

## Short Communication

# The Use of Citicoline in Pediatric Neurology and Pediatric Psychiatry

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Citicoline is the generic name of cytidine 5-diphosphocholine (CDP-choline, cytidine diphosphate choline) when used as an exogenous sodium salt. Cytidine diphosphate choline is a mononucleotide made of ribose, pyrophosphate, cytosine and choline. It is a water-soluble naturally occurring substance that is generally grouped with the B vitamins. It is also considered a form of the essential nutrient choline. Citicoline is a safe substance with generally minor side effects which may include digestive intolerance after oral administration. Citicoline has become available throughout the world and recently it has become available in the United States as a dietary supplement [1].

An accumulating research evidence suggests that citicoline is endowed with interesting pharmacological properties that can make it useful in the treatment of various disorders that has no universally accepted effective treatment including neurological conditions such as Parkinson disease, brain ischemia, hemorrhagic stroke, Alzheimer's disease, and ocular conditions such as glaucoma, non-arteritic ischemic neuropathy and amblyopia. Neuroprotective effects of citicoline in neurological disorders promised the emergence of a useful therapeutic agent for several disorders [1].

In addition, citicoline has been recently used with benefit in treatment of childhood neuro-psychiatric disorders including mental retardation [2,3], pervasive developmental disorders including Rett syndrome [4,5], brain atrophy [6], kernicterus [7], and cerebral palsy [8,9].

**Neuroprotective effects of citicoline have been attributed to [1-9]:**

1-As a phosphatidylcholine precursor, exogenous citicoline can help in maintaining and repairing the structural and functional integrity of the neuronal membrane through:

A: Increasing synthesis of phosphatidylcholine.

B: Activating the biosynthesis of structural phospholipids in the neuronal membranes.

C: Repairing damaged cholinergic neurons by the provision of

choline for acetylcholine production.

D: Reducing free fatty acid buildup at the site of nerve damage.

2-Citicoline can counteract the deposition of beta-amyloid which is a neurotoxic protein.

3-Maintaining sphingomyelin and cardiolipin levels which are constituents of the inner mitochondrial membrane.

4-Increasing the activity of glutathione reductase and increasing the synthesis of glutathione which is one of the most important endogenous antioxidant defense systems in the brain.

The neuroprotective effect of glutathione is also attributed to decreasing lipid peroxidation.

5-Decreasing lipid peroxidation.

6-Increasing cerebral metabolism and affecting various neurotransmitters.

7-Potentiating dopamine release in the brain by stimulating the release of acetylcholine.

8-Enhancing noradrenaline release in the brain.

9-Restoring the activity of mitochondrial ATPase and membranial Na<sup>+</sup>/K<sup>+</sup> ATPase.

10-Inhibiting the activation of phospholipase A2.

Therefore, citicoline has pharmacological activities that can provide neuroprotective effect in hypoxia and ischemia, and can improve learning and memory performance in the aging brain [1].

Citicoline was mostly used as a part of multi-factorial therapies in the treatment of childhood neurologic and psychiatric disorders including brain atrophy, cerebral palsy, kernicterus, idiopathic mental retardation, and autism [2-9].

The use of a multi-factorial therapies including citicoline (oral and intramuscular), oral pyritinol, intramuscular piracetam, intramuscular cerebrolysin, and intramuscular nandrolone decanoate has been reported to have a beneficial effect in a very severe form of spastic cerebral palsy associated with evidence of significant brain atrophy[6].

Al-Mosawi (2018) used citicoline 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 citicoline, oral pyritinol, intramuscular piracetam, and intramuscular cerebrolysin. 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 [2].

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 indicating improved coordination. The patient also developed improved ability to hold a pen [7].

The combined use of intra-muscular citicoline and cerebrolysin was considered to be associated with rather dramatic improvement of the neurological dysfunction caused by kernicterus in this patient [7].

A retrospective observational study [4] 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 [4].

Al-Mosawi (2019) [8] used citicoline 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.

In a retrospective observational study, Al-Mosawi [8] described the treatment of spastic cerebral palsy with individualized treatment plans providing a new combination of interventions including nutritional support, muscle relaxants and the use of oral pyritinol, intramuscular piracetam, citicoline (oral and intramuscular), intramuscular cerebrolysin, and intramuscular nandrolone decanoate. Treatment aimed primarily at improving motor development particularly standing and walking.

Al-Mosawi treated six patients (3 girls and 3 boys) with spastic cerebral palsy and marked motor disability. The patient 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 [8].

The work of Al-Mosawi [8] 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.

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