Analysis of treatment methods for arginase deficiency

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Abstract. Arginase deficiency is a rare, critical and highly lethal inherited metabolic disorder which may lead to impaired motor skills and neurodevelopmental deficits. Three mainstay treatment options have been arisen: drugs, liver transplantation surgery, and dietary control. Drugs are categorized as nitrogen scavengers and recombinant human arginase pharmaceuticals. They are fast-acting and less harmful but costly and may have complications. Liver transplantation has become possible in recent years with the development of minimally invasive surgery. This approach is highly effective but harmful to the patient. Dietary control is the least expensive and less harmful but less effective. The researchers should continue to focus on the long-term effects of the medications that are already available, improve surgical treatments and procedures, and investigate the effects of long-term dietary control on the disease. This article briefly analyzes and evaluates the therapeutic options that have already been developed, and looks forward to new treatments that may be developed in the future.

Keywords: arginase deficiency, treatment, inherited metabolic disorder.

1. Introduction

Arginase 1 deficiency (ARG1-D, OMIM207800) is a rare inherited metabolic disorder, caused by a double allele pathogenic variant in the ARG1 gene (HGNC663), which impairs the enzymatic activity of arginase 1 (ARG1, EC3.5.3.1), resulting in persistent elevation of plasma arginine (pArg) levels, leading to progressive and debilitating neurologic manifestations. The prevalence is estimated to be from 1 in 141,331 to 34,602,076 [1]. Arginase catalyzes the hydrolysis of arginine to ornithine and urea. At least two isoforms (type I and type II) of mammalian arginase exist, which differ in tissue distribution, subcellular localization, immune cross-reactivity, and physiological function. The type I isoform encoded by the AGR-1 gene is a cytoplasmic enzyme that is one of the essential components of the urea cycle. The vast majority of this enzyme is located in the liver, with a few presents in erythrocytes. As shown in Fig. 1, Diz-Fernandez et al. summarized data on all published ARG1 mutations and 12 new ARG1 mutations, totaling 66 mutations from 112 patients [2]. Of these, missense mutations were the most common, totaling 30, followed by 15 base deletions, 10 gene splices, 7 nonsense expressions, 2 gene duplications, 1 missense insertion, and translation initiation codon mutations [2].

ARG1-D is characterized by conspicuous and progressive spasticity in the lower limbs, which leads to irregularities in gait, difficulties walking and climbing, and reliance on assistive aids. Most patients eventually experience decreased movement and overall motor function, with some even becoming wheelchair-dependent and immobile. At the same time, there are also possibility for developmental delay and developmental extinction, which maybe means cognitive impairment while seizures are possible too. Overall, the characterization of this disease focused on motor impairment and neurodevelopmental disorders.

The treatments that have been produced so far fall into three categories: medication, liver transplantation surgery and dietary control. Drug therapy, as the classic option of conservative treatment, has its own characteristics of low injury, fast onset of action and obvious feedback, making it the most acceptable treatment option. However, the process of developing drugs for ARG1-D has been slow due to the fact that the researchers have not analyzed the mechanism of ARG1-D thoroughly enough. Liver transplantation, as a representative of direct intervention, is characterized by direct access to the lesion, high efficiency, and high recovery rates, making it the early treatment option of choice. However, due to the early onset of the disease, the generally young age of the

patients, and the developmental impact, this treatment option is less likely to become a practical treatment option. With the continuous development of technical means in recent years, liver transplantation in younger children has become possible. This approach is also becoming more accepted and tried. Dietary control, as the most convenient and simple treatment method, cannot improve the existing status quo, but it can improve the quality of life and prolong the life expectancy of patients. Although the effect is not very obvious, there is no doubt about the results that this method can produce.

The purpose of this research is to provide a summary of the therapeutic approaches and drugs that have been used in recent years in relation to arginase deficiency. The available pharmacological, surgical and dietary control methods are briefly described, respectively, and their advantages and disadvantages are analyzed and summarized, and finally possible improvements of the existing techniques and treatments that could be developed are suggested.

