OUTCOMES

REMARKABLE CASES IN NEURORECOVERY

A collection of practice-based evidence

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A collection of practice-based evidence

"The ***good*** physician treats the disease;
the ***great*** physician treats the patient who has the disease."

Sir William Osler (1849-1919)
Founding Professor of Johns Hopkins Hospital

Table of Contents

Dafin F. Mureșanu, MD, PhD

President of the European Federation of NeuroRehabilitation Societies (EFNR)

Foreword

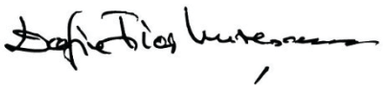
In the times of evidence-based medicine, patient outcomes have seen quintessential improvement, as health policies are informed by well-designed and rigorously conducted clinical trials. In addition to robust quantitative research methods, practice-based approaches draw information from complementary sources, like clinical cases, effectiveness or registry studies, to support the transfer of clinical experience into future practice, ultimately leading to successful patient treatment. Clinical cases highlight individual patients, allowing insight into the complex clinical judgement of physicians.

In this context, case reports are of utmost importance. These lie at critical points of the "evidence pyramid" and, especially in rare neurological diseases, may serve as the first step in the development of scientific evidence. Complex methodological constructions cannot always provide appropriate answers or do not exist when new treatment concepts are under development.

This booklet showcases case reports and mini-series in neurorecovery. Patients in this collection were treated with Cerebrolysin – a combination of peptides and amino acids with similar effects to endogenous neurotrophic factors. Important recovery was observed in a wide variety of indications such as acute ischemic stroke or traumatic brain injury, and after neurosurgical interventions.

This special booklet contains well-documented clinical cases from an international team of physicians, who have kindly agreed to share their experience with the medical community. The final goal of our dissemination effort is to promote new research avenues and to aid physicians' clinical decision-making process.

I want to acknowledge and address a warm thank you to all authors, reviewers, and editors who have contributed to the production of this booklet.



Dafin F. Mureșanu, MD, PhD

President of the European Federation of NeuroRehabilitation Societies (EFNR)

Introduction: The Goal of OUTCOMES

Medical experts are aware that the armamentarium of pharmacological treatment options for stroke, traumatic brain injury, and related disorders is limited. It is, therefore, all the more important that clinicians working in this field of medicine share their experience about treatment concepts, which have shown promising results.

One of these treatment concepts includes Cerebrolysin, a neuropeptide preparation with neurotrophic factor-like effects that has shown to promote neurorecovery. Each chapter is introduced by the current understanding of Cerebrolysin's mechanism of action.

The presented cases focus on the clinical experience with Cerebrolysin in the treatment of:

- Ischaemic stroke
- Hemorrhagic stroke, subarachnoid haemorrhage, and vascular surgery
- Traumatic brain injury
- Post-stroke and post-TBI complications
- Disorders of consciousness

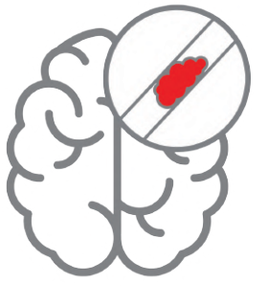
An individual chapter is dedicated to the combined treatment of Cerebrolysin and recanalization therapies.

This collection of cases and case series shows impressive treatment outcomes in therapeutic niches such as brain hypoxia after cardiac arrest, neurorecovery in post-stroke spasticity, and hemianopia.

Clinicians worldwide may find an inspiration by the shared experience when other treatment options do not result in the expected outcome.

Chapter 1

ISCHAEMIC STROKE



Dr. Michael Chopp
United States of America

Chapter 1.1

The role of Cerebrolysin as stand-alone therapy...

Cerebrolysin is used in many countries for the treatment of stroke. Some fundamental breakthroughs on the mode of action and fundamental pharmacological parameters of Cerebrolysin were deciphered by studying clinically relevant models of ischaemic stroke. Treatments were initiated hours and days (e.g., 3 days) post-ictus. Among the most clinically relevant stroke models in which Cerebrolysin has demonstrated therapeutic efficacy is middle cerebral artery occlusion (MCAo) which is induced by placement of a preformed clot at the origin of the MCA to induce a malignant stroke. Significant reductions of the volume of cerebral infarction and improvement in multiple indices of functional outcome were evident in a dose-response manner with Cerebrolysin therapy.

How does Cerebrolysin provide effective treatment for acute stroke? To address this question, we must realize that Cerebrolysin as a therapeutic agent acts on multiple targets, e.g., the cerebral microvasculature to reduce the spread and expansion of the ischaemic penumbra and to reduce secondary thrombosis as well as on cerebral parenchymal cells and tissue in ways that promote not only neurovascular protection but also initiate restorative processes. Such restorative processes include neurogenesis (production of new brain cells), angiogenesis (production of new blood vessels), neural plasticity, and white matter remodeling (remyelination and axonal growth and integrity). Cerebrolysin accomplishes these multifold therapeutic tasks by activating various neurovascular protective and restorative factors (to be described below). These restorative processes act in concert to enhance neurological recovery, and extensive data directly correlate these factors with neurological recovery.

The functional benefits induced by treatment of acute stroke with Cerebrolysin likely result from the coupling and amplification of concurrent neurovascular protective and restorative events.

Dr. Slaven Pikija
Christian Doppler Klinik
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1.1.1 ...in the treatment of brainstem stroke

Case Report

A 60-year-old male patient was admitted to the hospital due to a sudden onset of horizontal double vision. The patient was unable to swallow and had left-side upper extremity palsy, initially reported by the patient starting more than 4.5 hours before admission and confirmed via Medical Research Council Scale for Muscle Strength at time of clinical examination. The symptoms were localized in the brainstem – pons area on the right side. A brain MRI showed no acute infarct in this area, and the intracranial vasculature was without irregularities (Figure 1). The diagnosis of acute ischemic stroke was established according to Sacco et al., who states that each episode of clinical symptoms lasting more than 24 hours is suggestive of a stroke. Since the patient presented outside the therapeutic window, no acute thrombolytic therapy was given.

On admission day and days after that, he received ASA, intravenous fluids, prophylactic low-molecular-weight heparin, statin, and 30 ml intravenous Cerebrolysin. Quite unexpectedly, the patient showed signs of rapid neurological recovery. On the third day, he retained all previously lost functions and was discharged without neurological symptoms. Since extensive diagnostic workup showed no other cause of stroke, the stroke etiology was deemed to be microangiopathic due to elevated blood pressure.

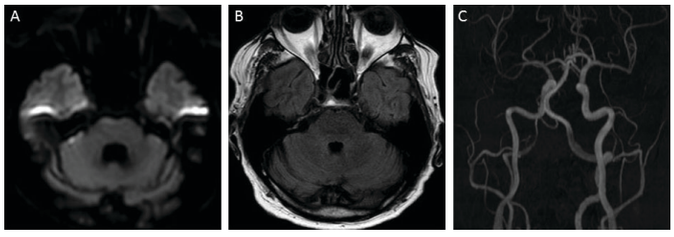

Figure 1 – Axial brainstem magnetic resonance images (MRI) showing diffusion weighted imaging (DWI) sequences, B-1000 (Panel A). Axial MRI fluid attenuated inversion recovery (FLAIR) images (Panel B). MRI - Time-of-flight (TOF) showing intracranial vasculature (Panel C).

Discussion

This is a case report of a brainstem stroke with quite unexpected fast recovery. While the MRI did not provide diagnostic clues, this is known for as many as 20% of brainstem strokes. Control imaging was not performed in this case. Cerebrolysin is an agent with established effects in anterior stroke syndromes and has a beneficial safety profile. We decided to administer the agent in this case of posterior stroke syndromes and were surprised by the dramatic improvement of the patient. It is not possible to reach a specific conclusion regarding the efficacy of Cerebrolysin on microangiopathic posterior-circulation, i.e. brainstem stroke, although it is tempting to do so, especially in a setting without acute clot-bust therapy (thrombolysis, endovascular intervention).

Conclusion

Cerebrolysin might have contributed to the beneficial outcome in this patient with posterior stroke syndromes and it seems warranted to investigate this treatment approach in prospective studies.

Dr. Saher Hashem

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Egypt

1.1.2 ...in the treatment of posterior cerebral artery occlusion (Wallenberg's Syndrome)

Case Report

A 60-year-old woman with a history of hypertension was admitted to an interventional stroke center with acute onset of impaired movement and swallowing, left-sided weakness, and partial ptosis. Initial examination showed left-sided hemiataxia, partial paralysis, vertigo, vomiting, palatopharyngeal bulbar palsy, facial numbness, and right-sided dissociated sensory loss. Her NIHSS score was 22; her previous medical history reported hypertension and heavy smoking. The patient was on angiotensin II receptor blockers (ARBs; antihypertensive medications) and selective serotonin reuptake inhibitors (SSRIs); she did not receive antiplatelet medication.

Physical examination, laboratory tests, diagnostic catheter after brain MRI of the lateral medullary syndrome, magnetic resonance angiography of the narrow left vertebral, and the left posterior inferior cerebellar artery (PICA), Scale for the Assessment and Rating of Ataxia, and continuous cardiac monitoring were performed. A diagnosis of left PICA - posterior cerebral artery occlusion (Wallenberg's syndrome) was established. Since the time of stroke, onset was unknown (wake-up stroke), and increased blood pressure (225/110 mmHg) and blood sugar level (160 mg/dL) needed to be managed first, alteplase was not given. The patient continued to deteriorate, became severely dizzy, and developed symptoms of left-sided hemiplegia with numbness in the right half of her body and the left side of her face. Vomiting continued. The consulted neuro-interventionalist decided to proceed with a diagnostic catheter angiogram after MRI indicating non-visualized left PICA (Figure 1).

Recanalization was attempted by endovascular thrombectomy, followed by left vertebral artery stenting. However, after thrombectomy, the blood vessel was still occluded (Figure 2). Thus, we injected TPA intra-arterially. Six hours later, the patient still showed signs of a stroke. The patient was treated with Cerebrolysin (20ml once daily for 15 days), dual antiplatelet therapy (aspirin and clopidogrel), ARBs, B12 and folic acid, anti-vertigo drugs, and anti-emetics. The patient also received physical therapy to improve strength and coordination. Treatment with Cerebrolysin was continued (10 ml on three days per week for three weeks and on two days per week after that for one year). Within one month after the stroke, the patient had improved rapidly and did no longer show bulbar palsy, vertigo, and eyelid drooping. Her NIHSS score decreased to 8; her quality of life had much improved; she was able to walk independently, drive, swim. The NIHSS score was four after two months post-stroke and two after one year, with no stroke recurrence and excellent recovery of functional abilities.

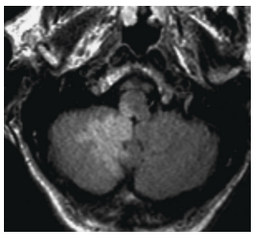

Figure 1 – Native CT showing hyperdense ACM left, and CT angiography showing occlusion of the M2 segment of the left arteria cerebri media.

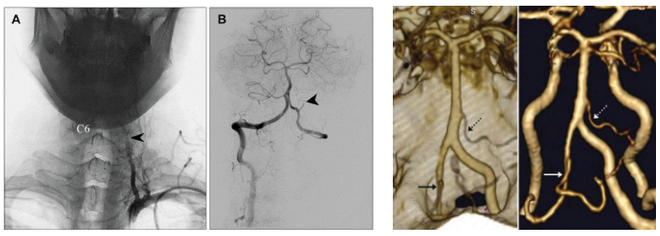

Figure 2 – Angiography and thrombectomy, showing only partial recanalisation (TICI 2B) of the ACM.

Discussion

Our case presented with symptoms of the Wallenberg's syndrome, which usually involves swallowing difficulties, dizziness, hoarseness, nausea and vomiting, nystagmus, and problems with balance. Some patients have uncontrollable hiccups, loss of pain and temperature sensation on one side of the face, and/or weakness or numbness on one side of the body as reported in our case. This syndrome is characterized by sensory deficits that affect the trunk and extremities contralaterally, and sensory deficits of the face and cranial nerves ipsilaterally. This cross-body finding was the main symptom for the diagnosis.

This case is a good example of stroke care with treatment coordination between multidisciplinary teams of the primary care and comprehensive stroke center aiming for early protection of the penumbral tissue and rapid delivery of recanalization therapies.

Conclusion

This patient presenting with the Wallenberg's syndrome did not benefit from recanalization therapies. However, the administration of Cerebrolysin in combination with aspirin and clopidogrel was found to be useful for improving the neurological outcomes.

Dr. Gerard Erikson Gonzalez

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1.1.3 ...in the treatment of recurrent ischaemic stroke

Case Report

A 73-years old, male Caucasian patient was examined in the outpatient department due to left-sided weakness and slurred speech starting two days before admission. The patient had a history of stroke (3 years back) with left-sided residuals (Modified Rankin Scale 2). Large vessel atherosclerosis was the mechanism of the prior stroke, and the patient was treated with aspirin and atorvastatin. He also had a history of diabetes mellitus maintained on Vildagliptin and Metformin, Dapagliflozin, and Insulin. At outpatient follow-up, the patient had moderate dysarthria without language problems; motor strength of 4/5 on both left upper and lower extremities; left hemisensory deficit and an NIHSS of 6. He was then advised for admission for the left-sided hemiparesis and dysarthria.

Upon admission, a brain MRI was done and revealed multiple non-haemorrhagic infarcts in the right basal ganglia and subcortex of the left parietal lobe. A Right parietal lobe encephalomalacia with haemosiderin deposition was likewise seen from the previous stroke. A repeat Carotid Ultrasound compared to three years back still showed a totally occluded right internal carotid artery. The 2D echo was unremarkable with EF of 54% while his 24-hour Holter monitoring only showed occasional premature ventricular contractions. Paroxysmal atrial fibrillation was the primary consideration of both neurology and cardiology services (CHA2DS2-VAsc score of 5) at this time. Since he was not eligible for thrombolysis, the patient was then started on Apixaban 5mg twice daily, Clopidogrel 75mg once daily, Atorvastatin 80 mg tab once daily and IV treatment with 10 ml Cerebrolysin per day. He was also referred to a diabetology and rehabilitation service with a note of his HbA1c at 9.9%. The hospital stay was unremarkable, and he was discharged on the 9th inpatient day.

On follow-up at the clinic (46th days post-ictus), motor strength was improved with manual motor testing of 4+/5, NIHSS of 4 with the same degree of mRS 2 (pre 2nd stroke). The plan was to maintain Clopidogrel for one year only with lifetime maintenance of Apixaban. No stroke recurrence was recorded since then.

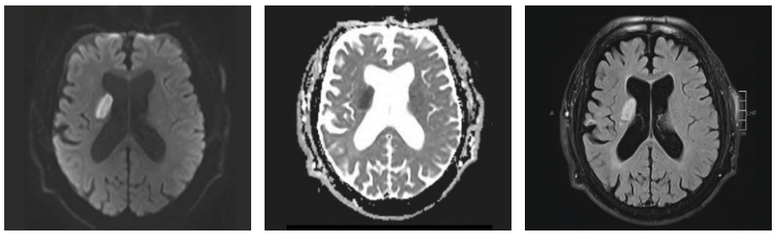

Figure 1 – DWI, ADC & FLAIR of patient upon admission (around 2 days post ictus)

Conclusion

Cerebrolysin as add-on therapy to standard treatment for ischaemic stroke contributed to improved functional outcome of the patient who has not received intravenous thrombolysis.

Dr. Nilufar Rashidova
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1.1.4 ...in the treatment of ischaemic stroke with co-morbidities

Case Report

A 60-year-old male patient fell due to weakness in his leg after getting out of bed in the morning. He was brought to the stroke department within 1.5 hours after the incident with symptoms of numbness and weakness in the right extremities. His arterial blood pressure was 205/100 mmHg. The patient was conscious, oriented in place and time, had no speech disturbances, slight flattening of the right nasolabial fold, palmar-chin reflex on the two sides was present. Tendon reflexes and positive Babinski reflex were expressed, in the right-sided extremities muscle tone was slightly declined and the strength was reduced (grade II in the Medical Research Council Scale for muscle strength). The patient suffered from hemihypoesthesia (right-sided) and had no meningeal signs. He was under treatment for hypertensive heart disease, his blood pressure was 160 over 90 mmHg, antihypertensive medication was taken irregularly.

Half an hour after admission, T2-weighted imaging of the brain showed an ischaemic area (1.3 x 0.7 cm) in the territory of the left MCA (Figure 1) and cerebro-cerebellar atrophic changes. ECG showed sinus bradycardia, a heart rate of 50–57 b/min, a possible scar in the lower wall of the left ventricle. Lab tests (including coagulogram) were within normal limits. The cardiological examination showed hypertensive heart disease (stage III) and post-infarction cardiosclerosis (duration unknown); duplex scanning of brachio-cephalic arteries showed atherosclerotic changes. The NIHSS was 10 and the mRS was 4. The lipid profile showed hypercholesterolemia (total cholesterol 6.4 mmol/l). Serological tests of HIV, viral hepatitis B, C and syphilis were negative. The clinical diagnosis was acute ischaemic stroke of moderate severity.

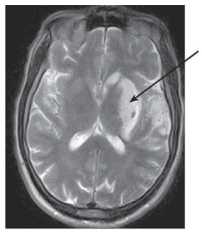

Figure 1 – T2-weighted imaging of the brain at admission

The patient received conventional stroke therapy (antiplatelet agents, statins, and antihypertensive drugs), kinesiotherapy and consultations at a medical psychologist. Cerebrolysin was administered at a daily dose of 30 ml IV during the first 10 days post-stroke. On the 3rd day of therapy, the focal symptoms improved markedly. The patient experienced an increase of strength in the lower limbs (grade 4 in the MRC scale) and showed minimal movements in the fingers. On the 11th day of treatment, hand paresis

had improved proximal to grade 4 in the MRC scale and to grade 3 in the wrist. The patient reported sensory improvement, both, the NIHSS and mRS were 3. The treatment was well tolerated, no adverse events were observed.

At discharge, the patient was transferred to a neurorehabilitation center for further therapy. Due to the very positive dynamics of the patient's clinical improvement, the rehabilitation program could be carried out more intensively.

Conclusion

The treatment concept applied to this patient who was diagnosed with ischaemic stroke was safe and is assumed to have contributed beneficially to the accelerated neurological and functional recovery of the patient.

Dr. Roberto Maturana Dasori
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Chile

1.1.5 ...in the treatment of chronic stroke

Case Report

A male, 51-year-old patient came for consultation four months after he suffered from stroke; he was already on physical and cognitive therapy. The onset of stroke occurred while he was at work. He was brought to an emergency room six hours after onset - beyond the therapeutic window for thrombolysis. The patient presented with left hemiparesis, hemi-hypoesthesia, and severe visuospatial neglect. A CT scan ruled out haemorrhage, no occluded vessels were found on angio-CT. He was thoroughly checked for the underlying etiology of stroke:

- 2D-echocardiography showed no remarkable alterations
- Angio-CT with no signs of atheromatosis at the aortic arch, cervical or intracranial vessels
- Brain MRI showed an area of hyperintensity, in the territory of medial cerebral artery (less than 1/3) present in DWI sequence as well as in FLAIR. No signs of haemorrhage in echo gradient sequences. Minimal unspecific periventricular gliosis on FLAIR.
- Transcranial Doppler with no significant findings
- Holter monitoring for rhythm disorders was negative
- Study for thrombophilia was negative

In the patient's family there is no history of stroke or other vascular diseases. The patient had a history of hypertension, which was under regular control and treatment before stroke. The patient was a nonsmoker. He was discharged with prescriptions for aspirin 100 mg, atorvastatin 80 mg and losartan 50 mgs daily and scheduled for neurorehabilitation. He remained at home for two months and participated in a rehabilitation therapy. By the time of his consultation, he had serious and progressive troubles at work, marital problems and could not keep up with his hobbies. He presented with marked irritability, disorders of sleep, and social isolation. At neurological examination he was cooperative, the speech was normal; moderate left-sided visuo-spatial hemineglect and inattention were found. However, the patient did not present dysarthria, cranial nerves alterations, hemiparesis, or superficial hypoesthesia. The patient presented difficulties compatible with ideatory apraxia had serious troubles performing fine movements with his left hand due to paresis of the hand. Two-point discrimination and graphesthesia were altered. The patient was still on aspirin, atorvastatin and losartan.

We decided to administer Cerebrolysin 30 ml IV daily for 10 days and increased the frequency of physical and occupational therapy from 2 to 5 weekly sessions for one month. One month later he

returned for control. Neurological examination showed a remarkable improvement on every aspect of his neurological deficits, particularly fine movements with the left hand and an outstanding improvement on hemineglect and inattention. In view of this good response he received a second course of Cerebrolysin two month after the initial one. No adverse events were observed. The patient continued to show a remarkably good response.

Conclusion

Two months after treatment the patient had been reassigned to previous responsibilities at work, which included outdoor work and also managing staff, under his supervision. Marital problems improved and he was socializing again. He reassumed his hobby of operating remote-controlled model airplanes with remarkable accuracy in handling the remote control.

Even four years after treatment, the patient was stable in the improvements achieved. No further administration of therapy was needed. He continued occupational therapy twice weekly.

Dr. Michael Chopp
United States of America

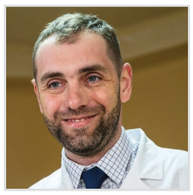
Chapter 1.2

The role of Cerebrolysin in combination...

Recanalization therapy for acute ischaemic stroke is presently relegated to fibrinolysis with tissue plasminogen activator (tPA) with a therapeutic window of 4.5 hours and to mechanical thrombectomy employed for endovascular removal of a surgically accessible large arterial clot, with a therapeutic window presently placed within 24 hours post stroke. For both tPA fibrinolysis and mechanical removal of the clot, the earlier the intervention, the better. Although these recanalization therapies have demonstrated therapeutic efficacy for acute ischaemic stroke, they are far from perfect, and the majority of patients in both (tPA and thrombectomy) subjected to each therapeutic intervention retain neurological and functional deficits and do not experience complete cerebral tissue reperfusion, i.e., although the therapies are called recanalization, they fail to restore tissue perfusion fully. It has been well known for decades that occlusion of an upstream artery damages both the arterial wall containing the clot and initiates a downstream cascade of events that induce secondary thrombosis leading to incomplete tissue perfusion and vascular and parenchymal cell dysfunction. Thus, there is a compelling need to enhance and augment the modest therapeutic benefits of recanalization therapies.

This can potentially be effectively accomplished by augmenting the thrombolysis and mechanical thrombectomy therapies with Cerebrolysin as an adjunctive therapy. Some clinical studies have supported the use of Cerebrolysin in combination with tPA thrombolysis. To obtain insight into how Cerebrolysin augments the standard recanalization therapies, we should focus on the microvasculature post recanalization. Stroke induces rapid disruption of the blood-brain barrier with increased vascular permeability and an upregulation within vascular cells, particularly endothelial cells, of inflammatory cytokines which create a prothrombotic, procoagulant, proinflammatory state in the microvasculature. Fibrin deposition in the microvasculature after stroke is a significant culprit in mediating this microvascular dysfunction, and tPA is well known to induce vascular permeability and as well as to increase vascular fibrin deposition.

Recent studies indicate that Cerebrolysin has a potent therapeutic effect directly on the microvasculature, ameliorating vascular permeability, and reducing the proinflammatory state of the endothelial cells. Thus, further studies are warranted to directly evaluate the effects of Cerebrolysin as a co-therapy for tPA thrombolysis and mechanical thrombectomy.



Dr. Maksim Domashenko

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Russia

1.2.1 ...with recanalization treatment (thrombolysis & thrombectomy)

Case Report

A female patient, 63 years old, underwent an in-patient treatment with the following diagnosis: cardioembolic ischaemic stroke in left middle carotid artery (MCA) M1 (TOAST) with sensory-motor aphasia and right-sided hemiplegia. Concomitant diseases: coronary heart ischaemia, angina of exertion, FC II, cardiac arrhythmia, a permanent form of atrial fibrillation, and arterial hypertension.

