Neuroscience and Behavioral Physiology, Vol. 38, No. 6, 2008

Effects of Cerebrolysin on Moderate Cognitive Impairments in Cerebral Vascular Insufficiency (a clinical-electrophysiological study)

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Translated from Zhurnal Nevrologii i Psikhatrii imeni S. S. Korsakova, Vol. 107, No. 5, pp. 32–38, May, 2007.

The efficacy of treatment with cerebrolysin was studied in 40 patients with cerebral vascular insufficiency. Cerebrolysin (20 daily i.v. infusions of 10 ml in 200 ml of physiological saline) was found to be an effective means of treating this group of patients. Courses of cerebrolysin treatment decreased the severity of memory and attention impairments, improving the overall cognitive status of the patients. Clinical observations and neuropsychological testing were supported by electrophysiological results, in terms of the P300 cognitive evoked potential. The effects of treatment at the doses used here were delayed and were seen three months after completion of treatment.

KEY WORDS: cerebral vascular insufficiency, impairment of cognitive functions, cerebrolysin, P300 cognitive evoked potentials.

According to the current classification of vascular lesions of the brain and spinal cord, cerebral vascular insufficiency (CVI) is a state involving progressive disturbances of brain function due to insufficiency of the cerebral vascular circulation and/or repeated episodes of circulatory failure, occurring either with marked clinical symptomatology or subclinically [19–22]. Vascular lesions of the brain lead to significant decreases in cognitive functions; the late stages can also impair the ability of patients to care for themselves. Mild, moderate, and severe cognitive impairments are distinguished [19]. Until recently, the main focus of attention was severe cognitive disorders (dementias) due to long-term progression of the disease. More attention in recent years has been paid to the question of moderate cognitive losses [8, 9, 14, 19, 33], especially in terms of early detection, which allows the timely provision of the appropriate treatment with consequent improvements in the prognosis [6, 8, 9, 14, 16, 19].

Apart from clinical and neuropsychological testing, neurophysiological investigations, particularly analysis of the cognitive evoked potential (EP), can be of value in the diagnosis of cognitive disorders of different severities.

Cognitive, or endogenous, event-linked potentials reflect electrical processes associated with brain activity and mental cognitive functions: the functions of anticipation, discrimination, memory, information processing, decision taking, response selection, etc. [35]. The clinical value of these potentials comes from the fact that they reflect higher cerebral integrative processes in central information processing and may thus serve as objective measures of the mechanisms of impairments in mental functions in humans [5].

Recent years have seen intense investigation of the development of instrumented electrophysiological methods in assessing these processes [10].

One widespread method in this area is analysis of the P300 wave of the cognitive EP, which is increasingly used in evaluating the preclinical stage of cognitive impairments and dementias of different types [5, 35]. The main changes in the P300 cognitive EP in neurological diseases are accompanied by impairments of mental processes, including reductions in the amplitude and increases in the latency of this wave [30]. Developments of methods for studying P300 by introduction of additional stimuli with the requirement to select, recognize, and retain in memory ver-

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0097-0549/08/3806-0639

bal and nonverbal material have allowed various psychophysiological aspects of brain activity to be evaluated objectively [11, 12].

In 1987, Goodin and Aminoff [27] first suggested use of cognitive EP in assessing these impairments. In subsequent reports, this methodology was actively used in studies of various diseases accompanied by cognitive disorders [5, 12, 34, 39]. Thus, detection of subclinical cognitive disorders in patients with cerebral atherosclerosis can be used for identifying increases in the risk of developing vascular dementia. Increases in the P300 latent period by 20–58 msec correlated strongly with results from neuropsychological tests, the extent of dilatation of the cerebral ventricles, and the severity of periventricular leukoareosis [38, 40]. In terms of the latent period and magnitude, the P300 wave can indirectly indicate the nature and extent of activity in defined areas of the cerebral cortex, which makes recording of this wave an important tool for studying human psychophysiology, providing a sensitive indicator of the temporospatial measures of cortical activity linked with the late cognitive stages of information processing.

The use of complex studies, including quantitative and qualitative neuropsychological investigations and analysis of the P300 wave of the cognitive EP, allows not only more precise determination of the nature of the neurological deficit and the state of higher brain functions of patients with chronic cerebrovascular insufficiency, but also determination of the timely onset of appropriate treatment and assessment of the efficacy of treatment.

