



ANTIOXIDANT PROPERTIES OF CEREBROLYSIN – AN OLD DRUG WITH NEWLY DISCOVERED CAPABILITIES

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Abstract: Cerebrolysin (cere) is a porcine brain derived peptide-based drug approved outside US for dementia, acute stroke, and stroke rehabilitation and after brain injury resp. brain surgery. The clinical efficacy of cere is mainly attributed to the neurotrophic properties of the peptides in its content. However, there is still new evidence arising on antioxidant properties of cere. In this study we analyze a case of a 37-year old police officer with bilateral brain calcifications, who was treated intravenously with cere with a spectacular cognitive improvement and significant, but short, daily functioning improvement. The patient was diagnosed with Fahr disease (FD) in psychiatry ward and followed-up in outpatients for one year. It cannot be excluded, that clinical improvement was due to cere antioxidant influence on calcium, phosphorus, iron, zinc, aluminum, copper, and magnesium, described to be a content of brain calcifications in FD. We encourage to perform in vitro investigation on interaction between cerebrolysin and brain calcification to provide effective Fahr disease treatment scheme. To our best knowledge this is the first case report on FD treated with cere.

Keywords: antioxidant effect, brain calcifications, cerebrolysin, neurodegeneration

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INTRODUCTION

Cerebrolysin (cere) is a porcine brain derived peptide-based drug, containing a mixture of low molecular weight peptides and amino acids, displaying neuroprotective and neurotrophic effects. Recently, new data is emerging that shows possible antioxidant properties of cere. It is not excluded, that significant cognitive improvement in the case of the described patient with bilateral brain calcifications can be due to antioxidant properties of cere content.

Primary bilateral calcifications in basal ganglia are described in the literature as Fahr disease (FD). It is a rare neurodegenerative disorder of unknown etiology, with multiple motor and neuropsychiatric symptoms. The most frequent manifestations of FD are motor symptoms: parkinsonism, chorea, tremor, dystonia, athetosis or oro-facial dyskinesia. Cognitive impairment is the second most common one, and the third one is cerebellar impairment and speech disorder [18]. FD is characterized by idiopathic symmetrical intracerebral calcifications in the brain. The extracellular calcium deposits occur in the walls of capillaries, small vessels, and perivascular spaces. They are already present before the onset of the symptoms and usually appear in the third decade of life. They induce progressive neuronal degeneration in surrounding areas. The usual onset of symptoms is in the fourth to sixth decade of life [16,17,18]. Deposits consist not only of calcium, but also of phosphorus, iron, zinc, aluminum, copper, magnesium [5].

Cere is a lipid-free preparation of free aminoacids (75%) and low molecular mass peptides (25%) of animal origin [12] which mimic the action of endogenous neurotrophic factors on brain protection and repair. Nuclear-emission analysis of the cere content revealed a presence of magnesium, potassium, phosphorus, and selenium which had neuroactive and antioxidant properties [11]. The summary of product characteristics states cere is approved as a supportive treatment in structural damage of the central nervous system and slight dementias (www.urpl.gov.pl). Its potential efficacy and safety is described also in patients after stroke, central nervous system injury and vascular dementia [4,20] and there is some data on cere treatment in progressive supranuclear palsy [10], Asperger syndrome and childhood autism [15] and amnesic syndrome [3,4].

A double-blinded, placebo-controlled, randomized study on patients with mild traumatic brain injury showed that patients requiring 30 ml cere daily intravenous infusion significantly improve in the long-term memory at third month after brain injury [6]. Chen et al. analyzed 6 randomized, controlled trials of cere for treating vascular dementia, without

a language restriction [7]. Cere showed a positive effect on general cognitive function and global clinical function. However, the authors concluded that there was insufficient evidence to recommend cere as a routine treatment for vascular dementia due to the limited number of included trials, wide variety of treatment durations and short-term follow-up in most of the trials.

Alvarez and Fuentes reviewed several randomized, double-blind, clinical trials on cere efficacy in Alzheimer disease and confirmed cognitive and global functioning improvement [1]. They found also that, the clinical benefits of cere were largely maintained for several months after treatment. However, they concluded that long-term studies with longer follow-up period were needed. Alvarez et al. qualified 279 patients with AD in randomized, double-blind study [2]. The patients scored in MMSE 14-25 points. It is noteworthy that cere showed indirect dose-dependent correlation with clinical improvement. It was shown that patients obtaining 10 ml cere daily for 5 days a week during four consecutive weeks and maintaining therapy of 10 ml cere daily twice a week for eight consecutive weeks, improved cognition function significantly higher than those obtaining 30 ml cere or 60 ml cere in same treatment scheme. Probably, the efficacy of cere in this group of patients results from its ability to reduce A β deposits [25].