The patient was admitted to the clinic 290 min after onset of first neurological symptoms. NIHSS score at admission was 18 points. CT imaging did not show any cross-sectional abnormalities of the brain, however, CT angiography verified an occlusion of the proximal segment of the left MCA (Figure 2). The patient underwent thrombolytic therapy with rtPA at a dose of 0.9 mg/kg with subsequent thrombectomy (thromboextraction and aspiration of the thrombus), reaching a level of reperfusion of TICI 3 (Figure 3). Despite technical success of the endovascular intervention, a small zone of ischaemia in the left part of the brain remained and was revealed by a CT scan done after 24 hours (Figure 4). No signals of haemorrhagic transformation were detected.

Right after endovascular reperfusion the patient received intravenous Cerebrolysin treatment at a dose of 30 ml per day for 10 consecutive days. Concomitantly, anticoagulation and basic stroke treatment in accordance to AHA-ASA recommendations were given. At discharge, a dramatic regression of the neurological deficit was noticed with only minor elements of sensory aphasia and light right-sided hemiparesis remaining. The patient was discharged with an NIHSS of 6.

Conclusion

This case demonstrates that administration of Cerebrolysin right after endovascular treatment is safe and may lead to an improved clinical outcome. However, further controlled clinical trials are needed to confirm the efficacy and safety of Cerebrolysin in combination with contemporary methods of reperfusion in patients with acute ischaemic stroke.

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1.2.2 ...with unsuccessful recanalization therapy (thrombolysis & thrombectomy) in severe stroke

Case Report

A 63 years-old male patient with an anamnesis of hypertension and myocardiopathy was admitted to the emergency department due to sudden right-sided hemiparesis and speech disturbance. Symptoms occured 53 minutes before arrival at the hospital, the NIHSS score at admission was 16. Urgent neuroimaging (native brain CT and CT angiography) showed a hyperdense middle cerebral artery (MCA) on the left side, without other brain parenchymal changes and occlusion of the M2 segment of the left MCA. Due to the fact that there were no contraindications, thrombolysis was started immediately (96 minutes after the onset of symptoms).

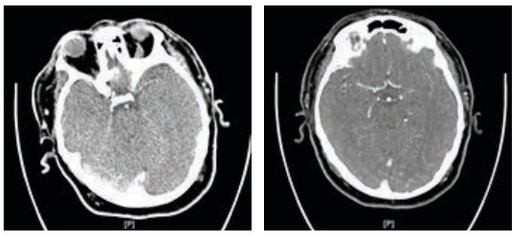

Figure 1 – Native CT showing hyperdense MCA left, and CT angiography showing occlusion of the M2 segment of the left arteria cerebri media.

However, after thrombolytic therapy hardly any clinical effect was observed, with the NIHSS remaining at 14. Thrombectomy was indicated and the procedure started about 2.5 hours from onset of symptoms. Partial recanalisation (TICI 2b) was achieved one hour later.

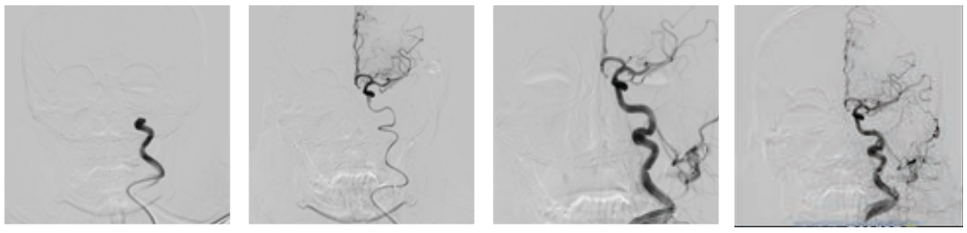

Figure 2 – Angiography and thrombectomy, showing only partial recanalisation (TICI 2B) of the MCA.

The NIHSS score after thrombectomy remained at 14. A control CT scan after the procedures showed an acute ischaemic lesion of the left hemisphere including insula, operculum and caudal parts of precentral and postcentral gyrus.

According to our clinical protocol, Cerebrolysin is indicated in this group of patients as early as possible, 24 hours after symptom onset at the latest. Our patient started with Cerebrolysin therapy (30 ml in 250 ml saline by intravenous infusion) 13 hours after symptoms onset and was continued until discharge on day 27.

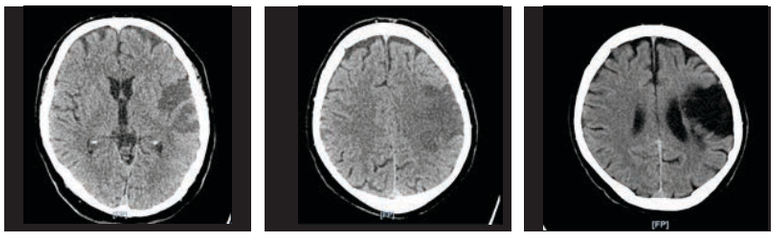

Figure 3 – CT labeled A and B showing early ischaemic changes 24 hours after thrombectomy
CT labeled C was done at one-year follow-up

On day 3, a neurorehabilitation program was initiated. The hospital stay was complicated by urinary tract infection and deep venous thrombosis in spite of prophylaxis. Anticoagulant therapy was initiated five days before referral to the stationary rehabilitation at day 27. At discharge the patient scored 4 points on the mRS and 12 points on the NIHSS.

After 25 days of rehabilitation the patient experienced a hemorrhagic shock due to rectorrhagia. He was admitted to the surgery ward for colectomy. By that time, before the operation, his NIHSS had improved to 8, with an mRS of 4. However, after the operation, at discharge, his general and neurological status had worsened again. While the mRS remained at 4, motorically he deteriorated back to the status he had reached one month earlier. He was transferred back to the stationary rehab therapy for another 10 days and received another 10 dosages of Cerebrolysin (30ml in 250 ml saline by intravenous infusion).

Eight months after the stroke, he developed a symptomatic partial epilepsy with consciousness disturbance and generalization which, in combination with antiepileptic therapy, further deteriorated his state. However, the patient continued with out-patient physical therapy and gymnastic, and slowly recovered. During our last out-patient visit, one year after the initial hospitalization, his mRS was at 3 with an NIHSS of 7 and he was strongly motivated to continue in his attempts for further improvement.

Conclusion

Cerebrolysin as add-on therapy to recanalization techniques, including IV thrombolysis, was safe in a patient with a large ischaemic stroke and an indication for anticoagulant therapy. In this particular case we did not notice any hemorrhagic neurological complications with a significant clinical improvement after a one-year period of follow-up in spite of unsuccessful reperfusion after thrombolysis and thrombectomy and complications resulting in anticoagulant therapy, surgical procedure and symptomatic focal epilepsy. Cerebrolysin may also have contributed to the clinical outcome for patients with acute stroke, which is in accordance with the neuroprotective and neurorestorative properties of Cerebrolysin. Based on our experience we can say that Cerebrolysin can be used safely in stroke even in the most complicated patients with a good chance for improvement of their clinical status.

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1.2.3 ...with recanalization therapy (thrombolysis & thrombectomy) after internal carotid occlusion

Case Report

This report focuses on a patient with acute ischaemic stroke due to internal carotid occlusion with Glasgow Coma Scale (GCS) 7 when transferred to our hospital. The onset of stroke was sudden with right hemiplegia and aphasia and 30 minutes later, her concsiousness was impaired. She was hospitalized 115 minutes after stroke onset in a state of coma, GCS 7/15, complete right hemiplegia, NIHSS 21 points.

The result of the CT scan showed images of early lesions in the left hemisphere, ASPECT 7 points. The patient is eligible for IV-tPA, the treatment was clearly explained to her family who consented. She was treated with IV – tPA 0.9mg/ kg, then had a CT Angiography, showing a left internal carotid occlusion. The patient was transferred directly to the vascular intervention room, the puncture into the femoral artery started 160 minutes after stroke onset. The thrombus was removed from the proximal part of the left internal carotid artery by a stent retriever. After two attempts of thrombus removal the vessel was recanalized (210 minutes after stroke onset) with a TICI score of 2b. During the intervention process, we also noticed insufficient collateral circulation in the internal carotid artery on the opposite hemisphere, as well as in the basilo-vertebral system. The left internal carotid artery also presented with severe stenosis due to atherosclerosis with obstructed blood flow and a risk to reocclude. Consequently, it was indicated to perform endovascular treatment placing a stent (X-ACT 6-8*30), into the left internal carotid artery.

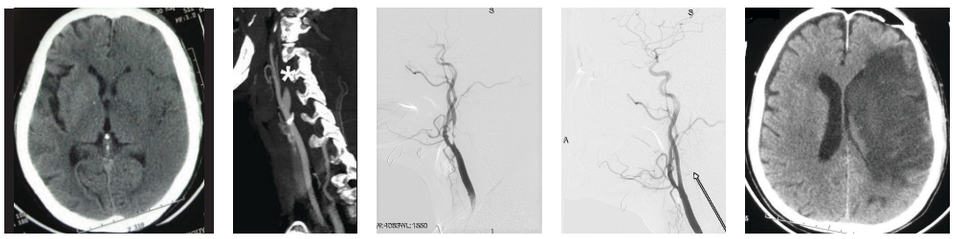

Figure 1 – a) CT scan at the time of hospital administration; b) CT-Angiography image of internal carotid artery occlusion; c) Digital subtraction angiography (DSA) image after thrombectomy, still narrow at the root of the left internal carotid artery; d) DSA image of the stent placed at the root of the left internal carotid artery; e) CT scan 24 hours after hospital administration.

Within 24 hours after surgery, the patient was still in a critical condition and was artificially ventilated. Her consciousness had not yet improved, GCS remained at 7 points. We understood that recanalization methods just solved the problem of revascularization to save the penumbra, so we decided to add Cerebrolysin 20ml IV, once daily to the treatment regimen. After 24 hours, the patient had another cerebral CT scan, the result showed a left temporo-parietal hypodensity, compressing the lateral ventricle and shifting the midline by 0.5 cm. The patient was maintained on artificial ventilation, anti-brain oedema treatment and Cerebrolysin 20ml per day for 14 days.

The patient's condition continuously improved and after 5 days her GCS increased to 10/15, she was able to breathe without the support of mechanical ventilation. Her clinical condition kept improving, another CT scan was conducted on the 10th day after stroke onset, showing left temporal hypodensity. However, the brain oedema had significantly decreased since the last CT scan.

The patient was discharged on the 15th day with a GCS of 13 points, right-sided muscle strength was 3/5 (for both upper and lower limbs), NIHSS 9 and mRS 3. The patient was transferred to a specialist rehabilitation center. On the last follow-up at day 90 after being discharged, the patient improved to GCS 15, NIHSS 6 and mRS 2. The patient was tested with the MoCA for cognitive assessment and achieved 25/30 points.

Conclusion

We present a case of a patient with severe ischaemic stroke due to internal carotid artery stenosis who experienced an excellent outcome after combining recanalization with Cerebrolysin treatment in the acute phase of the stroke. Since there is no gold strandard in the treatment of ischaemic stroke due to internal carotid artery occlusion, treatment has to be individualized according to evidence-based methods, personal experience and the specific requirements of each case. New data from well-conducted randomized clinical trials will help to improve treatment for stroke patients, especially those with severe stroke. In the future, a multimodal approach using recanalization techniques together with neurotrophic pharmacotherapy to support neuronal plasticity and neurorestorative processes complemented with intensive rehabilitation programs will likely achieve the best outcome for patients with acute ischemic stroke. Based on our experience and the results from randomized clinical trials, Cerebrolysin clearly has an important role in this multi-modal treatment approach for stroke patients.

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1.2.4 ...with thrombolysis and early initiation of rehabilitation

Case 1

A 38-year-old male patient was admitted to the emergency department with motor deficits on the right side and speech disturbances; the onset of symptoms was three hours before admission. There was no significant medical history, no tobacco, alcohol, or recreational drug use. However, his father died at the age of 67 years due to multiple strokes, hypertension, and diabetes. Neurological examination showed psycho-motor agitation, ocular deviation to the left, right central facial palsy, right hemiplegia, and severe global aphasia. The NIHSS score was 18. Vital signs and blood samples showed no abnormalities. Non-contrast CT scan showed left middle cerebral artery (MCA) hyperdensity, and minor sulcus effacement in the left temporal and parietal regions (Figure 1). Angio-CT scan showed thrombosis of the left M1 segment (Figure 2).

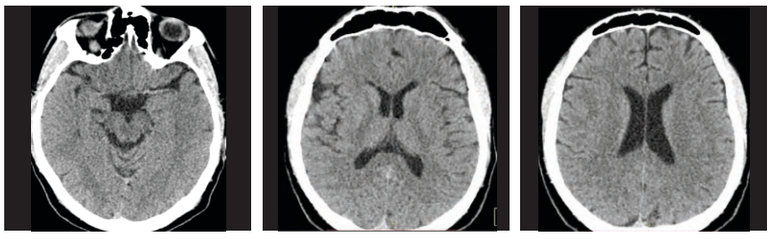

Figure 1 – Non-contrast CT scan before iv thrombolysis showing left MCA hyperdensity, sulcus effacement

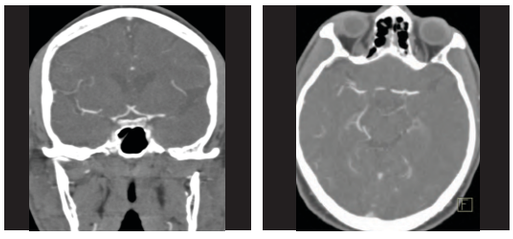

Figure 2 – Angio-CT scan showed left M1 segment thrombosis

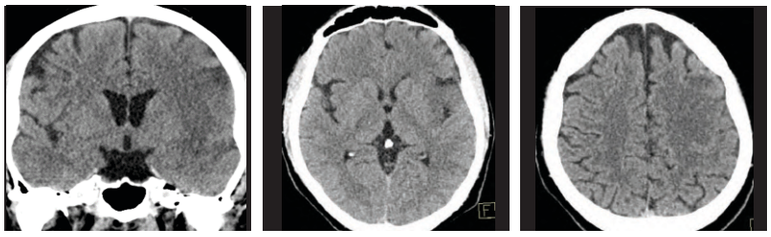

Figure 3 – Control Head CT scan performed 8 hours after thrombolysis shows hypodensity in the left ACM teritorry.

Intravenous (IV) thrombolysis with tissue-type plasminogen activator was initiated 3.5 hours after stroke onset. At the end of thrombolysis, the NIHSS score was 16. Thrombectomy procedures were not available in our region. In the next hour after thrombolysis we started IV treatment with 30 ml Cerebrolysin, and this dose regimen was continued for the next 13 days. Standard rehabilitation started 48 hours

after stroke onset. Extended lab tests showed a heterozygous mutation of methylene tetrahydrofolate reductase (MTHFR) with reduced enzymatic activity (T mutation- C677T) and a heterozygous mutation of factor V Leiden. The patient received chronic oral anticoagulation medication together with folic acid (1 mg/day), vitamin B6 (10 mg/day), and vitamin B12 (0.4 mg/day).

After seven days the NIHSS score was 10 and at discharge (14 days post-stroke), the NIHSS improved to 9 and the mRS score was 4. Rehabilitation and Cerebrolysin treatment (10 ml/day, for 10 consecutive days, for the next 3 months) were continued at home. Three months post-stroke, the NIHSS score was 4 and the mRS score was 2.

Cerebrolysin as add-on therapy to IV thrombolysis markedly improved the functional outcome of the patient.

Case 2

A 68-years old male patient was admitted to the emergency department due to sudden onset of left-sided motor deficits, visual field disturbances, and dysarthria 90 minutes earlier. His medical history was significant for hypertension and type II diabetes. He smoked 20 cigarettes a day for 40 years. The neurological examination showed disorientation in time and space, non-forced gaze deviation to the right, left hemianopia, left central facial palsy, left hemiplegia, moderate dysarthria, and left sensory loss. The NIHSS score was 14. Head CT scan showed hypodensity in the territory of the right MCA, suggestive for acute ischaemic stroke (Figure 1).

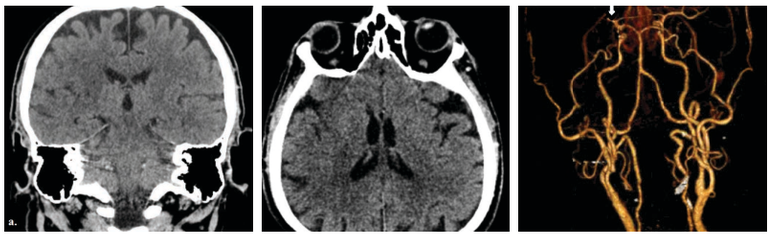

Figure 1 – Initial CT scan showed hypodensity in the territory of right MCA. (a. coronal view; b. axial view). Angio-CT showed right M1 segment occlusion (white arrow).

IV thrombolysis with rt-PA was initiated two hours after stroke onset. The NIHSS score after thrombolysis was 16. Thrombectomy procedures were not available in our region. In the next hour after thrombolysis, treatment with 30 ml Cerebrolysin per day started and was continued for the next 13 days. Standard rehabilitation started 48 hours after stroke onset.

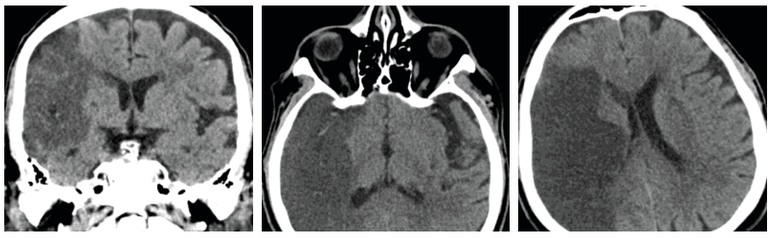

Figure 2 – Head CT scan performed 24 hours after thrombolysis showed a large ischaemic stroke in the right MCA territory

The CT scan performed 24 hours after thrombolysis showed further evolution of the infarction, which

was extensive and covered most of the right MCA territory (Figure 2).

After seven days the NIHSS score was 12 and at discharge (14 days post-stroke) the NIHSS was 10 and the mRS score was 4. Rehabilitation and Cerebrolysin treatment (10 ml/day, for 10 consecutive days, for the next three months) were continued at home. Three months post-stroke, the NIHSS was 8 and the mRS score was 3.

Conclusion

Cerebrolysin as add-on therapy to IV thrombolysis markedly improved the neurological and functional outcome of the patients. It can also be observed that even if the strokes were large, haemorrhagic transformation after thrombolysis was not noticed, suggesting that treatment with Cerebrolysin, started immediately after IV thrombolysis can potentially prevent hemorrhagic transformation.

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1.2.5 ...with systemic thrombolysis at a higher daily dose (50ml)

Case 1

A male patient, 71 years old, was admitted in a critical condition with obtundation, aphasia, and right-sided hemiparesis. Time from onset of symptoms to hospitalization was one hour and 40 minutes. Breathing was autonomous, effective, vesicular. Arterial oxygen saturation (SaO2) was 95% (when breathing ambient air). No rales. Bradycardia with a heart rate of 48 bpm. Blood pressure was 165/90 mmHg, weakened heart sounds with rhythmic activity. Body weight was 108 kg.

Laboratory findings: signs of haemoconcentration (red blood cells - 5.34 ×1012/l; hemoglobin - 162 g/l; hematocrit - 51.7 %). Activated partial thromboplastin time (aPTT) – 21 sec. Prothrombin time index (PTI) – 75%. Blood glucose – 5.9 mmol/l.

Neurological status: conscious, Glasgow Coma Scale (GCS) 13, NIHSS 12. Eyes and pupils dexter (D) = sinister (S). Photoreactions are preserved. Central insufficiency of cranial nerve pairs 7 and 12 on the right side. Elements of motor aphasia. Swallowing is not impaired. Tendon and periosteal reflexes (TPR) D>S. Right-sided hemiparesis. Right-sided hemihypesthesia. Babinski's sign on the right. No meningeal signs.

On multispiral computed tomography (MSCT) of the brain, no signs for haemorrhage, on MRI a decrease in the diffusion coefficient in an area covering 2.9 x 2.4 cm is seen subcortically in the left temporal region. No MR signal from the left MCA. After 20 min (neuroimaging), negative neurological dynamics are observed: deep obtundation, GCS 11-12, sensorimotor aphasia, right-sided hemiplegia.

Clinical diagnosis: Acute ischaemic stroke in the left MCA circulation (atherothrombotic subtype), sensorimotor aphasia, right-sided hemiplegia. He also presented with mild cognitive disorder and stage III hypertensive disease (HD), cerebrasthenic syndrome (CAS).

2 h 30 min after the first symptoms onset, thrombolytic therapy (TLT) per clinical protocol was initiated with rtPA of 0.9 mg. One hour after TLT, the patient was conscious, communicative. Decreased facial asymmetry and deviation of the tongue to the right. Elements of motor aphasia. Moderate right-sided hemiparesis. Right-sided hemihypesthesia. The control MSCT and MRI 24 h after thrombolytic therapy confirmed artery recanalization - the infarct size had not increased, the signal from the left MCA was restored. After thrombolytic therapy, Cerebrolysin was administered at a daily dose of 50 ml/day for 10 days. The NIHSS score before initiation of Cerebrolysin treatment was 7

Neurological status at the time of discharge: Full recovery with a GCS of 15, an NIHSS of 1, and an MRS of 0. The face is symmetrical. Speech, muscle strength and sensitivity have been restored. TPR D≥S. No meningeal signs.

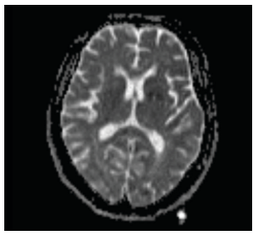

Figure 1 – MRI of the brain: limited diffusion area of 2.9 x 2.4 cm is seen subcortically in the left temporal region. No MR signal from the left MCA.

Case 2

Male patient, 76 years old, was admitted with complaints of numbness in the left half of the face and weakness in the left extremities, which appeared about two hours earlier.

Breathing was effective, slightly weakened in the lower respiratory tract. SaO2 - 96% (when breathing ambient air). No rales. Hemodynamics stable. Heart rate was 66 bpm, blood pressure145/85 mmHg. Heart sounds were weakened, the activity was rhythmic. Body weight was 80 kg.

Neurological status: conscious, communicative. GCS of 14. NIHSS of 9. Eyes and pupils D=S. Photoreaction was preserved. Smoothed left nasolabial fold. Deviation of the tongue to the left. TPR S>D. Moderate left-sided hemiparesis. Increased tone in the left extremities. Left-sided hemihypesthesia. No pathological plantar and meningeal signs.

Laboratory findings: platelets - 342×10^9 g/l; thrombin time - 11 seconds; aPTT - 22 seconds; blood glucose - 6.3 mmol/l.
Duplex scanning of brachycephalic vessels showed atherosclerotic artery disease with stenosis ACC 30-32%, ACE on the right up to 38% and on the left up to 30%. Right ACI stenosis of more than 80% with signs of thrombosis.

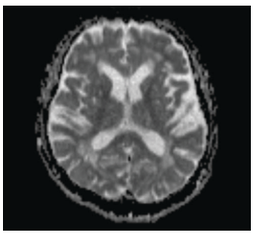

Figure 3 – NMRI of the brain - hyperintensive foci of 2 to 4 mm are visualized subcortically and periventricularly and in the area of the right putamen (6x3 mm). Foci of 7 x 4 mm and 2 x 3 mm in the projection of the right precentral gyrus.

Clinical diagnosis: Acute ischaemic stroke in the right MCA circulation (atherothrombotic subtype), moderate left-sided hemiparesis, left-sided hemihypesthesia. He presented with mild cognitive disorder, stage III HD, cerebrasthenic syndrome (CAS).

3 h 10 min after the onset of symptoms, thrombolytic therapy was initiated with rtPA at a dose of 0.9 mg.

One hour after TLT, the patient was conscious, communicative. GCS of 15, NIHSS of 3, mRS of 1. Eyes and pupils D=S, photoreaction is rapid. Decreased smoothness of nasolabial fold and tongue deviation. TPR D=S. Muscle strength restored, muscle tone normal. Left-sided hemihypesthesia. No pathological plantar and meningeal signs.

