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Gene therapy in the treatment of aromatic L-amino acid decarboxylase deficiency

Zastosowanie terapii genowej w leczeniu niedoboru dekarboksylazy L-aminokwasów aromatycznych

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Abstract

Aromatic L-amino acid decarboxylase deficiency is an autosomal recessive neurodevelopmental disorder caused by pathogenic variants of the *DDC* gene. The disease manifests already in newborns and infants. The presentation includes neurological symptoms, a significant delay in motor development and oculogyric crisis. Currently, gene therapy is successfully used in the treatment of aromatic L-amino acid decarboxylase deficiency. Until recently, no effective treatment for the disorder was known. The affected children died in the first decades of life. Gene therapy is a new and promising therapeutic strategy. The first genetic therapies for aromatic L-amino acid decarboxylase deficiency were implemented in the United States. The treated children recovered very quickly, began to sit up, stand, and even attempted to walk. For the first time in Europe, this method was used in 2019 in Poland, at the Interventional NeuroTherapy Centre at Bródno Hospital in Warsaw, with the involvement of a team of specialists under the leadership of Professor Mirosław Ząbek and Professor Krzysztof Bankiewicz. The therapy involves a real-time magnetic resonance imaging-guided introduction of a copy of the defective gene directly into the substantia nigra and the ventral tegmental area. Spectacular changes were observed in the first Polish patients treated with this innovative method. The children began to raise their heads soon after the procedure. Early accurate diagnosis and prompt implementation of appropriate treatment can minimise the consequences of deficient neurotransmitters in paediatric patients. This can be achieved with gene therapy, which is a chance for children affected by this rare disease.

Keywords: aromatic L-amino acid decarboxylase deficiency, adeno-associated viruses, gene therapy, AADC, AAV

Streszczenie

Niedobór dekarboksylazy L-aminokwasów aromatycznych to autosomalne recesywne zaburzenie neurorozwojowe wywołane przez patogenne warianty genu *DDC*. Choroba ujawnia się w wieku noworodkowo-niemowlęcym. Objawia się dolegliwościami neurologicznymi, znacznym opóźnieniem rozwoju motorycznego i występującymi kryzami oczno-zakrętowymi. Korzystne efekty w leczeniu tego schorzenia uzyskuje się obecnie dzięki terapii genowej. Jeszcze do niedawna nie była znana żadna skuteczna metoda leczenia niedoboru dekarboksylazy L-aminokwasów aromatycznych. Dzieci dotknięte tą chorobą umierają w pierwszych dekadach życia. Terapia genowa stanowi nową, obiecującą strategię terapeutyczną. Pierwsze na świecie zabiegi z jej wykorzystaniem przeprowadzono w Stanach Zjednoczonych. Dzieci poddane takim zabiegom bardzo szybko dochodziły do zdrowia, zaczynały siadać, pionizować się, a nawet podejmowały próby chodzenia. Po raz pierwszy w Europie ta metoda leczenia została zastosowana w 2019 roku w Polsce, w Interwencyjnym Centrum Neuroterapii Szpitala Bródnowskiego w Warszawie, przy zaangażowaniu zespołu prof. Mirosława Ząbka i prof. Krzysztofa Bankiewicza. Terapia polega na wprowadzeniu kopii defektywnego genu bezpośrednio do istoty czarnej i brzusznej części nakrywki śródmózgowia chorego w czasie rzeczywistym pod kontrolą rezonansu magnetycznego. U pierwszych polskich pacjentów leczonych tą innowacyjną metodą widoczne były spektakularne zmiany, w krótkim czasie od zabiegu dzieci zaczęły podnosić głowę. Wczesna trafna diagnoza i szybkie wdrożenie odpowiedniego leczenia mogą zminimalizować niekorzystny wpływ braku neuroprzekaźników u pacjentów pediatrycznych. Może na to pozwolić wdrożenie terapii genowej, będącej szansą dla dzieci cierpiących na rzadkie schorzenie, jakim jest niedobór dekarboksylazy L-aminokwasów aromatycznych.

Słowa kluczowe: niedobór dekarboksylazy L-aminokwasów aromatycznych, wirus związany z adenowirusami, terapia genowa, AADC, AAV

AROMATIC L-AMINO DECARBOXYLASE DEFICIENCY (AADC)

Aromatic L-amino acid decarboxylase (AADC) deficiency is a very rare autosomal recessive metabolic disorder. As a result of a mutation in the *DDC* gene (7p12.2-p12.1), the patient does not produce dopamine and serotonin – critical neurotransmitters. The incidence of AADC deficiency is estimated at less than 1 in 1,000,000. The disease was first described in 1990. So far, it has been confirmed in about 130 people worldwide, including 2 children in Poland. The onset of symptoms is observed in the neonatal/infant period. Surprisingly, the patients appear healthy and normal immediately after birth. Most often, however, the first manifestations in the form of reduced muscle tone appear already in the first month of life. Due to the limited motor function, patients usually remain in the supine position. They develop breathing problems and, as a result, very often require mechanical ventilation. This is accompanied by serious neurological disorders, oculogyric crisis with dystonia. The children present with increased muscle tension, with a stiff, tilted body posture. These episodes cause significant suffering and prevent normal food intake, which contributes to electrolyte imbalance. After such an episode, the child needs longer recovery time, during which the muscle tone gradually normalises. Intellectual development is usually normal, but there are difficulties communicating due to the lack of active speech. AADC deficiency can be diagnosed based on the analysis of cerebrospinal fluid biogenic amines. The diagnosis can be confirmed based on an assay for AADC activity, which is currently only available abroad, or molecular testing[1,2]. The treatment regimen is complex and includes the use of dopamine agonists, monoamine oxidase inhibitors, pyridoxal phosphate (PLP), anticholinergics and antiepileptic drugs, as well as additional therapeutic methods, such as physiotherapy or speech therapy[3].