There are very limited data on antioxidant properties of cere. Some were delivered on 163 patients with primary ischemic stroke admitted within the first 12 h after stroke onset. At baseline, patients had their lipid spectrum analyzed, level of free-radical lipid oxidation measured with chemiluminescent method, and hemostasis system parameters assessed. Patients were stratified into 3 groups: group 1 (n=59) received traditional treatment and mexidol during the first 10 days in dose 500.0 mg intravenously and cere in dose 1.0 ml intramuscular; group 2 (n=60) received cere in dose 1.0 ml intramuscular during 10 days in addition to traditional treatment; group 3 (n=44) received only traditional treatment. It was shown that administration of neuroprotective drugs, mexidol and cere, improved the lipid spectrum, reduced the intensity of free-radical lipid oxidation, and stabilized hemostasis parameters. Moreover, patients of group 1, while examined on the 21st day after stroke, showed increase in survival rate and more rapid reversal of neurological deficits [13].

A blood level of oxygen active forms were measured using chemiluminescent method before and after cere treatment in 41 former Chernobyl "liquidators" who have developed a complex of mental disorders of exogenous-organic type. Two groups

have been distinguished: (1) with marked effect of therapy and (2) with slight therapeutic effect. In the first group, cere significantly decreased oxygen active forms level [26].

Here reported patient and his family members gave a written informed consent and the case report protocol had been approved by the Local Bioethics Committee No. RNN/466/13/KB.

CASE REPORT

A 37-year-old police officer was admitted to the psychiatry ward for a diagnosis of progressing change in behavior, cognitive impairment and urine incontinence. The patient had a history of treatment for neurasthenia (F48.0 of ICD-10) [24] since he was 31 and alcohol dependence since he was 20 (F10.2 of ICD-10) [24]. There was no history of other, than alcohol and cigarettes, psychoactive substances intake. The history of concomitant somatic disorders and severe brain injuries were also silent.

The analysis of medical records and interview obtained from the family members revealed progressive changes in behavior of the subject after he reached 28 years. He has become euphoric or irritated and aggressive, sexually disinhibited and overfamiliar with strangers. He had no history of developmental delay in childhood. He graduated with good results from two university faculties. There was no family history of neurological disease. His consecutive treatment consisted of tianeptine, carbamazepine, valproic acid, and risperidone. Due to progressing behavioral disinhibition and urine incontinence, he was admitted to psychiatry ward for further diagnosis.

DIAGNOSTIC PROCEDURE BEFORE THE FIRST INTRAVENOUS CERE CYCLE

His brain computed tomography (CT) revealed massive bilateral calcifications in basal ganglia (lenticular and caudate), thalamus (Fig. 1. a-d) and in cortex of fronto-parietal border (Fig. 1. e-f). Apart from this, CT showed also cortico-subcortical atrophy of the brain, massive calcifications in the mucous of the left frontal sinus and Sieve cells and slight calcifications in the sphenoid sinus mucosum. It is difficult to state if the mucous calcifications were related to the etiopathogenesis of FD or would have revealed even though. The patient presented neutral mood, flat affect and tangentiality. He was suspicious, without delusional thinking or disturbances in perception. He showed apparent disturbances in episodic memory, operating memory and short attention span. His speech was

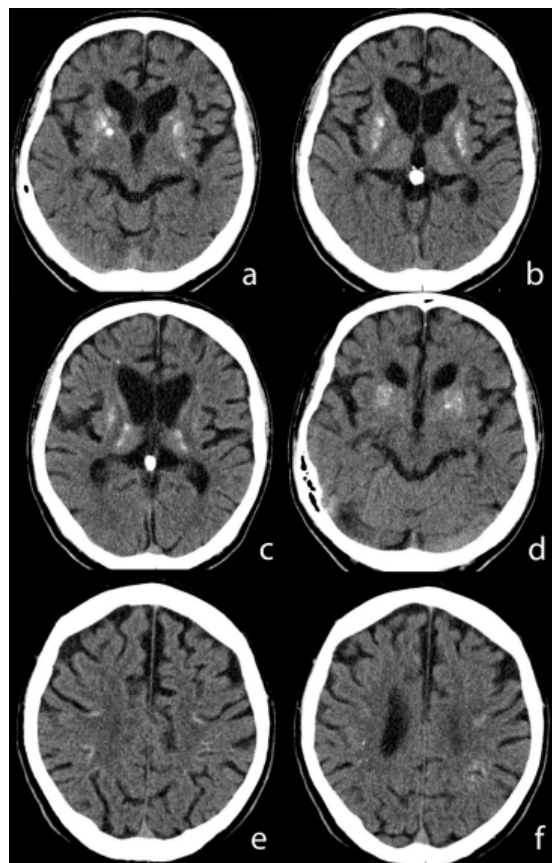


Fig. 1. Brain computed tomography of the patient.