MRI of the brain and MR angiography of the head and neck arteries after 24 hours: acute cerebral circulation disorder (ACCD) of ischaemic type in the right MCA circulation. Partial artery recanalization. Overt stenosis of arteria carotis interna (ACI) up to 90%.

The day after thrombolytic therapy, Cerebrolysin was administered at a daily dose of 50 ml/day for 8 days. Clinical signs of stroke fully regressed.

The patient was discharged without neurological deficits.

Due to overt vascular changes, the patient underwent total cerebral angiography, which showed right ACC stenosis of 75%, right ACI critical stenosis of > 90%, left vertebral artery stenosis of 75%. Elective stenting of the right ACI was performed.

NMRI of the brain - hyperintensive foci of 2 to 4 mm are visualized subcortically and periventricularly and in the area of the right putamen (6x3 mm). Foci of 7 x 4 mm and 2 x 3 mm in the projection of the right precentral gyrus

Case 3

Female patient, 61 years old, hospitalized with complaints of overt dizziness and nausea, repeated vomiting, impaired swallowing and double vision. Complaints occurred 2.5 hours ago.

Due to an irregular heart rhythm, warfarin was administered once daily with a dose of 4.5 mg but was stopped four days earlier while preparing the patient for elective surgery. No bridging therapy was offered.

The state was critical but stable. Pale skin, acrocyanosis. Breathing rate - 22/min. SaO2 - 93% with oxygen supply (2 l/min). Auscultatory breathing wass weakened in the lower respiratory tract on both sides. BP was 115/90 mmHg, pulse rate 58 bpm and heart sounds were weakened, with arrhythmic activity. Heart rate was 108/min with pulse deficiency of 50/min. Lower leg and feet were edematous.

Neurological status: conscious, communicative. GCS of 14. NIHSS of 7, divergent strabismus, homonymous hemianopia. Gross permanent horizontal nystagmus. Dysarthria. Dysphonia. Decreased pharyngeal reflex. Elements of dysphagia. TPR D=S. No paresis. Sensitivity disorders are not shown. Bilateral Babinski's sign. Ataxia. No meningeal signs.

Laboratory findings: prothrombin index - 71%; APTT - 32 seconds; plasma fibrinogen - 9 g/l. Blood glucose - 7.2 mmol/l.

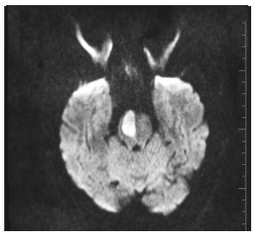

Figure 3 – MRI of the brain: limited diffusion area of 10 x 15 mm is visualized in the right stem sections.

ECG: HR - 96/min with atrial fibrillation of tachysystole form. Left ventricular hypertrophy.

Clinical diagnosis: Acute ischaemic stroke in the vertebrobasilar circulation (cardioembolic subtype). Bulbar palsy. Ischaemic heart disease (IHD). Diffuse cardiosclerosis. Atrial fibrillation of tachysystole form. Grade II B heart failure. 3 h 20 min after onset of stroke, rtPA perfusion was initiated and after 25 minutes the neurological deficits began to decrease progressively. The patient became conscious, communicative, adequate. GCS of 15, NIHSS of 4, MRS of 2. Homonymous hemianopia. Fine horizontal nystagmus. Elements of dysarthria. Swallowing preserved. TPR D=S. No paresis or sensitivity disorders. Atactic disorders decreased. Bilateral Babinski's sign. No meningeal signs. MRI after TLT: signal intensity reduction in diffusion - weighted images and T1 - scanning mode.

Cerebrolysin was administered at a daily dose of 50 ml/day for 12 days in order to normalize neurological disorders and reduce neurological deficits still persistent after thrombolysis.
Neurological status at the time of discharge:

Full recovery. The patient was conscious, communicative. GCS of 15, NIHSS of 0, mRS of 0. No strabismus, hemianopia, or nystagmus. Dysarthria, dysphonia and dysphagia were resolved. TPR D=S. No paresis. No sensitivity disorders. No meningeal signs.

Conclusion

The combination of thrombolytic therapy and neuroprotection is a safe and effective stroke treatment. According to the results of many studies, Cerebrolysin treatment results in a positive effect on the regression of neurological symptoms, reduced mortality and a faster recovery of patients.

Our experience of combining TLT with Cerebrolysin at maximum therapeutic doses also shows excellent therapeutic effects and a fast onset of action, in the absence of adverse effects and complications. This indicates that the use of Cerebrolysin in the early period of ischaemic stroke can prevent the formation and spread of cerebral edema, stabilizes microcirculation, and normalizes neurological and cognitive impairment.

Summary Table of GCS, NIHSS and mRS at admission and discharge

CASE	**GCS**		**NIHSS**		**MRS**
	Admission	Discharge	Admission	Discharge	Discharge
1	11--12	15	18	1	MCS
2	14	15	9	0	0
3	14	15	7	0	0

Based on the positive experience of combining TLT with Cerebrolysin, we plan to extend the use of high therapeutic doses both in patients who underwent thrombolysis as well as in patients who did not receive TLT.

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1.2.6 ...with concomitant administration of thrombolysis

Case 1

A white male 53-year-old patient was admitted to the stroke unit 1 h after onset with left-sided weakness and numbness, and speech difficulties. He had a history of coronary artery disease, atrial fibrillation, and hypertension. His pre-admission medications were an angiotensin II receptor inhibitor, a beta-blocker, and aspirin. At admission, his blood pressure was 140/90 mm Hg, pulse rate was 80 bpm, body weight was 95 kg, and the National Institutes of Health Stroke Scale (NIHSS) score was 8. An atrial fibrillation rhythm was registered on his ECG. Carotid ultrasound showed a right internal carotid artery stenosis of 50% and left common carotid artery stenosis of 30%. The ejection fraction of the left ventricle was 36% on his echocardiogram. His complete blood count, biochemical, and coagulation blood tests were within a normal range. At admission (Figure 1), the infarct core was clearly visible on DWI, ADC, CBV maps and occupied less than 1/3 of the right middle cerebral artery (MCA) territory.

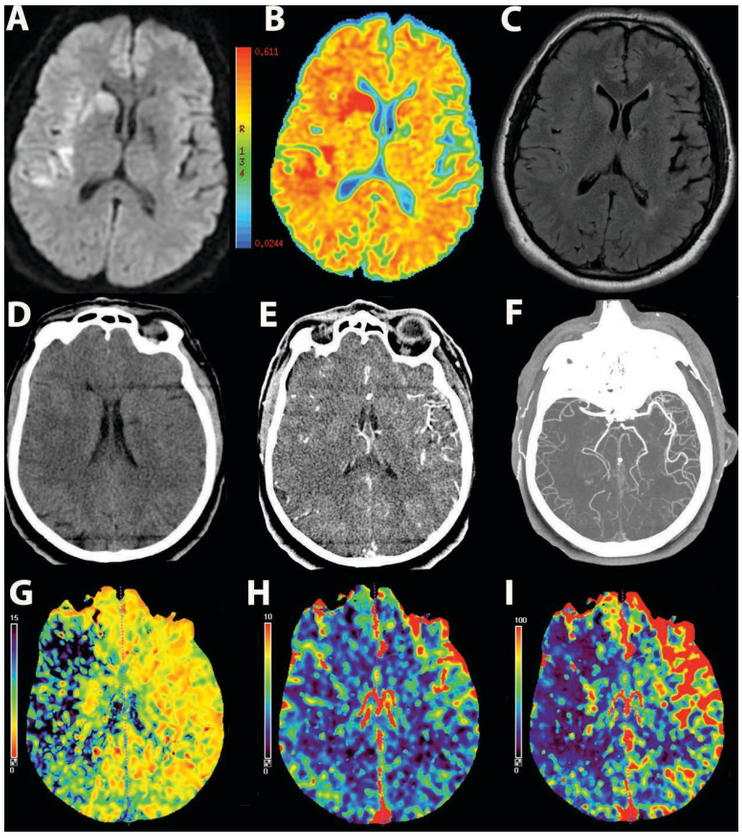


Figure 1 – Case #1. Neuroimaging at admission. A-C. Magnetic-resonance imaging (MRI): A. Diffusion weighted imaging (DWI). B. The apparent diffusion coefficient (ADC) map. C. Fluid-attenuated inversion recovery (FLAIR). D-I. Computed tomography (CT) scans: D. Non-contrast CT. E. CT-angiography source images (CTASI). F. Maximal intensity projection (CT-angiography). G-I. CT-perfusion study: G. The mean transit time (MTT) map. H. The cerebral blood volume (CBV) map. I. The cerebral blood flow (CBF) map.

However, it was presented neither on FLAIR nor on non-contrast CT scans indicating the stroke happened within less than 6 h. Occlusion of the right MCA was determined on CT-angiography, and poor collateral filling was confirmed on CTASI. His CT-perfusion study showed a huge area of hypoperfusion occupying completely the right MCA basin. Thus, the patient had a favorable diffusion-perfusion mismatch — the penumbra — for reperfusion therapy. Recombinant tissue plasminogen activator (rtPA, alteplase, 0.9 mg/kg) was started intravenously with concomitant Cerebrolysin infusion (30 ml). Cerebrolysin was continued at the same dose once daily over the next 14 days. Aspirin was administered on the day 2 (100 mg OD) and continued for the next 3 days followed by dabigatran (150 mg BID).

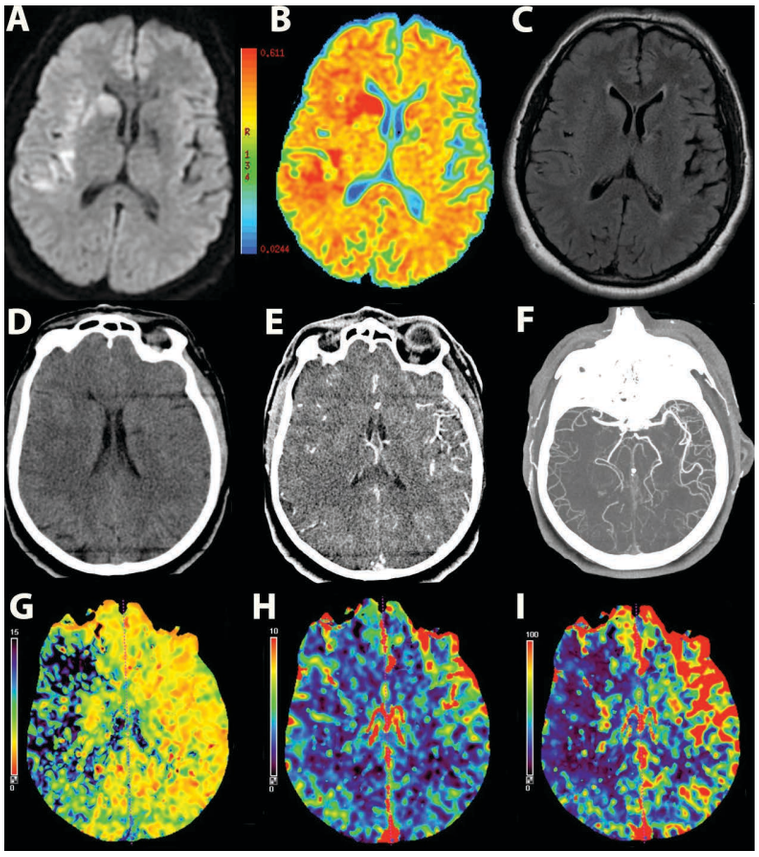


Figure 2 – Case #1. Neuroimaging in 24 h. A-C. Magnetic-resonance imaging (MRI): A. Diffusion weighted imaging (DWI). B. The apparent diffusion coefficient (ADC) map. C. Fluid-attenuated inversion recovery (FLAIR). D-I. Computed tomography (CT) scans: D. Non-contrast CT. E. CT-angiography source images (CTASI). F. Maximal intensity projection (CT-angiography). G-I. CT-perfusion study: G. The mean transit time (MTT) map. H. The cerebral blood volume (CBV) map. I. The cerebral blood flow (CBF) map.

The patient was almost free of any neurological deficit (NIHSS score of 1) on day 2. No haemorrhage was seen on his follow-up CT scans. His CTASI, CT-angiography, and CT-perfusion study showed full recanalization and reperfusion of the affected vascular territory. Some of the hyperintense foci disappeared on the DWI and ADC maps indicating early reperfusion (rtPA). Neuroprotection with Cerebrolysin could resolve some hyperacute ischaemic lesions (Figure 2). On the day 14, the patient was discharged without neurological deficit.

Case 2

A white female 72-year-old patient was admitted to the stroke unit 4.5 h after onset with left-sided weakness and numbness. She had a history of coronary artery disease, atrial fibrillation, and

hypertension. A few years ago, she survived an intracerebral haemorrhage, which left her with mild left-sided hemiparesis. Before admission, she was on antihypertensive medication and aspirin. At admission, her blood pressure was 130/90 mm Hg, and the NIHSS score was 17. An atrial fibrillation rhythm was registered on her ECG. Carotid ultrasound showed multiple carotid artery stenosis up to 50%-60%. The ejection fraction of the left ventricle was 50% on her echocardiogram. Her complete blood count, biochemical, and coagulation blood tests were within a normal range. At admission (Figure 3), the infarct core was barely visible on DWI and the CBV maps, which was presented neither on FLAIR nor on non-contrast CT scans. However, there was an area of restricted diffusion on the ADC maps mostly affecting the right MCA brain cortex. Notwithstanding the fact that the scans were taken 4.5 h after onset, this was a signature of hyperacute ischaemic changes. Susceptibility-weighted angiography (SWAN) revealed a small cyst with a hypointense rim in the left basal ganglia, a sequela of the intracerebral haemorrhage. The cyst was also clearly seen on non-contrast CT scans and FLAIR. Occlusion of the right MCA was determined on CT-angiography, and poor collateral filling was confirmed on CTASI.

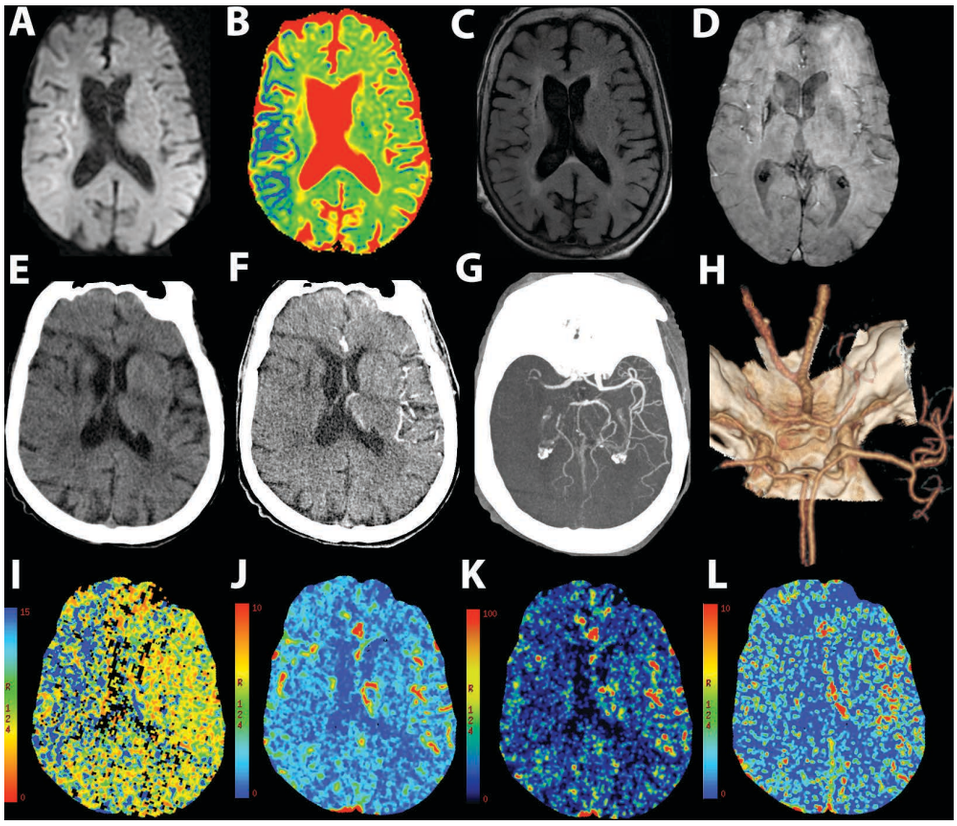


Figure 3 – Case #2. Neuroimaging at admission. A-D. Magnetic-resonance imaging (MRI): A. Diffusion weighted imaging (DWI). B. The apparent diffusion coefficient (ADC) map. C. Fluid-attenuated inversion recovery (FLAIR). D. Susceptibility-weighted angiography (SWAN). E-L. Computed tomography (CT) scans: E. Non-contrast CT. F. CT-angiography source images (CTASI). G. Maximal intensity projection (CT-angiography). H. Volume rendering (CT-angiography). I-L. CT-perfusion study: I. The mean transit time (MTT) map. J. The cerebral blood volume (CBV) map. K. The cerebral blood flow (CBF) map. L. The permeability–surface area product (PS) maps.

The CT-perfusion study showed a huge area of hypoperfusion completely occupying the right MCA basin. The permeability–surface area product (PS) maps showed no increase of the blood-brain barrier (BBB) permeability in the infarct core and the penumbra. Thus, the patient had a favorable neuroimaging and clinical data for reperfusion therapy. Recombinant tissue plasminogen activator (rtPA, alteplase, 0.9 mg/kg) was started intravenously with concomitant Cerebrolysin infusion (30 ml). Cerebrolysin was continued at the same dose once daily over the next 14 days. Aspirin was administered on the day 2 (100 mg OD) and continued for the next 6 days followed by dabigatran (150 mg BID). The patient's

neurological deficit dropped to her preadmission level (the NIHSS score of 10) on day 2. No haemorrhage was seen on her follow-up CT scans and SWAN. CTASI, CT-angiography, and CT-perfusion study showed full recanalization and reperfusion of the affected vascular territory. Some of hyperintense foci disappeared on the ADC maps indicating early reperfusion (rtPA). Neuroprotection with Cerebrolysin could resolve some hyperacute ischaemic lesions. Compared with the PS maps at admission, there was a mild decrease in BBB permeability of the whole brain on the day 2 (Figure 4). This could be evidence of the BBB stabilizing probably due to the neuroprotective effects of Cerebrolysin. On day 21, the patient was discharged with her preadmission neurological deficit.

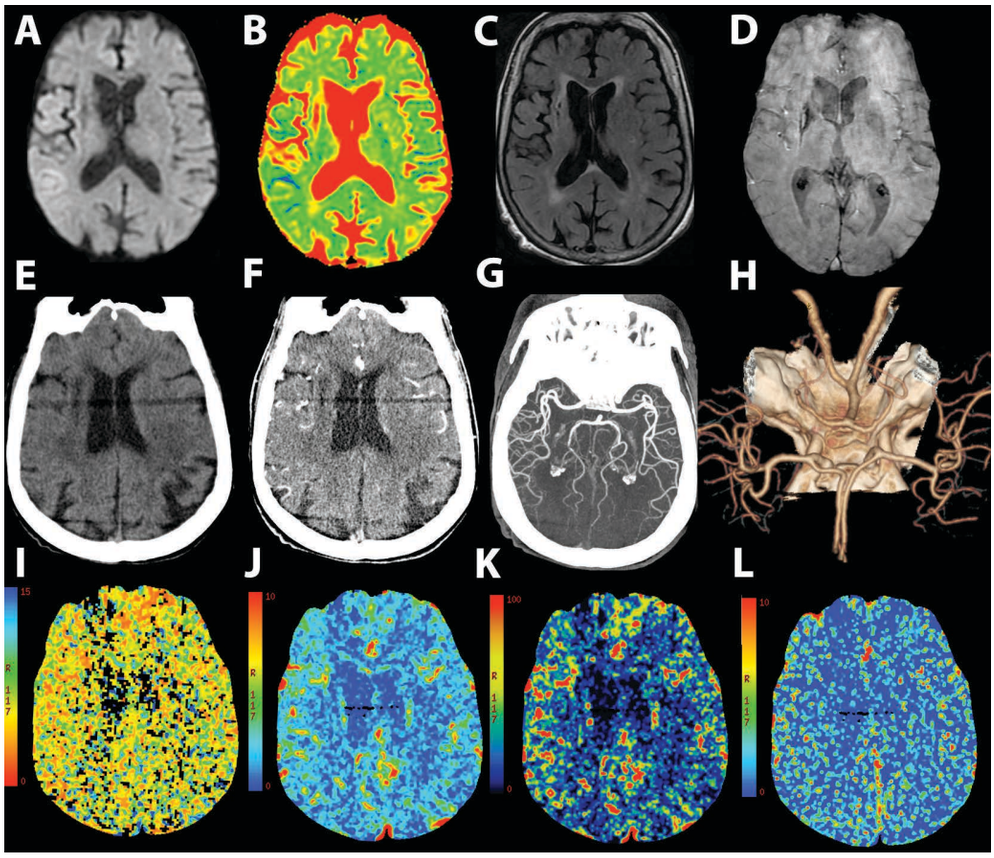


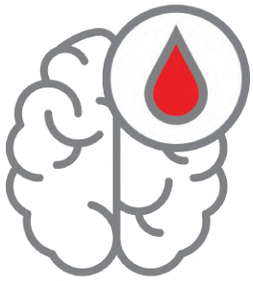
Figure 4 – Case #2. Neuroimaging in 24 h. A-D. Magnetic-resonance imaging (MRI): A. Diffusion weighted imaging (DWI). B. The apparent diffusion coefficient (ADC) map. C. Fluid-attenuated inversion recovery (FLAIR). D. Susceptibility-weighted angiography (SWAN). E-L. Computed tomography (CT) scans: E. Non-contrast CT. F. CT-angiography source images (CTASI). G. Maximal intensity projection (CT-angiography). H. Volume rendering (CT-angiography). I-L. CT-perfusion study: I. The mean transit time (MTT) map. J. The cerebral blood volume (CBV) map. K. The cerebral blood flow (CBF) map. L. The permeability–surface area product (PS) maps.

Conclusion

We present two cases of Cerebrolysin add-on therapy to IV thrombolysis with markedly improved functional outcome of the patients. The administration of Cerebrolysin concomitantly to IV thrombolysis is safe and well tolerated with no signs of hemorrhagic transformation after thrombolysis. The outcome was a full regression of the neurological deficits which, on the basis of the initial severity of the stroke, would not have been expected for each of the treatments alone. We therefore speculate that Cerebrolysin and IV thrombolysis act synergistically – recanalization and restoration of blood flow in the affected brain areas together with neuroprotection and the stimulation of neurorecovery. Further controlled clinical trials are warranted to confirm and extend our findings on the efficacy and safety of Cerebrolysin in combination with contemporary methods of reperfusion.

Chapter 2

HAEMORRHAGIC STROKE, SUBARACHNOID HAEMORRHAGE & VASCULAR SURGERY



Dr. Michael Chopp
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Chapter 2.1

The role of Cerebrolysin...

Cerebrolysin may act to ameliorate cerebral damage due to a cerebral bleed, whether caused by an intracerebral haemorrhage or a subarachnoid haemorrhage (SAH), as well as to act in a prophylactic manner to reduce potential iatrogenic adverse effects resulting from transient ischaemia and embolization evoked by vascular surgery. Cerebrolysin has a remarkable capacity to upregulate the expression of important vascular protective and neurovascular restorative molecules.

