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Hyperglycinemia: Innate Errors of Metabolism

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Abstract

Innate errors of metabolism are biochemical disorders of genetic origin that cause a specific defect in the structure or function of the protein molecules involved in a metabolic pathway. Hyperglycinemia, or elevation of glycine in the blood, occurs in different metabolic diseases related to a disorder of the metabolism of the amino acid glycine. It is inherited with recessive autonomic character. Two varieties are distinguished: primary or nonketotic hyperglycemia and secondary or ketotic hyperglycemia. The so-called primary or non-ketotic hyperglycemia corresponds to a congenital disorder of glycine metabolism and presents with an elevation of cerebral glycine, without an increase in ketoacids. It is the most common of the hyperglycinemia's due to a congenital deficiency of the glycine converting enzyme. Ketotic hyperglycinemia is secondary to organ acidemias, thus differing from the previous ones in that there are ketoacids and glycine increases little in the nervous system. They occur due to a blockage of the glycine converting enzyme and are due to external inhibition.

Keywords: Inborn errors of metabolism, glycine, nonketotic hyperglycemia primary, and ketotic hyperglycinemia secondary.

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1. Introduction

The concept of inherited metabolic disease was developed by Garrod in the early 20th century, with his studies on alkaptonuria. Garrod observed that patients with this disease excreted large amounts of homogentisic acid and that the inheritance of the disease could be explained according to Mendel's laws. After several years of study Garrod defined the concept that certain diseases occur due to the absence of an enzyme in a metabolic pathway. In 1945, Beadle and Tatum established the concept that genes encode enzymes, a concept that was later redefined and extended to include all existing variations and complexities. In 1949 Pauling and Ingram discovered the molecular basis of sickle cell disease and in 1953 Watson and Crick marked a milestone in science with the discovery of the structure of the double helix. In the following decades, the mechanism of protein synthesis was described and the genetic code deciphered. In 1977 the methods for DNA sequencing were discovered and the chromosomal location and identification of the genes responsible for many of the innate errors of metabolism (IMD) have been achieved [1,2].

Hyperglycinemia, or elevation of glycine in the blood, occurs in different metabolic diseases related to a disorder of the metabolism of the amino acid glycine. It is inherited with recessive autonomic character, that is, the parents carry mutations in some of the genes involved, although they do not suffer the effects of the deficiency. Two varieties are distinguished: primary or non-ketotic hyperglycemia and secondary or ketotic hyperglycemia [2,3].

The so-called primary or non-ketotic hyperglycemia corresponds to a congenital disorder of glycine metabolism and presents with an elevation of cerebral glycine, without an increase in ketoacids. It is the most common of the hyperglycinemias due to a congenital deficiency of the glycine converting enzyme. Data published in 2008 by the American Society of Clinical Pediatrics collect prevalence figures of 1/250.000 live births [4]. According to data published by the Ministry of Health and Social Services in relation to rare diseases, the prevalence as of May 2012 is 0.2/100.000 [5].

Ketotic hyperglycinemia is secondary to organoacidemias, thus differing from the previous ones in that there are ketoacids and glycine increases little in the nervous system. They occur by blocking the glycine converting enzyme and occur by external inhibition. The most frequent ketotic hyperglycinemias are propionic and methylmalonic acidemias [2,3].

Glycine is a simple, nonessential amino acid; it is the simplest and most abundant amino acid that is part of proteins. It is not essential in the human diet, since it can be synthesized and we can form it from other compounds, especially from another amino acid, serine. 50% of its daily dietary intake is destined to the synthesis of proteins, to which it is incorporated as glycine, serine or to a lesser extent

as aspartic or glutamic acids. It is present in high concentrations in collagen and gelatin and is abundant in most animal proteins (Figure 1) [6,7].