Cerebrolysin is an agent with a marked neuroprotective action. Its clinical efficacy and multimodal neurospecific action have been demonstrated in a variety of experimental studies, and its clinical efficacy has been supported in prospective randomized double-blind placebo-controlled clinical studies [7, 17, 24, 26, 28, 29, 36, 37, 41].

Cerebrolysin is a hydrolysate of pig brain containing biologically active polypeptides and free amino acids. This agent, containing low molecular weight biologically active neuropeptides and free amino acids, has been used in Russia and elsewhere for more than 40 years for the treatment of dementias of various origins [1–4, 6, 24, 26, 28, 29, 36, 41]. Cerebrolysin increases the efficiency of aerobic energy metabolism in the brain, protects neurons from the adverse effects of lactic acidosis, prevents the formation of free radicals, increases the survival and prevents the death of neurons in hypoxia and ischemia, and decreases the damaging neurotoxic action of glutamate [2, 3, 41].

Considering the need to seek effective treatments for the earlier forms of cognitive impairments, there is particular interest in studying the efficacy of cerebrolysin in CVI with moderate cognitive impairments.

The aim of the present work was to evaluate the effects of neurotensin on cognitive functions in patients with a syndrome consisting of moderate cognitive disorders of vascular origin.

MATERIALS AND METHODS

A total of 43 patients (23 female, 20 male) aged 40–80 years with clinical diagnoses of moderate cognitive impairment (MCI) took part in the study.

Diagnoses were made in accord with the modified MCI-Revised criteria [33]. At the moment of the initial investigation, patients scored at least 25 points on the Mini Mental State Examination (MMSE) scale [25]. There were no indications in the patients' histories of stroke or craniocerebral trauma for at least one year before inclusion in the present study.

All patients were given the diagnosis "cerebral vascular insufficiency, stage II, moderate cognitive impairment." The diagnosis of CVI was established in accord with the classification of vascular brain lesions [18, 20]. Moderate cognitive impairments were regarded as cognitive impairments beyond age norms but not reaching the level of dementia [8, 14, 19]. All patients taking part in the study had long (many years) histories of arterial hypertension. A total of 62.5% had ischemic heart disease. Acute cerebrovascular accidents (ACVA) were present in the histories of only two patients (with residual mild paresis (up to 4 points) at the start of the study).

Patients with severe motor or sensory impairments were excluded from the study, as these could hinder the neuropsychological testing; patients with severe or unstable somatic diseases, severe depression, or other clinically significant neurological or mental diseases were also excluded. Simultaneous treatment which might alter the results of the study (central acetylcholinesterase inhibitors, nootropic agents) was also excluded.

Cerebrolysin was given as daily i.v. infusions at a dose of 10 ml in 200 ml of physiological saline, with breaks on rest days. Treatment courses consisted of 20 infusions with subsequent evaluation of the therapeutic effect immediately and three months after courses of infusions ended.

During observations, three patients were lost to the study because of protocol failures (interruption of the therapeutic regime). It is important to note that these patients did not experience any side effects. The remaining 40 patients completed the study.

All patients underwent complex clinical, neurological, and neuropsychological testing, along with analysis of cognitive EP with assessment of the P300 wave using verbal and nonverbal stimulation. Investigations included use of the MMSE before treatment, after courses of treatment, and three months after courses ended [25].

Neurophysiological testing included the Mattis Dementia Rating Scale (MDRS) [31], the trial making test (TMT), and memory impairments in a test involving listening to 10 words (number of omissions) on the ADAS-Cog scale. Speech richness was assessed in terms of naming nouns beginning with the letter "s" in 1 min (verbal associations) and in terms of naming any plants (categorial asso-

TABLE 1. Quantitative Assessment of Cognitive Functions on the MMSE Scale Before and After Cerebrolysin Treatment, Points

Time point	Scale sections				
	Total points	Counting	Memory	Phrase repetition	Drawings
Before treatment	27.48 ± 0.91	4.18 ± 0.81	2.00 ± 0.83	0.61 ± 0.50	0.88 ± 0.33
On treatment day 30	29.06 ± 0.93*	4.73 ± 0.52*	2.67 ± 0.54*	0.91 ± 0.29*	0.97 ± 0.17
Three months after treatment	29.16 ± 0.99*	4.74 ± 0.54*	2.74 ± 0.45*	0.91 ± 0.29*	1.00 ± 0.00

Note. Here and in Tables 2 and 3: *significant differences compared with baseline ($p < 0.05$).