A major and therapeutically efficacious molecule upregulated by Cerebrolysin is the morphogen Sonic Hedgehog (SHH). SHH is present in developing brain and as a transcription factor upregulates highly restorative molecules, including endogenous tissue plasminogen activator (tPA). Beyond its thrombolytic effects, tPA has been directly employed to treat intracerebral haemorrhage. In addition, tPA has been shown in the developing brain, to exert potent effects on brain plasticity and upregulation of endogenous tPA thus may enhance neurological recovery post neurological injury/bleed. By upregulating endogenous tPA expression in parenchymal cells, e.g., neurons, astrocytes as well as in endothelial (vascular) cells Cerebrolysin likely promotes neurological recovery and also, enhances microvascular integrity after a brain haemorrhage. Another essential molecule demonstrated to be increased in endothelial cells by Cerebrolysin is Angiopoietin 1 (Ang1). Ang1 plays a very prominent role in maintaining the integrity and health of the brain vasculature and promotes maturation of brain microvasculature and the tight junctions of the blood-brain barrier. In addition, Ang1 has been shown to enhaence neural plasticity, and there are substantial data that Ang1 mimetics have therapeutic effects on stroke recovery and other forms of vascular injury.

Thus, given the potential of Cerebrolysin to activate “developmental” transcription factors, such as SHH, that subsequently promote increases in neurovascular protective and restorative proteins, further studies are warranted for application of Cerebrolysin as a means to treat brain bleed, whether induced by SAH or ICH. We also have multiple reasons to believe that Cerebrolysin, as a neurovascular protective agent, may be effectively employed prophylactically before surgery to reduce ischaemic and other adverse effects of surgery and anaesthetics. Further studies in this area are also warranted, so as not to miss the opportunity to extend the therapeutic benefits of Cerebrolysin therapy significantly to the millions of patients whom each year undergo surgery.

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2.1.1 ...in the treatment of poor grade aneurysmal subarachnoid haemorrhage

Case Report

A 43-year-old Chinese woman, with good past health, was admitted under neurosurgical care after she collapsed following an episode of acute severe headache and vomiting. Her initial Glasgow Coma Score was 10/15 and her pupils were equal with normal reaction to light. A computed tomography (CT) brain scan revealed diffuse subarachnoid haemorrhage (SAH) of modified Fisher grade III (Figure 1). A catheter angiogram confirmed the presence of a right internal carotid artery aneurysm (Figure 2). The diagnosis of a World Federation of Neurosurgical Societies (WFNS) grade IV SAH (a poor-prognostic grade) was made. The patient was mechanically ventilated and an emergency operation for external ventricular drainage of cerebrospinal fluid (CSF) with endovascular therapy by placement of a flow-diverter device along with endosaccular coiling was performed in the acute phase (Figure 3). The procedure was uneventful, and no treatment-related complications occurred.

The patient was subsequently managed with standard care for aneurysmal SAH that included the administration of systemic nimodipine and hypertensive therapy. Both interventions were employed to reduce the risk of DCI. The patient was also considered eligible to enter the Cerebrolysin for Aneurysmal Subarachnoid Haemorrhage Randomized-Controlled Trial (CESAR) (ClinicalTrials.gov Identifier: NCT01787123) and consent was obtained from her next-of-kin. She was recruited into the study, randomized and was assigned to receive intravenous Cerebrolysin 30ml per day for 14 days. This was started on day three of her SAH before the onset of DCI. Transcranial Doppler ultrasound was performed for the patient every four days for the detection of vasospasm, a predictor for the development of DCI, and was not observed.

The patient tolerated Cerebrolysin and completed the two-week course without experiencing any adverse effects. Throughout the entire course of her inpatient stay DCI did not occur. The patient had improved significantly recovering full consciousness with no focal motor neurological deficit. However, she developed post-SAH communicating hydrocephalus that required the implantation of a ventriculoperitoneal shunt for CSF diversion. A CT scan showed no evidence of cerebral infarction (Figure 4).

After one-month of hospitalization the patient was able to be discharged home relying on a single person for assistance in walking. Upon discharge her functional performance was a modified Barthel Index of 70, a mRS of 4 (moderate severe disability, unable to attend to bodily needs without assistance and unable to walk without assistance) and an extended Glasgow Outcome Scale (GOS) of 3 indicating severe disability (lower). Cognitively the patient had a Montreal Cognitive Assessment (MOCA) score of 13/30. Regarding quality of life her SF-36 scores were 49 and 55 for the physical and mental domains respectively. Six months after stroke the patient experienced further remarkable recovery. Not only

could she walk unaided, functional performance assessments at this time point showed a modified Barthel Index score of 100, a mRS of 0 (asymptomatic) and an extended GOS of 8 reflecting good recovery (upper). Comparable progress was also noted cognitively where the patient achieved a MOCA score of 25/30, considered to be acceptable for her level of education. Finally, there were considerable improvements in her quality of life with SF-36 scores of 89 (physical health) and 87 (mental health).

Conclusion

The extent of the patient's recovery from SAH over six months was remarkable. Based on its neuroprotective and neurorestorative effects, early administration of Cerebrolysin may have been a contributing factor to the patient's recovery and may have reduced the risks of delayed cerebral ischaemia. This should be further investigated in a clinical study, especially, because early administration of Cerebrolysin over two weeks in the early phase after acute SAH was safe, tolerated, and feasible.

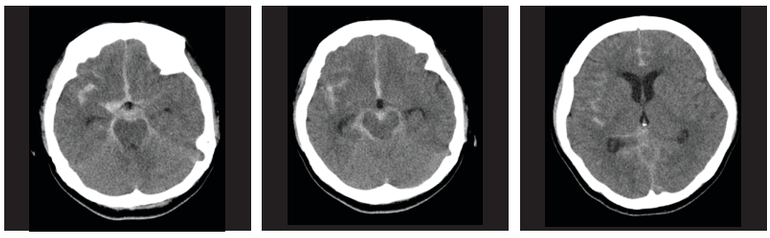

Figure 1 – An axial non-contrast enhanced CT brain scan revealing diffuse SAH of modified Fisher grade III with hydrocephalus.

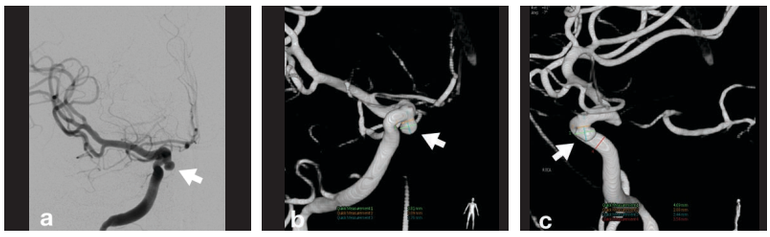

Figure 2 – A catheter angiogram showing the presence of a ruptured right internal carotid artery aneurysm, white arrow (a, anteroposterior projection; b, 3D anteroposterior projection, c lateral projection)

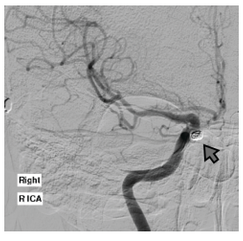

Figure 3 – Post-endovascular intervention catheter angiogram (right internal carotid artery injection) showing obliteration of the intracranial aneurysm, grey arrow (anteroposterior projection)

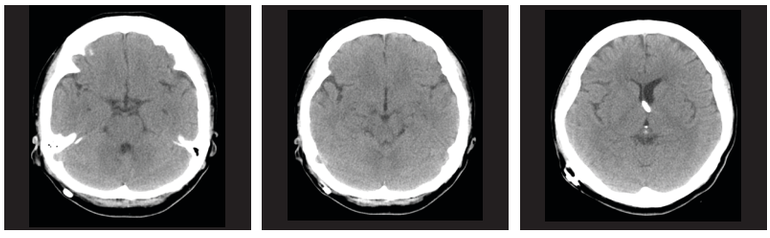

Figure 4 – An axial non-enhanced CT brain scan performed a month after admission showing the presence of a ventricular catheter after shunting with resolved SAH and hydrocephalus. There was no evidence of cerebral infarction.

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Mexico

2.1.2 ...in the treatment of an ischaemic vascular event secondary to vasospasm after aneurysm embolization

Case Report

Female patient aged 70 years, with a diagnosis of rheumatoid arthritis for one year, which is characterized by distal joint pain and treated with low dose of methotrexate. Chronic neuro-degenerative history was denied, however, her daughter reported episodes of occasional forgetfulness with increasing frequency in the last six months. At a first medical consultation, it was considered that she may meet the criteria for mild cognitive impairment, however, no treatment was initiated. The patient presented sudden and intense pulsatile left hemicranial acute headache followed by physical exertion that was accompanied almost instantaneously by nausea and vomiting as well as drowsiness. For this reason, the patient was taken to the emergency room with pain, generalized hyperreflexia, with presence of signs of meningeal irritation. However, strength and sensitivity were preserved.

Pharmacological management was initiated, and a simple brain tomography was performed showing subarachnoid haemorrhage at the level of the Willis polygon, with extension to the frontal and parietal lobes on the left side (Figure 1).

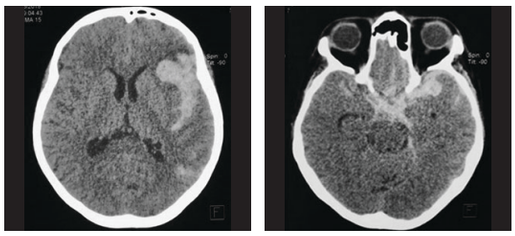

Figure 1 – Computerized Axial Tomography upon admission to the emergency department.

The vital signs remained stable with a blood pressure of 140/90 mmHg with a heart rate of 92 and a respiratory rate of 26 breaths per minute. Headache persisted and was relieved with analgesics. An angiotomography was performed (Figure 2) confirming the suspicion of an aneurysmal lesion in the M1 portion of the left middle cerebral artery.

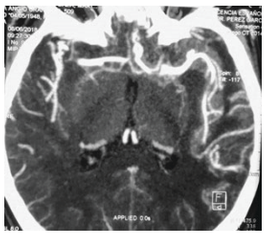

Figure 2 – Aneurysmal lesion in the left middle cerebral artery.

At 48 hours after admission, the patient was alert with complete mental functions, without alteration of

the cranial nerves, with discrete right hemiparesis 4/5 with ipsilateral hemi-hypoesthesia, no cerebellar alterations, although the signs of meningeal irritation persisted. The intervention of the endovascular therapy service was requested, performing digital subtraction angiography to corroborate the aneurysmal lesion with a 2.37 mm neck, a diameter greater than 2.33 mm, length of 3.56 mm at the bifurcation level, with a caudal dome and rostral to the neck, in the origin of the temporal branch (Figure 3). The aneurysm was embolized without apparent complications (Figure 4).

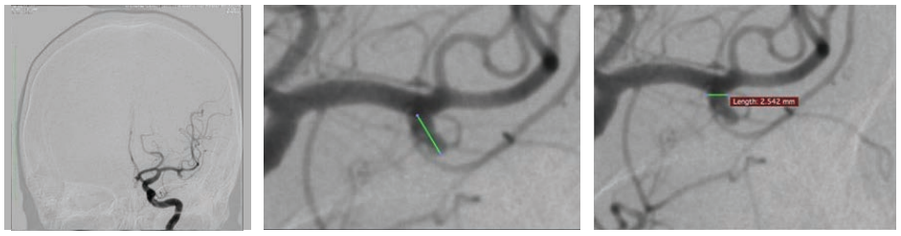

Figure 3 – Characteristics of the aneurysmal lesion observed in the angiography of the patient.

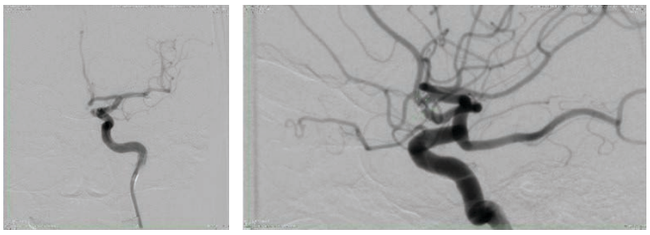

Figure 4 – Aneurysm embolization procedure.

Two hours after the procedure, the patient presented an increase in right hemiparesis at 1/5, associated with motor aphasia, which was considered to be due to an ischaemic event, most likely secondary to vasospasm, due to haemorrhage and embolization. Intravenous treatment with Cerebrolysin was initiated at a daily dose of 30 ml and citicoline IV at a dose of 1 g every 8 hours. This regimen was maintained for 12 more days until her discharge. The evolution of the patient was favorable, starting with physiotherapy and language therapy 48 hours after the event. The patient was sent to Neuropsychology for evaluation and multi-disciplinary treatment, showing a functional performance in verbal communication with a fluent type of aphasia over time, continuing difficulties in accessing the lexicon, which increases in stress and emotional conditions. It is important to mention that the age of the patient, as well as the extension and area of the lesion are determining factors in the evolution of the rehabilitation, which will always be dependent on an adequate cerebral plasticity.

The patient scored 29/30 points on MMSE - within the normal cut-off point. Regarding the global cognitive performance, with respect to the verbal comprehension index (Wechsler Adult Intelligence Scale, WAIS-IV), the performance was average (ICV 100).

In the evaluation of orientation, attention and concentration, the level of wakefulness was adequate throughout the evaluation sessions. In terms of orientation in space, time and person, the performance was correct with no errors. In attention and concentration, an adequate performance was observed in tasks of visual attentional amplitude and selective attention in both visual and auditory modalities. The evaluation of learning and memory, in memory tasks of coding at the auditory level, the patient presented an adequate performance in tasks of lists of words and pairs of words (ascending memory curve), in the register of stories and for the codification of names associated with faces. In the tasks of visual coding, she presented a performance according to what was expected for her age. In the memory of auditory evocation, the performance was adequate before the spontaneous memory, by

semantic association and by recognition, as well as in the evocation of associated pairs and stories. At a visual level, she achieved an adequate performance in face recognition, showing a slight alteration to the recovery of a semi-complex. For comprehension of language, an adequate performance was observed, as well as in the repetition of automated sequences (numbers, days of the week and months of the year), repetition of sentences, as well as in tasks of semantic and phonological fluency. In verbal denomination the performance was average, showing a performance with slight to moderate alteration in the written denomination.

The evaluation of executive functions showed that, in the tasks of abstraction, which aim to establish relationships between concepts, the patient presented an average performance in auditory and visual tasks. In the working memory tests, where the capacity to retain information and actively manipulate it is evaluated, she presented an average performance in tasks of visual type but had difficulties in tasks of auditory type (numbers in regression). With regard to fluency tasks, she achieved scores according to the norm in tasks of semantic, phonological and nonverbal fluency. Motor functions tests presented an average performance. With regard to the task of inhibitory control, which aims to measure the capacity of inhibition against automatic responses, the patient presented an average performance.

Conclusion

Currently the patient is without motor deficits and has recovered 90% of the language capabilities. She is fully functional and drives her vehicle to do her daily activities, with fully returning to normal life. It was reported by the evaluator that: “The patient presented herself to the evaluation sessions showing an adequate dressing; her attitude was collaborative, and she was committed to the completion of tasks.”

According to the applied neuropsychological tests, the patient presented a mean cognitive performance status with respect to the Verbal Comprehension Index (ICV 100), as well as an adequate performance in orientation (space, time and person), attention (visual amplitude and selective attention), learning and memory (auditory) and executive functioning in abstraction, working memory (visual), semantic, phonological and nonverbal fluency, as well as inhibitory control. However, she had difficulties in cognitive domains related to auditory amplitude, visual memory and written denomination, as well as executive functioning related to working memory (auditory).

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2.1.3 ...in the treatment of aneurysm surgery

Case Report

A female patient, 64 years old, right-handed, presented with severe headache, impaired consciousness and neck stiffness in January 2018. She had no history of medical problems and surgical interventions before. Her GCS was 13/15. Her systemic examinations and routine blood tests (FBC, U&E, Cr, lipid profile) were normal. Her ECG and chest X-ray were normal.

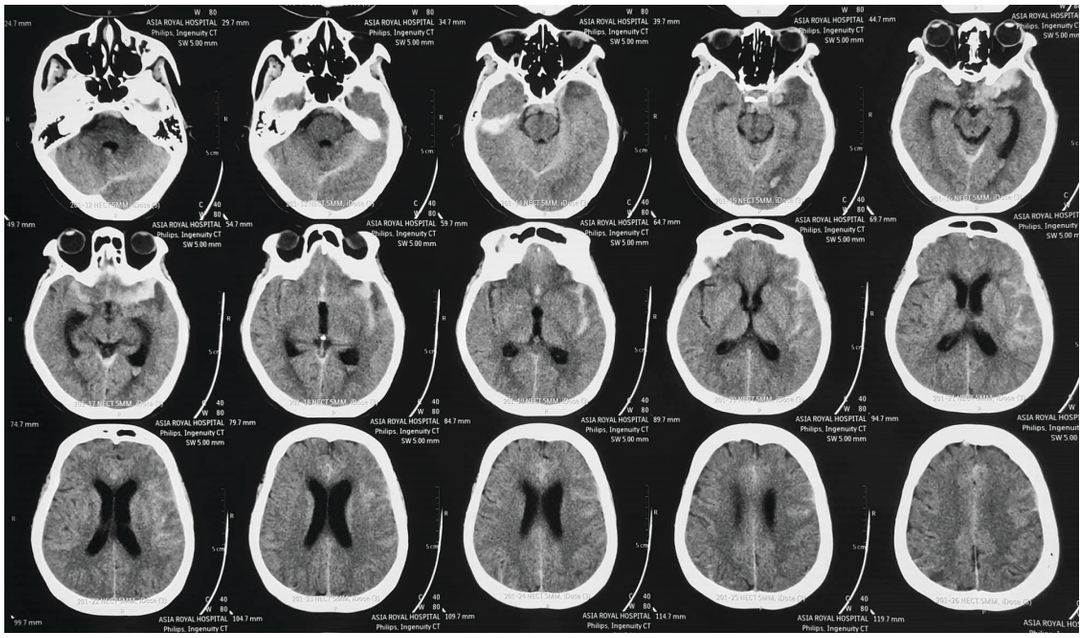

Figure 1 – Head CT indicating diffuse SAH, Fisher grade 2.

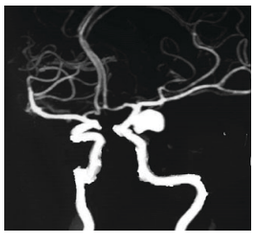

Figure 2 – CT brain angiogram indicating a wide neck aneurysm in the left internal carotid – posterior communicating artery.

She was treated as WFNS grade 2 SAH. She was given oral nimodipine 30mg every 6 hours, sodium valproate 200 mg every 12 hours and other symptomatic treatments. She underwent surgery, a left pterional craniotomy and clipping of a left ICA-PCOM aneurysm. On the second day post-surgery, she developed a right-sided hemiplegia (power 0/5), aphasia and reduced consciousness, the Glasgow Coma Scale decreased to 10/15.

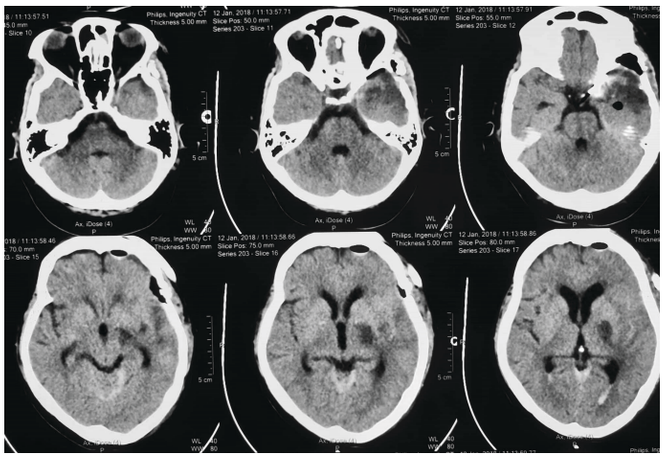

Figure 3 – A re-evaluated CT (head) showed ischaemic changes, an infarct and surrounding edema at the posterior limb of the left internal capsule and basal ganglia area.

Post-SAH vasospasms were assumed to cause delayed ischaemic deficits and/or compromise the left anterior choroidal artery perfusion. She had intensive physiotherapy treatment and medical therapy, which included nimodipine 30 mg every 6 hours for three weeks and IV Cerebrolysin 20 ml in normal saline 100 ml for 20 days. Two months after surgery, her condition improved gradually. On examination, she had a significant improvement in swallowing, speech, right-sided weakness from power 0/5 to right upper limb motor power 2/5 and right lower limb power 3/5. She continued with regular physiotherapy, additionally IV Cerebrolysin 10 ml OD for 20 days every three months was administered. Fourteen months after surgery, her condition improved significantly. On examination, she was fully conscious, could speak and swallow well. Her right upper limb regained power to 3/5 and the right lower limb power improved to 4/5. She can enjoy normal daily activities at home but needs some support from her family for outdoor activities.

Conclusion

Aneurysm clipping is a very invasive form of brain surgery, many neuronal connections have to be separated before the aneurysm can be reached and the clip or clips can be placed. In our experience the recovery process after aneurysm clipping was speedier, motor and cognitive functions showed less impairments when Cerebrolysin 30ml daily by IV infusion was administered for at least 14 days. We therefore advocate to study the efficacy of Cerebrolysin after aneurysm clipping surgery more intensely in prospective clinical trials, especially in more severe cases.

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Slovakia

2.1.4 ...in the treatment of non-surgical subarachnoid haemorrhage in the brainstem territory

Case Report

Male, born in 1951, with a diagnosis of subarachnoidal haemorrhage and multi-infarct encephalopathy showed a history of hypertension and stenosis of the spinal channel C3-7 with clinical signs of cervical myelopathy. One afternoon, he experienced a sudden violent headache. A blood pressure of 220/105 was measured. An emergency CT scan (Figure 1) showed subarachnoid bleeding with its maximum in the brain stem territory with suspected aneurysm in the a. basilaris territory. A CT angiography did not confirm an aneurysm.

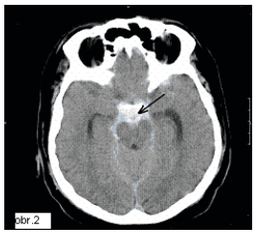

Figure 1 – CT scan with subarachnoid bleeding.

The neurological intensive care unit (ICU) started a comprehensive treatment of the subarachnoid bleeding consisting of antihypertensive treatment, prevention of vasospasm by nimodipine, analgesics, and Cerebrolysin 30 ml IV once daily for 10 days. Digital subtraction angiography (DSA) of cerebral circulation on October 1, 2008 did not show any aneurysm. The patient suffered from continuous headache and significant meningeal symptoms.

Control CT scans did not confirm a hydrocephalic development. Sixteen days after the blood pressure increased, a right-sided hemiparesis of medium degree and aphasia developed (NIHSS 11 points). An MRI scan of the brain showed two lesions temporally and frontally on the left. Cerebrolysis 30 ml IV was added to the daily treatment. During the next eight days motor deficits and speech improved. The neurological diagnosis showed a central paresis NCII on the right with discrete right-sided hemiparesis.

After 24 days, the patient was discharged home from hospital (mRS 1, NIHSS 3) and remained under medical supervision by an internal and neurological professional. The patient was treated with a combination of four antihypertensive medications. The patient mentioned worsening memory. Six months later, a control MRI scan detected ischaemia without motor deficiency. He was hospitalised again at the neurological department and was treated with Cerebrolysin 20 ml IV for 10 days. Ultrasonography did not show any stenosis. Psychological and psychiatric examinations showed a mild cognitive deficit, his neurological status has been stable and the mRS remained 1.

Conclusion

The use of Cerebrolysin in non-surgical treatment of a subarachnoidal haemorrhage in the brain stem territory was safe and had a beneficial effect on the clinical status of the patient.

Chapter 3

COMPLICATIONS

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Chapter 3.1

The role of Cerebrolysin...

There are various aspects of post-stroke complications directly emerging from the damaged cerebral tissue. These include motor and somatosensory dysfunction and deficits such as aphasia and depression, personality changes, and cognitive dysfunction. Additional complications may also include secondary organ dysfunction, including cardiac and renal dysfunction. Cerebrolysin by acting as a multimodal neurovascular protective and restorative agent may reduce both the primary and secondary adverse effects of the post-stroke complications.