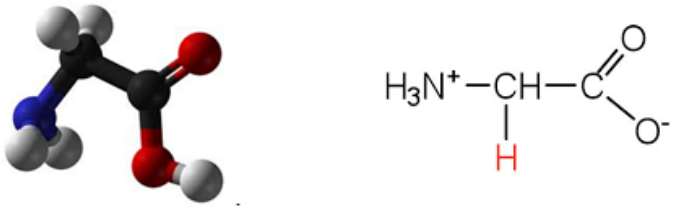

Figure 1. Glycine amino acid and its structure

In addition to being a precursor to multiple compounds, glycine is a brain neurotransmitter. Neurotransmitters are chemical messengers released by neurons to communicate with each other. Some neurotransmitters cause the initiation of the activity of the neurons that receive them (excitatory neurotransmitters), while others inhibit this activity (inhibitory neurotransmitters). Glycine is one of the most abundant neurotransmitters, along with glutamate and gamma amino butyric acid (GABA). It has a double function: on the one hand, it is an inhibitory neurotransmitter, acting on specific receptors in the brain stem and spinal cord. On the other hand, it is an excitotoxic neurotransmitter, which acts by modulating the N-methyl-D-aspartate (NMDA) receptor in the cerebral cortex. This NMDA receptor is actively involved in the development of the nervous system, brain plasticity and also in degenerative processes (figure 2) [7,8].

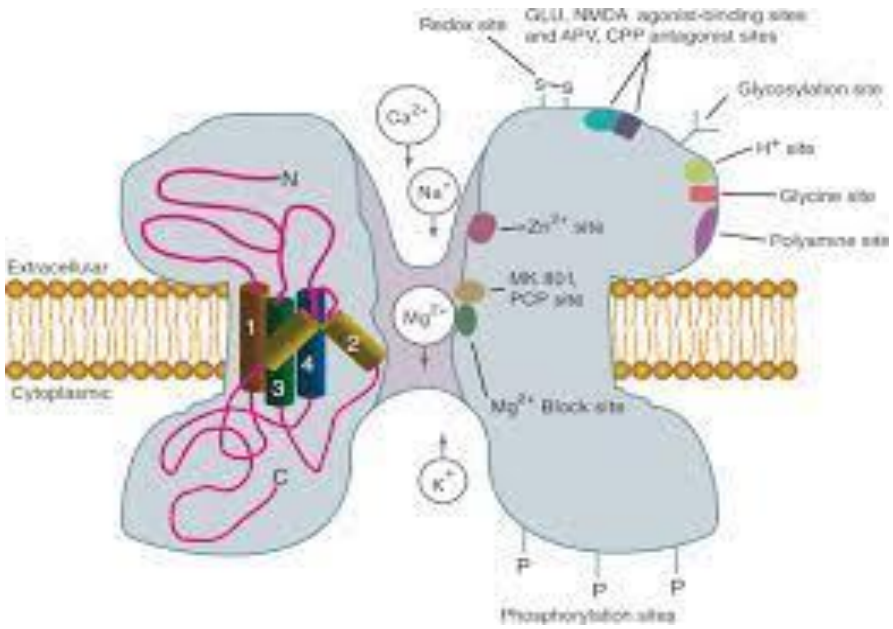

Figure 2. N-methyl-D-Aspartate (NMDA) receptor.

Glycine and serine have a joint metabolism since both amino acids are originally derived from an intermediate of glycolysis which is 3-P-glyceric acid. This precursor is successively oxidized and transaminated to form 3-P-serine, which finally by hydrolysis of the phosphate will form serine. The main synthesis pathway for glycine is a one-step reaction, catabolized by serine hydroxy methyl transferase (SHMT). This reaction involves the transfer of the hydroxymethyl group from serine to the tetrahydrofolate cofactor (TFH), producing glycine and N5, N10-methylene THF [9]. Glycine is metabolized in two different ways. The main catabolic pathway for glycine conversion is carried out in the liver at the mitochondrial level, through the enzymatic glycine conversion complex (CGF) that catalyzes the transformation of glycine and tetrahydrofolate into CO2, NH3 and methylene tetrahydrofolate (figure 3).