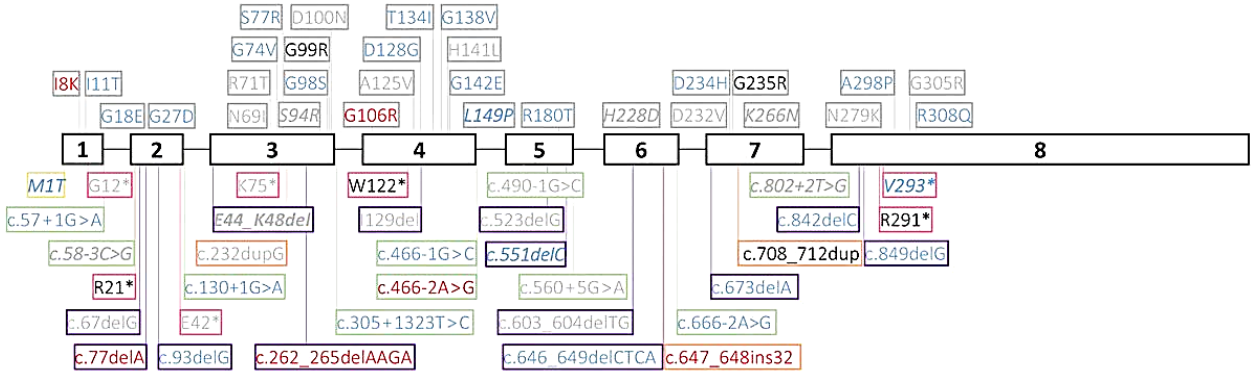

Figure 1. Distribution of mutations along the coding ARG1 exons and patients' arginine levels [2].

2. Different treatment methods

2.1. Drug therapy

2.1.1. Pegzilarginase

Russo's team developed a novel human arginase 1 enzyme therapy called pegzilarginase [3]. The drug uses cobalt in order to replace part of the original active site to speed up the reaction, and uses polyethylene glycol as a substrate to host the recombinant human arginase. To verify the drug's effectiveness, they conducted a phase 3, multicenter trial in several developed countries. The trial is randomized. For the accuracy and reliability of the statistics, it is also double-blinded and placebo-controlled. In the trial, they randomized patients with ARG1-D in a 2:1 ratio into an experimental group and a control group. The experimental group received weekly intravenous pegzilarginase injections, while the control group received placebo injections. They looked after the experimental subjects for other medical conditions. The experimental data was based on blood arginine levels (pArg), Gross Motor Function Test Scale Part E and 2-minute walk test. They compared the data and analyzed it using Full Analysis Set. The final results showed that the drug had excellent control of pArg levels in the blood, better improvement in patient's gait and excellent safety profile. The drug can be considered as an effective therapeutic drug for arginase deficiency [3].

2.1.2. Nitrogen scavengers

As the most conventional and common treatment, nitrogen scavengers reduce nitrogen in the blood by combining with amino acids involved in the urea cycle to form amides and eliminating them in the urine. Common nitrogen scavengers on the market today include sodium benzoate, sodium phenylbutyrate and glyceryl phenylbutyrate. Sodium benzoate breaks down into benzoic acid in the body and combines with glycine to produce marinic acid, while sodium phenylbutyrate and glyceryl phenylbutyrate break down into phenyl butyric acid and other substances in the body. Phenyl butyric acid undergoes β-oxidation to produce phenylacetic acid, which then combines with citrulline and

arginine succinate, which are involved in the urea cycle, and finally is eliminated in the urine [4]. These drugs are effective in reducing the accumulation of endogenous arginine, but they also have an effect on the levels of other amino acids in the body.

2.1.3. Polyethylene glycolized human recombinant arginase 1 (AEB1102)

Burrage's team developed a polyethylene glycol-based human recombinant arginase 1 (AEB1102) and experimented with it in mice, a model of arginase deficiency, and in healthy Crab-Eating Monkeys. Experiments in mice showed that AEB1102 is not an effective therapeutic drug because it only effectively reduces blood arginine levels, does not enter the liver, and has a short dosing cycle. Experiments on healthy crab-eating monkeys further showed that the drug was only effective in plasma. It can be concluded that the drug is not effective [5].

