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SCIENTIFIC LETTER

Carglumic acid (Carbaglu®) treatment in hyperammonemia post liver transplantation

Tratamiento con ácido carglúmico (Carbaglu®) en la hiperamoniemia post transplante hepático

We report the case of a male patient presenting with hyperammonemia after liver transplantation that was successfully reduced after treatment with carglumic acid and L-arginine. Carglumic acid can be a useful tool to reduce high ammonia levels that frequently appear after liver transplantation.

Case report

Our patient is a 60-year-old male who received a first liver transplant to remove a hepatocellular carcinoma due to a virus B infection. He received the liver of an 80-year-old donor who had a double venous system and poor blood flow, which hampered the operation. In the first 48 h he had a graft dysfunction secondary to ischemia. While waiting an urgent retransplantation procedure, he began to manifest encephalopathic symptoms. His ammonia levels were found to be 155 μmol/L (normal < 50 μmol/L), but no measures were undertaken. He then received parenteral nutrition containing 8 g of nitrogen per day. Given his progressive neurological impairment, 12 h later ammonia levels were measured again and had reached 199 μmol/L. The inborn errors of metabolism specialist was contacted, exogenous protein nutrition was stopped and pharmacological treatment was initiated with 5 g of arginine and 2 g of carglumic acid administered via a nasogastric tube. In the follow-up blood test performed 3 h later, ammonia levels had decreased to 122 μmol/L, thus ruling out the need for dialysis or other drugs. A second course of 3 g of arginine and 1 g of carglumic acid achieved a further reduction of ammonia levels to 98 μmol/L 6 h after the initiation of treatment. The patient regained consciousness. In the following hours he received his second liver transplant. His ammonia levels after surgery were 78 μmol//L and it was decided to maintain treatment with 3 g of arginine every 8 h until 48 h later, by which time the patient had begun normal nutrition and had normal ammonia levels.

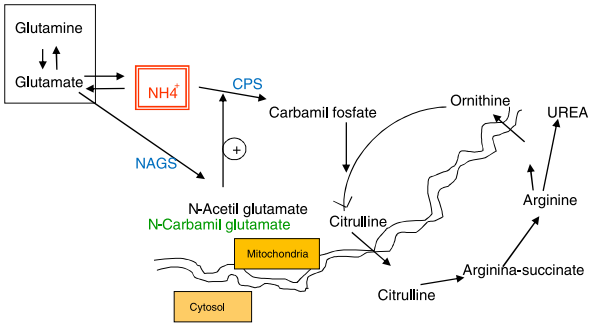

Figure 1 Urea cycle.

Discussion

Following liver transplantation, hyperammonemia is a frequent complication and it is due to the inability to eliminate ammonia through ureagenesis during the time the patient has no functional liver before, during and in the early post-implantation stages. After transplantation, the urea cycle is less effective because of a defect in glutamate synthetase activity[1,2] but we believe it is also due to a secondary N-acetyl glutamate synthase (NAGS) deficiency as a result of possible acetyl-CoA depletion. A transplanted liver is invariably subjected to ischemic injury due to the transient lack of blood perfusion during transportation [3] and, as in our case, due to surgical complications. Ischemia depletes hepatocyte stores of ATP[4] since, in the absence of aerobic respiration, mitochondrial oxidation of the enzymatic cofactors NADH and FADH2 does not take place. Lack of respiration also prevents the generation of acetylCoA from aerobic glycolysis or from beta-oxidation (since acylCoa dehydrogenase is FAD dependent), which is likely to promote an overall acetylCoA depletion in hepatocytes. As acetylCoA is one of the two substrates of NAGS, its deficiency induces a lack of NAGS activity in hepatocytes, resulting in reduced levels of N-acetyl glutamate (NAG) and therefore a reduced activity of the initiating enzyme of the urea cycle, carbamoyl phosphate synthase (CPS) (see Fig. 1).

All these factors can contribute to impairing the ability of the graft to eliminate the excessive ammonia accumulated. In these patients, hyperammonemia is not usually very high, but it can sometimes be a major complication as it induces cerebral edema and leads to neurological symptoms that can leave sequelae. Measures against cerebral edema and dialysis may be necessary treatments at this stage. Ammonia levels should be measured routinely after liver

transplantation, and treatment should be started as soon as possible. Although the posttransplantation hyperammonemia episode can hardly be avoided, its duration and intensity could be minimized contributing to actívate the urea cycle in the newly transplanted liver. Patients could benefit from the intake of arginine and carglumic acid (currently commercialized as Carbaglu®), a structural analog of NAG that can bind to and activate the CPS enzyme.[5,6]

Conflict of interest

There is no conflict of interest at work.

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Current situation of adult women with Turner syndrome in Spain

Situación actual de mujeres adultas afectas de Síndrome de Turner en España

Turner syndrome (TS) is a result of X chromosome monosomy and affects 25–50 per 100,000 females at birth. Several advances at the treatment level have lead to a reduction in part of the morbidity associated with the syndrome; however, its follow-up must be multidisciplinary.[1,2] During childhood, pediatric endocrinologists are responsible for their follow-up and they coordinate all the other medical specialists. In adult life, this coordinating role can be lost; therefore, it is advisable to create specialized units which offer long-term follow-up and allow a correct transition to adult care systems.[2–4] We develop a cross-sectional descriptive study, with patients older than 16 years old who suffer from TS in our country, using a questionnaire that contains 5 sections: demographic data, clinical items, employment situation, educational level, current health situation and follow-up in the last year. The questionnaire was sent by email or made by telephone and by means of self-report. All patients gave informed consent either verbal if the questionnaire was made by telephone or written if the questionnaire was sent by e-mail and the study was carried out according to the indications of the ethics committee of the center.

The inclusion of subjects was carried out thanks to the collaboration of five associations of women with TS (Andalucía, Salamanca, Aragón, Galicia, Madrid) and three third level hospitals (Hospital Materno Infantil de Málaga, Hospital Materno Infantil de Badajoz, Hospital Virgen de la Victoria de Málaga).

A total of 70 questionnaires were received. The median age was 29.5 years (interquartile range [IQR] 18) with median age at diagnosis of 7 years (IQR 4). Seventy women (70%) reported having been treated with growth hormone (GH) with median age at starting of 8 years old (IQR 6.5). The median height was 150 cm (IQR 10) with median body mass index (BMI) 24.74 kg/m^2 (IQR 5.73). There were no significant differences in adult height, weight or BMI between the women treated with GH and those non-treated. However, treated women had lower weight and lower BMI but this difference was not statistically significant.

Regarding the educational level, 80% had a medium-high level of education (secondary school, middle grade or higher studies, university degree) and 41.4% were currently studying. Eighty percent were working and/or studying and 20% reported being unemployed, retired or with permanent disability. Comparing the group of women with TS between 25 and 44 years of age with women the same age from