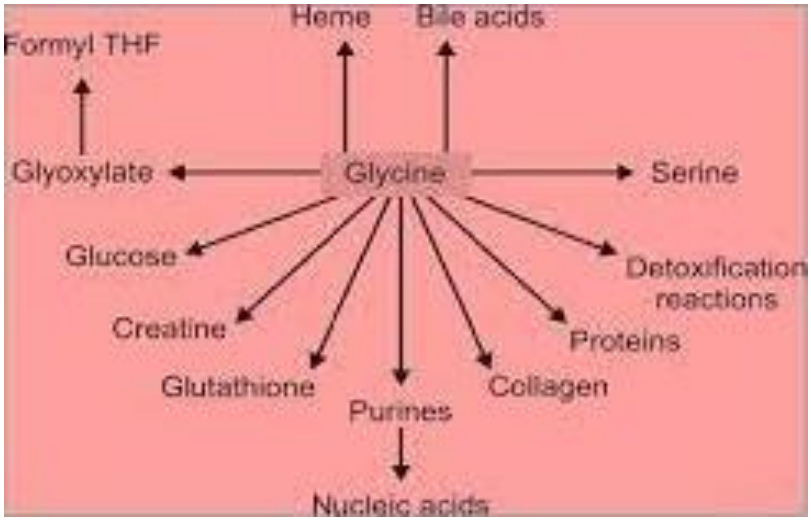

Figure 3.- Glycine metabolism.

The enzyme complex is made up of four protein components, a protein P (pyridoxal phosphate-dependent glycine decarboxylaxa), a protein H (protein amino methyl transferase containing lipoic acid), protein T (a tetrahydrofolate-dependent enzyme) and protein L (dehydrogenase-dependent of lipoamide [2,6].

First, the carboxyl group of glycine is released, by the action of proteins P and H, with the production of CO2 and the participation of pyridoxine as a catalyst. The next step, catalyzed by the T protein, requires the help of tetrahydrofolate and consists of the liberation of the amino group of glycine as NH3 and transfers to the alpha carbon of glycine to tetrahydrofolate, forming 5,10

methylenetetrahydrofolate. Finally, protein L, which is a lipoamido dehydrogenase, and NAD reoxidize the dithiol form of protin H to the bisulfite form (Figure 4) [9].

