

Case studies of intranasal administration of C-peptide to persons with brain damage

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Abstract

In the beginning of 2020 a team of special education teachers, speech-therapists, a psychologist and a health visitor conducted a pilot study in order to evaluate the experiences of clients using the intranasal C-peptide spray. Our study was based on two sources: video-recordings documenting the cases and a questionnaire filled in during a conversation with the parents or carers of the clients. The aim of the questionnaire was to find out information we could not find in the videos.

In the case of children with ASD we interviewed their parents obtaining data that is "weak" on one hand and "strong" on the other. This approach reflects our belief that parents know their children best, they can observe even minimal changes in their behaviour and abilities in everyday life. This information wouldn't be available in school or any other institutional settings. At the same time we have to keep in mind that they may be biased, they want to see the positive changes, therefore they may over-emphasize the improvements.

The data we collected, evaluated and summarized is soft data, but we verified it, and analyzed it applying our professional knowledge and tried to exclude any false information.

Our findings include that the main favourable changes parents and family members reported are longer and more relaxing sleep, improved social skills in autistic children and better expression of emotions in clients with acquired brain injury (ABI).

Since we involved in our study people in a very sensitive situation, e.g. families with a child with ASD, adults after ABI and their family members, and a few persons with schizophrenia, we have to count with the positive transfer affects. Even a slight positive change can bring hope to these people. The results may bring them in a better mood and give them hope, which may cause them to overestimate the effects of the spray.

As a conclusion we recommend to start clinical examinations concerning the effects of the usage of the intranasal C-peptide spray.

Background

C-peptide is the abbreviation of *connecting peptide* a short 31-amino-acid polypeptide that connects insulin's A-chain to its B-chain in the proinsulin molecule. The C-peptide, after separating from the proinsulin in the beta-cells of the pancreas, it enters the blood circulation in an amount equimolar to the insulin. While its half-life is significantly longer than that of the insulin (approximately seven times longer), it has become an important measure of the beta-cell function.

Later, after the 90s a number of clinical trials found that the replacement of C-peptide resulted in the improvement of several consequential problems in diabetes mellitus type 1.

In animal models it was beneficial for kidney function, the peripheral and the central nervous system. It was also noticed in several clinical investigations that C-peptide was able to improve the functioning of the impaired parasympathetic nervous system.

Intranasal administration was first tested in animal experiments. An investigation involving diabetic rats in 2018¹ revealed that insulin is absorbed through the blood-brain barrier into the cerebrospinal fluid five times more effectively than C-peptide². Intranasally administered C-peptide passes by the blood-brain barrier³, therefore the intranasal use of C-peptide could be the most effective way of administering it into the central nervous system. Successful application in animal tests raises hopes concerning future use in human brain damage prevention⁴.

Insulin has been administered intranasally „off label” since 2005 in children with Phelan-McDermid syndrome, which causes severe disturbances in the central nervous system, often resulting in autistic symptoms. In a publication by Schmidt⁵ on the effect of intranasal insulin it was found to improve cognitive and motor functions, as well as non-verbal communication in children with Phelan-McDermid syndrome. Later it was confirmed by randomized double-blind tests that the administration of intranasal insulin led to significant improvement of cognitive abilities and social skills in children with Phelan-McDermid syndrome above the age of 3⁶.

One of the most important genes responsible for the symptoms of the Phelan-McDermid syndrome is Shank3. During the research of Shank3 groundbreaking biological discoveries were made, which shifted the focus of therapeutic solutions from intranasal insulin to intranasal proinsulin C-peptide. The decrease of Shank3 protein, an important feature of Phelan-McDermid syndrome, leads to the disruption of the healthy actin network of the cytoskeleton. When researchers in animal tests inhibited the protein cofilin that was too active in the separation of actin, the impaired, typically autistic social abilities of animals significantly improved.⁷

Too active cofilin can be also responsible for the disruption of the blood brain barrier and the increase of its permeability⁸. The role of cofilin in the inflammation processes in the brain is even more relevant, since it has a significant role in over-activating the cerebral immune cells, the microglial cells and in amplification of the neurotoxic processes⁹.

