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Webinar EVER Pharma

Is there sufficient evidence to include Cerebrolysin into treatment algorithms in AIS?

March 18, 2025

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Webinar EVER Pharma (March 18, 2025)

Is there sufficient evidence to include Cerebrolysin into treatment algorithms in AIS?

MODERATOR

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EXPERTS

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INTRODUCTION

Acute Ischemic Stroke (AIS) remains a leading cause of disability and mortality worldwide, necessitating continuous advancements in treatment strategies. Cerebrolysin, a neuropeptide-based drug, has gained attention for its potential cytoprotective effects in AIS management. However, is there sufficient evidence to include Cerebrolysin into treatment algorithms in AIS, therefore facilitating its clinical use routinely?

This webinar aimed to evaluate the current scientific and clinical data supporting Cerebrolysin's role in AIS treatment. Two experts, Dr. Sławomir Michalak and Dr. Yakub Krespi, presented insights on Cerebrolysin's mechanisms of action, clinical trial outcomes and real-world applications.

Introduction by Dr. Andrei Alexandrov

Prof. Andrei Alexandrov opened the webinar by emphasizing the growing evidence supporting the inclusion of Cerebrolysin in treatment algorithms for acute ischemic stroke. He highlighted several published clinical trials demonstrating that early use of Cerebrolysin improves:

- **Motor functions**
- **Aphasia**
- **Activities of daily living**
- **Overall quality of life**

These trials have contributed to Cerebrolysin's inclusion into European guidelines, particularly for patients with moderate to severe stroke (NIH Stroke Scale score ≥ 8). The recommendation is to administer Cerebrolysin within the first week after stroke to maximize its benefits (Figure 1).

A major topic of discussion was whether Cerebrolysin could be incorporated into routine treatment during the hyperacute/acute phase of stroke.

Prof. Alexandrov highlighted that thrombectomy is one of the most effective reperfusion therapies, with a low number needed to treat. However, he emphasized that while thrombectomy significantly improves outcomes, there is still room for improvement because only about 50% of AIS patients reach a favorable day 90 outcome. This applies particularly to patients experiencing hemorrhagic complications – even if they are asymptomatic. Additionally, these complications can limit secondary prevention strategies in the subacute and chronic phases of stroke recovery.

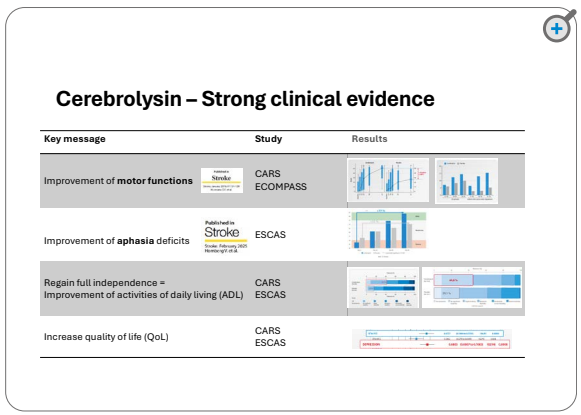

Figure 1: Overview of published clinical trials demonstrating improvements in motor function, aphasia, activities of daily living and quality of life with early administration of Cerebrolysin.

Why wait to protect the brain when providing reperfusion therapy?

He suggested that when administering reperfusion therapy (such as **thrombectomy or thrombolysis**) to stroke patients, it is essential to consider:

- **Protecting the blood-brain barrier**
- **Reducing hemorrhagic complications**
- **Maximizing the effectiveness of reperfusion therapy**

He emphasized Cerebrolysin's unique value, highlighting its ability to deliver key biological components that support recovery. He also pointed out its multi-target effects, offering both acute neuroprotection and long-term regenerative benefits. He also announced his upcoming participation in the Stroke Treatment Academy Industry Roundtable (STAIR) meeting in Washington, D.C., where experts, industry representatives, and regulatory agencies discuss integrating cytoprotection with reperfusion therapy to enhance treatment strategies.

In conclusion, Prof. Alexandrov underscored the importance of combining reperfusion therapy with cerebroprotective strategies to maximize stroke recovery outcomes.

