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Clinical uses of Cerebrolysin in Pediatric Neuropsychiatry

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INTRODUCTION

In 1949, Austrian scientist Gerhart Harrer from the University of Innsbruck reported that the process of enzymatic hydrolysis of the brain tissue producing a protein-based liquid, cerebrolysin can stimulate nerve cells. Cerebrolysin which was probably first registered in Austria in 1954, and was also called (FPF1070) is a protein-based liquid mixture of free amino acids (85%) and 15% biologically active low molecular weight amino acid sequences which include low molecular weight neuro-peptides [1-5]:

1. Brain-derived neurotrophic factor.
2. Glial cell line-derived neurotrophic factor.
3. Nerve growth factor.
4. Ciliary neurotrophic factor.

Cerebrolysin has been considered as a peptidergic substance with a multimodal mechanism of action. The active brain neuro-peptides contained in cerebrolysin penetrate the barrier of blood and brain and used by neurons to communicate with each other. The safety, tolerability, and efficacy of neuroreparative cerebrolysin therapy have been established in experimental studies and clinical trials. Cerebrolysin is associated with a relatively wide therapeutic time window [1-15].

Cerebrolysin acts as a neurotrophic and neuroprotective agent. This function may contribute delaying the progression of brain disorders [1-15]. Table 1 summarizes the mechanisms behind neuroreparative effects of cerebrolysin.

Table 1: The possible mechanisms contributing to the neuroreparative effects of cerebrolysin [1-15]

1	Inhibition or minimizing cell death rate which is called apoptosis. This function may contribute to improving many brain disorders.
2	Improving synaptic plasticity.
3	Induction of neurogenesis which is a process of development of new nerve cells.
4	Induction of neurogenesis is especially necessary in the hippocampus to enhance the memory formation process.
5	Augmenting the proliferation, differentiation, and migration of adult sub ventricular zone neural progenitor stem cells that contribute to neurogenesis.
6	Induction of stem-cell proliferation in the brain.
7	Promoting synaptic repair in the region of the hippocampus leading to enhancing overall neurotransmission.

Cerebrolysin has been used in the treatment of various neurological disorders. Table-2 summarizes the early Clinical uses of cerebrolysin during the 1970s, 1980s and 1990s.

In 2011, Alvarez et al, reported safe and beneficial use of cerebrolysin in moderate to moderately severe Alzheimer's disease in a randomized, double-blind, controlled trial. In 2012, Menon et al showed in an experimental study that cerebrolysin induces marked neuroprotection in spinal cord injury following intoxication of engineered nanoparticles from metals [30]. In 2013, Chen et al reported that cerebrolysin enhances

Table 2: The early Clinical uses of cerebrolysin during the 1970s,1980s and 1990s

Cerebral atherosclerosis (Zhovnir and colleague, 1973) [16].
Prenatal brain injuries and cerebral palsy (Gershman and Vasilenko, 1975) [17].
Traumatic brain injuries **(**Wanderka, 1975) [18].
Chronic encephalopathy (Wenzel, 1976) [19].
Dementias (Vereshchagin et al, 1991 [20]; Rainer et al, 1997 [21]) Degenerative dementias including senile dementia of Alzheimer's type (Rüther et al, 1994) [22]. Vascular dementias (Iakhno et al, 1996) [23] including multi-infarct dementia (Vereshchagin et al, 1991 [20]).
Acute ischemic stroke (Gusev et al, 1994 [24]; Domzał and Zaleska, 1995) [25].
Partial optic atrophy in children (Sidorenko et al, 1995) [26].
Prolonged extrapyramidal complications of neuroleptic therapy (Kontsevoĭ et al, 1997) [27].
Painful diabetic neuropathy (Biesenbach et al, 1997) [28].

cognitive recovery of mild traumatic brain injury patients in adouble-blind, placebo-controlled, randomized study [31]. In 2017, Allam and colleagues reported that 4 weeks treatment with cerebrolysin was safe and effective for improvement of cervical spondylotic myelopathy as compared to placebo [32].

Cerebrolysin has recently been used in the treatment of a variety of childhood neurological and psychiatric disorders including brain atrophy, cerebral palsy, kernicterus, and agenesis of the corpus callosum, idiopathic mental retardation, pediatric juvenile spinal muscular atrophy, Charcot Marie Tooth disease, myelomeningocele autism, and Rett syndrome [1-15].

The use of cerebrolysin as a part of multi-factorial therapies in the treatment of brain atrophy has been recently reported. Multi-factorial therapies including intramuscular cerebrolysin, citicoline (oral and intramuscular), oral pyritinol, intramuscular piracetam, and intramuscular nandrolone decanoate was used with a beneficial effect in a very severe form of spastic cerebral palsy associated with evidence of significant brain atrophy [1].

