Cerebrolysin®
Use in Children

Selected Literature

- Hyperactivity Attention deficit disorder
- Head / Brain Injury
- Cerebral Palsy
- Rett Syndrome
- Childhood Autism / Asperger's Syndrome
- Hypacusis
- Tissue disorders
Attention deficit Hyperactivity Disorder

Attention Deficit Hyperactivity Disorder, often called ADD or ADHD, is a diagnostic label that is given to children and adults who have significant problems in four main areas of their lives:

- Inattention,
- Impulsivity,
- Hyperactivity,
- Boredom.

Attention Deficit Hyperactivity Disorder is a neurologically based disorder

The Attention Deficit Disorder children show excessive slow brainwave activity (theta and alpha ranges) compared to non-ADD ADHD activity. The slow brainwave activity indicates a lack of control in the cortex of the brain.

Zavadenko from the Moscow University, Russia investigated the efficacy of nootropic drugs in 180 children with ADHD. The treatment was given for one month.

Five groups of the kids get nootropics, one group Thioridazine, a tranquilising medication with antipsychotic action and the control group multivitamins. The medication was given for one month.

Responderrate was in the Nootropic group 50%, in the Thioridazine 22% and 10% in the Multivitamin-group. In the Nootropic group, Cerebrolysin had the highest Responderrate (60%).

Cerebrolysin was given in the dose of 0.1 ml/kg of bodyweight i.m.

The results of this open study were presented 1998 at the 8th International Child Neurology Congress in Ljubljana, Slovenia and 1999 at the 3rd EPNS Congress - European Paediatric Neurology society in Nice, France.
Nootropics effects on behaviour, motor functions, attention and memory of children with ADHD

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<th>Measures</th>
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<th>Semax</th>
<th>Piracetam</th>
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Semax is a Russian drug contains seven natural amino acids
Phenibut (β-Phenyl-GABA): A Tranquillizer and Nootropic Drug
Instenon contains: hexobendin, hydroxytheophyllin, etamivan

Conclusion of Zavadenko:
"Containing biologically active substances, like neuropeptides, neurotransmitters and nerve growth factors-like substances, nootropics are able to stimulate the development of interneuronal connections and brain plasticity mechanisms. Taking into the account the underlying mechanisms of ADHD, the usage of nootropic agents, aimed to improve the deficient cognitive and motor functions, can be especially important in childhood, when intensive processes of brain development and maturation occur."

The conclusion of another study in children with ADHD, conducted by Badalian, Moscow Medical University, Russia was similar. Also here, Cerebrolysin was given for 30 days in a dose of 1ml /10kg of Bodyweight.
Head / Brain Injuries

- Head injury is the leading cause of death and disability from birth to age 44.
- Each year more children will die or be disabled by an injury than by any other disease or cause.

"Severe head injuries in children are uncommon while minor head injuries are common. The most common cause of minor head injury is falls followed by blunt injuries from rocks or golf balls. Severe head injuries are often associated with motor vehicle accidents. The child is not a small adult; this is especially true in the child's response to injury.

The child's brain has the ability to recover better from trauma, whether it is surgical or accidental, than adult's brain. This is probably due to plasticity of the child's brain. Also children rehabilitate better and quicker than adults."

PAEDIATRIC NEUROSURGERY
WOMEN'S AND CHILDREN'S HOSPITAL NORTH ADELAIDE SOUTH AUSTRALIA

Causes of Injuries in Children & Adolescents

Most acquired brain injuries result from a fall, car accident, or a sporting accident. The head striking an object, or a sudden change of movement causes the brain to move within the skull. There are two stages of damage after ABI.
Brain injuries can be described as focal or diffuse. A focal injury may cause disabilities such as paralysis of one part or side of the body. Diffuse damage may cause difficulties in thinking, memory, and behaviour. The injured child may think, move and act very differently than before the accident.

**Cognition (Thinking)**
ABI may cause a general loss of overall thinking functions. Or, it may cause specific deficits (problems or weaknesses) in understanding, judgement or being able to pay attention or concentrate. Memory problems, especially short term memory problems, are very common after head injury.

**Personality (Emotions and Behaviour)**
Personality may be very different after brain injury. Changes are not always permanent. Most of the time when people are recovering from brain injury they go through stages of agitation. An agitated person seems to be bothered by almost everything - sounds, lights, movement, touching. He or she may be irritable, combative, impatient and rude. Some even have emotional outbursts.

