The use of cerebrolysin in pediatric Wohlfart Kugelberg Welander syndrome

Abstract

**Background:** Juvenile spinal muscular atrophy which is also called Wohlfart Kugelberg Welander syndrome, 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 appear gradually leading to a variable degree of disability. There is no known satisfactory therapy for the treatment of Wohlfart Kugelberg Welander syndrome. The aim of this paper is to describe the novel use of cerebrolysin in the treatment of pediatric Wohlfart Kugelberg Welander syndrome.

**Patients and methods:** 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.

**Results:** 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.

**Conclusion:** A study enrolling more patients is recommended.

**Keywords:** wohlfart-kugelberg-welander syndrome, treatment, cerebrolysin

Introduction

Juvenile spinal muscular atrophy which is also called Wohlfart Kugelberg Welander syndrome, is generally 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.1-3

Wohlfart Kugelberg Welander syndrome is a genetic disorder results from degeneration of the anterior horn cells and motor fibers to the proximal muscles of the limbs. It presents with lower motor neuron signs including weakness, wasting, and loss of tendon reflexes especially of the quadriiceps.

The disorder is associated with a steady, slowly progressive course, and weakness affects first the large muscles of the buttock and thighs. Weakness may affect later the muscles of the upper arm. Late in the course of this condition, the more distal limb muscles may also be affected. Muscles of the face and neck are not affected.

There is no known satisfactory therapy for the treatment of juvenile spinal muscular atrophy (Wohlfart Kugelberg Welander syndrome). The aim of this paper is to describe the novel use of cerebrolysin in the treatment pediatric Wohlfart Kugelberg Welander syndrome.

Patients and methods

Two unrelated Iraqi boys pediatric with 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 can not 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.

Results: 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.

Conclusion: A study enrolling more patients is recommended.

Keywords: wohlfart-kugelberg-welander syndrome, treatment, cerebrolysin
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Right ulnar nerve.
Right and left sural nerve.
Right and left common peroneal nerves.
Tibial nerves.

b. The nerve conduction study (Table 1) showed
   Reduced amplitude of the compound action potentials.
   Normal sensory parameters.
   Prolonged distal motor latencies.
   Lower border and reduced motor conduction velocities.
   Prolonged F-wave latencies.
   No responses were obtained from EDB and abductor hallucis muscles.
   No evidence of focal conduction block.

Needle electromyography (EMG) study was performed on
Right FDI.
Right deltoid.
Right brachioradialis
Right and left vastus medialis.
Right and left tibialis anterior.
EDB muscles.

c. Needle electromyography (EMG) study (Table 1) showed
   Spontaneous activity grade 1-2 in the form of fibrillation, positive sharp,
   myotonic discharges, and no peripheral fasciculations.
   The average duration of 20 motor units:
   Right deltoid=22.8msec (n=10.5msec)
   Right biceps=22.9msec (n=10.3msec)
   Right vastus medialis=22.2msec (n=10.5msec)
   Left vastus medialis=22.5 msec (n=10.5msec)
   Right tibialis anterior=14.2 msec (n=10.5 msec)
   Polysphasia of long duration high amplitude was observed in 50-60%.

The second patient was more severely affected than the first patient. The boy was also first seen at the age of four years at the Children Teaching Hospital of Baghdad Medical City. The parents thought that his walking was rather awkward, and he was running rather slowly. He also had difficulty when climbing stairs.

When the patient walked at the clinic, his gait was rather awkward, and he was about to fall when he squatted (Figure 2). However, Gower’s sign was negative, and the sensory examination was normal. Like the first patient, the second patient was also unable to stand on one foot momentarily.

Figure 1 The less severely affected patient. (A) The boy walked at the clinic and no obvious gait abnormality. (B) The boy was unable to stand on one foot without holding the furniture.

