THE USE OF CEREBROLYSIN AND CITICOLINE IN AUTISM AND ASPERGER SYNDROME

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ABSTRACT

There is no known curative therapy for pervasive developmental disorders (PDD) which include autism, Asperger syndrome, and atypical autism. Marked improvement or disappearance of autistic features in these disorders has not been reported with any therapy before.The aim of this paper is report a retrospective observational study describing the use of a new therapeutic approach for the treatment of eight of 19 patients with PDD. The treated patients ages ranged from 3 to 16 years. The new therapeutic approach which included injectable cerebrolysin as the main therapeutic component. The patients 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 PDD 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 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.

***Key words*:** Autism, Asperger syndrome, cerebrolysin, citicoline

INTRODUCTION

Pervasive developmental disorders include five chronic disorders marked byearly impairment in socialization, communication, and behavior. Pervasive developmental disorders have recently been called Autism spectrum disorder mostly by the American Psychiatric Association, and the term pervasive developmental disorders has been used with the term autism spectrum disorder interchangeably. The pervasive developmental disorders include:

1-Autism

2-Asperger syndrome accounting for less than 10% of autism diagnoses.

3-Childhood disintegrative disorder

4-Rett syndrome

5-Pervasive developmental disorder not otherwise specified (PDD-NOS) including atypical autism is the most common accounting for about 47% of diagnoses. PDD-NOS are sometimes called Atypical autism (Al Mosawi, 2018). The onset of pervasive developmental disorders generally begins during infancy. However, the condition is usually not recognized until the age of three.Manifestations usually marked by social and communication impairment, and behavioral problems including:Difficulties in using and understanding language.Impaired social interaction marked by lack of eye contact, lack of facial responses and not responding to own name appropriately.Repetitive body movements or behavior patterns including hand flapping There is no known curative therapy for PDD which include autism, Asperger syndrome, and atypical autism (Al Mosawi , 2018)..

Marked improvement or disappearance of autistic features in these disorders has not been reported with any therapy before.The aim of this paper is to report a retrospective observational study describing the use of a new therapeutic approach for the treatment of PDD.

Materials and Methods

During a period of 14 months (December,2017-January,2019), nineteen patients with PDD particularly autism and Asperger syndrome were observed at the pediatric psychiatry clinic at the Teaching Hospital of Baghdad Medical City. Sixteen patients were males and three patients were females. The patients ages ranged from 3 to 16 years. Eight of the nineteen patients (Seven males and one female) were treated with a new therapeutic approach which included injectable cerebrolysin as the main therapeutic component.

The patients ages ranged from 3 to 8 years. Seven patients had a diagnosis of autism and one patient had a diagnosis of Asperger syndrome (Patient-5).The new approach aimed at improving the cardinal feature of PDD 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.

Most patient also required neuroleptics to control hyperactivity and other abnormal behaviors. Trifluoperazine and prochloperazine were used as necessary. Risperidone was also used in one patient. Some patients also received citicoline as an adjunctive therapy to improve speech development. It is expected that improving social interaction will contribute to improving other features especially verbal communication and speech. Courses of intramuscular cerebrolysin were given in individualized regimen depending on the age and severity of the illness and with aim of improving social interactions including response to name, looking at faces, and eye contact.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) www.wma.net/e/policy/b3.htm.

Table 1 summarized the courses of therapy received by the eight treated patients.

Table 1: courses of therapy received by the eight treated patients

	Age (year)	Sex	Treatment
Patient-1	Four	Male	Ten intramuscular injections of cerebrolysin, four ml given every third day over one months
Patient-2	Three	Male	**The first course** consisted of ten intramuscular injections of cerebrolysin, one ml given every third day over one months. **The second course:** A-Six intramuscular injections of cerebrolysin, one ml given every five days over one months. B-Six intramuscular injections of citicoline, two ml given every five days over one months. **The third course:** A-Ten intramuscular injections of cerebrolysin, three ml given every three days over one months. B-Citicoline syrup , three ml orally daily as a single dose in the morning. **The fourth course** of therapy consisted of ten intramuscular injections of cerebrolysin, four ml given every three days over one months.
Patient-3	Three	Male	**The first course:** A-Ten daily injection of cerebrolysin, one ml intramuscularly over ten days. B-Oral trifluoperazine 1mg at night.

			The second course: A-Ten daily injection of cerebrolysin, three ml every third intramuscularly over one month. B-Oral trifluoperazine 1mg at night. C-Citicoline syrup , three ml orally daily as a single dose.
Patient-4	Five &half	Male	A-Ten daily injection of cerebrolysin, thee ml intramuscularly over ten days. B-Oral trifluoperazine 1mg at night.
Patient-5	Eight	Male	Ten doses of 1 ml cerebrolysin by intramuscular injection every other day.