TABLE 2. Assessment of Cognitive Functions on the MDRS Scale Before and After Cerebrolysin Treatment, Points

Time point	Scale sections						
	attention	initiation and perseveration	speech richness	graphomotor functions	constructive praxis	conceptualization	memory
Before treatment	35.48 ± 1.15	32.18 ± 3.76	15.97 ± 3.51	3.64 ± 0.65	5.82 ± 0.39	37.33 ± 1.16	21.45 ± 2.91
On treatment day 30	36.27 ± 0.84*	34.58 ± 2.50*	18.00 ± 2.40*	3.88 ± 0.33*	6.00 ± 0.0*	38.00 ± 1.06*	23.15 ± 1.99*
Three months after treatment	36.33 ± 0.59*	34.44 ± 3.05*	17.93 ± 2.98*	3.88 ± 0.33*	5.92 ± 0.22	37.95 ± 1.11*	23.66 ± 1.55*

ciations). For studies of memory, each trial consisted of presentation of different words; constructive capacity was assessed by drawing various pictures.

Studies of cognitive EP were performed using a programmable EEGA-21/26 Entsefalan-131-03 electroencaphalogram-analyzer (NPKF Medikom MTD, Taganrog). For analysis of the P300 wave, patients were presented with series of verbal and nonverbal visual stimuli, among which they recognized the target stimulus and responded to it by pressing a button. The ratio of target and non-target stimuli was 1:4. The duration of stimulus presentation was 550 msec and the frequency of stimulus presentation was 1 per sec. Stimuli were presented in random order. Verbal stimuli were individual words of 3–6 letters, from a set of 20 words, presented on the screen in random order. The series consisted of 300 presentations. In preliminary training, patients were presented with five words on the screen; they studied them for 1 min, and these words were subsequently used as the target stimuli. A similar method was used to form the paradigm for nonverbal stimulation using a set of subject images (objects and animals) designated by the same words. Cognitive EP traces were obtained from two active leads using the 10–20 scheme with two ipsilateral reference ear electrodes. Artifact rejection was performed using additional EOG, ECG, and EMG channels. The P300 wave was taken as the peak positive component with a latency of ≥300 msec.

Results were analyzed statistically using a personal computer running the standard SPSS version 10 bundle. Analysis of dependent sets was performed using the *t* test for paired sets and the Wilcoxon test. Correlation analysis was also performed.

RESULTS

At the start of the study, the mean score on the MMSE was 17.48 ± 0.91 points. Three months after treatment was completed, as immediately after infusions, there were significant improvements in cognitive functions as compared with the baseline level (Table 1). There were significant improvements in measures such as counting, memory, and repetition of phrases spoken by the physician on the background of treatment, which persisted after treatment ended. There were no differences in the results obtained on any of the MMSE scales immediately after the end of treatment and three months later.

Assessment of cognitive functions using the MDRS showed that by treatment day 30, patients showed statistically significant improvements in all measures, with reductions in the extent of fronto-subcortical dysfunction (increased attention, initiation, richness of speech, conceptualization), and improvements in constructive praxis and both short-term and long-term memory (Table 2). Measures on this scale three months after the end of treatment were also significantly higher than at baseline (providing evidence of retention of improvements in the patients' states). The only measures not reaching statistical significance were those of constructive praxis. Comparison of these results on this scale in patients immediately after the end of treatment and at three months,

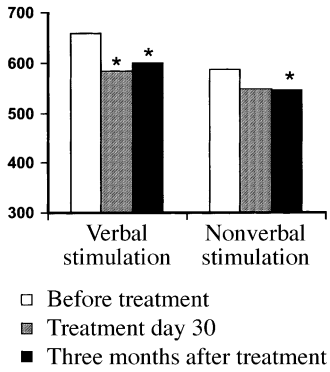

Fig. 1. Dynamics of MRT (msec) based on results of studies of cognitive EP before, during, and after cerebrolysin treatment. *Significant differences, $p < 0.001$, compared with the pre-treatment period.

