of damage to the cerebellum and its connections was characterized by gross violations of statics and walking, frequent and pronounced intensive tremor of the hands, head and trunk, horizontal nystagmus of various amplitude, crude, gross intention and incoordination during coordinator trials, adiadochokinesis.

Stem symptoms were more often recorded in a secondary process. It was characterized by diplopia in different planes, inter-core ophthalm paresis, vertical nystagmus, bulbar syndrome (piercing, a decrease in the excursion of a soft sky, a decrease or lack of a pharyngeal reflex, dysarthria).

Disorders of the functions of the traumatic brain nerves, along with oculomotor and bulbar disorders, were manifested by frequent damage to n. Opticus in the form of partial atrophy of optic nerves. Sensitive disorders according to the conduction (often) and segmental (less often) types were often combined with impaired proprioceptive sensitivity.

Violations of complex types of sensitivity were extremely rare. At the same time, impaired function of the pelvic organs was often decompensated and manifested by a delay, urinary incontinence or their combination, persistent constipation, less often - fecal incontinence.

For the vast majority of patients, especially with the progredient types of the multiple sclerosis course, cognitive and emotionally affective disturbances were characteristic. In some

patients, they combined with chronic pathological fatigue syndrome, diverse in nature, localization and duration of cephalgia.

Atypical syndromes in the form of epileptiform, subcortical, pseudotumorous, rarely rarely found (Table 1).

**Table 1.** The frequency of the main syndromes in the progredient types of the course of the multiple sclerosis course, %.

No.	Syndrome	Secondary-progredient type (n=42)	Progredient type (n=34)
1.	Violations of the optic nerve	78,6	88,2
2.	Symptoms of damage to the pyramid system	100,0	100,0
3.	Coordination disorders	100,0	100,0
4.	Sensitivity disorders	52,4	44,1
5.	Lesions of the cranial nerves	73,8	61,7
6.	Disorders of the function of the pelvic organs	83,3	88,2
7.	Cognitive and emotionally affective disorders	66,6	91,2
8.	Chronic pathological fatigue	83,3	73,5
9.	Other syndromes	35,7	41,2

Integral assessment of the characteristics of the clinical course, including the pace and options of progression, made it possible to distinguish the main criteria of a probable unfavorable prognosis in patients with predictive forms of multiple sclerosis, which showed the endolumbal introduction of glucocorticoids [21]:

- beginning of the disease under the age of 16 and after 40 years, especially in male persons;
- beginning of progression immediately after the debut with the progredient types of the multiple sclerosis current;
- following the remissions after the debut, bypassing the recurrent stage, with a secondary and transgressive course;
- short-term remission after a debut in combination with a short stage of recurrence before switching to secondary and transgressive course;
- real and/or recurrent variants of the current with a rapid rate of progression, the formation of a pronounced and persistent neurological deficiency, early deep disability;
- resistance to traditional pathogenetic therapy.

Before treatment, the severity of disability on the EDSS scale was estimated at 5.0-8.5 points (on average  $6.14 \pm 0.76$  points). Independent walking (5.0 and 5.5 points) was preserved in 29 (38.1%) patients, walking with support (6.0 and 6.5 points) – in 33 (43.5%), used wheelchair and wheelchair. They needed constant extraneous care (7.0-8.5 points) 14 (18.4%) patients (Table 2).

**Table 2.** Evaluation on the EDSS disability scale before and after endolumbal administration of Glucocorticoids in patients with predictive types of multiple sclerosis (N=76).

No.	Indicator	Before treatment and immediately after treatment	6 months after treatment	Number of patients with an estimate on EDSS scale
1.	4,5 points	-	3	1
2.	5,0 points	5	13	10
3.	5,5 points	24	22	22
4.	6,0 points	17	14	16
5.	6,5 points	16	12	14
6.	7,0 points	7	6	7
7.	7,5 points	4	3	3
8.	8,0 points	2	2	2

9.	8,5 points	1	1	1
	Average EDSS, points 6,14±0,76    5,93±0,85 6,03±0,81			

The effectiveness of the endolombal administration of glucocorticoids was not dependent on the age of the debut, the duration of the disease, the duration of the recurrent stage in the secondary process.

Based on the results of the studies, criteria for the effectiveness of endolumbal introduction of glucocorticoids are established:

- ✓ spasmodic improvement with partial regression of neurological symptoms after the first session of the introduction of dexamethasone;
- ✓ subsequent administrations potentiated the initial effect of administration;
- ✓ gradual achievement of the therapeutic effect after each subsequent endolumbal administration according to the type of summation;
- ✓ improvement through deterioration or through a multidirectional effect against the background of treatment, followed by stabilization of different durations;
- ✓ stabilization without regression of neurological symptoms after the course of endolumbal administrations of different durations;
- ✓ slowdown in the pace of progression in the absence of a clinical effect after the course of endolumbal introductions.

Thus, the efficiency of endolumbal administration of glucocorticoids was formed taking into account the dynamics of points on the EDSS scale and the rate of progression.

Four gradations of the effectiveness of the treatment were identified:

- good efficiency – regression of neurological deficiency and lack of progression for 6 months;
- moderate efficiency – an unstable regression of symptoms with the resumption of progression that occurs at a slowest pace, or the absence of positive dynamics according to the EDSS scale, but with the stabilization of the process in the future;
- low efficiency – lack of regression and stabilization of clinical symptoms, but slowing down the rate of progression;
- lack of effect – preservation of high rates of steady progression.

Due to the analysis of the dynamics of neurological symptoms, a selective and differentiated nature of positive effects was established, taking into account the temporary factor and individual sensitivity.