Researchers highlighted the fact that several neurological diseases including stroke, bipolar disorder, autism, schizophrenia, Alzheimer's disease can be improved by the reduction of cofilin activity or recovering adequate functioning of it¹⁰. Brain researchers suggest that finding the appropriate peptid therapy for this purpose could regulate cofilin activity without toxic side effects¹¹.

In the sample of our cases there are three children with Phelan-McDermid syndrome, who have been administered intranasal C-peptide for over a year. Two of them have previously been given off-label intranasal insulin therapy already recommended by several physicians as a possible therapeutic intervention. It is remarkable that in these two cases further improvement, such as development of cognitive, communication and social skills were experienced – more intensively than in the case of intranasal insulin therapy. Based on this observation our assumption is that the effect of intranasal C-peptide exceeds that of the intranasal insulin. The experience with the intranasal insulin therapy was that the positive tendency slowed down and stopped after a period of half or one year of administration.

The Phelan-McDermid syndrome is considered nowadays as one of the most important models of autism, schizophrenia, bipolar disorder, Alzheimer's disease, since each of these disorders feature the significant reduction of Shank3 protein. Therefore the regulation of cofilin can be a common issue in researching possible therapeutic interventions for these disorders.¹²

The Phelan-McDermid syndrome is characterized by regressions, therefore appropriate therapy to counteract these would be a major benefit for the families of these patients.¹³

Occasionally Alzheimer's disease¹⁴ is present in children with this syndrome, and the severe white matter damage is also a typical additional feature¹⁵. In certain forms of autism developmental regression is common possibly due to increased proinflammatory cytokines, oxidative stress and neuronal cell loss.¹⁶ In a mouse model of autism significant oxidative stress was measured due to the accumulation of 3-nitrotyrosin¹⁷.

Considering clients with traumatic brain injury in our sample it is important to note that according to clinical investigations those patients in coma have the least chance of recovery, who have the highest level of 3-nitrotyrosin indicating oxidative stress in their cerebro-spinal fluid¹⁸. Also elevated 3-nitrotyrosin was measured in the cerebro-spinal fluid of patients after stroke¹⁹.

Experiments with animals confirmed that in the case of traumatic brain injury, if nitrostatic and oxidative damage can be reduced by brain cooling, damage to the brain can be decreased. Researchers identified 3-nitrotyrosin as the direct cause of neuronal cell loss²⁰.

It is worthwhile pointing out that C-peptide can reduce nitrostatic stress and the amount of nitrotyrosine, which is elevated by the stress caused by high levels of glucose²¹. This is one of the effects of C-peptide in our study that most probably contributed to the remarkable improvement of the developmental level of children with neurological disorders and the chances of survival and recovery of patients with traumatic brain injury. Another very important effect of C-peptide is that it can favourably influence the parasympathetic nervous system, that can be measured by heart-rate variability (HRV). This was proven both in animal models and in clinical experiments^{22,23}.

The state of the parasympathetic nervous system is considered as one of the most important indicators of human health. Lower HRV predicts shorter life expectancy²²:

HRV in children and adults with autism spectrum disorder is significantly lower than in their healthy fellows^{24,25}. In children diagnosed with autism higher HRV correlates with better expressive and receptive language skills²³.

In persons with traumatic brain injury higher HRV means significantly better chances of survival²⁴.

Proinsulin C-peptide is able to adequately inactivate overactivated cofilin, so its ability to regulate brain cells and immune cells can be of greater importance than assumed by researchers until now²⁵.

The mechanism of action of C-peptide, stopping neuronal cell loss can contribute to the improvement of quality of life and chances of survival not only for persons with traumatic brain injury, but also for people with other brain disorders, such as autism spectrum disorder or stroke²⁶. The relevance of therapy using intranasal C-peptide is confirmed by the fact that the pharmacological therapies to cure traumatic brain injury and stroke did not prove to be effective enough in clinical experiments²⁷.

Study design

The study we undertook in the beginning of 2020 was based on the analysis of the video recordings and the evaluation of a questionnaire. The project team consisted of the following experts:

Tímea Gyertyán-Ági special education teacher, Nikolett Horváth and Erika Szücsné Göblyös speech therapists, Anikó Szepesi psychologist, Anita Varga and Magdolna Virág nurses. Designing our questionnaire we bore in mind the aspects of our analysis.