Presentation by Dr. Sławomir Michalak

Prof. Slawomir Michalak discussed the concept of futile reperfusion, a phenomenon where patients undergoing mechanical thrombectomy achieve successful recanalization of large arteries but fail to show clinical improvement. He emphasized that despite the high technical success of the procedure, many patients do not achieve meaningful functional benefits, underscoring the complexity of stroke care and the need for comprehensive, ongoing treatment beyond just restoring blood flow (Figure 2).

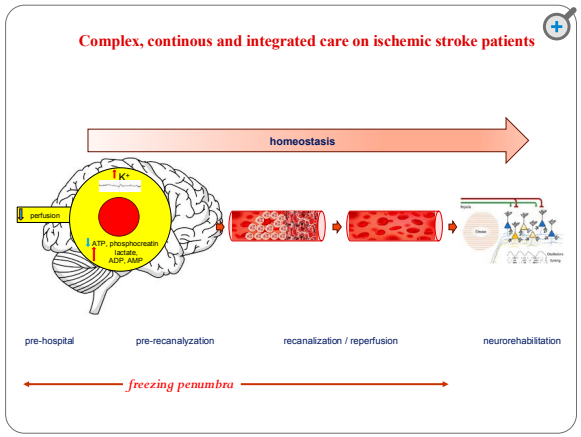

Figure 2: Complex continuous, and integrated care in ischemic stroke management. The figure illustrates the sequential stages of stroke care – beginning with pre-hospital and pre-recanalization phases, followed by recanalization/ reperfusion and extending into neurorehabilitation.

Dr. Michalak emphasized the need to preserve the ischemic penumbra through additional therapies to prevent further brain damage. He explored why some patients do not improve clinically despite successful reperfusion, identifying several key mechanisms:

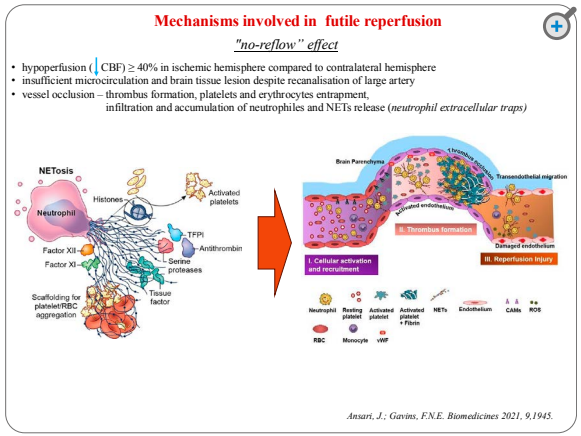

Figure 3: Mechanisms involved in futile reperfusion e.g. the No-Reflow phenomenon. Illustrates key pathological processes – such as cellular activation and recruitment, thrombus formation and susequent reperfusion injury.

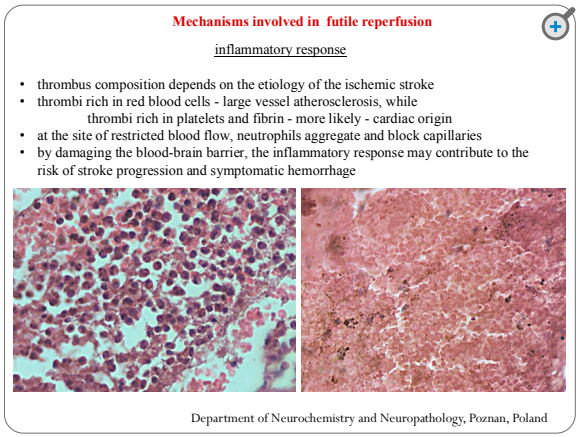

Figure 4: Mechanisms involved in futile reperfusion, focusing on the inflammatory response. Highlights how thrombus composition varies based on stroke etiology, with red blood cell-rich thrombi associated with large vessel atherosclerosis and platelet/fibrin-rich thrombi often linked to cardioembolic sources.

1. **No-Reflow Effect** – Microcirculatory dysfunction prevents proper blood flow to small brain vessels, limiting oxygen and nutrient delivery (Figure 3).