Vascular dysfunction, including blood-brain barrier disruption and inflammation, directly induce cerebral parenchymal tissue damage, which expands the lesion leading to progressive and permanent neurological and functional deficits. These microvascular pathologies induced by stroke, particularly vascular inflammation, increase the risk for dementia and systemic inflammation, which can adversely impact secondary organs. Based on a model of the blood-brain barrier employing human cerebral endothelial cells, we find that Cerebrolysin ameliorates microvascular dysfunction and vascular inflammation. In addition, the neurorestorative processes which support brain plasticity are substantially amplified with Cerebrolysin treatment. For cognitive dysfunction and depression, experienced by many stroke patients, current studies suggest that Cerebrolysin therapy may ameliorate these symptoms.

We have shown that Cerebrolysin stimulates expression of sonic hedgehog (SHH). SHH also significantly upregulates a family of important microRNAs, e.g., miR-17-92. MiRNAs are non-coding RNAs which have an enormous capacity to regulate post-transcriptional gene translation of hundreds of molecular pathways concurrently. There is convincing literature that the miR-17-92 plays a primary role in the development of depression and anxiety. Having an agent such as Cerebrolysin that upregulates this vital family of microRNAs, thereby likely provides means to reduce depression and anxiety often brought on by a stroke. Thus, the multifaceted protective and restorative roles of Cerebrolysin have a wide range of therapeutic effects which will improve a multiplicity of neurological outcomes post stroke and neural injury.

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3.1.1 ...in the treatment of upper motor recovery combined with rehabilitation and tDCS therapy after recurrent ischaemic stroke

Case Report

A 69-year old male patient was admitted to our rehabilitation facility following a second, probably embolic stroke of undetermined source (ESUS) in the area of the right middle cerebral artery in March 2017 (proximal ACMD, M1 segment). He suffered a first ischaemic stroke in the same vascular area in October 2016. When he was admitted to our clinic in May 2017, he already had completed 4 weeks of rehabilitation as an inpatient in another rehabilitation facility with only minor improvements in his motor functions.

The patient presented with left sided hemiparesis, left hemianopia and left hemineglect. He was able to walk with a cane and the hemiparesis was affecting especially his left upper limb with distal weakness (distal MCR Grade 1-2, proximal MCR Grade 3-4). He was not able to manipulate small parts or perform isolated finger movements (e.g. to pick up coins, using the cutlery etc.)

The patient was treated with Clopidogrel 75 mg in combination with Aspirin 100 mg for secondary stroke prevention. His diabetes, hypertension and hyperlipidemia were medically well controlled. As the patient was already ambulatory, the primary goal of our rehabilitation efforts was aiming to improve the motor activity-level of his left upper extremity and to promote manual dexterity. In early June 2017 we decided to offer the patient a 2 weeks course of multimodal therapy including:

1. Intensive occupational therapy with a minimum of one hour of task-oriented training per day,
2. Daily anodal transcranial direct current stimulation (atDCS 2x20 minutes, over the left motorcortex M1) on five days a week from Monday to Friday
3. A 2-week treatment course with Cerebrolysin 30 ml IV infusions once daily for 14 days

Before and after providing 14 days of this triple combination therapy, we assessed specific outcomes of arm function and hand dexterity (Table 1). The patient improved in the ARAT score (Action Research Arm Test) from 38 to 49 out of 57 points (corresponding to a 60% proportional recovery rate). This presents a clinical meaningful improvement as the patient was now able to

perform fine motor tasks with his paretic hand and was able to transfer these improvements into motor tasks of everyday use (picking up small pieces, performing a pinch grip and using the cutlery properly etc.). He could also improve manual dexterity and performance speed (Nine Hole Peg Test) and expand his active range of motion of the left shoulder, especially arm abduction. He could also slightly improve handgrip strength.

Table 1 – Arm Function and Hand Dexterity Assessments.

Test	On Admission	Day 14
9 Hole Peg Test	r: 25,42 sec l: 2min 47 sec	r: 20,84 sec l: 1min 48 sec
Hand grip force	r: 38/39/31 kg l: 10/9/9 kg	r: 38/40/40 kg l: 11/10/10 kg
Functional Hand Scale (1-5)	r:5 l:3	r:5 l:4
ARAT Score	38/57 pts.	49/57 pts.
AROM left shoulder	ABD – 90°	ABD – 135°

Conclusion

This is the first ever reported case of a patient with a chronic stroke who, although there was virtually no motor recovery seen during the early phase of recovery and rehabilitation, showed profound improvements in functional motor recovery by using a two weeks triple therapy including Cerebrolysin 30 ml IV/day.

Dr. Nataliia Chemer
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3.1.2 ...in the treatment of post-stroke spasticity in a chronic stroke patient

Abstract

Recent studies show that spasticity occurs in 20–30% of all stroke victims, especially in younger patients. Botulinum toxin is a very effective treatment; however, it is not reimbursed in the Ukraine, thus leaving patients untreated and unable to use the paralyzed limb. Finally, this might result in longterm disability with economic consequences and negative impact on the psychological state of patients. Therefore, alternative and affordable treatment options are of high interest. This case report describes the therapeutic experience with Cerebrolysin on post-stroke spasticity in a chronic stroke patient from both the investigator's and the patient's perspective.

Cerebrolysin was administered for 30 days at a daily dose of 10 ml by intramuscular (IM) injections into the spastic limb of a 56-year-old chronic stroke patient. Therapeutic effects were assessed by the Modified Ashworth Scale (MAS), the mRS, and manual muscle testing (MMT).

After completing the treatment course with Cerebrolysin, spasticity-related outcome measures like MMT had improved by 70% and the MAS by 2 points. The patient reported a beneficial effect on mood and motivation.

Intramuscular treatment with Cerebrolysin of post-stroke spasticity was safe and effective in this patient. The experiences observed in this patient are in line with the findings of a larger cohort study treated in the same way in the Philippines.

Patient's Experience

I had a stroke 5 years ago. It was a severe hemorrhagic stroke. During the first 3 months I was not very well aware of my situation and do not remember what has happened then. I was able to move independently and to walk with support after 3 months, but my left hand did not function at all. I was determined to improve the situation! Indeed, I made progress in walking by reducing spasticity in the leg muscles, but the hand remained immovable. A few months later, I suffered from a deep achy pain in the paralyzed hand and in the leg, like muscle pain after an intense physical training. At the beginning, this pain appeared sporadically, but later it became my permanent companion. It was associated with spasticity as my doctor explained to me. The spasticity in my leg actually helped to straighten it, and I could walk more confidently with a stick without support. The situation with the hand was different: the fingers were bent into a fist and I could not straighten them, only with assistance and considerable effort. However, I did not give up and tried to continue doing exercises as it was advised earlier in the clinic. Over time the situation worsened and it became almost impossible to do exercises with my left hand and leg. Moreover, the pain became permanent. I consulted my doctor and he recommended botulinum toxin injections as a

possible solution to my problem. I am not the person who gives up easily, so I agreed immediately despite the high price. At the beginning, we decided to try treatment only on the left hand. To my disappointment, I did not notice any effect of the procedure: my fist remained clenched and my wife helped me to unbend my hand to get dressed. Since it was already 2 years after the stroke, I began to despond and my hopes for recovery were disappearing. Nevertheless, I started to work again as car mechanic, which gave me additional opportunity to network with people and did not allow me to become depressed. My family was very supportive as well. Once I met an employee with the same problem at a gas station—his left hand was paralyzed, but he was able to use it to perform his duty. I asked him how he was living with this problem. He advised me to continue exercises despite everything and try to use the affected hand as much as possible. It incredibly supported and inspired me. Just a few months later I learned from my doctor about a possibility to take part in a clinical research for patients with a similar problem. The doctor explained that Cerebrolysin's ability to reduce spasticity in paralyzed limbs will be explored. One month later, after daily injections, I was able to dress myself and to raise my hand, and it became possible to unclench the fingers with assistance, which was previously impossible. I continued my exercises and my achy pain disappeared. At the end of the treatment course, I could walk without a walking stick for long distances! I continued to use my left hand as often as possible: when repairing cars, I tried to hold a wrench with my left hand, I tried to turn off lights and to take a shower without any assistance. I felt a sensation in my left hand, which was absent before; "a shape of an object in my hand" sensation returned, and coordination and accuracy of movements improved. I was especially happy that the effect was persistent and improved over time. It inspired and stimulated me to continue exercises. Now I can unbend the fingers, use my left hand at work and at home, and drive a car. Ten months have passed since the treatment course with Cerebrolysin. I still feel the effects of the treatment and plan to repeat the course.

Physician's Perspective

The history of this patient is unusual for two reasons. First, the treatment of spasticity with Cerebrolysin is a new method, initially described by Martinez [2]. Cerebrolysin has not been used previously for spasticity treatment in our practice. Secondly, it is rare that a patient remains highly motivated and continues exercises with such persistence to restore his motor functions. Usually, patients are more likely to rely on rehabilitation specialists and do not continue exercising at home properly after discharge from the clinic, and they often lose the hope for recovery. Spasticity is an important factor influencing rehabilitation progress negatively. Post-stroke spasticity causes painful sensations and the inability to use a paralyzed limb in everyday routine, which leads to the demotivation of the patient. I was intrigued to use Cerebrolysin in spasticity treatment for two reasons:

- Cerebrolysin intramuscular administration into a paralyzed spastic limb at a dosage of 10 ml daily over 1 month was shown to be effective and reduced spasticity symptoms in the long term [2]. Furthermore, it can be combined with physical exercises within a standard rehabilitation program [1].
- Additionally, its perceived antidepressant effect should improve the patient's general mood, increases motivation for physical activity, and improves cognitive function and motivation, which altogether may results in a significant positive outcome.

The patient of this case study was male, born in 1959, and suffered from stroke on June 24th, 2013 with spasticity diagnosed on July 4th, 2013. The spasticity-related rehabilitation program was initiated on September 12th, 2017; at that time, the patient had an NIHSS score of 6. At

follow-up 180 days later, the NIHSS score was 5 and the distal motor function score decreased from 2 to 0–1. In the manual muscle testing, the patient improved by approximately 70% and by 1–2 points in the Modified Ashworth Scale.

Taking into account the small number of centers and insufficient number of specialists providing quality rehabilitative treatment in our country, the access to this type of care is limited. Therefore, treatment of spasticity with Cerebrolysin is an encouraging approach as it is easy to use, accessible, and affordable, and—most important—safe to use in outpatient care. However, a key factor for success in post-stroke spasticity management is the motivation of the patient and people supporting him/her to continue rehabilitation. If a rehabilitation program has a clear goal and achievable tasks that go beyond daily routine and allows patients to participate in social life again, it will make therapy more successful!

References

1. Martinez RM. Efficacy of Cerebrolysin in reduction of spasticity during stroke rehabilitation. J Med Life. 2017;10:161–6.
2. Muresanu DF, Heiss WD, Hoemberg V, et al. Cerebrolysin and recovery after stroke (CARS): a randomized, placebo-controlled, double-blind, multicenter trial. Stroke. 2016;47:151–9.

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Azerbaijan

3.1.3 ...in the treatment of global aphasia without hemiparesis

Case Report

We present the case of a 38-year-old right-handed male who arrived by ambulance six hours after reports of symptom onset. The patient's wife noticed that her husband suddenly developed right-sided weakness, headache, dizziness, and speech repetition. The patient presented elevated blood pressure (220/110 mmHg) on admission to emergency care.

A neurological examination showed an NIHSS score of 17, global aphasia (Western Aphasia Battery), and right-sided hemiparesis (3/5) - a transient symptom. An MRI of the brain showed an acute infarct in the left middle cerebral artery, located in the anterior frontal region.

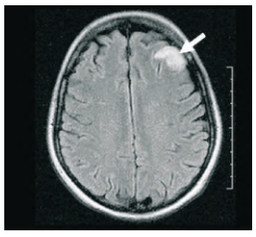

Figure 1 – Brain MRI: white arrow indicates site of acute infarct.

The patient's family history included migraine (mother), heart attack (father, 15 years earlier), and haemorrhagic stroke (maternal grandfather; at the age of 75). The patient was undergoing treatment with enalapril 10mg daily for three years prior to admission to treat hypertension but had recently stopped for unknown reasons.

We prescribed valsartan, aspirin, clopidogrel, Cerebrolysin, and piracetam for the treatment acute ischemic stroke. Cerebrolysin was administered at a dose of 20 ml once daily for 10 days, every three months. Piracetam was administered at a dose of 2.4 mg twice daily for six months. In addition, the patient received speech and language therapy.

We observed the clinical course of the patient for one year. At onset, the WAB score indicated global aphasia, four weeks later Broca's aphasia with an NIHSS score of 12. At the next follow-up seven months later, the WAB scores indicated transcortical sensory aphasia and the NIHSS score had decreased to 8. After one year, the NIHSS score was 6.

Conclusion

The use of Cerebrolysin in aphasia without hemiparesis was safe and well-tolerated and may have contributed to the unexpectedly good outcome in this patient. However, further studies are needed to better understand the functional connection between language recovery and neuroplasticity in GAWH patients.

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3.1.4 ...in the treatment of post-stroke hemianopia

Case Report

A male patient, born in 1949, was treated in the cardiology department for cardiac ischaemia, exertional angina, two cardiac infarcts in 2011 and 2013, post-infarct cardiac sclerosis in 2011 and in 2013. Two days before admission on February 15th 2017, the patient reported a loss of vision in the peripheral and central zones on both hemispheres, predominantly to the left and he also reported dizziness. The patient was conscious, responsive without any obvious sensory or motor impairments. According to the patient's request, he was discharged and continued the treatment in another private clinic, where he had a brain MRI on 15th of February, 2017, which showed a picture typical for simultaneous onset of acute ischaemic and hemorrhagic stroke in the left occipital lobe, multiple foci of demyelination in both hemispheres with presence of active structures in the cerebral peduncle and the thalamus, both on the right side. A hydrocephalus is visible as well.

The patient was admitted to the neurology department for additional investigations. He was oriented to time and location but suffered from a gaze paresis on the left side and a double-sided central hemianopia predominantly to the left. No paresis in the extremities, no sensory impairments were shown. In the hospital the patient received Cerebrolysin 30 ml diluted with 200 ml saline solution by IV infusions for 10 days, mannitol 200mg IV infusions for 5 days and nimodipine 30 mg twice per day for10 days orally. Due to the lesion's localization - occipital lobe on the left, cerebral peduncle on the right and thalamus on the right, the most pronounced clinical symptom was vision impairment in the form of loss of sight of the central scatoma in the left hemisphere. During the treatment dynamical MRI and perimetry results were evaluated.

On the MRI (Figure 1) dated February 15th, 2017, taken in the acute phase prior to the initiation of treatment, an extensive impairment of the occipital lobe on the left of mixed type with prevalence of haemorrhage sized 5 cm x 3.5 cm was shown together with lesions in the structure of cerebral peduncle on the right side and thalamus on the right side.

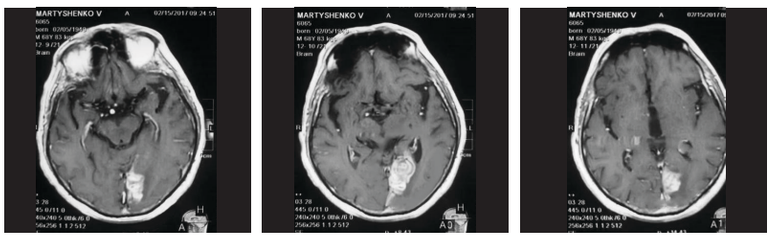

Figure 1 – MRI - extensive impairment of the occipital lobe on the left

Eleven days later, after the end of the treatment with Cerebrolysin, the MRI scan showed a significant reduction of the lesions in the occipital lobe (3.5 x 2.8 cm), as well as a complete regression of the lesions in the cerebral peduncle and the thalamus.

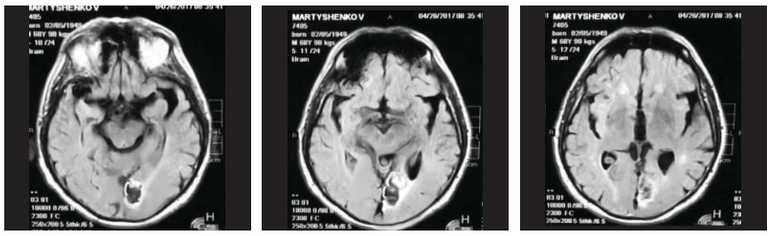

Figure 2 – MRI illustrating reduction of lesions

The patient also consulted with an ophthalmologist who conducted a perimetry examination.

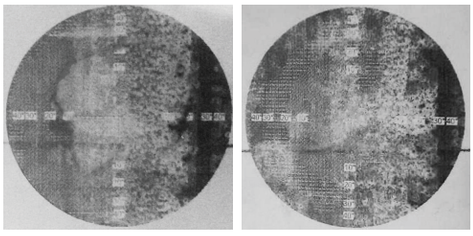

Figure 3 – The image on the left side, taken 24 hours after onset of symptoms and prior to the initiation of treatment, showed an extensive vision loss in the form of a central scatoma.

Five weeks later, after treatment with Cerebrolysin, the perimetry analysis showed that the scatoma lesion had significantly decreased in size and became fractional.

Conclusion

In my clinical practice, I have seen many patients who were transferred to our rehabilitation clinic after suffering from acute coronary accidents. My general observation is that patients who received Cerebrolysin already during the acute or subacute phase are generally arriving at the rehabilitation ward with lower degrees of impairment and milder symptoms. Clinical studies have demonstrated that even an initiation of treatment with Cerebrolysin in the post-acute phase (eight days post-stroke) improves motor functions, which is in line with my own clinical observations. In my experience, a standard treatment course of 30ml Cerebrolysin once daily for 10 days also improves gait, reduces aphasia symptoms and improves cognitive functions. The improved hemianopia observed after the treatment course with Cerebrolysin is remarkable and should be further investigated, especially since up to 60 percent of patients suffer from related problems after stroke.

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Dr. Tzu-Lun Huang, Far Eastern Memorial Hospital
Taiwan

3.1.5 ...in the treatment of hydroquinolone retinopathy

Case Report

A 55-year old female patient was diagnosed with systemic lupus sclerosis (SLE) for more than 10 years and she received hydroquinolone as immunomodulation therapy from 2000 to 2015. Progressive impairment of night vision developed since 2015 and hydroquinolone retinopathy was diagnosed by the ophthalmologist. This is a rare adverse effect of hydroquinolone therapy for which no effective treatment currently exists.

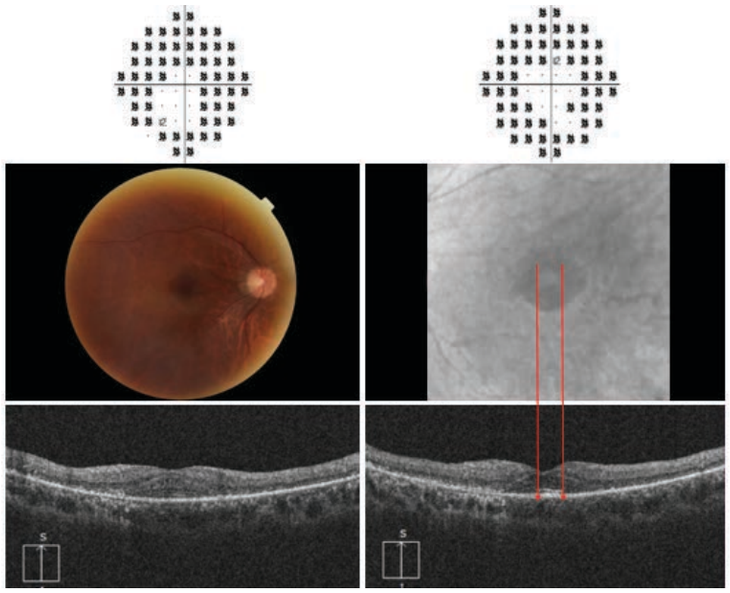

Figure 1 – Evidence of hydroquinolone retinopathy

A treatment course of Cerebrolysin 30ml/day IV for 5 days was repeated every two weeks. After three months, the patient preserved her vision and her visual field was improved (Figure 2, 3).

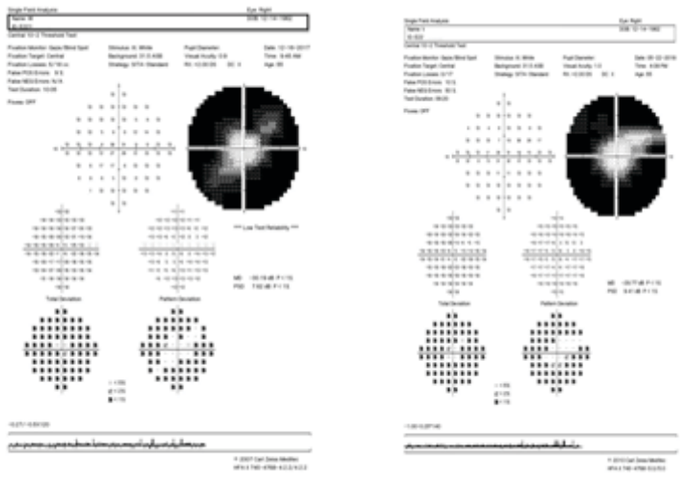

Figure 2 – Right eye before and after Cerebrolysin therapy.

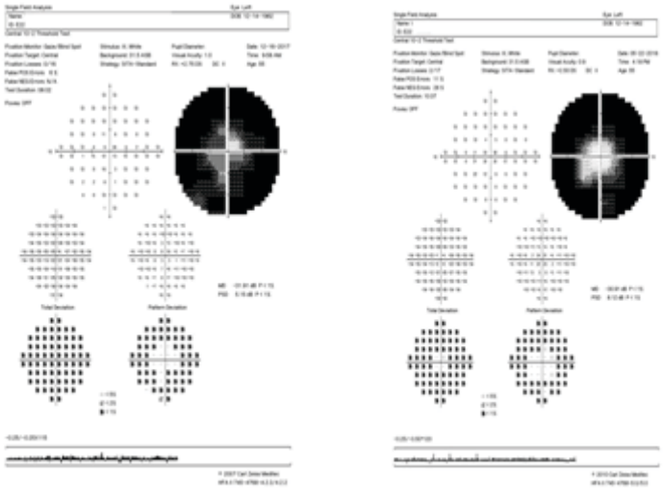

Figure 3 – Left eye before and after Cerebrolysin therapy.

Conclusion

The patient reported that she can see much more clearly even at night time after three months of Cerebrolysin therapy. Repeated visual field tests also showed the improvement in this patient: her visual field was getting wider and the quality of her vision improved as well. Currently she continues Cerebrolysin therapy. We continue her follow-up in our ophthalmology clinic. Cerebrolysin is an off-label therapy in patients with retinoneuropathy. More clinical experience or studies are essential to further evaluate the therapeutic effect of Cerebrolysin in this indication.

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3.1.6 ...in the treatment of haemorrhagic transformation, combined with intensive subacute rehabilitation

Case 1

The first case was a 69-year-old male patient who sustained a large MCA infarction with haemorrhagic transformation 6 weeks prior to his admission for neurological rehabilitation to the Samrong General Hospital. At admission he required maximal assistance for balance, mobility and ambulation. Regarding bed mobility, he suffered from a severe contraversive pushing behavior, had difficulties to maintain his balance, always leaned to the hemi-paretic side and it required continuous external support to keep him upright. He was also unable to initiate any arm or hand movement voluntarily, had severely impaired joint proprioception which was demonstrated by a failed “Thumb finding test” and he also had a left hemi-spatial inattention which was diagnosed in a line cancellation; he missed 39 out of 50 targets. He also reported a mild to moderate central burning arm and leg pain.

We started treatment with a daily infusion of Cerebrolysin 30ml dosage in conjunction with one month of intensive multidisciplinary in-patient rehabilitation which included the following:

- Robotic end-effector gait rehabilitation
- Physiotherapy, with emphasis on mobility, balance and ground walking with supports and intensive feedback.
- Vojta therapy (reflex locomotion therapy, following the method of Prof. V. Vojta)
- Perfetti method (cognitive sensory motor training therapy, following the method of Prof. C. Perfetti)
- rPMS (Repetitive Peripheral Magnetic Stimulation) to the limb muscles.
- HPLT (High Power Laser Therapy)
- Occupational Therapy, with focus on kinetic activities, speech training, and swallowing rehabilitation.