**Motor (Movement)**

Zavadenko from the Moscow University, Russia investigated the efficacy of nootropic drugs in 110 children with cognitive problems after a closed brain injury. The children suffered CBI in the period from 6 months - 4 years prior to the study. He divided the study population into four treatment groups and the treatment was given for 20 days.

The dose for Cerebrolysin was 2ml /d.
The other three groups were treated with Instenon or Semax and the control group received Multivitamins.

The Responderrate was 80% in the Cerebrolysin group, 70% in the Instenon-, 67% in the Semax- and 10% in the Control group.

The children showed a relief in headaches, tiredness, emotional stability, restlessness, poor concentration, memory and sleep disturbances.

In another study, Zavadenko compared the efficacy of Cerebrolysin with two different doses of Piracetam. 62 children with postcontusional syndrome were treated for 30 days, either with Cerebrolysin 2ml i.m., 1.2 g Piracetam, 2g Piracetam or Nicotinamide (Vit B3) as control. On day 60, one month after the last treatment day, a follow up assessment was performed.

The respondderate was best in the Cerebrolysin- and in the high-dose Piracetam group.

"...On day 60 assessment, 82% of the children in the Cerebrolysin group demonstrated definite improvement compared with the day 0 results. So, the effects of Cerebrolysin therapy were characterised by long duration
possibly due to its neurotrophic activity. In the other
groups of children with PCS dynamics of individual measures to day 60, when
compared with day 0 results was the same as to day 30…"

Gromova and colleagues, evaluated in 36 children of 3-8 years old with minimal
cerebral dysfunction the dynamics of malonic dialdehyde antioxidant status in
plasma, erythrocytes and platelets and the content of 25 elements (K, Mg, Ca,
Na, P, Se, Zn, Co, Cr, Cu, Fe, Mn, Mo, Si, Li, Ni, V, Pb, Sn, Cd, Al, As, Be, Bi, Ti).
It was done by hair analysis. These indices were measured before and after
treatment with Cerebrolysin (dose 2-5 ml intramuscularly during 1 month). A
clearly marked positive dynamic in the content of nervous system structural
elements, Mg and K has been demonstrated. The positive tendencies in
eliminating neuroactive trace element deficiency, Mn, Se, Cu, Zn and in reducing
the content of neurotoxic elements Al, Pb have been observed. Spectral analysis
of Cerebrolysin element structure was performed. It has been identified
sufficient presence of structural neuroactive elements Mg, K, P and of essential
trace element Se with marked antioxidant properties.
Cerebrolysin therapy in children with MCD results in positive clinical effect and
improvement of antioxidant and element homeostasis.
The dosage of Cerebrolysin was 0,1ml/kg of bodyweight given for 1 month.
Cerebral palsy

Cerebral palsy is a group of chronic disorders impairing control of movement that appear in the first few years of life. It is a developmental disability that is caused by damage to the developing brain either before or after birth. The brain damage cannot be repaired. However, cerebral palsy is not progressive.

It can affect a child's vision, hearing, speech, coordination and mental abilities. The damage to the brain may also result in mental retardation, seizures or trouble with learning, breathing, eating and digesting.

The degree of disability depends on the severity and location of the damage to the brain. Because other disorders mimic the symptoms of cerebral palsy, a thorough evaluation is essential to a proper diagnosis. Early detection may also reduce development problems.

In the United States and Europe, about 10 to 20 percent of children who have cerebral palsy acquire the disorder after birth. The figures are higher in underdeveloped countries. Acquired cerebral palsy results from brain damage in the first few months or years of life and can follow brain infections, such as bacterial meningitis or viral encephalitis, or results from head injury -- most often from a motor vehicle accident, a fall, or child abuse.

Congenital cerebral palsy, on the other hand, is present at birth, although it may not be detected for months. In most cases, the cause of congenital cerebral palsy is unknown. Some specific events during pregnancy or around the time of birth that can damage motor centres in the developing brain have pinpointed. Some of these causes of congenital cerebral palsy include:

- Infections during pregnancy.
- Jaundice in the infant.
- Rhesus incompatibility.
- Severe oxygen shortage in the brain or trauma to the head during labour and delivery.
There are no treatments that can undo the damage and symptoms of cerebral palsy. Treatment for cerebral palsy includes different therapeutic approaches to help better manage the potential physical and mental aspects of a child. Physical therapy, drug therapy, or surgery may be implemented as part of a cerebral palsy treatment depending on the individual's needs.