The questionnaire covered the following functions:

- * sleeping cycle, quality of sleep, level of wakefulness
- * eating, drinking, appetite, digestion
- * motor functions: gross and fine motor skills
- * cognitive abilities (attention, interest, memory)
- * learning (reading, writing, accepting rules, discipline)
- * speech and communication (understanding, expressive speech, non-verbal communication)
- * emotions (mood, expressing emotions. reactions to others' feelings)
- * social skills (relationship with other people)
- * behavioural problems, neurological symptoms (stereotypical behaviour)
- * level of independence (eating, dressing, using the toilet)

Selection of the cases

There were three groups of people with similar problems and symptoms, where the users of the spray or their families reported a quick and significant positive effect: the first group were children with autism spectrum disorder, the second group were persons with acquired brain injury and the third group were adults with schizophrenia.

After collecting video recordings of people from these three groups, contacting them or their families and obtaining their permission to participate in our study, we found 12 children, 9 persons with ABI and 3 persons with schizophrenia, and we established the sample of our pilot-study. The duration of using the intranasal C-peptid spray was between 3 to 12 months.

Description of the applied proinzulin C-peptid spray

The participants of our study used Vargapeptide skin-spray off label as an intranasal spray, on their own responsibility. The spray is produced and distributed by Max-Immun Ltd.

It was applied in the same way as the intranasal insulin, and administered among children with Phelan-McDermid syndrome. A 20 ml bottle contains a solution of 18 ml C-peptide.

One puff of the spray contains 0.108 mg proinsulin C-peptid. In Vargapeptide 0.5 the corresponding amount is half of that, 0.05 mg, in Vargapeptide 2 the amount is 0.216 mg.

The spray contains 0.8 % NaCl. The other ingredients meet pharmaceutical grade purity standards. The purity of proinsulin C-peptid is 98-99%.

Introducing the cases

The age range of the children in the sample was 3-4 to 14 years. Among the 12 children there were 4 girls and 8 boys. The diagnosis was Phelan_McDermid syndrome in 3 cases, in 6 cases it was autism spectrum disorder, two cases were born extreme prematurely, with a birth-weight under 1000 grams, and one child was diagnosed with mental retardation. In the former three cases the behaviour of the child in the video film and the parents' description were clearly suggestive of autism, therefore we considered them as children with ASD, not yet diagnosed.

The second group was persons with aquired brain injury. Their age ranged from 13 to 29 years, 4 of them women and 5 men. The onset of the brain damage ranged from 10 years to almost one year.

The third group consisted of three men diagnosed with schizophrenia at the age of 27-29 yers.

Results

Children with ASD

The parents of the target group reported the following changes:

- **SLEEPING**

There was no change in the sleeping habits of children sleeping well already prior to using the spray. In each case where sleeping problems were present it ended after administering the spray. A typical problem was not sleeping long enough and waking once or several times during the night. After a few weeks of using the spray these children slept through the night and the night wakings stopped altogether.

- **SPEECH AND COMMUNICATION**

Analyzing the video recordings and interviewing the parents we were interested in the changes in comprehension and production of speech, and nonverbal communication. In each case parents reported significant progress in the speech function and communication. There were five non-verbal children, in their cases comprehension skills and the non-verbal reactions improved, e.g. nodding or shaking the head to express 'yes' and 'no'.

When evaluating verbal children, we compared their level of speech at the onset of the treatment and at the time of our study. In each case we found an expansion of their vocabulary. In the cases of children in the starting phase of speech development this meant using new words, while those who already communicated by words, started to construct simple sentences. In one case the parents observed much better articulation.

- **SOCIAL SKILLS**

6 parents reported the appearance of longer and more intensive – or any – eye-contact as an important change. Longer eye-contact is a prerequisite to the ability to read and interpret mimics and facial expressions a factor in achieving better social skills. In 5 cases the parents perceived a clear change in their children's relationship with unfamiliar people. These children had difficulties in accepting the presence of any strangers, e.g. physical contact with unknown people. All these 5 parents reported that their child now accepts the presence of visitors, and can also tolerate other children around them (e.g. on a play-ground, visiting another family and meeting their children, etc.)

In four cases the parents did not find significant change in this field.

- **COGNITIVE ABILITIES: ATTENTION, MEMORY, LEARNING**

There were two domains in the improvement of children's cognitive abilities: attention, and reaction time.