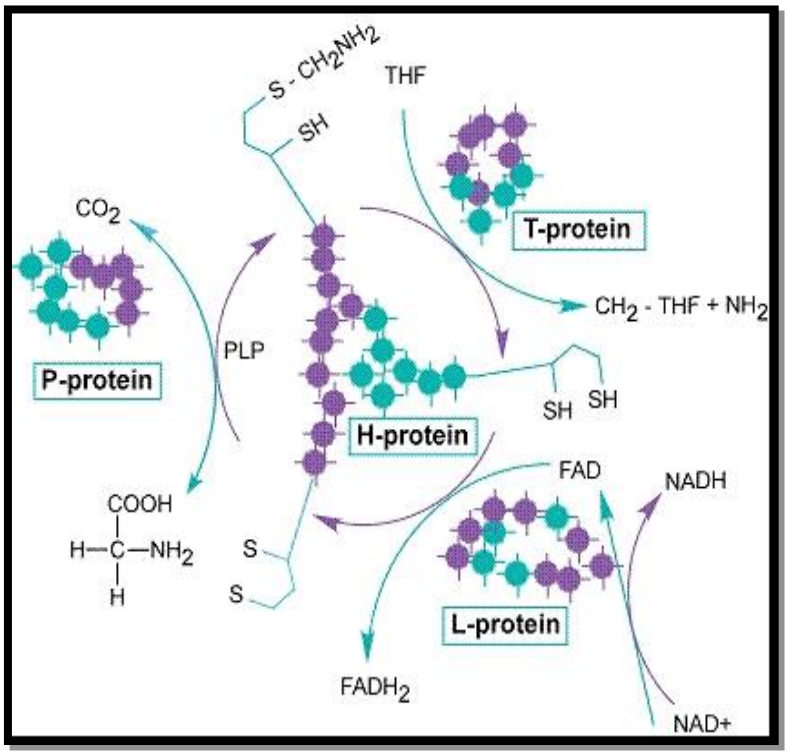

Figure 4.- Glycine converting enzyme. Protein P: Glycine decarboxylase. Protein T. Aminomethyltransferase. Protein H. Dihydrolipoamide. Protein L: Dehydrogenase.

The proteins in the complex dissociate easily, except for the P and L proteins which are loosely bound. The activity of this enzyme complex in the liver can be stimulated by glucagon. Diets rich in protein produce an increase in its secretion and give rise to a glucagon: insulin ratio, the result of which is an increase in the activity of the aforementioned system, mediated by an increase in cyclic AMP and free calcium; something similar occurs with the stimulation of alpha-adrenergic receptors [9].

The second pathway of glycine catabolism is less important than the previous one and is carried out by the enzyme glycine hydroxy methylase, an enzyme located at the cytoplasmic level. Through this route, glycine is converted to serine, in the presence of CO2 and NH3. This reaction is reversible and under normal conditions the net flux is in the direction of the conversion of serine to glycine. In a fasting state, this reaction constitutes an important source of serine and pyruvate. Other minor catabolic pathways are the conversion of glycine by the enzyme glycine oxidase to glyoxylate and the condensation of glycine with acetyl CoA to form aminoacetone [9].

When there is an alteration or error in metabolism, some metabolic process does not take place with due efficiency, this can cause the accumulation of a compound that is toxic to our body, such as glycine, which is neurotoxic. These alterations have pathological consequences.

2. Etiology

The origin of nonketotic hyperglycinemia, also called glycine encephalopathy, has been attributed to alterations in the component proteins of the glycine-converting enzyme complex. The name Glycine Encephalopathy is due to the pathology that produces this hyperglycinemia [2,5].

Mutations include genes that encode P protein (GLDC), T protein (CGTS), and H protein (GCSH). Most patients have a defect in the GLDC gene and therefore lack P protein or said P protein is altered. This entity is transmitted in recessive autonomic form, the glycine decarboxylase gene is located on the short arm of chromosome 9, the gene having been mapped to chromosome 9p13 or 9p23-24. Carrier status can be difficult to discover from a biochemical point of view [5].

Defects in the activity of this system lead to the accumulation of glycine mainly in the central nervous system, where it activates two different receptors. The classic receptor, located in the spinal cord, has inhibitory functions, causing apnea and hiccups in these patients. The receptor in the cerebral cortex, N-methyl-D-aspartate (NMDA), has excitatory functions and its activation causes brain injury and seizures.

3. Pathophysiology

There are several clinical phenotypes associated with nonketotic hyperglycinemia. Typically, the activity of the glycine converting enzyme system is absent or very low and the CSF/plasma glycine ratio is in the range 0.098-0.9. In the atypical form of the disease, there is residual activity of the glycine converting enzyme system and the CSF/plasma ratio is in the range of 0.09-0.097 [9].

In the pediatric age there are several forms of clinical presentation: neonatal, transitory and infantile.

- Typical neonatal form

It is the most impressive and frequent way, in which patients usually come from uncomplicated pregnancies and deliveries. In the typical neonatal form, normal patients at birth, in the first days of life, present hypotonia and inability to suck and refuse to feed. Infants present with myoclonic movements, episodes of apnea, and hiccups. Many of them present with myoclonic or generalized seizures, almost always difficult to control. They also show profound lethargy that, as encephalopathy and compromised consciousness progresses, progresses to coma [9,11].