After finishing the treatment, the patient was able to maintain good sitting balance without support and he was able to ambulate with a tripod cane under moderate to maximum assistance of one person (FAC 1 - Functional Ambulation Classification 1 weight bearing support). This much assistance was still needed despite his good (grade 3) leg muscle recovery, due to the residual pushing behavior still manifesting itself during walking and standing, necessitating assistance from other people. He was also able to initiate active elbow flexion and forearm pronation. However, these were bound to a mass movement or synergy pattern, and no active hand function has been observed. The arm and leg pain has been resolved almost completely by prescribing oral Gabapentin and treating the painful sites with high power laser therapy.

Even though the patient had sustained severe multiple disabilities, the combination of intensive task specific therapy in combination with Cerebrolysin infusions resulted in a significant recovery in all problematic domains.

Case 2

This case was a 72-year-old male with left MCA infarction with hemorrhagic transformation 3 weeks before admission to the in-patient rehabilitation department at Samrong General Hospital. This patient was older and even more severely affected than the first case. At admission he had a severe receptive and expressive aphasia, complicated by severe speech, oral motor, and swallowing apraxia. The left arm which was not considered to be affected was severely dyspraxic as well. The patient was neither able to make or imitate gestures nor reliably make or imitate head nodding or head shaking, so even gestural expressive communication was severely limited. Bed mobility and sitting balance were poor and were only possible with a person helping him. For one month after admission, he was prohibited to do any therapy in an upright position due to orthostatic hypotension, a side effect of his anti-hypertensive medication. This patient also received Cerebrolysin treatment with 20 ml daily infusions for 20 days plus 4 months of intensive inpatient rehabilitation. The list of therapies and devices used was similar to that of the first patient, details of his therapy programs were tailored to suit his individual impairments.

After finishing the treatment, the patient was able to turn in bed to the left side with minimal assistance and he was able to maintain good sitting balance. He walked with a tripod cane and one person's assistance, swallowed normal food and has stopped using a nasogastric tube. He regained his ability to repeat and to understand spoken words and points correctly to relevant pictures most of the time. His understanding of short sentences became possible, but his performance is not consistent. Naming and spontaneous conversation was at this time not possible as well, but the patient expressed his wishes reliably by making head nodding and head shaking plus other hand gestures. Imitation of hand gestures was not a problem, but many times he still had a problem showing the right gesture because he was unable to understand long or complicated words. This was confirmed by an abnormality in the Token Test in which the patient can correctly point when he listens to a one word- but not multiple word instructions.

Conclusion

These two illustrative cases, both had relatively large cortical and subcortical lesions with resulting complicated multiple disabilities, in which the judicious use of medication and intensive evidence-based, impairment appropriate rehabilitation therapies significantly changed the disability profile within a relatively short period.

Both patients are still making progress and have not reached their full rehabilitation potential. Therefore, it is reasonable to expect that a better recovery of their functions may be observed in the near future provided that the combination of Cerebrolysin and intensive rehabilitation can be continued.

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Military 103 Hospital
Vietnam

3.1.7 ...in the treatment of post-stroke aphasia including AVANT program

Case Report

The AVANT (Austrian Vietnamese Advancement Neurorehabilitation Treatment) is a collaboration program between Vietnam and Austria to standardize and systemize neurorehabilitation after stroke practice in Vietnam. The intervention procedure is divided into 2 groups: direct and indirect intervention (Figure 1).

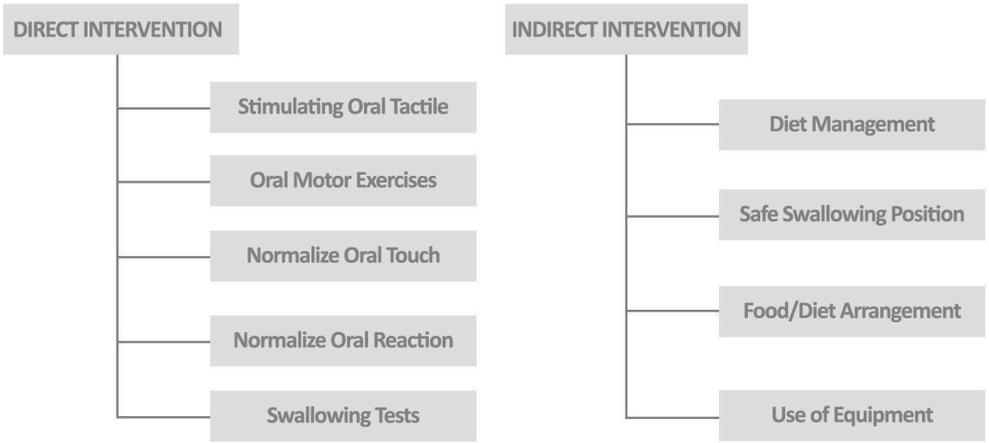

Figure 1 – Dysphagia intervention by the AVANT program

This case study refers to a 63-year-old male patient who suffered from ischaemic stroke in September 2018 (fully recovered), February 2019, and March 2019. His medical history included in addition dyslipidemia and hypertension. In the morning of February 16, 2019, the patient presented with hemiplegia on the left side of the body, aphasia, and dysphagia. He received 1.5mg of indapamide/day (for hypertension), 10mg of atorvastatin/day (for dyslipidemia), and 75mg of clopidogrel/day (platelet aggregation inhibitor). There was minor improvement of motor functions, no improvement on swallowing, the patient could consume liquids only, and choked when drinking water. The patient was assessed as a high-risk patient for recurrent ischaemic stroke with a low chance of recovery from dysphagia and a high chance of aspiration. Within three weeks, on March 3, 2019 at 3 PM, the patient suffered from another ischaemic stroke with right-sided hemiplegia, increased aphasia, and he was unable to swallow. He was hospitalized on March 4, 2019. A feeding tube was inserted through the abdomen and the patient's condition at hospitalization can be described as:

- Conscious
- Dysphagia: GUSS score = 0; mandatory use of a feeding tube
- Aphasia: patient understood words but had difficulty in pronunciation; speech was difficult to understand
- Quadriplegia: MRC Grade 2 for right and Grade 3 for left extremities
- Cranial nerves: undamaged
- No sphincter disturbance
- Blood pressure: 120/75mmHg, pulse 75bpm
- mRS 4
- Brain MRI: there are two ischaemic lesions in the left and right hemisphere (Figure 2)

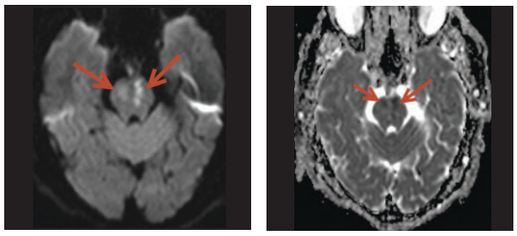

Figure 2 – Brain MRI shows two areas affected by cerebral ischaemia on the right and left hemisphere.

The patient required intensive care and received the previously described treatment and slow intravenous administration of 10ml of Cerebrolysin, twice per day.

Since recovery of swallowing function is challenging, yet vital to the patient, we decided to additionally involve a team of medical professionals trained in the AVANT program. This "recovery team" conducted a detailed evaluation of the patient's dysphagia, designed an exercise program for muscles involved in swallowing (lips, sets of teeth, tongue, cheeks, fauces, etc.), assessed daily the condition, explained the patient and his family the mechanism and causes of dysphagia, and gave them instructions on correct positions for eating and drinking, suitable types of food and drinks for each phase. In addition, a rehabilitation therapy was initiated for recovery of motor functions and communication. The patient was assessed for dysphagia (GUSS, Gugging Swallowing Screen), paralysis (MRC, Medical Research Council), and disability (mRS, modified Rankin Scale).

Day 7 (after hospitalization): The feeding tube was removed on day 6. From day 7 the patient could eat semi-liquid food (soup) and drink 5ml sips of water from a spoon. Medication was crushed and mixed with water to reach a slightly thinner consistency. GUSS score = 11. The patient could pronounce 2-3 syllable words quite clearly. MRC Grade 2 for right extremities, MRC Grade 4 for left extremities, mRS 4.

Day 14: The patient could eat pieces of soft food such as tofu, potato, gourd, fish, etc., and drink water in 10ml sips. Medication was crushed and mixed with water to reach a slightly thinner consistency. GUSS score = 15. The patient could pronounce 2-3 syllable words quite clearly. MRC Grade 3 for right extremities, MRC Grade 5 for left extremities, mRS 4.

Day 21: The patient could eat normal food such as rice, noodles, vegetables, etc., albeit slowly. Medication in small tablets could be swallowed. GUSS score = 17. The patient could speak complete sentences, albeit slowly and with difficulties. Speech made by the patient could be understood. MRC Grade 4 for right extremities, MRC Grade 5 for left extremities, mRS 2. The patient could walk without assistance.

Day 25: The patient was discharged with mRS 2, and he was given instructions on the administration of drugs and exercises at home.

Conclusion

In the present case, the recovery of the swallowing function seemed difficult due to the severe dysphagia. However, the combined intervention of the AVANT program on swallowing function and the neurotrophic effects of Cerebrolysin as part of the treatment regimen resulted in improvements on dysphagia after the first week of treatment. By the end of the third week, considerable improvements were observed, and the patient was able to do daily activities such as walking, communicating, and eating without assistance. Early adoption of an appropriate rehabilitation program, combined with neurotrophic drugs such as Cerebrolysin, showed improved swallowing function in this stroke patient.

Chapter 4

TRAUMATIC BRAIN INJURY

Dr. Michael Chopp
United States of America

Chapter 4.1
The role of Cerebrolysin...

Our data and those of others show that Cerebrolysin has a potent therapeutic effect in significantly reducing neurological damage and improving outcome in various models of traumatic brain injury (TBI) including severe penetrating head injury and mild/moderate closed head injury in rodents. Double-blinded placebo-controlled dose-response and therapeutic window studies have demonstrated an extended therapeutic window up to days post (and probably beyond) TBI and a clear dose-response of the treatment.

These robust preclinical data provide a compelling argument to fully translate Cerebrolysin from the laboratory to the clinic for treatment of TBI. Mechanistically, Cerebrolysin functions consistently with the extensive observations found for the treatment of stroke. This includes neurovascular protection, remodeling, and augmentation of plasticity, thus contributing to the reduction of proinflammatory conditions and amelioration of functional deficits. We have also shown that plasticity, including enhanced axonal outgrowth and neurogenesis, among other parameters, has a remarkable and highly significant correlation with multiple aspects of functional and neurological recovery. Thus, our data demonstrate that Cerebrolysin induced plasticity drives functional recovery. A significant adverse effect of TBI, even mild TBI, such as concussion is reduced cognitive function and memory.

These aspects of TBI have been extensively evaluated in our laboratory on multiple tests, including memory, anxiety, social integration, and general learning and memory. Our data demonstrate a potent therapeutic effect of Cerebrolysin in significantly reducing neurological as well as cognitive and emotional dysfunction post-TBI.

Dr. Rhoderick M. Casis
St. Luke's Medical Center
Quezon City, Philippines

4.1.1 ...in the treatment of severe traumatic brain injury from clinician's and patient's perspectives

Abstract

We hypothesize that the combination of Cerebrolysin and atDCS induces a milieu of heightened neuroplasticity, possibly by promoting BDNF-mediated synaptic plasticity. This enhances the therapeutic benefit of the concomitant neurorehabilitation program, which includes a conventional rehabilitation protocol as well as task-oriented training, on motor function recovery.

Traumatic brain injury is a challenge for general practitioners and specialists worldwide due to the heterogeneous clinical picture, secondary injuries and complex treatment including surgery, medication, intensive care, nutrition and rehabilitation. This case report is about a TBI patient with a score of four on the Glasgow Coma Scale when she was transferred from the primary hospital to our center. Her condition, treatment options and expectations were discussed with the relatives. The patient was subjected to surgery and received pharmacologic intervention including a neurotrophic drug and extensive rehabilitation measures including occupational therapy. Considering the patient's remarkable recovery, a combination of multiple treatment approaches seems promising in patients with severe traumatic brain injury.

Introduction

Traumatic brain injury (TBI) is a global health problem and a common condition seen by every clinician. It is a major concern in all countries because it consumes healthcare resources and puts a tremendous strain on a government's healthcare budget. A large percentage of TBI patients suffered from vehicular accidents. In a meta-analysis of individual patient data in moderate and severe TBI, the IMPACT study group found a very similar distribution: the percentage of TBIs caused by road traffic incidents varied between 53% and 80%, and the percentage of TBIs caused by falls varied between 12% and 30% [1, 2]. Furthermore, a significant number of survivors was dependent on a caregiver in their activities of daily living. Similarly, in St. Luke's Medical Center in Quezon city, Philippines, almost 40% of the admission and referral patients suffered from traumatic brain injury. However, improving treatment should not only result in increased survival but also in improved functional outcome. Thus, new treatment concepts that improve the benefits for the patients should be explored.

The primary aim of this article is to provide help and information on additional treatment of traumatic brain injury, especially severe TBI. Improving the treatment of severe traumatic brain injury through better understanding of its pathophysiology and information about innovative treatment will help clinicians in treating TBI. Hopefully, new and well-designed studies will open avenues for new and

innovative treatments to be accepted as beneficial to patients. Eventually, this will help in improving clinical guidelines on its treatment, which will potentially benefit patients with TBI.

Patient's Case

My patient, a 57-year-old female, was involved in a vehicular accident. She was hit by a speeding vehicle while crossing a busy street. Immediately after the accident, she was still able to say her name and talk to people around her. After 2 h she became drowsy. When she was brought to the primary hospital, she had a Glasgow Coma Scale (GCS) score of 13/15. According to the initial CT scan, she suffered from an acute right frontotemporoparietal subdural hematoma. She was still in the emergency room when she started to deteriorate, now with a GCS score of 7/15. The right pupil was noted to be dilated and non-reactive to light. With a GCS score of 6/15, she was intubated and was transferred to the emergency department of St. Luke's Medical Center. She received mannitol at a dose of 20 mg every 4 h intravenously. Unfortunately, she deteriorated further to GCS 4/15. She received another bolus of 40 mg of mannitol upon consultation with the neurosurgeon. Her GCS score improved to 6/15, and the decision for emergency surgery was made.

All procedures performed in this study involving the patient were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the patient or her representative for all the procedures done.

Physician's Account

When I was informed about the patient in the emergency department and that her condition was deteriorating, I immediately asked them to give 40 mg of mannitol as a bolus dose and to repeat the cranial CT scan. I told the doctor in the emergency room that I was on my way to the hospital. I entered a nearly full emergency room with every physician taking care of a patient. In the critical area, I saw the patient hooked to a ventilator. She still had traces of blood on some areas of her face. She had a periorbital haematoma on the right side, making examination of her right eye difficult. I noticed that her right pupil was dilated with no reaction to light. Her left pupil was 3 mm reactive to light. On further examination, she was responding to painful stimulation by withdrawing her left upper extremity with no eye opening. I asked for the CT scan images and saw that besides the right acute subdural hematoma, she also had multiple contusion hematomas of the right frontal, temporal and parietal lobes (Figure 1a). There was a significant midline shift and signs of uncal herniation. All of these CT scan findings indicated a serious prognosis for the patient. I talked to her daughter and emphasized the need for immediate surgery, discussing the procedure to be done and and possible outcomes. The high possibility of death even with surgery and the probable neurologic deficits if the patient survived were also discussed. She gave her consent for the surgery. The patient was prepared for immediate surgery and brought to the emergency department operating suite. The planned surgery was craniotomy with evacuation of the acute subdural haematoma and intracerebral haematoma with possible decompressive hemicraniectomy.

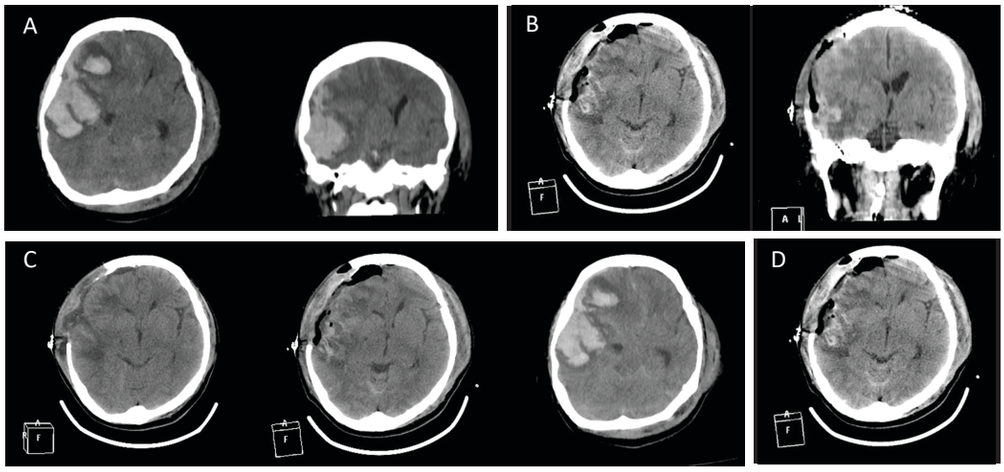

Figure 1 – Patient's cranial CT scans. a Cranial CT scan at the emergency department showing multiple hemorrhagic contusions, a subdural haematoma and midline shift. b Cranial CT scan 24 h after the first surgery with decreased mass effect and bone defect. c Cranial CT scan 28 days after the first surgery compared with 24 h after the surgery and preoperatively. d Cranial CT scan 9 months after injury with cranioplasty showing minimal encephalomalacia

A burr hole was made in the temporal area and enlarged to expose the tense dura. The dura was opened, and the acute subdural haematoma was suctioned. After a significant volume of blood had been evacuated, we proceeded with the frontotemporoparietal craniotomy. Upon lifting off the bone flap, the dura was noted to be tense with blood underneath. The exposed dura was opened, and a substantial volume of acute subdural haematoma was evacuated. Burst frontal and temporal lobes were noted, and a significant amount of intracerebral haematoma was evacuated. Bleeding areas of the brain were cauterized, and devitalized brain tissues were also removed. The brain was noted to be pulsating but still significantly swollen. It was decided to do duraplasty and not to put back the bone for decompression of the swollen brain. Intracranial pressure monitoring was not done because it is not a standard procedure in our hospital for large decompressive craniectomies. The scalp was closed by layer with a closed drain placed through a separate stab incision.

The patient was then brought to the neurocritical care unit, still maintained on a ventilator. She was given medical decompression using mannitol. The need for medical decompression was explained to the relatives including how it would be progressively decreased. An anticonvulsant was also given. The surgery including the findings were explained to the patient's children and also that her condition was still critical. A follow-up cranial CT scan showed near complete evacuation of the contusion hematomas and acute subdural haematoma with good expansion of the brain (Figure 1b).

Less than 24 h after the surgery, the patient was still in critical condition. Knowing the limitations of surgery for the other problems of TBI, I decided to try other means to help the patient in her recovery. I informed her daughter about a medicine that is used for treatment of brain injuries caused primarily by stroke but is also used in TBI. I explained that Cerebrolysin® consists of purified peptides from porcine brain and is given intravenously. I gave examples of my patients who had good recovery after brain injury but mentioned that these were mostly from strokes. The daughter agreed to the added treatment. The medicine was to be given at a dose of 50 ml once a day for 14 days. No other neuroprotective or neuroregenerative drug was given to the patient.

The patient improved and was eventually weaned off the ventilator. She progressively improved, and a repeat cranial CT scan was done 28 days after her first surgery (Figure 1c). She underwent cranioplasty

where the bone that was removed to accommodate the brain swelling was put back. This was done 41 days after the first surgery. The patient was discharged 5 days after the repair of the decompressive craniotomy. On the patient's last follow-up 9 months post-TBI, she had a Glasgow Outcome Scale score of 5, indicating good recovery. She was examined and showed good cognitive function including understanding and judgment. Her visual examination was normal including gross confrontation tests. She mentioned that she had started to work but was taking things slowly with her work load. A repeat cranial CT scan was also done during this time (Figure 1d).

The treatment options used for this patient were in accordance with the institutional guidelines on the care of patients with severe traumatic brain injury. Furthermore, no study was conducted on humans or animals in this article.

The following interview with the patient and her daughter reflects their impressions regarding the treatment and their feelings throughout the whole recovery process.

Conclusion

There is no magic bullet in the treatment of severe TBI. Our treatment has to be individualized based on EBM, personal experience and our environment. However, we have to remember that the future is bright with better research and understanding of TBI. Newer information, from well-conducted randomized clinical trials, will definitely help in the treatment of TBI patients, especially those with severe TBI. In the future, the combined treatment and the multispecialty approach in the treatment of TBI will greatly benefit our patient.

References

1. Theadom A, Feigin V, Reith F, Maas A. Epidemiology of traumatic brain injury. In: Winn HR, editor. Youmans and Winn neurological surgery. Philadelphia: Elsevier; 2017.
2. Finkelstein E, Corso P, Miller T. The incidence and economic burden of injuries in the United States. New York: Oxford University Press; 2006.
3. Wakai A, McCabe A, Roberts I, Schierhout G. Mannitol for acute traumatic brain injury. Cochrane Database Syst Rev. 2013;8:CD001049.
4. Servadei F, Picetti E. Intracranial pressure monitoring and outcome in traumatic brain injury: the probe does matter? World Neurosurg. 2015;83:732–3.
5. Christensen B, Colella B, Inness E, Hebert D, Monette G, Bayley M, Green RE. Recovery of cognitive function after traumatic brain injury: a multilevel modeling analysis of Canadian outcomes. Arch Phys Med Rehabil. 2008;89(12 Suppl 2):S3–15.
6. Anderson J, Schmitter-Edgecombe M. Recovery of time estimation following moderate to severe traumatic brain injury. Neuropsychology. 2011;25(1):36–44.
7. Powell J, Heslin J, Greenwood R. Community based rehabilitation after severe traumatic brain injury: a randomised controlled trial. J Neurol Neurosurg Psychiatry. 2002;72:193–202.
8. Shakur H, Roberts I, Bautista R, CRASH-2 trial collaborators, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010;376:23–32.
9. Olivecrona M, Koskinen LO. The IMPACT prognosis calculator used in patients with severe traumatic brain injury treated with an ICP-targeted therapy. Acta Neurochir (Wien). 2012;154:1567.

10. Grigorakos L, Alexopoulou A, Tzortzopoulou K, Stratouli S, Chroni D. A predictors of outcome in patients with severe traumatic brain injury. J Neurosci Clin Res. 2016;1:1.
11. Martins ET, Linhares MN, Sousa DS, Schroeder HK, Meinerz J, et al. Mortality in severe traumatic brain injury: a multivariated analysis of 748 Brazilian patients from Floriano´ polis city. J Trauma. 2009;67(1):85–90.
12. McMillan TM, Teasdale GM, Weir CJ, Stewart E. Death after head injury: the 13-year outcome of a case control study. J Neurol Neurosurg Psychiatry. 2011;82:931.
13. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. Lancet Neurol. 2008;7:728.
14. Skolnick BE, Maas AI, Narayan RK, et al. A clinical trial of progesterone for severe traumatic brain injury. N Engl J Med. 2014;371:2457.
15. Wright DW, Yeatts SD, Silbergeit R, et al. Very early adminstration of progesterone for acute traumatic brain injury. N Engl J Med. 2014;371:2457.
16. Brain Trauma Foundation TBI Guidelines 2016. Guidelines for the management of severe traumatic brain injury, 4th ed. Neurosurgery 2016;3:p76.
17. Giacino JT, Whyte J, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. N Engl J Med. 2012;366:819–26.
18. 18. Secades Julio. Citicoline for the treatment of head injury: a systematic review and meta-analysis of controlled clinical trials. J Trauma Treat. 2014;4:227.
19. Zafronte RD, Bagiella E, Ansel BM, et al. Effect of citicoline on functional and cognitive status among patients with traumatic brain injury: Citicoline Brain Injury Treatment Trial (COBRIT). JAMA. 2012;308:1993–2000.
20. Brain Trauma Foundation TBI Guidelines 2016. Guidelines for the management of severe traumatic brain injury, 4th ed. Neurosurgery 2016;0:3
21. He J, Fan J, Geng S. Efficacy of cerebrolysin in acute brain trauma. Chin J Clin Pract Med. 2002;4:71–2.
22. Ko¨nig P, Wannders R, Witzmann A, et al. Cerebrolysin in traumatic brain injury—a pilot study of a neurotrophic and neurogenic agent in the treatment of acute traumatic brain injury. J Neurol Neurochir Psychiatr. 2006;7:12–20.
23. El Sayed I, Zaki A, Fayed AM, Shehata GM, Abdelmonem S. A meta-analysis of the effect of different neuroprotective drugs in management of patients with traumatic brain injury. Neurosurg Rev. 2018;41:427–38.
24. Muresanu DF, Heiss WD, Hoemberg V, et al. Cerebrolysin and recovery after stroke (CARS): a randomized, placebo-controlled, double-blind, multicenter trial. Stroke. 2016;47:151–9.