pressured and blurred. The patient displayed no insight into his signs and symptoms, and his only claim were sleep disturbances. Parents delivered a history of urine incontinence during the night and day since about 2 years.

Before the first course of cerebrolysin treatment, the patient underwent a neuropsychological examination which showed decreased cognitive functioning related to the frontal lobe disturbances [23]. A decreased extent and permanence of direct visual memory was confirmed. His MMSE [8] score was 24. He did not manage to put any number on circle in the clock drawing test [22]. His intelligence quotient measured with the revised Wechsler adult intelligence scale (WAIS-R) was 68 [9].

The laboratory tests and physical examination did not reveal any possible secondary nature of brain calcifications. There was no abnormalities observed on fundoscopic examination. Neurological examination revealed blurred pressured speech, bilateral positive Babinski sign, no other abnormalities were found. His EEG recordings before the first cere treatment course revealed no epileptic activity. The α rhythm was moderately abundant, symmetrical, irregular, with a correct spatial organization of 10-11 Hz, amplitude of 25 μ V. The stop reaction was bilaterally poor. We

observed generalized, irregular low-voltage fast activity with diffused theta waves 6-7 Hz. His EKG tracings were normal. Laboratory investigations including blood count, serum electrolytes (calcium, chlorates, potassium, sodium) level, sedimentation rate, renal and liver function tests, glucose level, thyreotropin and free thyroid hormones serum levels did not reveal any abnormality.

After analysis of the above listed diagnostic procedures and exclusion of any secondary cause for brain calcifications, a probable diagnosis of Fahr disease was established.

TREATMENT

The patient was initially put on carbamazepine and chlorprothixene (50mg/day). After 2 days treatment with carbamazepine in a daily dosage of 400 mg patient developed side effect as an erythema located in the area of head, thoracic, abdomen and thighs. Carbamazepine was stopped and antihistaminic agents were introduced. The patient displayed sexual disinhibition towards female patients and medical personnel and became even aggressive as submitting sexual proposals and grabbing women in the ward. He displayed urine incontinence during the day and night and had no insight into it, which made urine incontinence more problematic and confusing for others than for himself. Zuclopentixol and sodium valproate were gradually introduced but after 2 days of 30mg/day zuclopentixol intake, he showed severe parkinsonism with parkinsonian posture, parkinsonian gait and upper limbs muscle rigidity. Zuclopentixol and chlorprothixene were stopped and biperiden was administered until the parkinsonism resolved.

When brain computed tomography and psychological examinations were completed (results indicating frontal lobe structural damage), the decision on cere treatment was made as FD can be defined as a disease with brain structural damage, here additionally with cognitive impairment. Patient underwent a 20 days cere intravenous treatment 10ml/day. There was no urine incontinence episode during the whole cere treatment and during 4 days after we finished cere treatment and discharged our patient. His sleep and behavior disturbances, cognitive functioning improved: he could focus, read book.

After the patient was discharged, he was provided with psychiatric follow-up in outpatients for 20 days with a cere maintaining therapy. He was receiving 10 ml cere per day intramuscularly twice a week. He received a total of 8 dosages cere a 10 ml within 20-days psychiatric follow-up. The treatment of sodi-

um valproate (1000mg/day) was continued. Additionally, choline alfoscerate was given in a dose of 800mg/day, as a supportive treatment to maintain current improvement of cognitive impairment. After 20 days of follow-up he was transferred to the psychiatric ward for a second cere intravenous treatment course. On admission a stable status of mental improvement was found. The patient was calm, with improvement in social and sexual disinhibition. There was no urine incontinence during outpatients follow-up. His second neuropsychological examination (before second cere treatment course, 80 days after the first neuropsychological examination) revealed improvement in extend and permanence of direct visual memory, however the results of some neuropsychological tests as previously used were still below the normative ranges. This time, he scored 30 points on MMSE.