Cerebrolysin was used in the treatment of a boy with idiopathic mental retardation which is a heterogeneous condition. Treatment included a new combination of interventions consisting of the use of intramuscular cerebrolysin, intramuscular citicoline, oral pyritinol, and intramuscular piracetam. Treatment was successful in advancing the mental function of the boy with moderately severe idiopathic mental retardation who was uneducable, but became perfectly educable after treatment [3].

Cerebrolysin was used in the treatment of cerebral palsy which is a heterogeneous condition associated with a non-progressive lesion, but permanent disorder of movement with limited mobility. Cerebral palsy is generally associated with gross motor developmental delay. In moderate to severe cases motor developmental milestones such as walking may never be achieved [3,4].

In a retrospective observational study, patients with spastic cerebral palsy were treated with individualized treatment plans providing a new combination of interventions including nutritional support, muscle relaxants and the use of oral pyritinol, intramuscular cerebrolysin,citicoline (oral and intramuscular), intramuscular piracetam, and intramuscular nandrolone decanoate. Treatment aimed primarily at improving motor development particularly standing and walking. Six patients (3 girls and 3 boys) with spastic cerebral palsy and marked motor disability were treated. The patients' age ranged from 22 months to three years. All patients were unable to stand or walk, and had poor speech development. Four patients had severe cerebral palsy and were even unable to sit. The other two patients had moderately severe disorder and were unable to stand or walk. All the patients were not saying any word or were saying only few words. After treatment, all the treated patients experienced improvement in motor development without the occurrence of any side effect. Five patients were able to stand with support, and four of them were also able to walk few steps with support. The sixth patient remained unable to stand and the limited benefit of treatment was attributed to some degree of deformity and muscle contracture. In all patients treatment was associated with initiation of speech development or improved speech. It was possible to demonstrate improvement in fine motor skills in three patients. This study suggested that treatment of patients with spastic cerebral palsy (moderate and severe) with this individualized treatment plans was associated with a beneficial effect on motor development particularly standing and walking [4].

The combined use of intra-muscular cerebrolysin and citicoline was has been recently been reported to be associated with rather dramatic improvement of the neurological dysfunction caused by kernicterus in this patient [5,6].

The combined use of intra-muscular citicoline (500 mg given by intra-muscular injections every third day in the morning, 10 doses over on month) and intra-muscular cerebrolysin (5ml given by intra-muscular injections every third day in the morning, 10 doses over on month) was associated with an obvious benefit in the treatment of a girl with kernicterus. Before treatment, the girl was not speaking and was not saying any word. She was lacking the balance (co-ordination) without obvious muscle weakness. She was also unable to maintain the sitting posture on a chair for few minutes and was unable to maintain straight standing posture at all even when supported on chair. She had difficulty in holding things. After treatment, speech development was initiating, and she was saying few words. She was able to sit normally on the chair and maintaining the sitting posture indefinitely. She was able to maintain more straight stable standing posture without holding a chair and with the ability to hold things at the same time indicting improved coordination. The patient also developed improved ability to hold a pen[5].

There is no curative or satisfactory effective therapy for the nervous tissue damage associated with myelomeningocele which generally results in a serious disability [7]. Recently a retrospective study described the treatment of four patients with myelomeningocele, three of them were treated with new therapies which included cerebrolysin .Three of the patients were referred for us for treatment and received new therapies aiming at treating the nervous tissue damage associated with myelomeningocele and improving the associated neurological dysfunction. The fourth observed patient was treated by other physicians mainly with physiotherapy, and received no specific medical therapy. All the patients had hydrocephalus of variable severity and three of them have already been treated with a ventriculo-peritoneal shunt. Parenteral cerebrolysin was used in three patients with the aim of regenerating the spinal cord cells. Nandrolone decanoate was used in one patient with aim of strengthening muscles of legs. Treatment of the three patients was associated with a significant improvement that has never been reported before with this condition, and without the occurrence of any side effects. The fourth patient who was not treated by us didn't show any improvement [8].

Corpus callosum is a large nerve tract consisting of a flat bundle of commissural fibers that runs below the brain cerebral cortex. It connects the left and right cerebral hemispheres. Absence of the corpus callosum because of failure of development is a rare congenital defect called "Agenesis of the corpus callosum" [9].

