Lysinuric Protein Intolerance in Pregnancy

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Lysinuric protein intolerance (LPI) is a rare inborn error of metabolism (IEM), classified as an inherited aminoaciduria, caused by mutations in the SLC7A7 gene, leading to a defective cationic amino acid transport. The metabolic adaptations to the demands of pregnancy and delivery cause significant physiological stress, so those patients affected by IEM are at greater risk of decompensation.

lysinuric protein intolerance | pregnancy | rare disease

1. Introduction

Lysinuric protein intolerance (LPI) is a rare disorder classified in the Inborn Error of Metabolism (IEM) group, with an autosomal recessive inheritance. It is caused by mutations in the SLC7A7 gene, which encodes the y+LAT–1 protein [y(+) L–type amino acid transporter 1]. A defective y+LAT–1 protein results in an abnormal cationic amino acid (AA) transport, leading to deficient gastrointestinal absorption and urine loss of arginine, ornithine, and lysine [1][2]. The reduced availability of arginine and ornithine compromises the normal functioning of the urea cycle (the major pathway for the disposal of nitrogen in humans) as both AA act as urea cycle intermediates [3].

Although LPI is characterized by protein intolerance and failure to thrive, it represents a severe multisystemic disorder in which almost any organ can be affected: gastrointestinal tract (vomiting and chronic diarrhea), lungs (pulmonary alveolar proteinosis (PAP)) and kidneys (tubulopathy, proteinuria, and renal failure). Hematological defects (anemia, leukopenia, thrombocytopenia, hemophagocytic lymphohistiocytosis/macrophagic activation syndrome (HLH/MAS)), altered immune response (autoimmune disorders, deficient B–cell function), and hypercholesterolemia/hypertriglyceridemia are also usual findings [1].

Therapeutical management is based on a low-protein diet, supplemented with citrulline (lysine can also be considered), L-carnitine, vitamins, and other micronutrients if necessary, along with nitrogen-scavenging drugs [1][2][4].

LPI integrative treatment has helped females to reach their reproductive age. As pregnancy and delivery constitute significant stressors, any woman is at greater risk of metabolic decompensation at this time [5][6]. When an IEM coexists, this risk becomes even greater [7].

A limited number of case reports on LPI in pregnancy and only one cohort study from Finland have been published thus far [5][8][9][10]. However, none of these cases have simultaneously faced: 1) the classical, but challenging, both medical and nutritional disorders of LPI in the pregnancy setting and 2) the patient's will of natural childbirth despite suffering a complex metabolic disorder. To contribute to the fulfillment of this gap in the literature, the case of a 28–year–old woman with genetically confirmed LPI who developed threatening complications in pregnancy but expressed her will for a natural delivery has been recently reported [11].

2. Lysinuric Protein Intolerance in Pregnancy

IEM were once considered exclusively pediatric conditions; however, they currently represent a growing challenge in adult medicine. Indeed, more patients with IEM are now reaching the childbearing age and pursuing pregnancy [12][13]. Furthermore, as independent adults, patients are the ones who actively take control of their diet (not their parents anymore) and so, tailored and supervised dietary management becomes essential for good health and well-being.

The clinical characteristics of patients with LPI go beyond the classical urea cycle disorder (UCD) [14], suggesting an increased risk for maternal complications during pregnancy and delivery [1][2]. There are a few reported cases of LPI and pregnancy [5][8][9][10] that shared some of our main medical challenges but did not face the patient's wish to have a natural delivery.

Through the revision of the case report of a young woman with LPI willing for a natural delivery, new knowledge has been acquired. The metabolic needs in pregnancy can be met through a tailored dietetic plan including a *shake* specially designed to avoid both essential and non-essential AA deficiencies. As previously reported in the Finnish cohort, plasma leucine and isoleucine appear to be decreased, along with cationic AA [5]. Meanwhile, in contrast to healthy pregnancies [15], methionine can be decreased across gestation while no significant changes in phenylalanine levels. It should be stressed that although ammonia concentration can remain within an acceptable range, plasma glutamine can be set further above the upper limit of normal. Indeed, in certain patients with UCD, glutamine may be chronically elevated without high ammonia levels at the same time point indicating metabolic instability. Even if glutamine does not cause brain edema as in acute hyperammonemia, glutamine itself is neurotoxic [16][17]. Among nitrogen scavengers, sodium phenylbutyrate and glycerol phenylbutyrate bind directly to glutamine allowing better clearance; on the other hand, sodium benzoate binds to glycine [18]. However, since the use of benzoate in pregnancy is more widespread, it is the most used option.

Bronchitis episodes may compromise the patient's calorie intake. Even though PAP might be the underlying cause, a deterioration of the phagocytic function leading to an abnormal immune response might also contribute to respiratory symptoms [2].

Renal involvement is another main concern in patients with LPI. Glomerular filtration rate (GFR) can be estimated using cystatin C to avoid the limitations derived from Cr, observing a GFR appropriate to pregnancy-related hyperfiltration [19].

With regards to liver enzymes, transaminases tend to increase after the second trimester and remain slightly elevated 1 year after pregnancy. A similar pattern can be observed for both cholesterol and triglycerides.

Moving onto the PE risk, an imbalance between proangiogenic (i.e., PlGF: Placental Growth Factor) and antiangiogenic factors (i.e., sFlt–1: Soluble fms-like tyrosine kinase-1), namely an increased sFlt–1/PlGF ratio, results in a net antiangiogenic state which favors the development of placental dysfunction [20]. The sFlt–1/PlGF ratio within the reference range (<38) has shown a very high negative predictive value for the short-term prediction of PE and is used to rule out an imminent threat in a pregnant woman with clinical or analytical suspicion of PE [21]. However, an elevated ratio does not necessarily indicate an increased risk as it can be caused by other factors (e.g., the presence of a small-for-gestational-age fetus). Angiogenic factors within the normal range at the time of the onset of arterial hypertension make the diagnosis of PE very unlikely. Moreover, other signs of PE, such as thrombocytopenia, mild proteinuria, and elevated liver enzymes might be explained by LPI pathology. Therefore, PE diagnosis in LPI should be considered with great care.

The monitorization of ammonia levels during delivery, as well as its concentration in the umbilical cord and the newborn, has just been reported once in the literature (10.3390/jcm12196405). In this case, as plasmatic ammonia determination was not readily available in the maternity hospital, capillary blood ammonia was also measured with a portable meter. This analyzer uses a single wavelength reflectance method and special reagent strips, with a measurement range from 10 to 400 µg/dL (conversion factor from µmol/L to µg/dL = 0.587). While a good correlation between plasmatic and capillary ammonia could not be established, since many external factors could have obscured the relationship [22], capillary levels constituted a good aid in tracking ammonia oscillations [23]. It has been described that ammonia is produced by deamination within both the fetus and the placenta. However, the arterial umbilical ammonia concentration exceeds the venous umbilical concentration, indicating a net ammonia production by fetal tissues in humans [24]. A better knowledge of ammonia levels evolution intrapartum could help to determine the plausibility of delayed cord clamping in IEM.

To conclude, careful nutritional and pharmacological treatment under the surveillance of integrative teams is crucial to ensure both maternal well-being and fetal development in any woman, especially when potentially threatening medical conditions such as LPI coexist [7].

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