Most newborns require mechanical ventilation and about 30% die in the first weeks of life. Many patients die quickly without the diagnosis being suspected. Those who survive have severe neurological damage. Those who survive usually resume spontaneous breathing around the third week of life, and survival ranges from a few months to 22 years. Some are able to suction again, but most require syringe or tube feeding [10,12].

Those without treatment have refractory seizures by twelve months; the seizure pattern begins with myoclonic movements and progresses to infantile spasms, partial or tonic motor seizures. Psychomotor retardation is severe with low adaptive behavior; initial hypotonia often progresses to spastic quadriplegic. [9,10].

- Transitory form

The transient form is clinically indistinguishable from the neonatal form, with elevated levels of glycine in plasma and cerebrospinal fluid that return to normal levels between two and eight weeks of life, with remission of clinical manifestations. It is related to an immaturity in the glycine conversion enzyme system in the liver and brain. The neurological prognosis of these patients, in general, is good [9.10].

- Infant Form

In the infantile form, the growth and development are normal until the six months of life and later they present apneas, hypotonia, seizures and moderate mental retardation. It is a milder presentation than neonatal and with a longer survival [10].

There are forms of late presentation. One of them from the second and third year with seizures and some degree of mental retardation. Another appears even in later childhood, with progressive spastic diplegia and optic nerve atrophy, but without cognitive impairment. There is dystonia, presenting the affected choreoathetosis movements. These late presentation forms appear as a consequence of abnormalities in protein H or T [9,10].

4. Diagnosis

• Clinical diagnosis

In any pathology or disease, making a good diagnosis taking into account the clinical symptoms is essential. However, in most cases, the clinical manifestations are not sufficient to establish the specific diagnosis and must be supported by complementary radiological, electroencephalographic or clinical laboratory tests. In the specific case of congenital metabolic diseases, including nonketotic hyperglycinemia, the most frequent symptoms, as we have seen previously, are those corresponding

to encephalopathy. It is therefore essential to carry out a differential diagnosis based mainly on specific laboratory tests.

• Differential diagnosis

In hyperglycinemia's, confirmation of the clinical diagnosis is made by determining the levels of the amino acid glycine in plasma and cerebrospinal fluid. It is important to establish the differential diagnosis between ketotic and nonketotic hyperglycinemia. In nonketotic hyperglycinemia the ratio of glycine in cerebrospinal fluid to glycine in plasma is greater than 0.09 and in ketotic hyperglycinemia this ratio is less than 0.04 [9].

The most frequent ketotic hyperglycinemia's are propionic and methylmalonic acidemias, therefore hyperammonemia and aciduria is a characteristic biochemical sign in this pathology caused by the accumulation of propionic or methylmalonic acid in the mitochondria. The finding in the blood of methyl citrate or isovalerylglycine rules out the possibility of nonketotic hyperglycinemia [2].

5. Diagnostic tests in non-ketosic hyperglycinemia. Lab tests

In the blood, there is a moderate to severe increase in glycine that can reach up to eight times the normal value, serine levels are low, and plasma pH is normal. In urine, high glycine values are also shown, appearing hyperglycinuria. In cerebrospinal fluid, the glycine value is 10 to 15 times the normal value.

A cerebrospinal fluid/glycine plasma ratio greater than 0.09 is diagnostic. In the typical form in which the activity of the glycine converting enzyme system is absent or very low, the CSF/plasma glycine ratio is in the range 0.098-0.9. In the atypical form in which there is residual activity of the glycine converting enzyme system, the CSF/plasma ratio is in the range of 0.09-0.097 [10].

The determination of the amino acid glycine can be done by thin layer amino acid chromatography and by Tandem mass spectrometry. This method is more effective today, it allows to measure the mass or molecular weight of a substance.

In research studies it is possible to make a prenatal diagnosis of the disease, but in clinical practice it is not done. Initially, it was postulated that the glycine / serine ratio in amniotic fluid could be useful, however, several authors report that this relationship is not reliable.