Recently, cerebrolysin has been used in the treatment of non-syndromic agenesis of the corpus callosum associated with colpocephaly. Two infants with non-syndromic agenesis of the corpus

callosum one infant with the isolated type and the second infant had agenesis of the corpus callosum associated with colpocephaly. Both infants had the clinical features of the syndrome resulting from the associated failure of neuronal migration including hypotonia with poor head control, no response to voice, not recognizing faces, and they didn't show any eye contact. They have never smiled and had poor spontaneous movements. The patient with colpocephaly was a girl and, she was treated with courses of intramuscular piracetam and cerebrolysin for three months with aim of improving brain functions and accelerating her development. The second patient was a boy and he didn't receive any specific therapy. Treatment was not associated with any side effects, and after three months of treatment, the patient experienced improvements in feeding, muscle tone, alertness and response to voice, and movements. The untreated patient didn't show any obvious improvement despite he didn't have colpocephaly [9].

A retrospective observational study described the use of a new therapeutic approach for the treatment of eight of 19 patients with pervasive developmental disorders. The treated patient's ages ranged from 3 to 16 years. The new therapeutic approach included injectable cerebrolysin as the main therapeutic component and citicoline was used mostly as an adjunctive therapy. The patient's ages ranged from 3 to 8 years. Seven patients had a diagnosis of autism and one patient had a diagnosis of Asperger syndrome. Treatment aimed at improving the cardinal feature of pervasive developmental disorders which is the impairment of social interaction which is mostly manifested by poor responsiveness to their name and infrequent engagement with others manifested by poor eye contact and infrequently looking to faces. All the treated children showed improvement and marked lessening of the autistic features with six patients showed complete disappearance of the main autistic features. No patient developed any side effects. The eleven patients observed during the same year who didn't receive this treatment or were treated with other treatments such as omega-3 and risperidone didn't show any lessening effect in the autistic features. However, one patient was treated with citicoline injection without cerebrolysin showed obvious improvement in the autistic features [11,12].

Cerebrolysin has been used with a beneficial effect in treatment of Rett syndrome which is a rare X-linked dominant genetic disorder that affects only girls.

A three-year old girl with Rett syndrome girl was treated with new therapies including intramuscular cerebrolysin. Before treatment, the girl was hypotonic, ataxic, and had abnormal movements of the upper limbs. She was not able to sit alone on the chair and showed no eye contact and was not responding to her name. She didn't have purposeful hand movement and was not able to hold things. She couldn't be held erect in the standing position. She was not saying any word nor was babbling. The girl received two treatment courses. The first course included cerebrolysin 1ml daily given by intramuscular injection for ten days. The second course of treatment was given over one month and included 10 cerebrolysin injections, 3ml every third day, and oral citicoline. After the ten-day course of cerebrolysin, she showed dramatic improvement in muscle tone and was able to sit on the chair, and she had no abnormal movements. It was also possible to hold her straight in the standing position without apparent ataxia. After the second course of treatment she showed marked improvement with the development of purposeful movement and the ability to hold feeding bottle with assistant of the mother and feed herself. She was able to stand and step one step holding furniture. She started babbling and showed some reduction in the autistic features [13].

Cerebrolysin has been used with a beneficial effect in treatment of juvenile spinal muscular atrophy which is also called Wohlfart Kugelberg Welander syndrome, it is an autosomal recessive condition which appears within the first few years of life. Most of the patients are able to walk during early life, but difficulties in walking appears gradually leading to a variable degree of disability [14].

Two unrelated Iraqi boys aged four years with pediatric Wohlfart Kugelberg Welander syndrome were observed, and the one who was more severely affected was treated with intramuscular cerebrolysin. The less affected boy received no treatment. The father of the boy with less severe condition mainly complained that his son cannot run as fast as his peers and he didn't have obvious gait abnormality, but he was unable to stand on foot which is a milestone commonly achieved at the age of three years. The more severely affected boy had noticeable gait abnormalities and obvious difficulty with squatting, and was also unable to stand on foot. Cerebrolysin treatment was not associated with any side effects. Cerebrolysin treated boy experienced improvements in gait and squatting, and was able to stand on one foot momentarily for 2-3 seconds, while the untreated boy with the less severe condition couldn't [14].

Cerebrolysin has been used with a beneficial effect in treatment of Charcot Marie Tooth disease which is a is a very chronic progressive hereditary motor and sensory neuropathy characterized by progressive weakness and loss of touch sensation across various parts of the body. A boy who was born on the seventh of November, 2009, and was first seen on 29th of January, 2018 at the Children Teaching Hospital of Baghdad Medical City and had Charcot Marie Tooth disease was observed. He had difficulty in walking and abnormal gait that made him left first grade primary school. The nerve conduction study and electromyography study supported the clinical diagnosis of chronic symmetric sensori-motor polyneuropathy of moderated severity. The boy was treated with a safe novel therapy for one month. He received ten doses of 3 ml intra-muscular cerebrolysin every three days. The short term effect of the therapy was dramatic with noticeable improvement that has never been reported before with this condition [15].

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