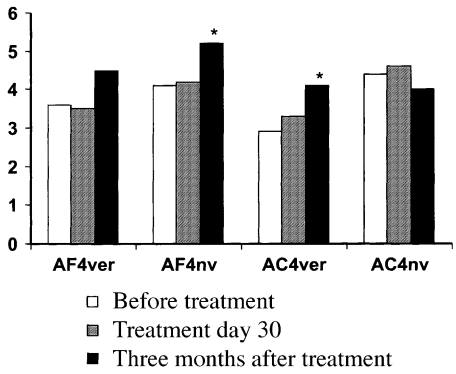

Fig. 2. Dynamics of cognitive EP P300 wave amplitude at different study times. P300 wave amplitudes (μV): AF4ver – in the right frontal lead on verbal stimulation; AF4nv – in the right frontal lead on nonverbal stimulation; AC4ver – in the right central lead on verbal stimulation; AC4nv – in the right central lead on nonverbal stimulation.

like comparison of MMSE data, showed no significant changes. There was also no deterioration in measures.

Studies of speech richness showed improvements in both literal and categorial associations during treatment; improvements persisted to three months after treatment (Table 3). In studies of attention, patients performed the tracking test much more quickly both immediately after completing courses of treatment and subsequently than at baseline (see Table 3).

Thus, as demonstrated by the neurophysiological results, there were statistically significant improvements in cognitive functions four weeks after courses of cerebrolysin treatment. There were reductions not only in frontal-subcortical dysfunctions, as indicated by improvements in measures of initiation, conceptualization, speech richness, and attention, but also in memory, constructive ability, and writing. It should be noted that this improvement, i.e., positive dynamics in improved spatial functions and memory, was not only seen immediately after completion of courses of treatment, but also persisted for three months after completion of treatment.

Neuropsychological data were supported by the neurophysiological results. Analysis of changes in measures of the P300 wave of the cognitive EP demonstrated reductions in the mean reaction time (MRT) on verbal stimulation both immediately after treatment was completed and over the subsequent three months. A similar dynamic was seen on nonverbal stimulation, though statistically significant differences from baseline were only reached three months after the end of treatment (Fig. 1). P300 amplitude only changed significantly three months after treatment, which may be evidence for a delayed neuroprotective effect of cerebrolysin treatment. Thus, there were significant increases in P300 amplitude in the right frontal lead on nonverbal stimulation and in the right central lead on verbal stimulation during investigation of patients three months after treatment (Fig. 2).

Correlation analysis identified a positive relationship between P300 wave amplitude and results obtained on the memory subtest on the MMSE scales (with verbal stimulation in the left frontal lead, $r = 0.43$, $p < 0.05$), the "graphomotor perseveration" test in the MDRS (verbal stimulation, right frontal lead, $r = 0.46$, $p < 0.05$), speech richness on the MDRS (right central lead, nonverbal stimulation, $r = 0.64$, $p < 0.01$), attention on the MDRS (left frontal lead, nonverbal stimulation, $r = 0.54$, $p < 0.05$), the "10-words" memory test (nonverbal stimulation, right frontal lead, $r = 0.60$, $p < 0.05$; right parietal lead, $r = 0.57$, $p < 0.01$; left parietal lead, $r = 0.59$, $p < 0.05$; verbal stimulation, left frontal lead, $r = 0.62$, $p < 0.05$; left parietal lead, $r = 0.45$, $p < 0.05$).

Correlation analysis identified relationships between MRT for both types of stimulation with the "drawing" subtest of the MMSE ($r = –0.49$, $p < 0.05$), literal associations ($r = –0.59$, $p < 0.01$), the "10-word" memory test ($r = 0.52$, $p < 0.05$), and the TMT ($r = 0.61$, $p < 0.01$).

There were also reductions in the latent period of the P300 wave in the parietal leads in verbal stimulation and in all leads in nonverbal stimulation, as compared with initial values at the end of treatment. The latent periods of this wave were also significantly shorter three months after treatment as compared with baseline and with latent periods after treatment ended (Table 4).