Xu Baozhen investigated the effects of Cerebrolysin in children with mild cerebral palsy. 132 children were included in the study. 90 received Cerebrolysin 2ml i.m. every second day for 3 months. The treatment protocol also included massage, function training, Bobath therapy, language training and cognitive training.

"...both the mean effectiveness rate and much improved rate in Cerebrolysin group were obviously higher than in the control group. The 90 cases, who received Cerebrolysin in this study, achieved much better result...It is highly recommended in the area where the medical facility is limited."

Tang Jiu-lai and his colleagues treated 81 children with cerebral palsy with Cerebrolysin and home training. Subsequent follow-up in five years showed that:
- 4 cases became normal
- 69 cases showed significant improvement
- 8 cases were not better

The dosage of Cerebrolysin was 2ml/d in 1 year old children
4ml/d in 3 year old children
5ml/d in 5 year old children
10ml/d in kid older than 5 years

Treatment was given daily for 10 days, after that ten day period once a week up to three months.

The effect in patients with spasticity and athetosis was more pronounced than in the other forms.
Rett Syndrome

Rett Syndrome (RS) is a neurological disorder seen almost exclusively in females, and found in a variety of racial and ethnic groups worldwide. First described by Dr. Andreas Rett, RS received worldwide recognition following a paper by Dr. Bengt Hagberg and colleagues in 1983.

The child with RS usually shows an early period of apparently normal or near normal development during the first 6-18 months of life. A period of temporary stagnation or regression follows during which the child loses communication skills and purposeful use of the hands. Soon, stereotyped hand movements, gait disturbances, and slowing of the rate of head growth become apparent. Other problems may include seizures and disorganized breathing patterns which occur when awake. Apraxia (dyspraxia), the inability to program the body to perform motor movements, is the most fundamental and severely handicapping aspect of RS. It can interfere with every body movement, including eye gaze and speech, making it difficult for the girl with RS to do what she wants to do. Due to apraxia and lack of verbal communication skills, an accurate assessment of intelligence is difficult. Most traditional testing methods require use of the hands and/or speech, which may be impossible for the girl with RS.

RS is most often misdiagnosed as autism, cerebral palsy or non-specific developmental delay. While many health professionals may not be familiar with RS, it is a relatively frequent cause of neurological dysfunction in females. The prevalence rate in various countries is from 1:10,000 to 1:23,000 live female births. Most researchers now agree that RS is a developmental disorder rather than a progressive, degenerative disorder as once thought. While there is strong evidence of a genetic basis, the origin and cause of RS remain unknown. Barring illness or complications, survival into adulthood is expected.

Rett syndrome has been found to be caused by mutation in the gene encoding methyl-CpG-binding protein-2 (MECP2). This gene is located on the X chromosome and, in some cases, may be transmitted as an X-linked dominant trait. Other mutations may be sporadic in nature. The course of Rett Syndrome can be improved by therapies aimed at slowing the progression of motor disability and improving communication skills.
Based on the suggestion that nerve growth factor plays a core role in the brain maturation process, which is altered in Rett syndrome, Gorbachevskaya investigated the influence of Cerebrolysin on motor and higher cortical functions in Rett syndrome girls.

The open pilot study was performed on 9 Rett syndrome girls (aged from 2 years and 2 months to 7 years and 6 months) at stage 3 of the illness, and included both clinical and quantitative EEG evaluations before and after Cerebrolysin treatment.

After Cerebrolysin treatment, increases in the behavioural activity, attention level, motor functions, and non-verbal social communication have been shown in Rett syndrome patients. EEG parameters after Cerebrolysin treatment also changed towards normal values, indicating an improvement of the brain functional state. EEG changes included: decrease of theta activity over all cortical regions, increase of beta activity in the frequency band 13-15 Hz, and some restoration of the occipital alpha rhythm (in the narrow 8-9 Hz band).