Side effects after manipulations were minimal and turned on:

- post-punching headache, which was short-term in nature – 56.7 % of patients;
- meningism – 5.3 % of patients;
- disorders of night sleep (difficulties with falling asleep and frequent awakening) – 34.2 % of patients.

It is important to note that all patients have passed the full course of endolumbal administration of glucocorticoids. There was no rejection of manipulations.

Positive dynamics of neurological status is marked mainly with spasticoparetic syndrome. The effectiveness of endolumbal administration of glucocorticoids with the regression of spinal symptoms was higher in the presence of several active spinal foci on magnetic and resonance imaging with contrast amplification. Less commonly, the functions of the pelvic organs and stem symptoms were impaired, extremely rarely – cerebellar symptom complex.

Partial regression of symptoms (on average by 1.0 points on the EDSS scale) immediately after the end of the treatment was detected in 32 (42.1%) of 76 patients, including in the form:

- jump-like improvement after the first session in 12 (37.5%) of 32 patients;
- gradual achievement of the therapeutic effect, reaching the maximum by the end of the course, in 18 (56.2 %) of 32 patients;

- improvements through deterioration or through multidirectional effects established at different introduction sessions in 2 (6.3 %) of 32 patients.

Positive dynamics in the neurological status corresponded to a decrease in the average score on the EDSS disability scale from  $6.14 \pm 0.76$  to  $5.93 \pm 0.85$  (Table 2).

6 months after the end of the endolumbal introduction course, the following picture shook, so in:

- 22 (28.9%) of 32 patients, a persistent regression of neurological symptoms was preserved, recorded immediately after the end of treatment (good efficiency);
- other patients of this group, the number of points increased, but they progressed in their slow pace than before treatment (moderate effectiveness);
- 39 (51.3%) patients observed stabilization of the process, despite the lack of regression of neurological symptoms after the end of the course of treatment (moderate effectiveness);
- 12 (15.9%) of patients, including 6 with severe neurological deficiency (7.5-8.5 points), a slowdown in the rate of progression in the absence of regression and stabilization of the process (low efficiency) was noted;
- 3 (3.9%) patients with an estimate of 6.5-7.0 points on the EDSS scale, the pace was preserved progression (lack of effect).

The EDSS score, 6 months after treatment, amounted to on average ( $6.03 \pm 0.81$ ) points (Table 2).

Thus, in patients with moderate and low efficiency, a transformation has occurred with switching a steady and recurrent variant of progression to the progressive version, which is characterized by a slower accumulation of neurological deficit, and therefore a more “benign” course of the progressive process.

The analysis of the reasons for the low efficiency of treatment revealed a close relationship with a high level of disability on the EDSS scale, a long stage of steady progression, the predominance of pronounced cerebellar symptoms in the clinical structure, multiple glucocorticoids in physiologically unreasonable schemes at the previous stages of treatment.

Repeated sessions of the endolumbal administration of glucocorticoids were recommended to patients with the next stage of rapid progression, which occurred with the predominance of a pronounced spastic-paretic syndrome and sphincter disorders, provided that the previous treatment course in the form of recourse of symptoms and their subsequent stabilization is good or moderate.

The ability of endolumbal introductions to cause not only direct (partial regression of clinical symptoms during the course of their conduct), but also a trace therapeutic effect (stabilization, slowing down the pace of further progression), contributed to the improvement of the psychological state of patients, increasing the quality of life with the formation of a more adequate model of personality behavior in conditions of serious illness.

It is known that the anatomical features of the blood supply to the spinal cord against the background of changes in the permeability of the hematoencephalic barrier with the multiple sclerosis contribute to the “chronic” of active foci of inflammation and complicate the maintenance of the optimal concentration of medicinal substances in the cerebrospinal fluid and medical structures. This leads to a decrease in bioavailability and effectiveness of parenteral and intravenous administration of drugs in spinal active foci of inflammation.

The local introduction of glucocorticoids directly into the cerebrospinal fluid space is one of the priority areas, especially in the treatment of spinal forms of the multiple sclerosis. In a similar situation, the cerebrospinal fluid acts as an intermediary during the transportation of medicines from blood to chronic foci of inflammation in the spinal cord.

The choice of the drug (dexamethasone) is due not only to its anti-inflammatory, but also a powerful dehydratic effect, which exceeds the prednisolone preparations, which, taking into account the limited space of the spinal cerebral canal, is an additional pathogenetic therapeutic factor.

**Conclusions.** The authors of the article optimized the treatment of predictive forms of the multiple sclerosis using the method of endolumbal introduction of glucocorticoids and its effectiveness was evaluated. The clinical characteristics and features of the course of progredient



forms of the multiple sclerosis have been studied. Indications have been developed for the use of glucocorticoids by endolombal administration in patients with a progredient type of multiple sclerosis. The clinical effectiveness of the proposed treatment method has been assessed. The advantages of the method of endolombal administration of glucocorticoids are justified compared to other treatment methods in patients with progredient types of multiple sclerosis. Principles of health care for improving rehabilitation services for patients suffering from neurological health disorders have been implemented. Multidisciplinary studies of Professor Voloshyn P.V. on the use of modern, safe, efficient and accessible glucocorticoids. The resulting clinical data indicates the effectiveness and appropriateness of the widespread use of this treatment method for severe progredient forms of the multiple sclerosis. Further studies are ongoing.

**Declaration of conflict interest.** The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding.** The authors state, that this research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Ethical approval.** Ethical clearance was obtained from the administration of the State Institution "Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine". Permission statement for conducting the experiments was received from the administration of State Institution "Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine". Before any data collection, the main purpose of the study was clearly explained to each department (concerned personnel).

**Data availability statement.** The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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