Correlation analysis showed that the latent period of the P300 wave in the parietal leads was significantly associated with virtually all measures obtained on neuropsychological testing regardless of the type of stimulation; the latent periods in the frontal leads were related to measures of the initiation and perseveration test ($r = 0.58$, $p < 0.05$), counting ($r = –0.51$, $p < 0.05$), drawing ($r = –0.49$, $p < 0.05$), and TMT ($r = –0.53$, $p < 0.05$).

TABLE 3. Quantitative Assessment of Speech Richness and Tracking Test

Time point	Literal association, points	Categorial association, points	Tracking test, sec
Before treatment	11.27 ± 4.46	15.64 ± 3.69	77.22 ± 38.08
On treatment day 30	13.58 ± 4.88*	17.33 ± 3.16*	63.81 ± 30.57*
Three months after treatment	12.25 ± 5.00*	17.49 ± 3.26*	53.75 ± 21.90*

TABLE 4. Dynamics of the Latent Period of the P300 Wave of the Cognitive EP by Study Group

Latent period	Baseline data	Treatment day 30	Three months after treatment
LPF3V	392.31 ± 44.25	391.15 ± 45.76	385.78 ± 32.65
LPF3nV	406.00 ± 38.14	411.35 ± 34.34	393.56 ± 38.86**
LPF4V	394.23 ± 73.74	379.85 ± 43.40	361.39 ± 32.75
LPF4nV	406.77 ± 29.43	414.46 ± 40.71	392.00 ± 33.35*,**
LPC3V	418.81 ± 80.27	412.58 ± 65.86	404.00 ± 64.12
LPC3nV	454.46 ± 46.91	436.15 ± 58.07	404.44 ± 52.35*,**
LPC4V	401.77 ± 71.67	409.38 ± 73.89	388.44 ± 64.54
LPC4nV	450.92 ± 51.41	440.31 ± 57.69	399.11 ± 41.90*,**
LPP3V	442.69 ± 80.40	465.15 ± 70.04	433.56 ± 62.74**
LPP3nV	463.85 ± 48.52	448.38 ± 67.65	430.67 ± 65.55*
LPP4V	459.46 ± 85.69	442.00 ± 71.55	416.22 ± 76.57*,**
LPP4nV	461.69 ± 60.07	447.77 ± 67.62	424.89 ± 64.08*

Notes. P300 latent periods, msec: LPF3V – left frontal lead, verbal stimulation; LPF3nV – left frontal lead, nonverbal stimulation; LPF4V – right frontal lead, verbal stimulation; LPF4nV – right frontal lead, nonverbal stimulation; LPC3V – left central lead, verbal stimulation; LPC3nV – left central lead, nonverbal stimulation; LPC4V – right central lead, verbal stimulation; LPC4nV – right central lead, nonverbal stimulation; LPP3V – left parietal lead, verbal stimulation; LPP3nV – left parietal lead, nonverbal stimulation; LPP4V – right parietal lead, verbal stimulation; LPP4nV – right parietal lead, nonverbal stimulation; *significant difference compared with baseline data ($p < 0.05$); **significant difference ($p < 0.05$) compared with values on treatment day 30 and three months after treatment.

Thus, the dynamics of electrophysiological changes supported the data obtained from neuropsychological investigation: after courses of treatment ended and for at least three months thereafter, patients showed improvements in neurodynamic functions, memory, and the rate and qualitative characteristics of thought processes.

Deterioration of cognitive functions did not occur during treatment or after treatment ended. There were also no side effects in any of the study patients during the treatment.

DISCUSSION

Considering the high risk of developing dementia when moderate cognitive impairments are present, timely diagnosis and treatment are of particular importance. Patients showed cognitive impairments in the form of frontal-subcortical dysfunctions. With relatively high MMSE measures, patients' performance of the conceptualization and initiation of mental activity and dynamic praxis were unsatisfactory. Patients had significantly reduced attention and elevated impulsivity, leading to degraded performance of tests for mnestic functions. Cerebrolysin treatment yielded gradual improvement in neuropsychological test measures and cognitive EP parameters, with reductions in the severity of cognitive dysfunctions. Neuropsychological tests immediately after the end of treatment demonstrated significant improvements in cognitive functions, with increases in the total MMSE points score; patients started to show improvements in orientation in time and in counting, became more able to concentrate, and experienced improvements in short-term memory.

