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A Novel Therapeutic Approach for Treating Rett Syndrome

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Abstract

Background: Rett syndrome is a rare X-linked dominant neuro-developmental and pervasive developmental disorder that has no satisfactory or effective treatment. The diagnosis is generally clinical and autistic feature is a typical finding in all patients. We have previously described the short-term treatment of an Iraqi girl with Rett syndrome who was first seen at the age of about three years. The girl was treated with intramuscular cerebrolysin and oral citicoline for 40 days. Treatment was associated with significant improvement with the development of purposeful movement and the ability to hold feeding bottle with assistant of the mother and feed her. She was able to stand and step one step holding furniture. She started babbling and showed some reduction in the autistic features.

Aim of the Study: The aim of this paper is to describe the extended treatment of the girl with Rett syndrome which was treated with a novel therapeutic approach which included intramuscular cerebrolysin, citicoline, and piracetam.

Patients and Methods: After the initial 40 days treatment, the girl received several treatment courses that included intramuscular cerebrolysin, citicoline, and piracetam.

Results: Several months of treatment resulted in improvements in behavior, autistic features, and mobility and she was walking confidently holding a wall or furniture**.** Treatment was not associated with any side effects.

Conclusion: Rett syndrome is a very complex neuro-developmental and pervasive developmental disorder that has no satisfactory or effective treatment. The use of novel therapeutic approach which included intramuscular cerebrolysin, citicoline and piracetam for the treatment of Rett syndrome resulted in within few months a significant improvement that have not been reported without treatment or with any other therapies before.

Keywords: *Rett Syndrome; Novel Treatment Approach*

Introduction

Rett syndrome is a rare X-linked dominant neuro-developmental disorder affecting only girls. The diagnosis is generally clinical and based on the characteristic abnormalities which include 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 [1-5]. We have previously described the short-term treatment of an Iraqi girl with Rett syndrome who was first seen at the age of about three years. The girl was treated with intramuscular cerebrolysin and oral citicoline for 40 days [1].

Aim of the Study

The aim of this paper is to describe the extended treatment of the girl with Rett syndrome which was treated with a novel therapeutic approach which included intramuscular cerebrolysin, citicoline, and piracetam.

Patients and Methods

The girl was seen for the first time at about the age of three years, she had 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 significant autistic features as she had no eye contact and was not responding to her name (Figure 1A) [1].

Figure 1A: *The girl was not able to sit alone on the chair and showed significant autistic features.*

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 was given over one month and included cerebrolysin 3 ml given by intramuscular injections every third day in the morning (Ten doses), and oral citicoline 2 ml (200 mg) daily. After the ten-day course of cerebrolysin, the girl showed dramatic improvement in muscle tone and was able to sit on a chair (Figure 1B) and she had no abnormal movements or apparent ataxia. It was also possible to hold her straight in the standing position.

Figure 1B: *After the first course of cerebrolysin, the girl showed dramatic improvement in muscle tone and was able to sit on a chair.*

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 (Figure 1C). She was able to stand and step one step holding furniture. She started babbling (Figure 1C). 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.

Figure 1C: *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.*

The girl was still having convulsions despite treatment with sodium valproate, but replacing valproate with carbamazepine was associated with disappearance of convulsions. Thereafter, the girl received intramuscular cerebrolysin 3 ml every third day in the morning (30 doses over three months), and oral citicoline 3 ml (300 mg) daily for three months. Oral melatonin was intermittently used at night to control nocturnal irritability and insomnia. However, no further important improvement was observed. Additional treatment courses were given (Table 1). Oral neuroleptics including trifluoperazine and prochlorperazine were used to control excessive irritability and episodes of crying. Nutritional support was also needed and was given mostly in the form of Royal jelly capsules.

The first course (One month)
Oral citicoline 2 ml (200 mg) once daily in the morning.
Oral prochlorperazine 5 mg once after lunch.
Oral trifluoperazine 1 mg once daily at night.
Royal jelly capsules three times daily.
The second course (One month)
Intramuscular cerebrolysin 3 ml given by intramuscular injections every third day in the morning (Ten doses).
Intramuscular citicoline 200 mg every third day (10 doses over 30 days).
The third course (One month)
Oral trifluoperazine 1 mg once daily at night.
Intramuscular citicoline 500 mg on alternate days (10 doses over 20 days).
The Fourth course (One month)
Oral citicoline 3 ml (300 mg) once daily in the morning.
Oral trifluoperazine 1 mg once daily at night.
Royal jelly capsules twice daily.
Intramuscular piracetam 3 ml (600 mg) on alternate days (10 doses over 20 days).
The Fifth course (Two month)
Oral citicoline 2 ml (200 mg) once daily in the morning.
Royal jelly capsules twice daily.
Intramuscular piracetam 4 ml (800 mg) on alternate days (20 doses over 60 days).

Table 1: *Additional treatment courses.*

Results

The earlier courses received by the patient and the first three courses in table 1 were used based on the available evidence provided by our published extensive experiences in the treatment of pervasive developmental disorders [2,4-12]. The courses in table 1 were associated with improvement in behavior and autistic features, and she responsive to her name and had some eye contact. was able to stand for long time without holding furniture with some anxiety and instability after the third course in table 1 (Figure 2A).

Figure 2A: *The girl was able to stand for long time without holding furniture with some anxiety and instability after the third course in table 1.*

The fourth and fifth courses which included intramuscular piracetam were based on the available evidence provided by our published extensive experiences in the treatment of various neurological disorders including various forms of brain damage and developmental

retardation [13-20]. After the fourth course and during the fifth course, she was standing confidently for long time was walking few steps holding a wall or furniture, but with some anxiety (Figure 2B). After the fifth course, she was walking more confidently holding a wall or furniture (Figure 2C).

Figure 2B: *After the fourth course and during the fifth course, she was standing confidently for long time was walking few steps holding a wall or furniture, but with some anxiety.*

Figure 2C: *After the fifth course, she was walking more confidently holding a wall or furniture.*

Discussion

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). After more than half century from the first description of the disorder, it remained without any specific or satisfactory therapies [1]. However, in this study several months of treatment with a novel therapeutic approach that included intramuscular cerebrolysin, citicoline, and piracetam, resulted in improvements in behavior, autistic features, and without the occurrence of any side effects.

Intramuscular cerebrolysin, citicoline, and piracetam have been used safely in a large number of neurological and neuro-psychiatric disorders with noticeable benefits [21-23].

Cerebrolysin, a mixture of free amino acids (85%) and 15% biologically active low molecular weight amino acid sequences. It contains low molecular weight neuro-peptides (Brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, nerve growth factor, ciliary neurotrophic factor [21]. Citicoline, a water-soluble natural substance is generally grouped with the B vitamins and is considered a form of the essential nutrient choline [22]. Piracetam can has a beneficial effects on impaired brain function, by improving neuronal and cognitive functions through increasing blood flow and oxygen consumption in the brain, and also improving the function of the neurotransmitters and brain neurotransmission. Piracetam has no significant side effect nor has acute toxicity at the doses used in human studies. The LD_{50} is 5.6 g/kg in rats and 20 g/kg in mice, indicating extremely low acute toxicity [23].

Conclusion

Rett syndrome is a very complex neuro-developmental and pervasive developmental disorder that has no satisfactory or effective treatment. The use of novel therapeutic approach which included intramuscular cerebrolysin, citicoline and piracetam for the treatment of Rett syndrome, resulted in within few months a significant improvement that have not been reported without treatment or with any other therapies before.

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Conflict of Interests

None.

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