"...The data obtained suggested possible perspectives of Cerebrolysin in complex therapy of Rett syndrome..."
Childhood Autism / Asperger's Syndrome

Autism (sometimes called “classical autism”) is the most common condition in a group of developmental disorders known as the autism spectrum disorders (ASDs). Other ASDs include

- Asperger syndrome,
- childhood disintegrative disorder, and
- pervasive developmental disorder not otherwise specified (usually referred to as PDD-NOS).

Asperger Syndrome or (Asperger’s Disorder) is a neurobiological disorder named for a Viennese physician, Hans Asperger, who in 1944 published a paper which described a pattern of behaviours in several young boys who had normal intelligence and language development, but who also exhibited autistic-like behaviours and marked deficiencies in social and communication skills. In spite of the publication of his paper in the 1940’s, it wasn’t until 1994 that Asperger Syndrome was added to the DSM IV and only in the past few years has AS been recognized by professionals and parents.

By definition, those with AS have a normal IQ and many individuals (although not all), exhibit exceptional skill or talent in a specific area. Because of their high degree of functionality and their naïveté, those with AS are often viewed as eccentric or odd and can easily become victims of teasing and bullying. While language development seems, on the surface, normal, individuals with AS often have deficits in pragmatics and prosody. Vocabularies may be extraordinarily rich and some children sound like "little professors." However, persons with AS can be extremely literal and have difficulty using language in a social context.

Pervasive developmental disorder (PDD) is rare and usually marked by autistic-type behaviour, hand-flapping, repetitive statements, slow social development, and speech and motor problems.

Childhood Disintegrative Disorder(CDD) was identified by Theodore Heller, a Viennese special educator, in 1908 but has only recently been ‘officially’ recognized. He proposed the term “dementia infantilis” to account for a major loss of skills after 2 to 4 years of apparently normal development in the children he observed.
The clinical presentation is similar to autism, but the onset is different, and the prognosis is usually worse. More females than males are affected, and the condition is perhaps 10 times less common than autism (<5 in 10,000 children)

**Autism** was first identified in 1943 by the physician Leo Kanner (born in Austria and educated in Germany, he immigrated to the United States in 1924), but appears to have existed throughout recorded history. It occurs in all ethnic and social groups. It is estimated that three to six children out of every 1,000 will have autism and boys are more likely to be affected than girls.

It is still not known what causes autism, but it is thought to be related to changes in brain structure and function and has a strong genetic component. *It is definitely not caused by poor parenting as was once believed.*

Autism is a puzzling disorder because it is difficult to understand the behaviour of autistic people and because the world is so confusing for them.

An autistic person will have significant difficulties in several areas of his/her development. The areas most affected are communication, social interaction and behaviour. People with these disorders are affected differently, but all require specialised assistance and support.

**COMMUNICATION:** Autism affects the ability of a person to understand the meaning and purpose of body language and the spoken and written word. Words can be misunderstood, interpreted literally or not understood at all. Other people’s feelings and emotions can also be difficult to understand.

**SOCIAL INTERACTION:** Social interaction is an essential part of life for most people. For autistic people being sociable is difficult, scary and very confusing. Some appear to withdraw and become isolated, others try very hard to be sociable but never seem to get it right. People with autism can find friendships difficult.

**BEHAVIOUR:** Impairments in Communication and Social Interaction produce a range of behaviours that have become linked with autism spectrum disorders. These may include:

**Speech** - absent, delayed or showing abnormal patterns.

**Play** - isolated, repetitive, unimaginative, destructive, obsessional.

**Tantrums** - can be a way of expressing extreme confusion and/or frustration.

**Sensory sensitivities** - to certain sounds, colours, tastes, smells, textures.

**Obsessions** - intensive interest with favourite topics, objects, places, people or activities.

**Insistence on sameness** - routines bring some order to the autistic person’s confusion - a change of routine can be very difficult to cope with.
**Body movements** - such as hand flapping, toe walking and occasionally behaviour that may cause self injury (such as hand biting).

Knowledge of autism has improved greatly over the years, although there is no known cure.

Krasnoperova and colleagues investigated the effect of Cerebrolysin on cognitive functions in Childhood Autism and Asperger's Syndrome.

In the study included were 19 children with Childhood Autism and 8 children with Asperger's Syndrome, aged 2 to 8 years.