Table 1 The findings of nerve conduction study and needle electromyography of the less severely affected patient

| Nerve                      | Sensory | Motor            |
|----------------------------|---------|------------------|
|                            | Latency msec/cm | Amplitude (uv) | SNCV m/sec | Muscle | DML msec/cm | WNCV msec/cm | F-wave Latency |
| Right median               | 2.5     | 22.6             | 55         | APB    | 4.2        | 50.3         | 25.6          |
| Right ulnar                | 2.3     | 25.6             | 56.3       | FDI    | 4.3        | 51.6         | 26.5          |
| Right common peroneal      |         |                  |            | Tibialis Ant |         | 4.6          |              |
| Left common peroneal       |         |                  |            | Tibialis Ant |         | EDB No response |
| Right tibial               |         |                  |            | Gastroenemious |     | 4.4          |              |
|                           |         |                  |            | Abductor Hallucis |   | No response |
|                           |         |                  |            | Tibialis Post |    | 5.9          |              |
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Serum creatine phosphokinase was measured during February, 2018 and it was 185u/L (Normal: 40-200u/L). However, Serum creatine phosphokinase was measured twice during July, 2018 and it was mildly elevated (210, and 255u/L).

g. Needle electromyography (EMG) study was performed on
   Right deltoid.
   Right biceps.
   Right brachio-radials.
   Right and left vastus medialis.
   Right and left tibialis anterior.

h. Needle electromyography (EMG) study (Table 2) showed
   Spontaneous activity grade 1-2 in the form of fibrillation, positive
   sharp, myotonic discharges, no peripheral fasciculations.
   The average duration of 20 motor units:
   Right deltoid=14.8msec (n=8.5msec).
   Right biceps=15.9msec (n=8.3msec).
   Right vastus medialis=15.2msec (n=8.5msec).
   Left vastus medialis=14.3msec (n=8.5msec).

   Right tibialis anterior=14.2msec (n=10.5msec).
   Left tibialis anterior=15.3msec (n=10.5msec).

   Polypaysia of long duration high amplitude was observed in 30-40%.
   Reduced recruitment pattern of high amplitude.

   The findings of the nerve conduction and electromyography (EMG) study showed no evidence of peripheral polyneuropathy or
   muscle disease.

   At about the age of four years and half year, during July, 2018, the
   boy was treated with ten intramuscular cerebrolysin given at a dose of
   3ml on alternate days.

Table 2 The findings of nerve conduction study and needle electromyography of the more severely affected patient

| Nerve                        | Latency m/sec/cm | Amplitudeuv | SNCV m/sec | Muscle     | DML Msec/cm | WNCVmsec/cm | F-wave Latency |
|------------------------------|------------------|-------------|------------|------------|-------------|--------------|----------------|
| Right median                 | 2.5              | 22.6        | 55         | APB        | 3.4         | 53.3         | 20.7           |
| Right ulnar                  | 2.3              | 25.6        | 56.3       | FDI        | 3.7         | 53.6         | 21.7           |
| Right common peroneal        |                  |             |            | Tibialis Ant | 3.7         |              |                |
|                              |                  |             |            | EDB        | 4.8         | 44.3         | 42.6           |
| Left common peroneal         |                  |             |            | Tibialis Ant | 3.9         |              |                |
|                              |                  |             |            | EDB        | 4.9         |              |                |
|                              |                  |             |            | Tibialis post | 5.5     |              |                |
|                              |                  |             |            | Tibialis post | 5.6     |              |                |

Figure 2 The more severely affected boy had noticeable gait abnormality and was about to fall when he squatted.

Table 2 The findings of nerve conduction study and needle electromyography of the more severely affected patient

c. Nerve conduction study was performed by surface and needle electrode on
   Right and left median nerve.
   Right ulnar nerve.
   Right and left sural nerve.
   Right and left common peroneal nerves.
   Tibial nerves.

d. The nerve conduction study (Table 2) showed
   Reduced amplitude of the compound action potentials on proximal
   and distal stimulation site.