-Electoencephalographic and radiological tests

The electoencephalogram performed in the first two weeks of life shows a characteristic burst-suppression pattern. This EEG pattern changes, and a hypsarrhythmia trace can be seen at three months of age. The burst-suppression pattern is not diagnostic of nonketotic hyperglycinemia, as other entities such as hypoxic-ischemic encephalopathy, meningitis, early childhood epileptic encephalopathy

(Ohtahara syndrome), early myoclonic epilepsy, and leucinosis have been reported as the cause of the burst-suppression pattern. . In general, it does not correlate with the patient's clinical activity status and after one year the tracings reveal slowing and frequent independent multifocal tip discharges. Auditory evoked potentials suggest a slowdown in conduction through the auditory pathway. Less frequently reported visual potentials may be abnormal [5,9].

Several publications have reported structural abnormalities of the nervous system such as hypoagenesia or agenesis of the corpus callosum, malformation of the gyri, ventriculomegaly, hydrocephalus, colpocephaly, and hypoplasia of the cerebellum. Corpus callosum dysgenesis or agenesis has also been described in other inborn errors of metabolism such as primary lactic acidosis, Zellweger syndrome, adrenoleukodystrophy, Menkes syndrome, and glutaric aciduria type II [5].

Nuclear magnetic resonance imaging (NMR) shows a delay in myelination and dysgenesis of the corpus callosum [5,10].

6. Forecast

The prognosis of patients depends fundamentally on the form of presentation, typical or atypical, and is correlated with the absence of the glycine-converting enzymatic system or the demonstration of some residual activity of the enzyme system.

7. Treatment

Currently, there is no specific treatment. Many strategies have been tried in order to decrease intractable seizures and slow the progression of brain damage. However, to date none have demonstrated uniform effectiveness. Therapeutic studies are aimed at lowering glycine concentrations and blocking its effect on the N-methyl-D-aspartate (NMDA) receptor [14].

One of the therapeutic alternatives used is dietary treatment, providing a hypoproteic diet and reducing daily glycine intake, providing a synthetic diet without glycine and eliminating serine, which is its precursor. However, the reduction of glycine in the diet has had no effect on the frequency of seizures or the progress of psychomotor development. [15,16].

The alternative to a diet low in glycine is the administration of sodium benzoate that is conjugated with glycine to form hippurate that is excreted in the urine. The benzoate doses range between 150 and 750 mg/Kg/day; Although glycine concentrations in plasma decrease reaching normal values, in cerebrospinal fluid the values do not decrease to normal. Therefore, it only produces a decrease in the frequency of seizures but does not achieve an improvement in the psychomotor development of affected patients [9,10,17].

Another therapeutic strategy is the administration of substances that block or compete for glycine receptors. Diazepam and other benzodiazepines are used as they are competitors for glycine receptors in the central nervous system, but no significant clinical changes are achieved either. Dextromethorphan, an N-methyl-D-aspartate (NMDA) receptor antagonist, at doses between 5 and 35 mg/kg per day has shown beneficial effects in some patients [9,10].

Oral administration of ketamine, a NMDA channel blocker at a dose of 8 mg/kg/day, produces partial neurological changes. Likewise, antagonist antidepressants at NMDA receptors are also used with relative results, especially in children with a later presentation [9,10].

8. Conclusions

Although congenital errors of metabolism are rare genetic diseases, their study is very important. And these are generally characterized by an enzymatic defect that blocks a metabolic pathway producing certain characteristics and clinical manifestations.

Hyperglycinemia, or elevation of glycine in the blood, occurs in different metabolic diseases related to a disorder of the metabolism of the amino acid glycine. It is inherited with recessive autonomic character

Two varieties are distinguished, primary or nonketotic hyperglycemia and secondary or ketotic hyperglycemia. The so-called primary or non-ketotic hyperglycemia corresponds to a congenital disorder of glycine metabolism and presents with an elevation of cerebral glycine, without an increase in ketoacids. It is the most common of the hyperglycinemias due to a congenital deficiency of the glycine converting enzyme.

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