

NEW THERAPIES FOR RETT SYNDROME

Aamir Jalal Al Mosawi

Children Teaching Hospital, Baghdad Medical City, Bab Al Muadham, Baghdad, Iraq

ABSTRACT

There is no satisfactory therapy for Rett syndrome, a rare genetic disorder. A three-year old girl with Rett syndrome was hypotonic, ataxic, and had abnormal movements of the upper limbs. She was unable to sit alone on a 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 intramuscular cerebrolysin 1ml daily for ten days. The second course 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 a 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. The use of these new therapies in Rett syndrome resulted in an obvious improvement that has never been reported before.

Key words: *Rett syndrome, cerebrolysin, citicoline.*

No: of Figures : 03
References:12

No: of

INTRODUCTION

Rett syndrome is a rare X-linked dominant genetic disorder affecting only girls. The disorder is generally regarded as a neurodevelopmental condition rather than a neurodegenerative disorder. The diagnosis is generally based on clinical findings which characteristically include (Galli et al.,1985; Peters, 1985):Delayed motor development and delayed speech development.Ataxia or fine tremor of hand movements.Repetitive hand-wringing movements and loss of purposeful and spontaneous use of the hands. Autistic feature is a typical finding in all patients.

Generalized tonic-clonic convulsions occur in the majority and are usually well controlled by anticonvulsants.

Many patients also develop respiratory abnormalities with intermittent periods of apnea that may be associated with cyanosis.Feeding problems and poor weight gain are common. Rett syndrome was most probably first described in German language in 1966 by Andreas Rett, a pediatrician in Vienna (Rett,1966) .

Bengt Hagberg, a Swedish pediatrician, published an English article in 1983 and named the condition after Rett (Hagberg et al.,1983).More than half century after the syndrome was first described, and there is no known effective therapy that can improve Rett syndrome, and treatment mostly includes anticonvulsants to control seizures.

Patients and methods

A girl with Rett syndrome was first seen at the age of about three years because of developmental delay, abnormal movements, and autistic features. The girl

had history of convulsions and was taking sodium valproate. She also had poor feeding and respiratory abnormalities with intermittent periods of apnea associated with cyanosis.The girl was not able to sit alone on the chair and showed no eye contact and was not responding to her name (Fig.1).

She didn't have purposeful hand movement and was not able to hold things. She was hypotonic and ataxic, and had abnormal movements of the upper limbs.She couldn't be held erect in the standing movement, and she was not saying any word nor was babbling. Audiogram showed normal hearing. Brain MRI showed mild ventriculomegaly.

The girl was initially treated with cerebrolysin 1ml daily given by intramuscular injections for ten days.A second course of treatment given over one month included:

Cerebrolysin 3ml given by intramuscular injections every third day, received ten doses.Oral citicoline 2ml (200mg) daily.The protocol for this research was approved by the scientific committee of Iraq headquarter of Copernicus Scientists International Panel and conforms to the provisions laid out in the Declaration of Helsinki (as revised in Edinburgh 2000).

Results and Discussion

After the ten-day course of cerebrolysin, the girl showed dramatic improvement in muscle tone and was able to sit on a chair (Fig. 2), and she had no abnormal movements or apparent ataxia. It was also possible to hold her straight in the standing position.After the second course of treatment she showed marked improvement:She developed purposeful

movements and was able to hold feeding bottle with the assistant of her mother and fed herself (Fig. 3).

She was able to stand and step one step holding furniture (Fig. 3). She started babbling. She showed some reduction in the autistic features according to the mother, but at the clinic she remained not responding to her name and didn't show obvious eye contact. There is no specific nor satisfactory therapy for many of the disabling neurological disorders such as Rett syndrome.

Cerebrolysin solution which can be given intramuscularly consists of low-molecular-weight neuro-peptides including nerve growth factor, glial cell line-derived neurotrophic factor, brain-derived neurotrophic factor, and ciliary neurotrophic factor. Cerebrolysin solution is a safe, well-tolerated, and efficacious neuroreparative agent that is associated with a relatively wide therapeutic time window (Al Mosawi, 2017).

Previous reports of the use of cerebrolysin in patients with Rett syndrome suggested that it can improve behavior, attention level, motor functions, and nonverbal social communication.

The EEG parameters of the patients with Rett syndrome could also be normalized with the use of cerebrolysin (Gorbachevskaya et al., 2001). The use of cerebrolysin in childhood autism and autism spectrum disorder was also associated with a beneficial. Krasnoperova et al., (2003) reported the use of cerebrolysin in the treatment of nineteen children with childhood autism and eight with Asperger's syndrome. Treatment with cerebrolysin was associated with improvement of cognitive functions (expressive and receptive

speech, fine motoring, playing). Positive effects were noted in all the patients with Asperger's syndrome and in 89% of the patients with childhood autism.