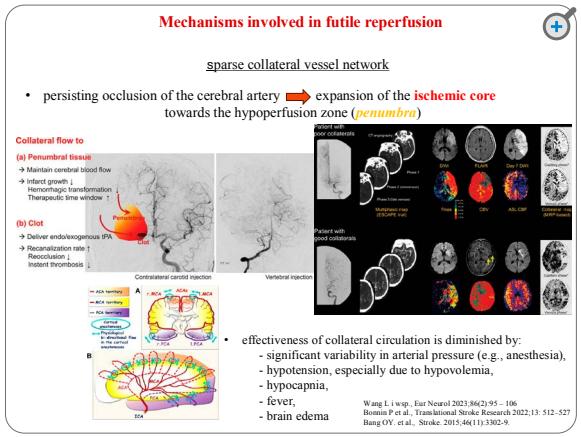

Figure 5: Mechanisms involved in futile reperfusion, exemplified by poor collateral circulation. Includes angiographic images illustrating collateral flow to the penumbral tissue and the occlusion site. It also highlights factors contributing to reduced collateral circulation.

2. **Thrombus Characteristics/Inflammatory Response** – Clot composition affects reperfusion success, with fibrin-rich thrombi being easier to treat than neutrophil-rich ones, which can worsen microcirculatory failure (Figure 4).
3. **Poor Collateral Circulation** – A weak collateral network reduces blood supply to ischemic tissue, even after artery reopening, shifting the focus from "Time is Brain" to "Collaterals are Brain" (Figure 5).
4. **Insufficient Venous Drainage** – Damage to the blood-brain barrier and impaired venous circulation can hinder recovery, increasing reperfusion failure.

Dr. Michalak also mentioned that maintaining homeostasis – stabilizing blood pressure, temperature, heart rate, ionic balance, glycemia and blood brain barrier integrity – is vital in the hyperacute phase of stroke treatment. Imbalances in these five different factors can worsen stroke damage, further reducing recovery potential.

This led to the introduction of the **TAKE 5 protocol**, which includes:

1. **Acetaminophen for fever control (T > 37°C)**
2. **Blood pressure stabilization using precise formulas**
3. **Magnesium infusion**
4. **Glycemia optimization**
5. **Cytoprotection agent = Cerebrolysin**

Dr. Michalak shared insights on the Take 5 protocol, which emphasizes the importance of acting quickly in stroke treatment (5 minutes = 10 million neurons lost). In Poland, the protocol has been introduced in several thrombectomy centers operating within the drip and ship system, where patients are transported over long distances for treatment in comprehensive stroke centres. A multi-center study is underway to evaluate its impact, and efforts are being made to publish the protocol in an international journal for a broader audience.

As evidence-based medicine Cerebrolysin is included in guidelines such as those of the EAN and those of leading reference countries such as Canada, Germany and Austria.

Dr. Michalak highlighted Cerebrolysin's multimodal effects, including its anti-inflammatory properties, protection against free radicals and apoptosis, blood-brain barrier stabilization and neurogenesis stimulation, making it a promising add-on therapy in both acute and hyperacute stroke phases.

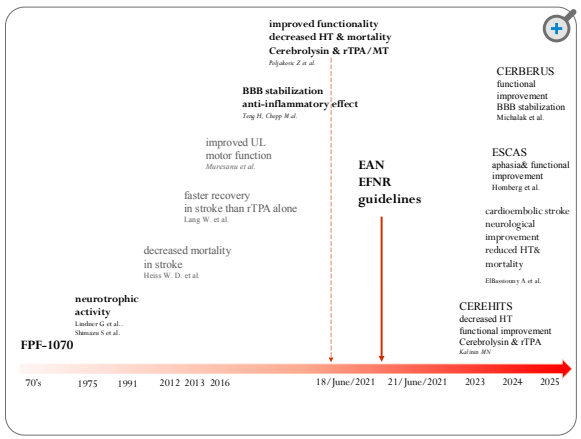

Figure 6: Development timeline of Cerebrolysin from the 1970s onward, highlighting key clinical trials, therapeutic milestones and its inclusion in stroke treatment guidelines.