2.2. Liver transplants

Campeau's team performed the treatment of multiple cases of 1-year old children with urea cycle disorders by liver transplantation. They used a developmental quotient to quantify symptoms. The children's developmental quotient was assessed by accredited testers using the Griffith Mental Development Scale. Prior to liver transplantation, these patients used the treatments available to control blood arginine levels at the time. To facilitate the intake and administration of drugs and foods, all patients received a gastrostomy tube shortly after deciding attending the experiment. Patients under one year old all underwent hemodialysis. This is also intended to control for arginine levels. They received transplanted livers from deceased donors. They were immunosuppressed with tacrolimus and steroids after undergoing transplantation. The patients had a 7-year survival rate of 80% after surgery. Developmental testing 7 years after transplantation showed an increase in mean developmental quotient (DQ) from 69 to about 90 in the group of children, who are younger than one year old while taking liver transplants. And the DQ increased from about 60 to 80 in the group of three-year-old patients who received transplants [6]. They concluded that early liver transplantation and early childhood therapies all work together to enhance neurological development in kids with urea circulation problems. It is also important to take a strict metabolic management. Arginase deficiency, a type of urea cycle disorder, could be considered to have the same results for arginase deficiency.

2.3. Dietary control

Mireia Tondo et al. experimented with dietary control therapy in l two cases of lysinase deficiency [7]. These two cases were diagnosed biochemically and genetically as hyperlysinemia type I at the ages of 2 and 8 years, respectively, and were started on a lysine-restricted diet. After three years of restricted lysine intake, Case 1 had no further seizures. In case 2, tremor and dysrhythmia improved, but fine motor clumsiness persisted. Despite dietary treatment, both patients had mild cognitive impairment [7]. Hyperlysinemia, as a type of inherited amino acid metabolic disease, can be considered as a mitigating effect of dietary control in inherited metabolic diseases and the earlier the dietary control is performed, the better the effect on the recovery of the patient's symptoms.

While taking dietary control, doctors can use some complementary drugs to achieve better results, such as lactulose. Lactulose inhibits proteolytic bacteria by promoting the growth of acidophilus bacteria in the intestines, thus converting ammonia into an ionic state and reducing absorption. However, this drug may cause diarrhea, so the drug should also be used with caution.

3. Conclusion

Arginase deficiency, as a rare inherited metabolic disease, is diagnosed only with a relatively crude combination of pArg level analysis and morphological abnormalities. The researchers should try to develop more efficient and accurate diagnostic methods. The early onset of the disease has a significant impact on the development of young children, and researchers should develop safer and more widely applicable drugs. As an inherited metabolic disease, can doctors treat patients by

performing gene editing? At the same time, researchers can try to build organoid organs in the body to construct a reflux system in capillary-rich areas, which is controlled by physical or chemical signals and receives signals to carry out the secretion of arginase in the body or to filter out the excess arginine.

In terms of drug therapy, it is conceivable to develop drugs that work by breaking down or inhibiting endogenous arginine, but at the same time there should be longer term and more effective monitoring of the drugs that are already available. For liver transplantation, can doctors consider donors other than human sources? Can they use less invasive methods? Is it possible to replace an organ by delivering an organ that is not yet fully differentiated? Regarding dietary control, since the main patients of this disease are young children, and young children are at the stage of development, doctors should control the amount of arginine in their body without affecting their normal development. The mainstay of treatment for arginase deficiency is in vitro synthesis of the enzyme, organ transplantation and control of the amount of arginine consumed. However, it should be noted that there are both in vitro and in vivo sources of arginine. As a metabolic genetic disease, aspects that can be effective in the long term, have low toxicity and low drug resistance, and cause little harm to the patient should be considered. Due to the importance of arginine for development, it should not be removed altogether, but maintaining a reasonable concentration is also necessary.

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