During the second cere treatment course there was no urine incontinence and significant improvement in lack of social and sexual inhibitions. However, despite the better results on neuropsychological examination, we observed worse compliance during intravenous treatment: the patient was irritated, interrupting cere intravenous flow and during the family members visits, he was becoming more irritated, with impulsive behaviors. The patient presented with poor upper limbs balance and bent posture. This time, the clinical outcome on cere was not as significant as recently. He obtained psychiatric follow-up with cere intramuscular maintaining treatment as previously. Unfortunately, progressive worsening of neurological and mental status is observed. His current main problems, referred in outpatients, are sexual disinhibition, urine and fecal incontinence.

DISCUSSION

Although our patient was treated with carbamazepine (400mg/day) about 2.5 year earlier, now he developed skin side-effects while treated with same daily carbamazepine dosage. The patient displayed hypersensitivity to typical antipsychotics. He developed severe parkinsonian signs after 2 days of treatment with zuclopentixol 30 mg daily. Parkinsonism resolved after the zuclopentixol had been stopped and the patient started on biperiden. In our opinion it can be due to progressive neurodegeneration of brain cortex and changes in drug receptors localization and balance. During the second hospitalization a bend posture and poor upper limbs balance was seen and consistent in the absence of neuroleptic treatment, which was a new patient's neurological sign. There are some

data that patients with Fahr's disease are at greater risk for extrapyramidal side effects. In one case series, four of seven patients with basal ganglia calcification were prone to extrapyramidal side effects with treatment with typical antipsychotics [9]. In patient described by Shakibai et al. [21], there was no extrapyramidal symptoms during treatment with risperidone (3mg/day). The authors conclude that it is probably more safe to treat psychosis or accelerated psychomotor drive in patients with Fahr's disease with atypical antipsychotics.

General cognitive and social functioning improved during the first intravenous cere treatment cycle and maintained for 2-3 weeks after that. Unfortunately it has declined during the second intravenous cere treatment. In our opinion, the possible reason of this decline requires wider discussion. It is possible that this decline was due to continuous progress of calcifications and secondary neurodegeneration. However, so far, it has not been determined if a critical amount must be reached before clinical signs and symptoms occur [16] or a patient gets worse.

So far, there is no causative treatment of FD. Selective removal of deposited calcium from the brain without affecting calcium from bone and other tissues appears to be an impossible task [18]. Further, there are several other than calcium minerals deposited. An attempt of treatment with central nervous system specific calcium channel blocking agents like nimodipine was unsuccessful [18]. Reduced 25-OH vitamin D3 with normal levels of 1.25(OH)₂ vitamin D₃, indicate an inborn error of vitamin D metabolism and was found in three members with FD [19] and suggest a new possible treatment strategy. It is noteworthy, in one patient, disodium etidronate showed symptomatic benefit without reduction in calcification [14]. It is interesting that cere contains magnesium, potassium, phosphorus, and selenium which had neuroactive and antioxidant properties [11]. Calcifications, located extracellularly, in the walls of capillaries, and small vessels, and in perivascular spaces contain calcium, mag-

nesium, phosphorus, iron, zinc, aluminum, copper [5]. It is a matter of question if microelements being a content of cere and administered intravenously act in chemical reactions with microelements in FD calcifications present in the walls of vessels and in the perivascular spaces. If they do, another question is coming, if it increases or reduces the size of FD deposits or maybe it is neutral according to this issue. Significant improvement of our patient's condition during the first cere treatment course and current stable cognitive improvement, encourages the use of this agent in FD. In our opinion it is an introduction to investigate cere influence on FD deposits in experimental or animal models. We think, it could deliver a guidelines according to optimal duration and daily dosages for intravenous cere treatment in FD to maintain the clinical improvement.

Conclusions:

1. It is possible, that patients with symmetrical brain calcifications can benefit from antioxidant properties of cerebrolisin.
2. It cannot be excluded that the significant clinical improvement in patient with basal ganglia calcifications was due to the interaction between other than protein contents of cerebrolisin and chemical elements of brain calcifications.
3. We encourage to perform in vitro investigation on interaction between cerebrolisin and brain calcification to provide effective Fahr disease treatment scheme.

Disclosure section:

The Author reports no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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AUTHORS' DECLARATION:

Study Design: Dominika Berent; **Data Collection:** Dominika Berent; **Manuscript Preparation:** Dominika Berent, Krzysztof Zbolarski; **Funds Collection:** Marian Macander. The Authors declare that there is no conflict of interest.

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