Improved attention was reported in regards to five children, all of them attend school, kindergarden or therapy sessions in special education classes. Both parents and teachers noticed and commented the changes of improved attention in the cases of these children. Parents reported that their two small children, who had not yet started the kindergarden are more ready to join games and playful learning activities. Earlier

one of them used to throw everything around, and the other was only engaged with his own activities. After starting to use the spray they gradually got involved in games and this created a chance of learning through acquisition.

There was a remarkable comment from parents about quicker reactions by their children. Each of the families concerned noticed that their child started giving quicker reactions when they were called by their name asked to do something. It was interesting to compare this comment with the original problem of more than half of the parents whose children became often easily agitated, restless, and unable to focus their attention. In their cases quicker reaction did not mean increasing their general restlessness, but the opposite. Quicker reactions made them capable of giving feedback, turning their attention to the person talking to them, and providing adequate response. These even made them calmer, eased their motor agitation and this was a prerequisite to activating other skills and abilities.

- **BEHAVIOURAL PROBLEMS, NEUROLOGICAL SYMPTOMS (STEREOTYPICAL BEHAVIOUR)**

The most important change for the parents in the field of behavioural problems was the lower levels of anger, and in some cases even the disappearance of bursts of anger. This was reported by five parents whose children's anger reactions were serious problems before. In one case the anger resulted even in self-abuse, which also stopped following the start of the treatment.

Probably the most severe case in our sample was a child with severe mental retardation showing aggressive behaviour. After the spray treatment started a favourable change unfolded, and the child's behaviour became gradually treatable and acceptable for the parents.

In one case a parent reported the stopping of the stereotypical behaviour of flickering hands in front of his eyes.

In two other cases the children had a repetitive activity. One kept opening and closing the door, and the other kept pulling out and pushing back the drawer. Both habits disappeared after starting to use the spray. The parents found that the improvement resulted from their children's ability to engage in games and play.

- **EMOTIONS (MOOD, EXPRESSING EMOTIONS, REACTIONS TO OTHERS' FEELINGS)**

The changes in the child's mood and emotional life was evaluated as significant by 5 parents. Two of them highlighted that their child, formerly prone to crying became balanced and happy. Two parents reported that their hyperactive, agitated child became calmer, and one parent said her distressed, moody child became emotionally more balanced and is more often in a good mood.

- **LEVEL OF INDEPENDENCE (EATING, DRESSING, USING THE TOILET)**

In one of our cases the biggest problem was the child's incontinence in stressful situations. The mother of that child experienced a great improvement in her son's life as they can now move around freely and attend programmes without the fear of incontinence.

In other areas of skills of independent living the parents did not mention any significant change.

- **MOTOR FUNCTIONS: GROSS AND FINE MOTOR SKILLS**

In the field of motor functions there was no significant change in our cases. A few parents reported that their child's walking became more stable and their sense of balance improved.

Experience gained from the cases of acquired brain injury

The prognosis of acquired brain injury depends on a number of factors, such as the localization, the extent, and the type of the damage, also the onset of the injury and time passed since the injury, along with many other medical and physiological factors. The hope is in the plasticity of the brain, which means that the neurons may modify their connections and re-wire the brain. In case of a damage neural pathways can replicate another's function, correct or overtake the lost function by rerouting signals along a different pathway. The question for us was if we can see signs of the effect of administering intranasal C-peptide that it may activate the neuron cells and connections to start recovery and the process of re-learning the lost functions and abilities. Reports of the clients highlighted the following improvements:

- **RELAXATION OF SPASM**

In each of our nine cases the clients perceived the relaxation of spastic posture of their limbs. In a number of cases this meant being able to open clenched hands, or at least that the therapist was able to open them. Also the passive movements of the trunk and the limb muscles implemented by the physiotherapist improved. Generally speaking, the regulation of, and change in the muscle-tone was experienced. This is very important both in nursing situations and for rehabilitation exercises.

- **MOTOR FUNCTIONS**

The family members of even the most severe case report the start of some conscious and independent movements. It specifically meant moving the legs and arms in a lying position and turning the head voluntarily. This made some kind of non-verbal communication possible for the client.

In one of our cases, after 8 years of total immobility, three months after starting to use C-peptide the client was able to keep up-right in sitting and standing position. He can stand up using support, and pull himself forward in his wheel-chair.