   Normal sensory parameters.
   Normal distal motor latencies, motor conduction velocities, and
   also normal
   F-wave latencies.
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The protocol for this therapeutic trial 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

The treatment was not associated with any side effects. Treatment didn’t affect muscle mass and atrophy of the upper thighs remained obvious. After treatment improvement in his stance and gait was reported by the mother and was also observed at the clinic.

Before treatment the boy had undeniable difficulty in squatting and was about to fall when he squatted, while after treatment the boy was easily squatting without any difficulty (Figure 3).

Both the first boy who was less affected and the cerebrolysin treated patient had difficulties in standing on one foot without support. However, although the second boy experienced some difficulty in standing on one foot without support after treatment, he was definitely able to stand momentarily on one foot for 2-3 seconds (Figure 3).

Discussion

Recent research evidence suggests that cerebrolysin is endowed with interesting pharmacological properties that can make it useful in the treatment of various childhood neurologic and psychiatric disorders including mental retardation, pervasive developmental disorders including autism, brain atrophy, cerebral palsy, Rett syndrome and myelomeningocele.

Cerebrolysin is a peptidergic therapeutic agent containing mainly biologically active neuro-peptides including brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, nerve growth factor, and ciliary neurotrophic factor. It has a nerve growth factor like activity on neurons, and growth promoting efficacy in different neuronal populations from peripheral and central nervous system.

Cerebrolysin has been shown to have neurotrophic and neuroprotective properties effects in vitro and in vivo.

The effects of cerebrolysin seems to be similar to the pharmacological activities of naturally occurring nerve growth factors.

The neuroreparative effects of cerebrolysin in various neurologic and psychiatric disorders may result from

- Inhibition of apoptosis.
- Improving synaptic plasticity and induction of neurogenesis.
- Augmenting the proliferation, differentiation, and migration of adult subventricular zone neural progenitor stem cells, contributing to neurogenesis.
- Induction of stem-cell proliferation in the brain.

This study suggested that intramuscular cerebrolysin is a promising agent for a new effective treatment of Wohlfart Kugelberg Welander syndrome.

Conclusion

A study enrolling more patients is recommended.

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Conflicts of interest

The authors report no conflicts of interest.

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References

1. Wohlfart G, FEX J, Eliasson S. Hereditary proximal spinal muscular atrophy, a clinical entity simulating progressive muscular dystrophy. *Acta Psychiatr Neurol Scand.* 1955;30(1–2):395–406.
2. Kugelberg E, Welander L. Heredofamilial juvenile muscular atrophy simulating muscular dystrophy. *AMA Arch Neurol Psychiatry.* 1956;75(5):500–509.
3. Ghetti B, Amati A, Turra MV, et al. Werdnig-Hoffmann–Wohlfart-Kugelberg-Welander disease. Nosological unity and clinical variability in intrafamilial cases. *Acta Genet Med Gemellol (Roma).* 1971;20(1):43–58.
4. Al–Mosawi AJ. *A novel therapeutic approach for the treatment of brain atrophy.* 1st ed. Saarbrücken; LAP Lambert Academic Publishing. 2018.
5. Al-Mosawi AJ. *A novel therapeutic approach for idiopathic mental retardation.* 1st ed. Saarbrücken; LAP Lambert Academic Publishing. 2018.
6. Al-Mosawi AJ. *A new therapeutic approach for cancer.* *J Bio Innov.* 2019;8(1):99–108.
7. Al-Mosawi AJ. New Therapies for the treatment of spastic cerebral palsy. *Med J Clin Trials Case Stud.* 2019; 3(2): 000209.
8. Al-Mosawi AJ. New therapies for Rett syndrome. *J Bio Innov.* 2019;8(3):301–307.
9. Al-Mosawi AJ. New Medical Therapies for The Treatment of Myelomeningocele. *Surgical Medicine Open Access Journal.* 2019;2(4):1–4.