Glutaric aciduria type I (GA1) is a rare inherited neurometabolic disease that affects the metabolic pathway of the amino acids lysine, hydroxylysine and tryptophan. It is caused by a severe deficiency of the activity of the enzyme glutaryl-CoA dehydrogenase, that leads to an accumulation of glutaric acid (GA) in the organism (Scriver, 2001).

Increased concentrations of GA are directly related to the clinical findings and brain damage involved in this disorder. GA1 is one of the most prevalent organic acidurias, with an estimated worldwide frequency of 1:30,000 to 1:100,000 newborns (Kölker et al 2000). Clinical symptoms include dyskinesia, dystonia, convulsions and muscle stiffness due to striatum degeneration that appear during or after encephalopathic crises triggered by fever, infections or prolonged fasting (Heringer et al 2010).

Diagnosis is performed by elevated levels of the metabolites in urine and glutarilcarnitine in blood of patients by chromatographic methods (Pfeil et al 2013).

Treatment is based on protein restriction and supplementation of L-carnitine, a compound that has demonstrated important anti-inflammatory effects in some organic acidurias (Gokmen-Oze et al 2012).
OBJECTIVE

Due to the severe symptomatology presented by GA1 patients and in agreement with several recent studies in the literature focusing the involvement of inflammation in neurodegenerative and metabolic genetics diseases, the aim of this work was to evaluate the inflammatory profile in GA1 patients.

MATERIALS AND METHODS

We studied nine patients with GA1 at diagnosis (mean age, 3.54 ± 2.25 years) and nine patients under treatment with L-car (mean age, 2.65 ± 2.38 years), with similar clinical symptoms, from the Medical Genetic Service of Hospital de Clínicas de Porto Alegre. The control group consisted of samples from nine aged-matched healthy children (mean age 3.0 ± 3.02 years). Plasma samples were used to determine the inflammatory profile.

Plasma Granulocyte-macrophage colony-stimulating factor (GM-CSF), Interleukine 1β (IL-1β), Interleukine 2 (IL-2), Interleukine 4 (IL-4), Interleukine 5 (IL-5), Interleukine 6 (IL-6), Interleukine 8 (IL-8), Interleukine 10 (IL-10), Interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) were simultaneous measured by the Human Ultrasensitive Cytokine 10-Plex Panel (LHC6004, Invitrogen Corporation, Carlsbad, CA, USA). Assays were performed in triplicate using 50 μl of sample and strictly according to the manufacturer's protocol, utilizing recommended samples dilutions and standard curve concentrations. The results were expressed as pg/mL.

All the analyses were performed using the GraphPad Prism® (GraphPad Software Inc., San Diego, CA, USA – version 5.0) software. For in vivo assay with biological samples, comparison between means was analyzed by one-way ANOVA followed by Mann–Whitney U-test. A P value lower than 0.05 was considered significant.

The Ethics Committee of HCPA, RS, Brazil, approved this study (15-0616). All patients in the present study or their parents gave informed consent.
RESULTS

Figure 1 Plasmatic concentrations of pro-inflammatory cytokines (A-G) in L-car treated GA-I patients (n=8-9). Controls consisted of samples from age-matched healthy children. Data are expressed as median (min:max). \( a \ P<0.05 \) compared to controls. Mann-Whitney test.
RESULTS

Figure 2 Plasmatic concentrations of anti-inflammatory cytokines (A-C) in L-car treated GA-I patients (n=8-9). Controls consisted of samples from age-matched healthy children. Data are expressed as median (min:max). Mann-Whitney test.
DISCUSSION AND CONCLUSION

We verified in a pioneering way that GA1 patients showed an increase in the pro-inflammatory cytokines IL-6, IL-8, GM-CSF and TNF-α, compared to the control group. Inflammation in this disease, is a key process that must be monitored in affected patients since this process can trigger a metabolic crisis and the appearance of the main symptoms and sequels left by GA1 disease (Scriver, 2001).

Our human findings agree with the animal data showing inflammation and oxidative stress in the genetic mouse GA1 model. Increased pro-inflammatory cytokines can be related to an excessive production of reactive species, contributing to inflammation (Rodrigues et al, 2015; Rodrigues et al, 2016).

In the present work we demonstrated that GA1 patients have a pro-inflammatory status allowing us to suggest that adequate monitoring and treatment are crucial for a good prognosis of patients affected by this severe disease.

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