Treatment was not associated with any side effect (Krasnoperova et al., 2003). Radzivil and Bashina (2006) described an open prospective clinical study of the use of cerebrolysin with a beneficial effect in the treatment of twenty five patients with childhood autism. Chutko et al (2017) reported that the use of cerebrolysin in the treatment of forty three children with autism spectrum disorders was associated with improvement observed in 27 patients (62.8%).

Cerebrolysin can improve brain functions through (Al Mosawi, 2017): Inhibition of apoptosis. Stimulation of neurogenesis through stimulating proliferation, differentiation, and migration of adult subventricular zone neural progenitor stem cells. Stimulation of stem-cell proliferation in the brain. Citicoline (cytidine diphosphate-choline) or cytidine 5 diphosphocholine is a nootropic agent with a very low toxicity and has been approved for treatment of head trauma, stroke, and neurodegenerative disease in Japan and Europe (Al Mosawi, 2017). As a safe neuro-protective agent, citicoline may improve brain functions through the following mechanisms (Al Mosawi, 2017):

Preservation of cardiolipin and sphingomyelin. Preservation of arachidonic acid content of phosphatidylcholine and phosphatidylethanolamine. Partial restoration of phosphatidylcholine levels. Stimulation of glutathione synthesis and glutathione reductase activity. Reduction of phospholipase A2 activity. Increasing glucose metabolism in the brain. Increasing cerebral blood

flow.Reducing oxidative stress and preventing excessive inflammatory response in the brain by inhibiting the

release of free fatty acids and reducing blood brain barrier breakdown.



Fig.1: A three-year old girl with Rett syndrome. The girl was not able to sit alone on a chair and showed no eye contact and was not responding to her name.



Fig. 2: After the first course of cerebrolysin, the girl showed dramatic improvement in muscle tone and was able to sit on a chair



Fig. 3: After the second course of treatment, the girl was able to hold feeding bottle with the assistant of her mother and fed herself. She was able to stand and step one step holding furniture

Enhancing cellular communication by increasing the availability of neurotransmitters, including acetylcholine, norepinephrine, and dopamine. Lowering increased glutamate concentrations and increasing the decreased ATP concentrations induced by ischemia. Increases dopamine receptor densities. Al Mosawi (2019) reported a retrospective observational study describing the use of cerebrolysin and citicoline for the treatment of eight of 19 patients with autism and Asperger syndrome. Seven patients had autism and one patient had Asperger syndrome.

All the treated patients 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 showed obvious improvement in the autistic features. In this study, the use of cerebrolysin and oral citicoline in the treatment of Rett syndrome resulted in an obvious improvement that has never been reported before.

References

- Galli V, Ciccarone V, Venuta A, Ferrari P, Cavazzuti GB.** Rett syndrome. Review of the literature and presentation of 2 clinical cases. *Pediatr Med Chir* 1985 Jan-Feb;7(1):23-7. PMID:4088913 [Article in Italian].
- Peters AC.** The Rett syndrome. *Tijdschr Kindergeneesk* 1985 Dec;53(6):232-4. PMID:4095698 [Article in Dutch].
- Rett A.** On a unusual brain atrophy syndrome in hyperammonemia in childhood. *Wien Med Wochenschr* 1966 Sep 10;116(37):723-6. PMID:5300597 [Article in German].
- Hagberg B, Aicardi J, Dias K, Ramos O.A** progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of 35 cases. *Ann Neurol.* 1983 Oct;14(4):471-9. PMID:6638958.
- Al Mosawi AJ.** A novel therapeutic approach for the treatment of brain atrophy (ed). LAP Lambert Academic Publishing, Germany, 2017.
- Gorbachevskaya N, Bashina V, Gratchev V, Iznak A.** Cerebrolysin therapy in Rett syndrome: clinical and EEG mapping study. *Brain Dev* 2001; 23 Suppl 1:S90-S93.
- Krasnoperova MG, Bashina VM, Skvortsov IA, Simashkova NV.** The effect of cerebrolysin on cognitive functions in childhood autism and in Asperger syndrome. *Zh*
- Nevrol Psikhiatr Im S S Korsakova** 2003; 103(6):15-8. PMID: 12872620 [Article in Russian].
- Radzivil MG, Bashina VM.** An effect of long-term cerebrolysin therapy in combination with neuroleptics on behavioral and cognitive disturbances in endogenous childhood autism]. *Zh Nevrol Psikhiatr Im S S Korsakova* 2006; 106(2):21-5. PMID: 16548370 [Article in Russian].

Chutko LS, Yakovenko EA, Surushkina SY, Kryukova EM, Palaieva SV. The efficacy of cerebrolysin in the treatment of autism spectrum disorders. Zh Nevrol Psikhiatr Im S S

Korsakova 2017; 117(9):71-75. PMID: 29053124 [Article in Russian].

Al Mosawi AJ. The use of cerebrolysin and citicoline in autism and Asperger syndrome. J Bio Innov 2019; 8(1), pp: 99-108.