He referred to several clinical trials, including the following (Figure 6):

- **Teng *et al.*:** Cerebrolysin reduces endothelial permeability caused by tPA/fibrin.
- **Poljakovic *et al.*:** Improvement in mRS after 12 months and reduction in hemorrhagic transformation.
- **CEREHETIS (Kalinin *et al.*):** Decreased hemorrhagic transformation, functional improved, and benefits of combining Cerebrolysin with rTPA.
- **ElBassiouny *et al.*:** Significantly higher proportion of mRS scores 0–2 at day 90, reduced hemorrhagic transformation, and decreased mortality.
- **ESCAS (Homberg *et al.*):** Improvement in aphasia-related deficits.

In the last part of his lecture, Dr. Michalak shared with the audience his decade-long research interest which focuses on investigating biomarkers related to stroke, particularly related to tight junction proteins, which play a crucial role in maintaining the integrity of the blood-brain barrier (BBB). His studies have identified claudin and occludin serum levels as predictors of hemorrhagic transformation in stroke patients.

In the context of the CERECAP program, he currently conducts the CERBERUS study with over 360 patients, divided into four groups (Figure 7):

1. **Thrombolysis and thrombectomy**
2. **Thrombolysis, thrombectomy and add-on therapy (Cerebrolysin)**
3. **No reperfusion and no Cerebrolysin**
4. **Cerebrolysin-only**

CERebrolysine effect on **B**lood-brain barrier / **E**ndothelium integrity during **R**eperfusion therapy of ac**U**te ischemic **S**troke **(CERBERUS Study)**

CERBERUS Study registered in Clinical Trials (Approval Number:392/23).

A prospective longitudinal study is performed in ischemic stroke patients who:
1. are included for reperfusion therapy (intravenous thrombolysis and/or mechanical thrombectomy – control (group A),
2. are included for reperfusion therapy (intravenous thrombolysis and/or mechanical thrombectomy plus Cerebrolysin (group B)
3. are not referred to reperfusion therapy nor Cerebrolysin (group C).
4. Cerebrolysin only, without reperfusion therapy (Group D)

Clinimetric evaluation of all patients included NIHSS every day for 7 days and at day 30
Modified Rankin scale (mRS) was evaluated at baseline, day 1 – 3, day 7th, at discharge and at day 30

Blood samples for TJ proteins analyses were withdrawn at baseline, day 1-3 and day 7th

All patients – N = 367 underwent current AHA Guidelines for the Early Management of Patients with Acute Ischemic Stroke – real life data

	males : females	hypertension	diabetes	atrial fibrillation	ischemic heart disease	cancer
N#	213:154	288	108	108	47	29
%	58 : 42	78	29	29	13	8

Figure 7: Overview of the CEREBERUS (CERebrolysine Effect on Blood-brain Barrier in acUte Ischemic Stroke) study, detailing its patient population.

In his study, Dr. Michalak identified the following preliminary findings (mRS 0-2 day 90 results , the primary endpoint – not yet available) (Figure 8-10):

- Patients treated with Cerebrolysin showed **clinically relevant improvements by the 7th day of treatment**, as measured by the decrease in NIH Stroke Scale (NIHSS) scores.
- The **add-on therapy group** (recanalization plus Cerebrolysin) demonstrated improvement as early as day 3, continuing through day 7.
- Serum levels of tight junction proteins, specifically **occludin and claudin**, were decreased in patients receiving Cerebrolysin, suggesting **reduced blood-brain barrier disruption**.
- The multiplate platelet function test showed that Cerebrolysin treatment does not cause any disturbances in platelet function.

Dr. Michalak's research underscores the importance of biomarker analysis in stroke management and highlights the potential of Cerebrolysin as an adjunct therapy.