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4.1.2 ...in the treatment of diffuse axonal injury

Case Report

A 24-year-old man suffers from a vehicular collision with the seatbelt in place. His car was hit between the two left doors and the car spun. He had to be evacuated by firefighters and was intubated at the scene due to unresponsiveness. He arrived at the emergency room (ER) at 6 AM, his physical examination showed coma (Glasgow Coma Scale [GCS] 4/15), miotic pupils, decerebration posturing to painful stimuli and spontaneous hyperventilation. A CT scan showed changes compatible with diffuse axonal injury, which was confirmed by MRI (Figure 1).

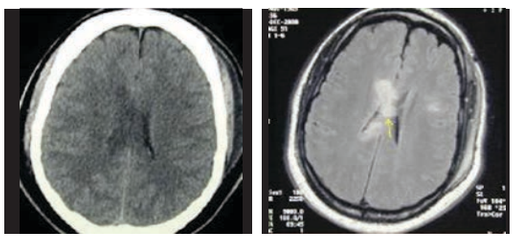

Figure 1 – CT scan and MRI showing lesions compatible with diffuse axonal injury (DAI). The arrow signals a shear lesion at the corpus callosum.

The patient was transferred to the intensive care unit (ICU). An intraparenchymal fiberoptic device was placed in the left parietal lobe for intracranial pressure (ICP) monitoring. He spent 45 days at the ICU during which he developed several medical complications including nosocomial pneumonia, septic shock, and a difficult weaning. He was transferred to a rehabilitation facility in a patent vegetative state with nocturnal mechanical ventilation requirements. He never developed seizures, had no symptoms of infections and normal laboratory values. We decided to administer Cerebrolysin 30 ml/day for 10 days. – the agent had only recently been approved by the Argentinian regulatory office (2012). Since we had no prior experience of its usefulness in TBI, we decided to use the dosage recommended in the literature. Diffuse axonal injury (DAI) had been traditionally considered an acceleration-deceleration injury resulting in widespread neuronal damage: small petechial haemorrhages in the corpus callosum and dorsolateral pons quadrants and axonal disruption (clusters and Wallerian degeneration) associated with brain edema, which could be seen on CT scan and MRI studies. Nevertheless, recent evidence has shown that DAI is present with any type of brain injury, focal or otherwise, and that it can be detected in more than 90% of TBI cases, especially in those patients dying immediately after TBI as well as those who remained in persistent vegetative state or severely disabled.

The cytoskeletal damage of DAI was initially assumed to occur rapidly, due to the transmission of shear forces throughout the brain. Modern research shows that tearing of the axons occurs

rarely; a progressive disruption of the axonal membrane is the norm, not only in severe but also in moderate and mild TBI cases. Mitochondrial disruption could play a central role in this process. Very recent evidence has pointed out that axonal damage and degeneration are not always associated with neuronal death, as it was assumed up to now. It may be possible for neurons to survive such insults and even attempt to regenerate, providing a further chance of recovery or intervention. This means neuroplasticity and neurotrophic action, which was indicative for the administration of Cerebrolysin.

A transcranial Doppler (TCD) was performed in order to establish cerebral blood flow velocities in the Circle of Willis and to calculate cerebral perfusion pressure (CPP) using Belfort´s formula (Figure 2). By the 7th day of Cerebrolysin administration the patient began to respond to simple orders (stick out your tongue, close your eyes) and could be weaned from nocturnal mechanical ventilation. A new TCD was performed, which showed a major improvement in blood flow velocities and CPP as compared to baseline (Figure 2).

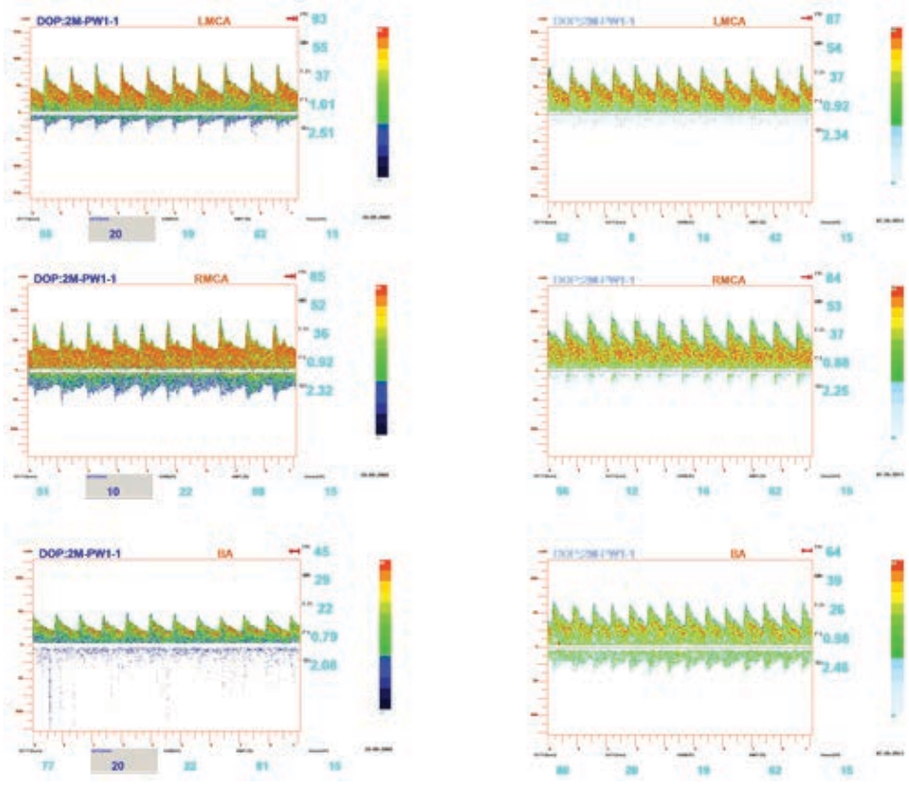

Figure 2 – Blood flow velocities after and before Cerebrolysin administration showed an improvement in diastolic velocities and in calculated CPP raising from 48 mmHg to 61mmHg.

On the 45th day after Cerebrolysin administration the patient was able to perform a MiniMental State Examination scoring 18/30. He also had pyramidal signs of the four extremities with a vicious position in flexion of both upper arms. After discussing with the patient's family, we decided to perform another Cerebrolysin treatment cycle with the 10 ml/day dosage for 21 days, the dose recommended for cognitive disorders, three months after the first administration. We also decided to administer botulinum toxin in the upper extremities and in the vocal cords. After the second Cerebrolysin treatment cycle the patient improved in the MMSE to 25/30 and a full cognitive battery was performed, including Benton´s test and verbal fluency (Figure 3). He also improved motor abilities, gained weight and muscular mass.

Occupational therapy was reinforced. A third Cerebrolysin treatment cycle was scheduled after another three months using the same dosage. Thereafter the patient improved his cognitive abilities, resulting in an MMSE of 28/30 (faults in recall) and improvement in Benton´s test and in verbal fluency (Figure 3).

Day	After Cycle 1	After Cycle 2	After Cycle 3
MMS	18	25	20
Benton (general efficiency)	NA	4	0
Verbal Fluency (mean/normal)	NA	7.5/18	13.5/18

Figure 3 – Cognitive evaluation

Conclusion

The patient's improvement was unexpected. He asked for a fourth Cerebrolysin treatment cycle because he felt a difference in cognitive functions and in mood after the third one. Due to the beneficial safety profile of Cerebrolysin and the possibility of cognitive improvement we agreed to this request. Although the patient felt better, he remained with recall failures. Nevertheless, he could return to work, not at his original position (casino croupier) but to an administrative one.

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4.1.3 ...in the treatment of severe traumatic brain injury and longterm follow-up

Case Report

The patient was a 20-year-old male student who suffered from a head injury during New Year's Eve 2014. He was admitted to the emergency room, where he presented with quantitative disturbances of consciousness with GCS sub-scores of 1/4, 1/5 and 2/6 and a total GCS of 4/15. A CT head scan showed an acute subdural haematoma in the right frontal area with a diameter of 7 millimeters as well as brain edema. The CT scan showed haemorrhagic foci in the left frontal lobe and the pons. A right-side craniotomy was performed on January 1st (Figure 1a). Hospital stay was otherwise uneventful.

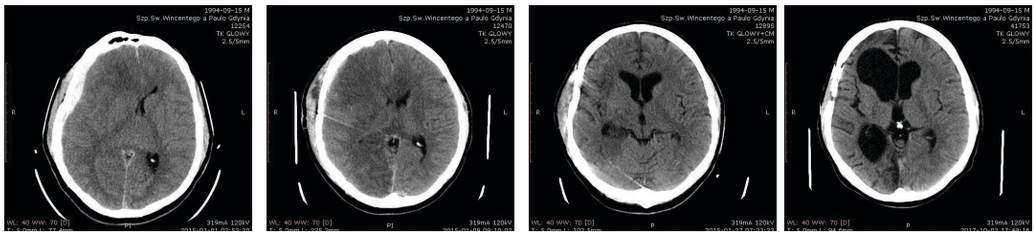

Figure 1 – CT head scans on January 1st, 2015 (a), January 9th, 2015 (b), January 27th, 2015 (c), and October 2nd, 2017 (d).

Nine days later, the patient was transferred to the surgical unit for further management. On admission the patient was alert, without verbal contact, but comprehended simple, verbal commands and performed voluntary movements with his right upper limb. Otherwise he was triplegic, with bilateral pyramidal signs. A control CT head scan (Figure 1b) was performed nine days after injury, showing a 5-millimeter residual subdural hematoma, focal brain edema and multiple hypodense areas in the right frontal, parietal and temporal lobes. Two weeks after injury, the patient was transferred to the local neurorehabilitation unit by a neurologist. His neurological status was stable, he was alert, performed only simple tasks, the right upper limb was fully operational, other limbs were plegic with bilateral pyramidal signs. Treatment with Cerebrolysin was initiated at a daily dose of 30 ml, lasting for 37 days. The patient was bedridden without the ability to maintain an upright position. He required personal assistance in performing activities of daily living. A psychological examination showed significant behavioural control deficits, which prevented assessment of the Mini-Mental State Examination (MMSE).

At discharge, three months after injury, the patient's condition had gradually improved. He presented with a slightly spastic left upper limb and right pyramidal signs. He was fully ambulatory and completely independent in his activities of daily living. Psychological

examination showed a significant improvement in cognitive abilities, scoring 28 points in the MMSE. His behaviour increasingly adjusted to his current life situation including adequate emotional reactions. However, impulsivity and a slight mood deterioration persisted due to his limitations.

During the following year, further improvement in motor functions has been achieved as outpatient treated by a multidisciplinary team (psychologist, speech therapist, physiotherapist). To further improve instrumental activities of daily living (IADL) the patient participated in psychological therapy for another 12 months. Currently, the patient is completely independent and has started working.

Case 2

A 66-year-old male patient with a history of hypertension suffered from head injury caused by a car accident on July 16th, 2017. Six weeks later, the patient was admitted to the neurosurgery unit. He was conscious, with full verbal contact. He scored 15 points in the GCS but complained about headaches; he scored 8 out of 10 in the visual analog scale (VAS). Furthermore, he also reported a subjective weakness in the lower limbs. The patient was diagnosed with bilateral subdural haematomas (Figure 2a) and was subjected to bilateral craniotomy.

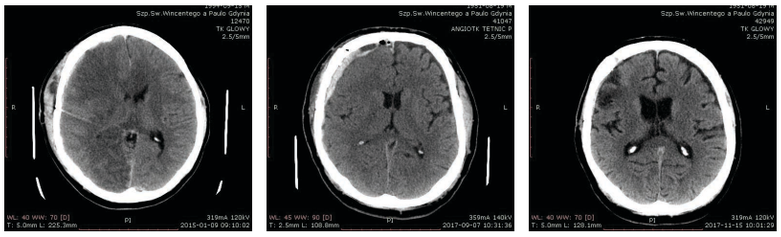

Figure 2 – CT head scans September 2nd, 2017 (a), 7th September, 2017 (b), 15th November, 2017 (c).

While staying in the neurosurgery unit for four days a single epileptic seizure occurred. Following collective epileptic seizures, the patient was seen by a neurologist and finally transferred to the neurology department. On admission he presented with quantitative disturbances of consciousness, was drowsy with a psychomotor downturn, oriented to time and place. Dysarthria and central lesions to the left facial nerve were present. The patient was quadriparetic (MRC 3/5) with decreased muscle tone in all limbs. A control head CT scan (Figure 2b) showed bilateral hematomas in the fronto-temporal areas. The patient was treated with valproic acid at a daily dose of 2000 mg to control the seizures. In addition, Cerebrolysin was administered at a daily dose of 30 ml for 29 days. Furthermore, the patient received rehabilitation therapy due to fluctuating qualitative and quantitative disturbances of consciousness, mainly escalating in the evening.

During the second week of hospitalization, the patient was auto- and allo-psychically disoriented. Occasionally, he was delusional. At night, IV infusions of benzodiazepines were sometimes required. During the day, the patient presented with attention disturbances, slurred speech, periodic disinhibition, and variability in affect and motivation. On discharge he needed continuation of psychological therapy. He was able to walk with crutches and required

assistance with ADL. About two months after craniotomy, the patient was re-hospitalized. A control CT scan (Figure 2c) showed a regression of brain haematomas and cerebral oedema. On neurological examination he presented left-sided pyramidal signs and psychomotor downturn. The patient required assisstance with IADL. No certain epileptiform waves were recorded in the EEG. He received valproic acid at a 2000 mg daily dose; no epileptic seizures have been observed.

Nine months after the injury, the patient continues neuropsychological therapy, remains independent in his ADL and plans to return to work.

Conclusion

These two cases both highlight the importance of the long-term therapy with Cerebrolysin - 37 days and 29 days respectively. We observed continuous and dynamic improvement over the course of treatment, and we associated functional recovery with the administration of Cerebrolysin. Patients treated in our institution for similar forms of TBI and who do not receive Cerebrolysin generally recover more slowly and most of them cannot regain a satisfactory status of independence. Thus, we consider Cerebrolysin as a rational choice for pharmacotherapy in severe TBI patients which is also documented by the two cases presented above.

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4.1.4 ...in the treatment of severe traumatic brain injury caused by a bullet wound

Case Report

A male patient, 21 years old, college student, right-handed, with a history of moderate alcohol and tobacco consumption since the age of 18. The patient suffered a head gunshot wound on June, 2014 with an entrance hole in the right temporal region and an exit orifice in the left parietal region (Figure 1). The initial Glasgow Coma score is unknown. It did not require neurosurgical treatment and was treated for two weeks in the intensive care unit also performing gastrostomy and tracheostomy. The patient did not present seizures during this acute phase. He was admitted four months later to the neurological rehabilitation area. The physical examination showed minimally conscious state (MCS): he only obeyed some simple commands, had visual tracking, and emitted only some monosyllables. The gag reflex was severely diminished, and he presented spastic quadriparesis with predominance to the left limbs, he was unable to walk, and incontinence of both sphincters was present. At admission he presented with a Barthel Index of 0/100, FIM (Functional Independence Measure) of 1/126, and DRS (Disability Rating Scale) of 20 (extremely severe disability); it was not possible to assess the MMSE. In the conventional digital EEG, there was no anteroposterior gradient, alpha activity (8-9 Hz) of low voltage (20 µV) was observed, with slow focal activity (5-6Hz) in central and parietal regions, with some left frontal and temporal spikes that indicated focal cortical hyperexcitability (Figure 2).

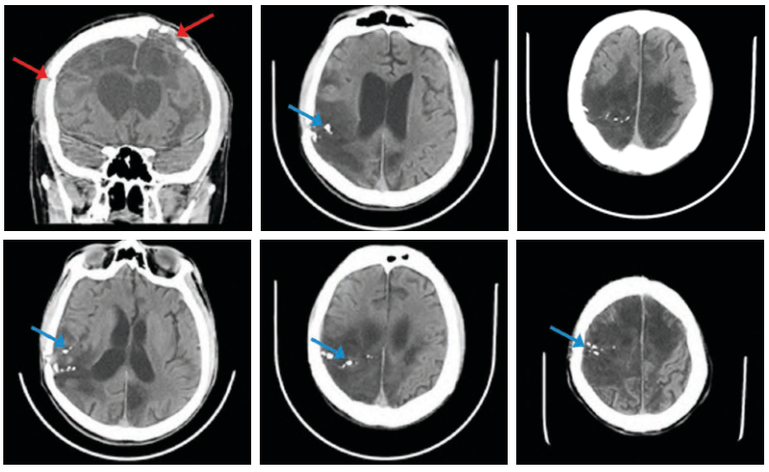

Figure 1 – Standard CT scan with a very large area of frontal and parietal encephalomalacia with right predominance; also, compensatory ventricular dilation and the presence of bone fragments at multiple sites of the lesion (blue arrows). The entry and exit sites of the projectile in the skull (red arrows) are also shown.

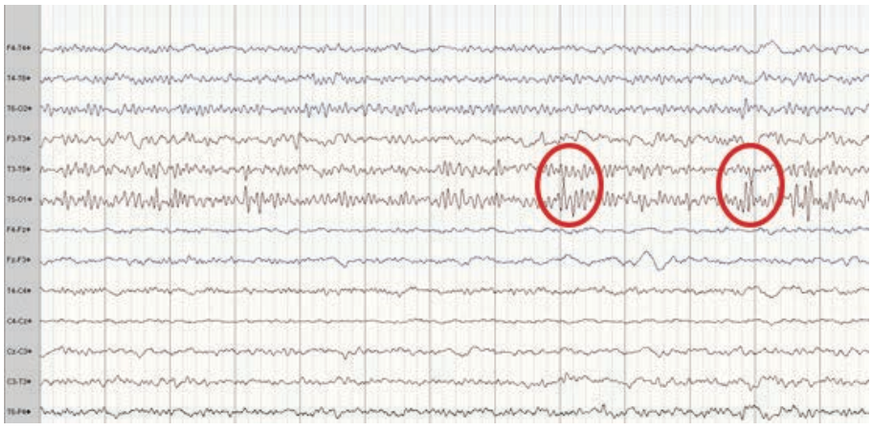

Figure 2 – The EEG trace showed some spikes in the left temporal derivations (T5)

The patient was hospitalized for an intensive rehabilitation program for four weeks, and during his stay, Cerebrolysin 50 ml was administered intravenously once a week for four weeks, as adjuvant treatment to rehabilitation. Simultaneously he received an integral neurological rehabilitation program, composed of physical, occupational, respiratory, swallowing and language therapies, as well as multidisciplinary treatment. At the end of his hospital stay a significant improvement was observed, especially in his state of alertness, attention and cognitive functions. The patient began to present spontaneous language, demonstrated better language comprehension and started to use some instruments of daily life; for this reason, it was considered that he had emerged from the MCS according to established criteria. At discharge the Barthel Index was 10/100, the FIM Scale was 33/126, the MMSE was 22/30, and the DRS was 11 (moderate severe disability). In the control EEG, an increase in the base rhythm (9-10 Hz) and an increase in voltage (40µV) were also observed.

Due to excellent therapeutic response, a new treatment cycle with Cerebrolysin was scheduled five months later with the same administration regimen (50 ml once a week for 4 weeks), but before its second administration the patient presented a focal seizure secondarily generalized; treatment with levetiracetam 1gr every 12 hrs was initiated and it was decided to continue with the application of the second cycle of Cerebrolysin with no complications reported. The patient continued to improve especially in the cognitive domain and received three additional cycles of Cerebrolysin administration every 4 to 6 months without any complications. The patient has not presented further seizures and has currently a Barthel Index of 50/100, a FIM of 66/126, an MMSE of 27 points (persisting anterograde amnesia), and a DRS score of 6 points (moderate disability).

Conclusion

This patient with sequelae of traumatic brain injury experienced a remarkable neurological recovery after combining conventional neurological rehabilitation and administration of Cerebrolysin, especially in the cognitive domain as well as in the activities of daily living. This treatment was safe and well tolerated despite a previously controlled post-traumatic epilepsy.

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4.1.5 ...in severe pediatric traumatic brain injury

Case Report

A 12-year-old female patient was admitted to the emergency department one hour after a motorcycle accident. There was no significant medical history, no tobacco, alcohol, or recreational drug use history. Her familial medical history was not assessed due to mass casualties. Neurological examination showed no spontaneous eye opening, no verbal response, no motor response. Her Glasgow coma scale (GCS) score was E1 (no spontaneous eye opening), M1 (no motor response), V1 (no verbal response), pupil right 5 mm left 4 mm fix dilated and no brain stem reflex. Vital signs and blood samples showed no abnormalities. The non-contrast CT scans (Figure 1) showed an acute subdural haematoma in the right temporal and frontal area and a hemorrhagic contusion, a right temporal and sulcus effacement in the right temporal and parietal regions with right uncal herniation with diffuse brain ischaemia and brain stem infarction due to hypoxia

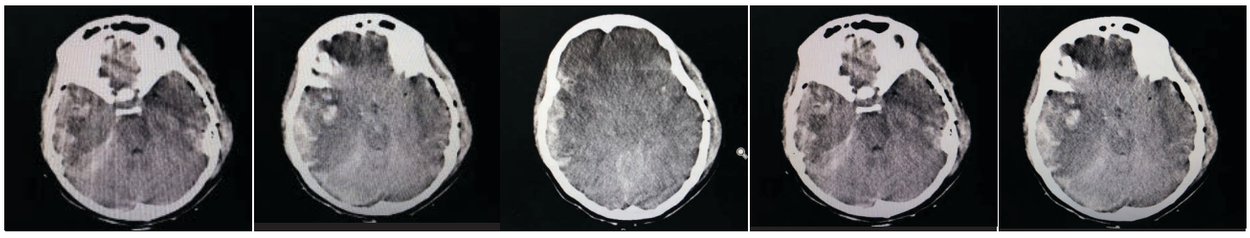

Figure 1 – The non-contrast CT scans showed an acute subdural haematoma in the right temporal (B) and frontal (A) area and a hemorrhagic contusion (C), a right temporal and sulcus effacement in the right temporal and parietal regions with right uncal herniation with diffuse brain ischaemia (D) and brain stem infarction due to hypoxia (E)

After consultation with the neurosurgery department, this patient was sent for a right wide craniectomy with clot removal and duraplasty emergency. In the post-op-period her GCS remained E1 (no spontaneous eye opening), M1 (no motor response), Vt (verbal cannot be evaluated due to endotracheal intubation), pupil right. 5 mm, left. 4 mm fix dilated and no brain stem reflexes. Vital signs and blood samples showed no abnormalities. In the critical care period, we treated her with intravenous (IV) mannitol, antifibrinolytics, antiepileptic drugs and analgesics and avoided hypoxia and hypotension. A few days after surgery her GCS improved to E1 (no spontaneous eye opening), M4 (motor response with withdrawal from pain), Vt (verbal cannot be evaluated due to endotracheal intubation), pupil right. 5 mm, left. 4 mm fix dilated but now with brain stem reflexes. Vital signs and blood samples showed no abnormalities. After her GCS score showed signs of slight improvement, we started IV treatment with 50 ml Cerebrolysin once daily for the next 10 days. On day 7 her GCS improved to E1, M5 and Vt, pupil right. 5 mm, left. 4 mm fix dilated. We successfully performed a

tracheostomy to enhance the probability to wean her off the ventilator; afterwards her GCS improved to E3, M5 and Vt. At discharge on day 30 her mRS was 4. Rehabilitation was continued for three months, thereafter, her mRS improved to 3.