Cerebrolysin was given each alternate day in the form of 0.1 ml microinjections intramuscularly and into perineural and periganglionic spaces (a course of 5 procedures over 6 months)

Status of the patients was assessed before the treatment and three months after the treatment completion. Basic method used was clinical and psychopathological method. Besides a standardised assessment of the developmental level of cognitive functions and communicative skills specially elaborated for this purpose by the authors.

**Results**

- Improvement of cognitive functions: expressive and receptive language skills, fine motor skills, playing activity.
- Different degree of improvement was noticed in all patients with Asperger's Syndrome and in 89% of patients with Childhood Autism

**Percentage of patients with cognitive function improvement after cerebrolysin treatment**

![Graph showing percentage improvement](image-url)
A therapeutic effect of Cerebrolysin on development of cognitive functions proved to be more effective in patients with Asperger's Syndrome as compared with the group of patients with Childhood Autism (p<0.005).
Pruszewicz from the University of Poznan, Poland examined two groups of children with hypoacusis. The purpose of his work was to present the dynamics of hearing thresholds and the progress in rehabilitation of hearing and speech according to the treatment applied and probable etiological factor of hypoacusis.

Two groups of children were examined. The first group consisted of children with deep sensorineural hypoacusis together with central component of hypoacusis, whereas the second group included children with sudden occurrence of hypoacusis or deterioration of diminished hearing ability. The first group received a treatment with Cerebrolysin, whereas the other one underwent typical therapy applied in case of sudden deafness (Mannitol, hydrocortisone, vitamins, enzymes).

Cerebrolysin was given in a dosage of 1ml twice a week, altogether 60 - 100 ampules per patient.

Both the groups were subjected to objective examination of hearing before and after the treatment.

The improvement in examination results in the Cerebrolysin group was observed in 36%. The biggest part of patients were children with hypoacusis associated with delivery complications.
Raynaud Syndrome

Osipenko investigated the effect of local administration of cerebrolysin in Raynaud’s disease in a 2-year-old child. A case of Raynaud’s disease in a 2-year-old child seen by the authors for 1.5 yr. is described. The paper treats of the basic reported data on the pathogenesis, clinical picture and treatment of Raynaud’s phenomenon and disease; the child’s disease history and the main clinical manifestations are described as are the results of examinations. The case is characterized by successful counteracting the main clinical manifestations of Raynaud’s phenomenon by the local metameric application of cerebrolysin (neuromeric, scleromeric puncturing) employed by the authors for the first time for the disease treatment. Interpretation of the effect obtained is briefed.

Mikovska-Dimitrova investigated the efficacy of Cerebrolysin in congenital connective tissue deficiency (CCTD).

- EHLERS-DANLOS SYNDROME
  - A disorder of collagen, characterized by articular hypermobility, dermal hyperelasticity, and widespread tissue fragility.

- MARFAN’S SYNDROME
  - A disorder of connective tissue resulting in ocular, skeletal, and cardiovascular abnormalities.

Cerebrolysin was administered to 45 children having CCTD in a dosage of 1ml s.c. three times a week. The duration of treatment was 6 months.

"...Due to the effect of Cerebrolysin the children...had a comparatively fast stabilisation (at the end of the first month already) of locomotor system. At the end of the course the effect was yet more efficient...Some stabilisation of the nervous system and mental state has been achieved....The durable use of Cerebrolysin was marked by its good endurance without side-effects..."

"...The polymerisation effect of Cerebrolysin in glucosaminglycans has been proved."
There was no improvement in all examined patients with probable congenital deafness and in those with hypoacusis associated with ototoxic drugs action in the infantile and early-childish period.

Sukhareva conducted a study with pharmacopuncture treatment (cerebrolysin, cavinton [VINPOCETINE], prozerin). It was given to 120 children with neurosensory hypoacusis aged 4-15 years. The treatment consisted of 3 courses 10 days each with 7-10-day interval. The drugs were injected in the dose 0.1 ml in biologically active points according to the original technique. The treatment lowered tonal thresholds more than by 15 dB in 36% children. Speech intelligibility increased, head ache and noise in the ears relieved in 85% cases. Adaptation to the hearing aid was positive. Clinical evidence was confirmed by REG picture indicating normalization of hemodynamics.

“Pharmacopuncture is a promising method in the treatment of children with neurosensory hypoacusis.”