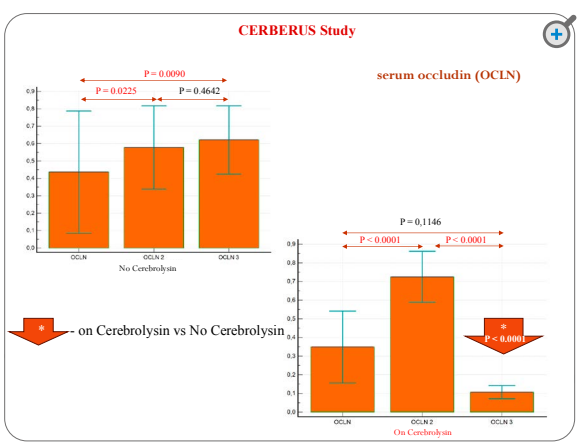

Figure 8

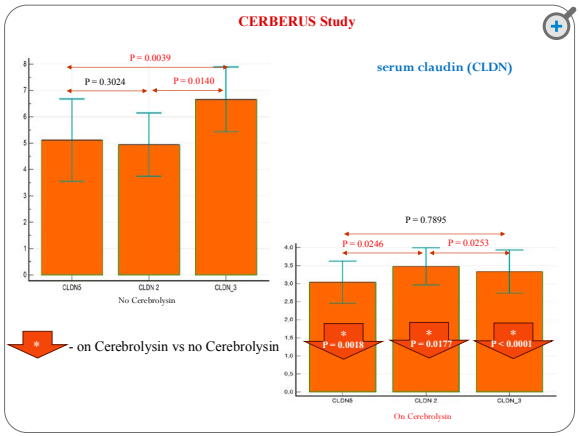

Figure 9

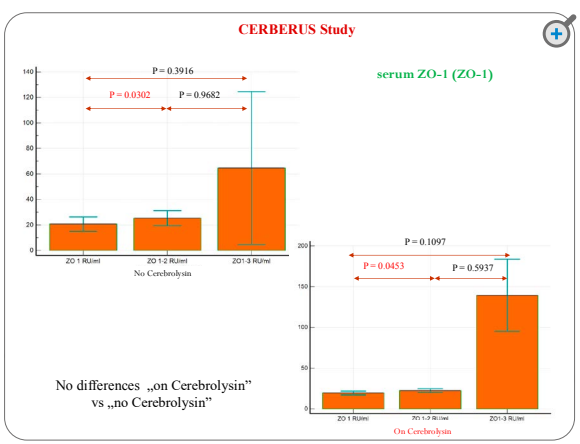

Figure 10

Figure 8-10: Results from the Cerberus study showing the reduction in serum levels of tight junction proteins, specifically occludin, claudin and ZO-1.

Presentation by Dr. Yakub Krespi

Prof. Yakub Krespi's presentation focused on the operational challenges and potential benefits of integrating Cerebrolysin into the management of stroke patients, especially in the hyperacute phase of stroke treatment. Despite advancements in stroke treatment options, including revascularization therapies, a large proportion of stroke patients still experience reduced mobility and difficulty performing daily activities, highlighting the urgent need for more effective treatment strategies to enhance patient recovery (Figure 11).

In low-income countries the direct costs of stroke are high, and although several treatment options exist, there remain limited therapeutic interventions for stroke patients. A significant number of stroke survivors continue to experience long-term disability, with a large proportion of patients having difficulty with activities of daily living. This raises the fundamental question:

How can stroke treatment be improved?

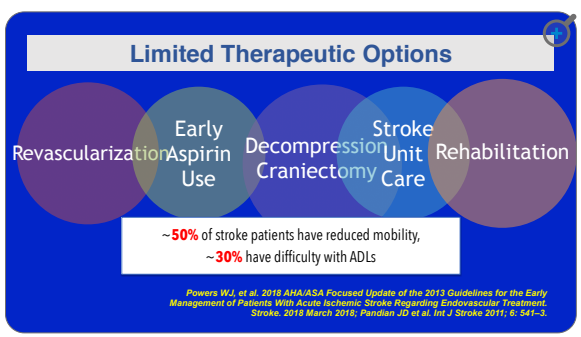

Figure 11: Represents the limited therapeutic options, with a particular emphasis on reduced mobility and difficulties with activities of daily living in stroke patients.

Dr. Krespi highlighted that stroke treatment is multifaceted, involving

- **Vascularization**
- **Cerebroprotection and**
- **Neuro-repair**

Cerebrolysin has gained attention for its potential cerebroprotective properties, with clinical trials and meta-analyses confirming its safety and tolerability, leading to its inclusion in stroke rehabilitation guidelines such as those in Canada, Europe and Korea. Recent hyperacute trials have shown that Cerebrolysin improves recovery in patients undergoing thrombectomy and thrombolysis, particularly by enhancing microcirculation and reducing hemorrhagic transformation rates.