The improvements in cognitive functions could not be explained by a learning effect, as each assessment of memory involved presentation of different words, assessment of constructive capacities used different drawings, different times were shown on clocks, etc.

Analysis of the electrophysiological data also demonstrated positive dynamics: measures of cognitive EP improved at three months post-treatment, the latent period

of the P300 wave decreasing in all leads on nonverbal stimulation but decreasing only in the parietal leads on verbal stimulation.

In the normally functioning brain, the parietal lobes, along with their systems of connections to each other and subcortical levels, operate as a single unit. The studies reported here showed reductions in neurodynamic impairments on the background of cerebrolysin treatment. The parietal areas concentrate all leading modalities and support complex synthesis in subject and verbal activity, so the cognitive potential, which is studied during the performance of cognitive tasks associated with some particular sensory stimulation, responds to changes in the functioning of cells in this part of the brain, which is supported by the correlation between the latent period of the P300 wave in the parietal leads with virtually all measures obtained from neuropsychological tests. Clinically, this is manifest as improvements in constructive praxis and spatial functions in the study patients.

It is now generally accepted that the P300 wave is generated [5, 35] as a result of the activity of a wide network of brain structures, both cortical and subcortical, interacting with each other during the execution of cognitive processes [5, 12, 13, 27, 34, 35]. As regards the later components of the cognitive complex, the involvement of structures including the frontal area has been demonstrated [34, 35]. An involvement of the frontal area in the cognitive component is not unexpected, as this area is connected with final stimulus recognition and decision taking [32]. Thus, analysis of the sources of the P300 wave demonstrates the involvement of a variety of brain structures in recognition, differentiation, and retention of target stimuli in memory. The reductions in the response latencies (the latent period of the cognitive EP) and mean reaction times of the patients in our study are evidently linked with improvements in processing activating mental activity, i.e., improvements in the functioning of the first "energy" block as defined by Luriya [15]. Clinically, this is manifest as improvements in attention measures and the tracking test.

Patients with CVI showed significant reductions in the P300 latent period in the frontal lead on nonverbal stimulation three months after treatment. Various investigations in patients with frontal-subcortical deficit of cognitive activity have demonstrated greater impairment to the subdominant hemisphere at the initial stages of the pathological process [10, 11, 13, 19, 22]. These data are completely consistent with results obtained in our studies of patients with vascular dysfunction with features of fronto-subcortical deficit. Thus, cerebrolysin treatment had positive influences in relation to fronto-subcortical cognitive disturbances for three months. One of the mechanisms of the neuroprotective action of cerebrolysin is an increase in glucose transport across the blood-brain barrier [23]. Ultimately, this improves aerobic metabolism, which may explain the positive effect of cerebrolysin in vascular lesions.

Subcortical-stem structures play an important role in the execution of higher mental functions. Lesions to structures in this area produce a cortical-subcortical "dissociation" syndrome, which underlies the development of cognitive deficits in vascular brain lesions, including moderate cognitive impairments of vascular origin [19–22]. Electrophysiological changes supported the clinical effects after courses of cerebrolysin, with reductions in the inertness and rigidity of mental activity (tracking test results). The dynamic factor in mental activity is also supported by the adequate functioning of the frontal lobes. Many mental functions can be regarded as processes developing over time and consisting of a series of stages which sequentially displace each other. Thus, decreases in the latent period of the P300 wave of the cognitive EP in the frontal leads also reflect improvements in the functioning of the third block (the "programming" block) in Luriya's scheme. Clinically, this is apparent as improvements in the memory and the mental activity initiation and perseveration subscales. Overall, there appear to be improvements in cortical-subcortical interactions on the background of cerebrolysin treatment; cerebrolysin acts directly on the lesioned substrate in moderate vascular cognitive impairment; in chronic cerebral circulatory insufficiency, this is known to be primarily the connections of the cerebral cortex with subcortical structures.

Thus, the results obtained here indicate that cerebrolysin is an effective substance for the treatment of patients with chronic cerebral dysfunction of vascular origin, which is manifest clinically as moderate cognitive impairment. Courses of cerebrolysin treatment were found to decrease memory and attention deficits and to improve the patients' cognitive status; treatment at adequate doses (20 i.v. infusions of 10 ml cerebrolysin in 200 ml of physiological saline) has a delayed effect which is seen three months after completion of courses of treatment.

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