MATERIALS AND METHODS

We performed a review of the literature on the use of gene therapy in the treatment of AADC deficiency based on the PubMed database. The following keywords were used: "gene therapy," "AADC deficiency," and "AAV vector." We additionally reviewed articles published on the Internet.

GENE THERAPY IN THE TREATMENT OF AADC DEFICIENCY

AADC deficiency is treated with gene therapy using adeno-associated viruses (AAVs) as vectors (carriers)[4]. AAVs belong to the parvovirus family and consist of single-stranded DNA encapsulated in proteins. Unable to replicate themselves, they depend on the viruses they accompany, i.e. most often adenoviruses[5].

The vaccine uses a recombinant adeno-associated virus (rAAV) vector devoid of viral genetic material except for the inverted terminal repeat (ITR) responsible for packaging the viral genome into the capsid. Instead of the viral genes, the genome contains the correct *DDC* gene enclosed in the viral capsid[6]. This structure enables the vector to transport and deliver recombinant genetic material to the nucleus[7]. AVV enters the host cell by binding to appropriate receptors and coreceptors on its surface, and then undergoes endocytosis and enters the nucleus through the pores[7]. Currently, single-stranded (ss) and double-stranded (self-complementary, sc) forms of AAVs are available. ssAAVs carry a single-stranded DNA that must be transformed into a double-stranded form before transcription, whereas scAAVs are transcribed and translated shortly after they enter the nucleus, ultimately forming a therapeutic protein[8,9]. The vector is administered directly to the substantia nigra and the ventral tegmental area of the midbrain under real-time magnetic resonance imaging guidance[10].

Depending on the desired effect, the vector can be modified (ITR, the promoter and the capsid). The effect will also depend on the transgene[11]. The ability to enter both dividing and non-dividing cells of various types is one of the advantages of AAV gene therapy[12]. Furthermore, these vectors are not pathogenic and are associated with low immunogenicity[13]. They are also characterised by highly stable expression. Small packaging capacity (up to 4.7 kb) and the risk of neutralisation by endogenous anti-AAV antibodies are the main limitations of their use[14].

GENE THERAPY OF AADC DEFICIENCY IN PARKINSON'S DISEASE

Parkinson's disease (PD) is a progressive neurodegenerative disease, the main symptoms of which include bradykinesia, stiffness, postural instability, and rest tremor[15]. PD involves the loss and degeneration of dopaminergic neurons in the midbrain substantia nigra and formation of Lewy bodies[16]. Treatment of PD is based on levodopa preparations which inhibit disease progression[17]. However, the efficacy of levodopa therapy decreases with PD progression. One of the reasons for this is the loss of the endogenous dopamine-synthesizing enzyme, i.e. L-amino acid decarboxylase (AADC), involved in the conversion of levodopa to dopamine[18]. The VY-AADC gene therapy for PD was developed by Neurocrine Biosciences and Voyager Therapeutics. The method uses a modified adenovirus that delivers the *DDC* gene to brain cells[19]. The *AADC* gene delivers information necessary for the production of AADC[20]. The effectiveness of a given method has been assessed in many studies. A phase I clinical

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trial has shown that a single administration of VY-AADC was sufficient to increase both the activity of the AADC enzyme and the effectiveness of levodopa. Patients also showed improved motor functions[21].

GENE THERAPY OF AADC DEFICIENCY IN POLAND

Since 2019, Poland has been a European pioneer in the treatment of AADC deficiency using gene therapy. The availability of this type of treatment in our country is considered a huge success. An 8-year-old girl and a 13-year-old boy were the first patients diagnosed with AADC deficiency in Poland. The children responded positively to the treatment, made attempts to speak, raised their heads and moved their limbs unassisted, which was not possible before the therapy[22].

Gene therapy can be used in Poland owing to the involvement of Professor Krzysztof Bankiewicz from the University of California (USA) and Professor Mirosław Ząbek and his team from the Bródno Hospital in Warsaw (Poland). The use of this modern therapeutic strategy made it possible to create a specially dedicated operating room, where intracerebral infusions under real-time magnetic resonance imaging guidance can be performed[23].

The Interventional NeuroTherapy Centre at the CMKP Department of Neurosurgery of the Bródno Hospital in Warsaw (INC Bródno) has a qualified team of specialists. The Interventional NeuroTherapy Centre is a sister facility of the Department of Neurosurgery at the University of California, San Francisco. Establishment of these centers paved the way for the development of medicine in the treatment of brain diseases. Currently, both institutions are conducting research on the use of gene therapy in the treatment of patients with malignant brain tumors, PD and other diseases of the nervous system. The procedures performed with the use of modern specialised equipment available in the hybrid operating room at the INC Bródno are guaranteed under the National Health Fund[10,22,23].

WNIOSKI

The treatment of aromatic L-amino acid decarboxylase deficiency is very difficult. Pyridoxal phosphate, monoamine oxidase inhibitors and dopamine agonists are usually used in patients with AADC deficiency. Additionally, physiotherapy and speech therapy are recommended. Treatment is not always effective due to symptom resistance. Until recently, the disease was considered incurable. However, advances in medicine and gene therapy have brought hope for patients with AADC deficiency.

Conflict of interest

The authors do not declare any financial or personal links to other persons or organisations that could adversely affect the content of this publication or claim rights thereto.

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