Table 1 (Cont.): courses of therapy received by the eight treated patients

	Age (year)	Sex	Treatment
Patient-6	Six	Female	**The first course:** A-Ten daily injection of cerebrolysin, three ml every third day intramuscularly over one month. B-Oral trifluoperazine 1mg at night. C-Prochlorperazine 5mg tablet daily taken during the afternoon. **The second course of:** A-Ten daily injection of cerebrolysin, five ml every third day intramuscularly over one month. B-Oral trifluoperazine 1mg at night. C-Prochlorperazine, 5mg tablet daily taking during the afternoon. D-Risperidone 0.5 mg daily at night during the first week, thereafter continued at 1 mg dose daily. **The third course** of treatment was the same as the third course, but with addition of Citicoline (Somazina) syrup, three ml orally daily as a single dose.
Patient-7	Six	Male	**Three courses** of treatment over three months and included: A-Intramuscular cerebrolysin 5ml every third day given over one month. B-Trifluoperazine in a daily dose of 5mg at night C-Prochloperazine in a daily dose of 5mg in the afternoon was added during the third month.
Patient-8	Six	Male	**Four courses** of treatment over four months included: Trifluoperazine in a daily dose of 5mg at night Prochloperazine in a daily dose of 5mg in the afternoon. Intramuscular cerebrolysin 5ml every third day given over one month.

Figure 1 shows patient-3 after treatment.

Figure 2: The sixteen year old boy

RESULTS

All the seven patients with autism and the patient with Asperger syndrome treated with this new approach showed improvement and marked lessening of the autistic features with six patients (Patients 1,2,3,4,7,8) showed complete disappearance of the main autistic features. Treatment was also associated with initiation of speech and improvement of repetitive behaviors.When these six patients were examined by physicians after treatment, the physicians couldn't identify any autistic feature and didn't make the diagnosis of pervasive developmental disorder or autism.It seems that the six patients who achieved complete disappearance of the main autistic features will need an intensive learning especially of speech to abolish the effect of the time when they were under the effect of autistic feature, and to push them toward a possible cure of their illness.

Figure 1 shows patient-3 after treatment. The boy showed normal social interaction manifested by appropriate response to his name, normal eye contact, responding to the doctor when asked him to take the pen and try to draw a line and a circle, waving goodbye when leaving the examination room.No patient developed any side effects. Ten of 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.A striking example of these patients was a sixteen years old boy who received before referral many therapeutic interventions and special education, but continued to have severe autistic features and was unable to say any word.

Figure 2: The sixteen year old boy who didn't received continued to have marked autistic features as he was not responding to his name, didn't show any eye contact, displayed repetitive in form of spinning and became occupied with washing basin at the clinic.However, one of the eleven patients was treated with citicoline injection showed obvious improvement in the autistic features.

Discussion

Impairment of social interactions is the most important distinguishing feature that makes autism and the pervasive developmental disorders (Autism spectrum disorders) distinctive from other developmental disorders.There is no known curative therapy for pervasive developmental disorders which includes autism and Asperger syndrome.Marked improvement or disappearance of autistic features in these disorders have not been reported with any therapy before.Cerebrolysin is a mixture of low-molecular-weight neuro-peptides including brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, nerve growth factor, and ciliary neurotrophic factor (Al Mosawi , 2017).

The safety, tolerability, and efficacy of neuroreparative cerebrolysin therapy have been established in clinical trials included adults with stroke and Alzheimer s disease. Cerebrolysin is associated with a relatively

wide therapeutic time window (Al Mosawi , 2017).

The use of cerebrolysin in girls with Rett syndrome improved behavior, attention level, motor functions, and nonverbal social communication. The EEG parameters of the patients were also normalized (Gorbachevskaya et al,2001).The use of cerebrolysin in childhood autism and autism spectrum disorder was also reported to be beneficial.

Krasnoperova et al (2003) treated 19 children with childhood autism and eight with Asperger's syndrome aged 2-8 year with cerebrolysin. All the patients of Krasnoperova et al received 10 microinjections (intramuscularly and perinervously) of 0.1 ml cerebrolysin daily during five days.

Treatment with cerebrolysin resulted in improvement of cognitive functions (expressive and receptive speech, fine motoring, playing). Positive effects were revealed in all the patients with Asperger's syndrome and in 89% of the patients with childhood autism. Treatment was not associated with any negative effects (Krasnoperova, et al 2003).Radzivil and Bashina (2006) conducted an open prospective clinical study that included twenty five patients with childhood autism aged from three to eight years (mean age 5 years 11 months).

The patients were treated with two therapeutic courses (15 intramuscular cerebrolysin injections of 1.0 ml every other day per course) with 2 months interval and basic antipsychotic therapy using typical neuroleptics in age adjusted dosages. The duration of the study was 180 days.Significant or very significant improvement was observed after the first cerebrolysin course in 38% patients.Significant or very significant improvement was observed after the second cerebrolysin course in 50% patients. Significant or very significant improvement was observed after 180 days in 71% patients.There were no cases of deterioration during the trial.Chutko et al (2017) treated forty three children with autism spectrum disorders, aged 4-6 years with cerebrolysin. Cerebrolysin therapy was associated with improvement in 27 children (62.8%).

Citicoline (cytidine diphosphate-choline) or cytidine 5 diphosphocholine is a psycho-stimulant/nootropic. Citicoline has a very low toxicity and has been approved for treatment of head trauma, stroke, and neurodegenerative disease in Japan and Europe (Al Mosawi , 2017).

This paper provided an evidence that autism can be cured but of course without abolishing the effect of the condition on learning and speech development.

Conclusion: Further studies are vital to study this new therapeutic approach.

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