A young client, who could only move his limbs when C-peptide was first administered to him can now walk independently after a period of 9 months.

- **SLEEPING**

The clients with acquired brain injury indicated they could return to their normal sleeping cycle. This is especially difficult when a patient is in bed day and night, their physical activity is minimal, and the opportunity is there to sleep during the day. In our cases most of the clients complained about different types of sleeping problems (waking up at night, napping too often during the day, superficial sleep at night, etc.) The feedbacks show that the effect of C-peptide was a better and more relaxing sleep at night, and several clients said they were more active during daytime (e.g. in therapy sessions).

- **ATTENTION, COGNITIVE ABILITIES**

Attention was said to have improved in seven cases in our sample. More intense visual and auditive interest in the surrounding world was shown by our clients, and also reactions to speech (turning their head or establishing eye-contact) was likewise observed.

There were two cases where a higher level of attention evolved, and the clients started re-learning letters and reading. One person showed interest in watching films by the end of a three months period of C-peptid administration, and he developed that as a source of entertainment while in bed.

- **SPEECH AND COMMUNICATION**

There were two functions that family members reported as having improved due to the use of C-peptide: the return of mimicry and certain reflexes. These enabled clients to start expressing feelings, e.g. smile for expressing interest or happiness when seeing someone. The return of the cough and sneeze reflexes, the sucking, grasping and search reflex enabled the client to start non-verbal communication, e.g. show sucking reflex when being thirsty or use the grasping reflex to call someone or to ask for something.

Expressive speech appeared in two cases. After a period of nine months using the spray a young man regained his ability to speak. Another person's abilities improved from saying a few single words to saying full sentences. That made him able to express anger and negative feelings, so his ability to swear also returned.

- **CHANGES IN MOOD**

It was reported in each case that the client is more intensively expressing his/her mood and feelings. This also means the expression of negative feelings or bad mood, but that means a positive change in their cases.

One client's family member indicates that instead of the former apathic and lethargic mood the clients can smile and also cry. Another person is said to be angry and sometimes expresses negative feelings, after he started using the spray.

Another change is that a formerly quiet, indifferent person is by now balanced and often smiles, while the other person used to be depressive now is enjoyed and is in more lively mood.

The expression of negative feelings is an important sign of the awakening consciousness. This shows us that the person is aware of his/her condition. Since coping with the trauma starts with mourning, the feeling of being angry about his/her own situation is a necessary phase before starting to work on the long and difficult process of accepting his /her state.

- **SENSATION OF HEAT**

In some cases the sensation of heat (e.g. the temperature of the room or the food) became re-activated.

The experiences of persons with schizophrenia

We cannot sum up or analyze any results about the experiences of people with schizophrenia because of the low number of participants in our sample, but we found the common features in these persons' feedback interesting and promising. Each client experienced positive changes. These include:

- two high functioning clients reported that delusions disappeared
- better mood;
- improvement of memory and cognitive abilities
- hand tremor reduced in one case, and stopped in two cases
- return of normal sleep cycle, longer and more relaxing sleep
- relaxing spasms, which improved clients' fluency in walking, fine motor skills and in one case also their ability to speak

Conclusion

The reports concerning the effect of intranasal C-peptide therapy in children with autism spectrum disorder, persons with acquired brain injury and schizophrenia highlight remarkable improvements. In our sample no side-effect or negative impact was mentioned. The changes after the administration of the spray should be investigated on children, and assessed by a team of specialists including a neurologist or psychiatrist, a psychologist and a special education teacher before starting the administration. The rate of development in motor functions, speech and communication, social skills and the possible behavioural problems, stereotypical behaviour, neurological symptoms should be tested. While administering the spray follow-up assessments should be conducted regularly.

In the cases of acquired brain injury the state of the patients should be tested by measuring it based on an objective scale such as the Glasgow Coma Scale before and during treatment.

In the cases of people with psychiatric diseases an investigation with a larger number of clients should be implemented involving the expertise of a psychiatrist.

It is important to note that the dosage of the spray must be carefully controlled.

Another significant result is that in some cases the proinsulin C-peptide could reduce or replace other medications such as muscle relaxants or tranquilizers in psychiatric cases.

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