Professor Krespi outlined his own ongoing "Cerebrolysin in Everyday Practice" observational registry study, which evaluates the practical use of Cerebrolysin in hyperacute stroke treatment (Figure 12,13).

He stated that their treatment algorithm begins with assessing the possibility of revascularization (Figure 14).

- **If the patient undergoes revascularization** Cerebrolysin is administered within 24 hours, particularly in the hyperacute phase, alongside intravenous thrombolysis and just before endovascular therapy.
- **If revascularization is not performed** Cerebrolysin is delivered within the first 72 hours to suitable patients.

Dr. Krespi explained that their study, using a propensity-matched analysis, aims to evaluate the global outcomes of patients receiving Cerebrolysin, including the rates of hemorrhagic transformation and cerebral edema, compared to patients who do not receive the treatment.

Figure 12

Another objective of the study is to generate real-world data to encourage broader adoption of Cerebrolysin across stroke networks. By the second year, a propensity score matching analysis will assess the impact of Cerebrolysin on stroke recovery, especially regarding hemorrhagic transformation in the subacute and hyperacute phases.

Figure 13

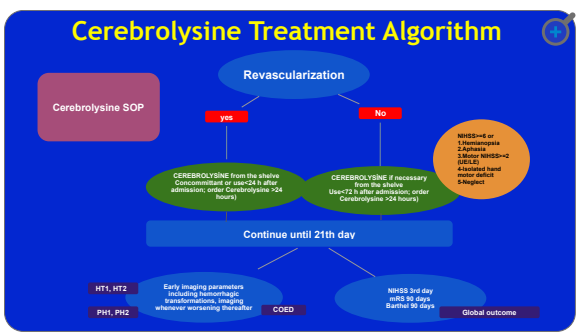

Figure 14

Figure 12-14: Illustrating the use of Cerebrolysin in everyday clinical practice, including a detailed overview of the study, the availability of Cerebrolysin in the hospital and the treatment algorithm protocol.

CONCLUSION

The webinar highlighted scientific and clinical evidence supporting the **integration of Cerebrolysin into treatment strategies for AIS,** especially in conjunction with reperfusion therapies like **thrombolysis and thrombectomy.**

Experts emphasized Cerebrolysin's multimodal cerebroprotective properties. **Dr. Alexandrov** pointed out the value of combining reperfusion with **cerebroprotection,** highlighting **Cerebrolysin as a key adjunct therapy** for moderate to severe strokes. **Dr. Michalak** presented the **TAKE 5 protocol,** showing how early use of **Cerebrolysin** may overcome futile reperfusion and contribute to **preserving the penumbra,** an important topic in **"drip and ship" systems,** supported by clinical and biomarker data. **Dr. Krespi** shared real-world insights, outlining both benefits and challenges in **implementing Cerebrolysin in routine stroke care.**

In conclusion, the growing evidence supporting the **integration of Cerebrolysin into AIS treatment,** particularly when combined with recanalization therapies, was highlighted. Experts emphasized the **cerebroprotective properties and clinical benefits of Cerebrolysin,** as well as the importance of ongoing research to optimize its use in routine stroke care.

ABBREVIATED PRESCRIBING INFORMATION. Name of the medicinal product: Cerebrolysin - Solution for injection. Qualitative and quantitative composition: One ml contains 215.2 mg of Cerebrolysin concentrate in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic indications: For treatment of cerebrovascular disorders. Especially in the following indications: Senile dementia of Alzheimer's type. Vascular dementia. Stroke. Craniocerebral trauma (commotio and contusio). Contraindications: Hypersensitivity to one of the components of the drug, epilepsy, severe renal impairment. Marketing Authorisation Holder: EVER Neuro Pharma GmbH, A-4866 Unterach. Only available on prescription and in pharmacies. More information about pharmaceutical form, posology and method of administration, special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, fertility, pregnancy and lactation, effects on ability to drive and use machines, undesirable effects, overdose, pharmacodynamics properties, pharmacokinetic properties, preclinical safety data, incompatibilities, shelf life, special precautions for storage, nature and contents of the container and special precautions for disposal is available in the summary of product characteristics.

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