Conclusion

Cerebrolysin has been widely used as a neuroprotective and neurorecovery enhancing agent in closed head injury. However, as add-on therapy in severe head trauma patients undergoing craniectomy surgery no clinical results have been reported so far. The encouraging results of the patient documented above demonstrate a potential benefit for the add-on therapy with Cerebrolysin after craniectomy surgery, but further studies are needed to confirm these results.

Chapter 5

DISORDERS OF CONSCIOUSNESS

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Chapter 5.1

The role of Cerebrolysin...

Disorders of consciousness are often directly induced by cerebral injury and are associated with the subsequent reduction of cerebral tissue perfusion. Disorientation and psychological deficits are also extensions of cerebral vascular dysfunction and brain tissue damage. Although to our knowledge experimental laboratory studies on the use of Cerebrolysin to treat such disorders have not been performed, the known effects of the drug on enhancing tissue perfusion and brain plasticity would warrant clinical investigations on the multiple sources of disorders of consciousness. Importantly, Cerebrolysin increases parenchymal and vascular cell levels of tissue plasminogen activator (tPA). Recombinant tPA has been employed for thrombolysis, e.g., for myocardial infarction and stroke.

However, endogenous tPA plays an essential role in mediating brain plasticity and neurite outgrowth. The observation corroborates that tPA is highly active in the developing brain and facilitates the essential plasticity required for cerebral structural development. Cerebrolysin by inducing tPA, via the morphogen and developmental transcription factor SHH, thus has an ontogenous effect on the injured mature brain fostering plasticity and neurite growth and neurite connections which may ameliorate disorders of consciousness. Low tissue perfusion, as noted, may also promote disorders of consciousness and dementia-like symptoms. The reduced tissue perfusion may also be somewhat attributed to microvascular thrombosis and fibrin deposition, which may be reduced by enhancing the endogenous cellular levels of tPA. Furthermore, the concurrent upregulation by Cerebrolysin of Angiopoietin 1 would work cooperatively with tPA to generate highly functional and intact microvasculature, which may reduce disorders of consciousness.

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5.1.1 ...after cardiac arrest

Case Report

A 57-year-old male patient suffered from cardiac arrest at an airport. He was resuscitated after a 20-minute-cardiopulmonary resuscitation (CPR), however, hypoxic brain injury (HBI) secondary to cardiac arrest resulted in a decreased level of consciousness. After hypothermia therapy for HBI for 12 days, he was transferred to a university hospital for further treatment. Five months later, he was admitted to the department of rehabilitation for comprehensive rehabilitation therapy. At the time of admission, he was stuporous, responding only to painful stimuli and suffered from spasticity in all extremities (upper extremities - grade 1 to 2 according to the Modified Ashworth Scale [MAS], lower extremities - grade 2 to 3 according to MAS). The patient was treated with Anorex 50 mg and Bacron 5 mg three times a day as anti-spasmodic agents. In addition, Orfil syrup 420 mg and Rivotril 0.5 mg three times a day, and Keppra solution 1000 mg twice a day were also administered as antiepileptics.

On the day of admission, 156 days after cardiac arrest, the total score of the initial Coma Recovery Scale - Revised (CRS-R) was 6 and the patient was responding locally to noxious stimuli. Three days later, treatment with Cerebrolysin 10ml IV twice daily started. An EEG performed on the next day did not show any epileptiform discharges.

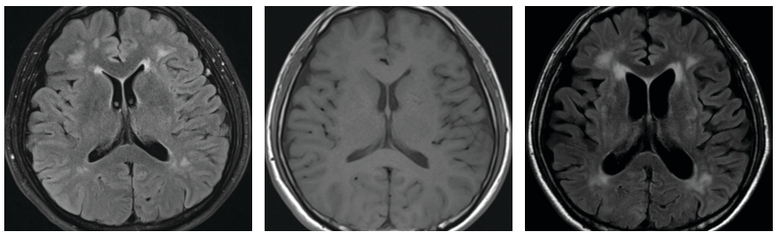

Figure 1 – Left: brain MRI (T2 FLAIR) taken at 2013.7.2 (premorbid); Middle: brain MRI (T1) taken at 2015.3.11 (4th day after the onset of illness); Right: brain MRI (T2 FLAIR) taken at 2015.5.1 (55th day after the onset of illness) showing prominent brain atrophy

On the fourth day of Cerebrolysin administration, the CRS-R increased to 10 and the patient was able to fix his eyes on a target. On the 11th day he started to make verbal output (CRS-R 11), and on the 28th day the patient was able to visually pursue targets (CRS-R 12).

Conclusion

This patient responded quickly to a Cerebrolysin supported therapy and improved remarkably his consciousness level. As therapy was started five months after cardiac arrest, recovery enhancing effects of Cerebrolysin might have contributed to this treatment success, which should be addressed in further studies.

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5.1.2 ...in the treatment of acute brain hypoxia secondary to cardiac arrest

Case 1

A 59-year-old female patient was brought to the Emergency Room by emergency medical service after cardiac arrest with a systolic cardiac arrest at home and successful resuscitation. The patient was intubated by the emergency medical service and ventilated by bag valve mask with passive oxygen therapy. Administered medications: adrenaline, atropine. In the ECG done at the ER, a discrete elevation of ST in the II, III, and VF leads was apparent. She was admitted to the Intensive Care Unit (ICU) in critical condition. Deeply unconscious, GCS 3 points, extensional spasms, narrow pupils, with delayed pupillary light reaction. Respiratory function was insufficient, she required mechanical ventilated on. Circulation unstable, HR 110/min, BP initially 140/80 mmHg and then 90/60 mmHg. Features of ischemia of the cardiac muscle in the ECG. Head CT was done. In the laboratory tests demonstrated high D-dimer concentrations as well as elevated creatinine and potassium levels. Resonium was administered. Treatment with amantidine 200mg/day, Cerebrolysin 30ml/day, piracetam 12g/day, as well as antithrombotic-, sedative- and bronchodilative agents was pursued as needed.

The result of the head CT on day one showed a focus of encephalomalacia in the caudate nucleus on the left side. Apart from that, the cortex presented with no other malatic changes. The ventricular system was placed midsagitally with normal width and symmetry. No signs of intracranial bleeding and no signs of fractures were detected. Passive rehabilitation started in the Intensive Care Unit on day 3. On day 6 the dose of piracetam was doubled (2x12g) and the doses of amantidine (200mg) and Cerebrolysin (30ml) were kept at the initial level. This treatment regimen was maintained until the end of hospitalisation in the ICU. On day 10 the patient's verbal communication became coherent. On day 12, the patient was taken off the respirator and extubated.

The patient stayed in the ICU for 13 days, and subsequently moved to the neurological department in a cardiovascularly and respiratorily stable and greatly improved condition with verbal communication. In the neurological unit the patient stayed for 17 days. At discharge, the patient presented with improvements of the neurological state and psychomotor functions, sphincter control, and independent feeding. The patient walked independently with minor support. Bilateral blindness with light sensitivity and colour recognition was still present.

Case 2

A 42-year-old female patient was admitted to the ICU after sudden cardiac arrest following ventricular fibrillation and resuscitation before arriving at the hospital. The anamnesis showed mitral valve regurgitation, ventricular arrhythmia. The general condition was very severe: the patient was unconscious, with a GCS score of 4-5 points, symmetric pupils, widened with delayed light reaction. Spastic tetraplegia and decerebrated flexion were present. The Babinski sign was absent bilaterally. Respiratory function was insufficient (the patient was ventilated mechanically) and she had an irregular cardiac rhythm for approximately 120/min with blood pressure 100/60 mmHg and the presence of numerous additional ventricular systoles. Laboratory investigations showed increased Troponin I, CK-MB, D-dimers, transaminases, CRP and leukocytosis. Head CT showed features of early brain edema.
The patient was mechanically ventilated for 7 days, followed by a tracheostomy (Griggs method), right pleura catheterisation (after iatrogenic pneumothorax) for 13 days, antibiotic treatment (at first empiric, later targeted), Clexane, Plavix, Polocard, Cordarone, Vivacor, Furosemide, Mannitol, Sedative drugs, Nootropil 12mg/day IV for 8 days and then 2x12mg/day PO (23 days), Amantix 200mg/day IV (23 days), Cerebrolysin 30ml/day (18 days). Bedside rehabilitation was initiated on day 7. The patient was released to the cardiology ward after 23 days of treatment in the ICU in good general condition. The patient presented conscious, logical verbal communication was possible with occasional non-logic periods.

The GCS score was 13, without paresis and with adequate circulatory and respiratory function.

Case 3

A 65-year-old male patient was admitted to ICU from ER after sudden cardiac arrest and long-term resuscitation. Respiratory and circulatory functions were insufficient. The anamnesis showed:

- state after acute coronary disease NSTEMI in April 2007, angioplastic surgery of left circumflex coronary artery.
- state after infarction of lower cardiac wall.
- arterial hypertension.

The patient was intubated in the emergency room. In the intensive care unit, the patient arrived deeply unconscious, GCS 3 with narrow, equal, reactive pupils. His heart rate was regular but rapid with approximately 150 beats/min. He was connected to life support and ventilated mechanically in SIMV FiO2 mode 1.0-0.7. Tetraparesis was observed. The Babinski sign was absent bilaterally. ECG showed features of acute coronary disease, high values of CK-MB as well as troponin I. Brain CT without contrast showed bilaterally inhomogeneous hypodense areas in the frontal lobes, no indication of pre-existing diseases and traumas, as well as generalized obliteration of grooves between brain curves especially around temporo-occipital region and cerebellum. No evidence of freshly extravasated blood was found. Ventricles were not compressed, not enlarged, not repositioned. Median structures were not repositioned. Post-traumatic skeletal changes were absent. Segmental thickening of frontal sinus's mucus was present. Left-sided curvature of nasal sinus with presence of bone spurs

(exostosis) was also observed. Mechanical ventilation was followed by administration of neurorestorative and neuroprotective treatment with Cerebrolysin 30ml/day IV, piracetam 12g/day IV, amantadine 200mg/day IV) and sedation with midazolam as needed. Cordarone, Vivacor, Palvix, Polocard, Clexane, Ebrantil, Tertensif SR, Piramil, Spironol, Furosemide, Diben, Aminoacids, SmofKabiven, Biofuroxym, Tienam, Lacidofil, Adiphos, Crystalloids. The patient was extubated on day 7 with good skills, he was able to follow commands and to answer basic questions.

On day 8, another sudden cardiac arrest (PEA mechanism) occurred. Resuscitation was performed and resulted in recovering cardiac haemodynamic function. The patient was reintubated and connected to life support again.

Due to prolonged intubation a tracheotomy was performed on day 18 of hospitalisation. During hospitalization, the patient had three cardiological and three neurological consultations. On his last two days, piracetam was discontinued. Cerebrolysin (30ml) and amantadine (200mg) were administered during the whole course of hospitalisation.

The patient was discharged from the ICU after 33 days and transferred to the neurology ward in a generally improved condition, with adequate respiratory and circulatory functions, conscious with superficial logical communication.

He was hospitalised in the neurology ward for 15 days. Administration of piracetam and amantadine were discontinued during last two days. Cerebrolysin (30ml/day) was maintained throughout the whole duration of stay at the neurology ward. The patient was lying, conscious, without verbal communication (total aphasia), with inability to follow commands, periodical psychomotor hyperactivity, tetraparesis, and presented Babinski sign on the right side. Physical rehabilitation was carried out and laboratory tests showed a significant increase in troponin levels.

The patient was transferred to the cardiology ward where he was mechanically ventilated for seven days, followed by a tracheostomy (Griggs method), right pleural catheterisation (after iatrogenic pneumothorax) for 13 days, antibiotic treatment (at first empiric, later targeted), Clexane, Plavix, Polocard, Cordarone, Vivacor, Furosemide, Mannitol, Sedative drugs, Nootropil 12mg/day IV for 8 days and then 2x12mg/day PO (23 days), Amantix 200mg/day IV (23 days), Cerebrolysin 30ml/day (18 days). Bedside rehabilitation was initiated on day seven.

The patient was discharged to the cardiology ward after 23 days of treatment in the ICU in good general condition. The patient presented conscious, logical verbal communication possible with occasional non-logic periods. The GCS score was 13, with no paresis and adequate circulatory and respiratory function.

Conclusion

Since many years optimal standards for procedures and pharmacotherapy are under discussion that aim for improving functionality of neural cells affected by hypoxia from various causes. We have been using neuroprotective agents such as amantadine, piracetam and other agents

in our practice for many years with reasonable success. Recently, we have added Cerebrolysin to our standard treatment regimen for patients suffering from brain damage following severe hypoxia with the intend to stimulate neurorecovery and neurorestoration in addition to the standard neuroprotective regimen. Here we presented three cases, which in our opinion represent a spectacular and highly satisfactory therapeutic outcome in view of the poor initial prognosis. The cases illustrate the effects we typically achieve in our clinic with our new standard treatment regimen Cerebrolysin, piracetam and amantadine. Our previous neuroprotective regimen typically resulted in a reasonably good clinical outcome in most cases, however, after adding Cerebrolysin we were able to see such a spectacular recovery in patients with severe brain hypoxia who typically have a very poor clinical prognosis. We are aware that for a reliable confirmation of our observations, long-term and well-planned controlled studies are required. Furthermore, a head-to head comparison of the individual components of our treatment regimen would help to assess their individual effects and to determine any synergistic effect by combining neuroprotective and neurorestorative treatments.

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5.1.3 ...in the treatment of delirium & cognitive complications

Abstract

A 68-year-old male patient with a medical background of atrial myxoma operated 10 years ago, definitive pacemaker, and mild cognitive amnesic impairment due to cerebrovascular disease (leukoaraiosis, ventricular enlargement with Evans´ Index of 0.29) was admitted to the medical Intensive Care Unit (ICU) with a diagnosis of community acquired pneumonia. He developed respiratory failure, so he was placed on mechanical ventilation for 12 days and received standard care, including intravenous antibiotics, sedoanalgesia with fentanyl and midazolam and muscular blockage with vecuronium. During his ICU stay he developed mixed delirium for at least four days. He was weaning from the ventilator on day 13 after admission with muscular weakness of the four limbs. It was interpreted as ICU-acquired weakness that includes critical illness polyneuropathy and critical illness myopathy. A differential diagnosis using needle electromyography was not possible due to the pacemaker. The patient was evaluated according to the Medical Research Council scale as grade 4 over 5 (movement against moderate resistance over full range of motion). The patient was sent to a rehabilitation facility in which he stayed for three months, improving his muscular weakness up to a normal state. However, his wife noted a worsened cognitive status, which was the reason we were consulted. His neurological examination was normal but with signs of wasting syndrome. His Mini Mental State Examination (MMSE) score was 25/30, with failures in orientation, memory and calculation. A complete neuropsychological evaluation showed verbal and visual memory impairment (Rey Auditory Verbal Learning Test [RAVLT]; z score – 1.8) as well as attention deficits (Trail Making A; z score -3.71) and executive function problems (Trail Making B; z score – 2.8), with a score of 0.5 in the Clinical Dementia Rating (CDR), which previously was 0.

Our diagnosis was cognitive impairment after critical care. We decided to perform a diffusion tensor imaging with tractography, which showed a reduction of the fibers of the superior longitudinal fascicles, cingulate beams and optical radiations to predominance of the left as well as a reduction of the fibers of the corpus callosum (Figure 1).

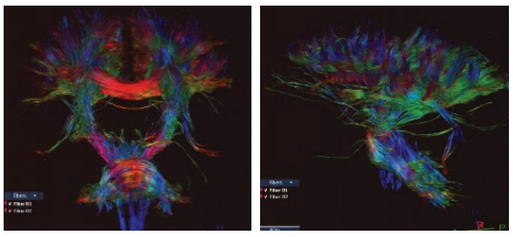

Figure 1 – Diffusion Tensor Imaging (DTI). DTI is an MRI-based neuroimaging technique which allows estimating the location, orientation, and anisotropy of the brain's white matter tracts. Starting from a seed region of interest (ROI), generally defined manually, the fiber tracking algorithm looks for adjacent voxels whose main diffusion direction is in the continuity of the previous one. In the left image the arrow shows a reduction of the fibers of the corpus callosum. In the right image the arrows show a reduction of the fibers of the optical radiations.

Treatment with donepezil (5 mg/day p.o.) and a neurocognitive rehabilitation program were started. The patient developed intestinal intolerance, so we changed to rivastigmine patches, which were well tolerated. After three months of treatment the patient showed no improvement, so we offered to administer Cerebrolysin taking into account the profile of this patient. We explained to the family the benefits reported in the literature and our own experience in demented patients, which showed a four points improvement in MMSE after Cerebrolysin administration. The dosage was 10 ml/day i.v. for 21 days and the patient continued with rivastigmine patches and neurocognitive rehabilitation. Two months after Cerebrolysin administration the neurocognitive evaluation was repeated and showed a marked improvement in the MMSE (30/30), in the RAVLT (z score 0.38) as well as in the Trail Making A (z score -0.08). Executive function remained impaired (Trail Making B, z score – 2.9). CDR improved to 0. This improvement persisted after one year of rehabilitation.

Conclusion

This type of dementia – cognitive impairment after critical care – is more frequently observed nowadays. Advancement in the treatment of critical illness over the last 30 years has resulted in reduced mortality and millions of patients who survive a critical illness. Cerebrolysin has shown beneficial effects on cognitive impairment of patients after critical care, thus, further studies should be performed with Cerebrolysin in this type of dementia.

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5.1.4 ...in the treatment of disorders of consciousness after subarachnoid haemorrhage

Abstract

A 55-year-old male patient was admitted to the emergency department due to severe headache and seizures. His initial CT scan with angiography showed a subarachnoid and intraventricular haemorrhage with a ruptured anterior communicating artery (ACA) aneurysm. His co-morbidities were significant; he suffered from hypertension, dyslipidemia, and type II diabetes. After his transfer to the neurosurgery department he received emergency coil embolization of the ACA aneurysm. On the same day he received an external ventricular drainage due to recurrent haemorrhage and aggravation of hydrocephalus and started to be managed in the neurological ICU. After two months of onset, a ventriculo-peritoneal shunt insertion was done due to uncontrolled ventriculomegaly.

After three months of onset, he was transferred to the department of rehabilitation medicine and received standard comprehensive rehabilitation treatment. His Coma Recovery Scale-Revised (CRS-R) score was 12 with the following subscores: auditory function 3, visual function 4, motor function 1, oromotor function 1, communication 1, and arousal 2, corresponding to Minimally Conscious State (MCS) of the CRS-R. The Korean version of the Mini-Mental State Examination (MMSE-K) was not assessable because of his impaired consciousness. Motor strength was evaluated at 2 to 3 grade on the British Medical Research Council Scale upon pain stimulation.

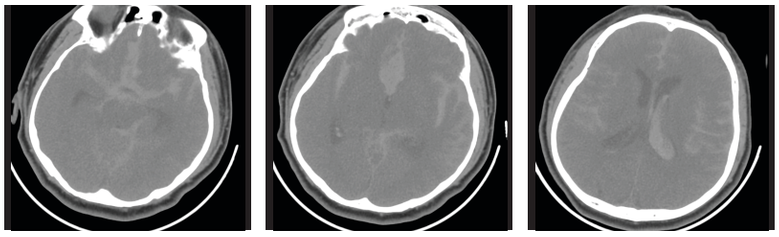

Figure 1 – Initial CT scan showing subarachnoid and intraventricular haemorrhage

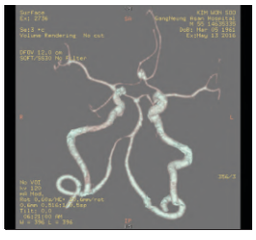

Figure 2 – Initial CT angio scan showing ACA aneurysm

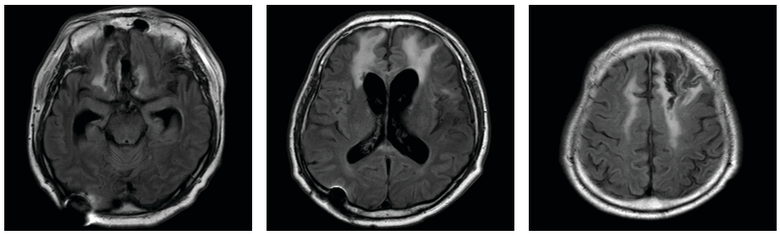

Figure 3 – MRI scan in T2 FLAIR sequence performed three months after onset showing encephalomalacia in bilateral frontal lobes with enlarged ventricles.

Three days after transfer to the department of rehabilitation medicine, Cerebrolysin was administered intravenously at a dose of 10 ml daily for 20 days. Cerebrolysin was diluted with normal saline and a total 100ml volume was infused over 20 minutes.

At discharge, seven weeks after initiation of Cerebrolysin treatment, the patient's total CRS-R score was 22 with the following sub-scores: auditory function 4, visual function 4, motor function 6, oromotor function 3, communication 2, and arousal 3. Thus, according to the criteria of CRS-R, the patient has emerged from MCS. He achieved a total MMSE-K score of 5 and he finally was able to obey to two-step verbal commands.

Conclusion

Cerebrolysin markedly improved the consciousness level and cognitive function of the patient.

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5.1.5 ...after intracranial haemorrhage

Case Report

A 41-year-old man without relevant medical history did not wake up in the morning and he had signs of vomiting around him. He was immediately brought to the emergency room and was found to be in stuporous condition responding only to painful stimuli. He was diagnosed with an intracranial haemorrhage in the left frontal lobe, combined with subarachnoid haemorrhage secondary to rupture of left posterior communicating artery aneurysm. He underwent coil embolization and surgery of craniectomy and haematoma evacuation at the day of onset. After postoperative monitoring in the intensive care unit, he was transferred to the department of rehabilitation for comprehensive rehabilitation therapy 28 days after the incidence. On the day of transfer, the total score of CRS-R was 8 (auditory function scale - 2, visual function scale - 2, motor function scale - 2, oromotor/verbal function scale - 0, communication scale - 1, and arousal scale - 1), which meant that he was barely able to fix his eyes on a target. He also showed definite sleep cycle. Keppra 500mg was administered as anti-epileptics twice a day.

On the 38th day after onset (Oct 30, 2018), Cerebrolysin (10ml IV, twice a day at 6AM and 6PM) treatment was started. Three days after the initiation of Cerebrolysin treatment, he began to raise his hands up to his head, which had not been observed before.

On the 7th day of Cerebrolysin administration, he started to reach objects purposefully with his arms (total score of CRS-R was 15 [auditory function scale - 3, visual function scale - 4, motor function scale - 3, oromotor / verbal function scale - 1, communication - 1, arousal scale – 3]).

On the 14th day of Cerebrolysin administration, he started to use the objects functionally, which meant that he had emerged from minimally conscious state.

On the 25th day of drug administration, the total score of CRS-R improved to 20 (auditory function scale - 4, visual function scale - 4, motor function scale - 6, oromotor / verbal function scale - 1, communication - 1, arousal scale - 3).

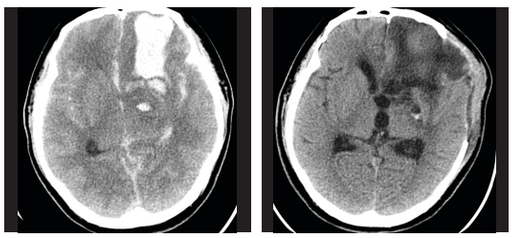

Figure 1 – Left: brain CT taken at 2018.9.23 (the day of illness onset); Right: brain CT performed at day 30 after onset and surgery.

Conclusion

This patient showed a clinically remarkable improvement of his level of consciousness during Cerebrolysin treatment. This therapeutic approach seems promising and should be assessed in a larger population.