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Cytokines levels in late-diagnosed Classical Homocystinuria patients

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Classical homocystinuria (HCU; CβS deficiency) is characterized by a blockage in homocysteine (Hcy) degradation, resulting in Hcy and methionine accumulation and cysteine deficiency. Studies in healthy and chronically ill individuals have found positive associations between proinflammatory cytokines and plasma total homocysteine (tHcy) [1–3], suggesting a role for immunomodulation in HCU pathogenesis. Therefore, we aimed to investigate 20 inflammatory cytokines in plasma of poorly controlled HCU patients and healthy controls.

The study sample comprised 9 late-diagnosed HCU patients and 10 age and gender-matched healthy controls from South Brazil. tHcy, cysteine, methionine, S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH) were measured in plasma by LC-MS/MS. The cytokines quantification assay was performed through EMD Millipore's MILLIPEX® MAP Human Cytokine kit, accordingly manufacturer's instruction. All samples were measured in duplicates for 20 cytokines (Table 1). Measurements with divergence ≥30% between duplicates

Table 1
Homocysteine-related metabolites and cytokine levels in HCU patients and controls.

		Patients (n = 9)	Controls (n = 10)	p
		Median (range)	Median (range)	
Homocysteine-related metabolites (μmol/L)	Met	165 (22–777)	24 (14–30)	0.007
	Hcy	130 (17–300)	6.7 (5.7–12)	< 0.001
	Cys	158 (67–297)	223 (174–241)	0.014
	SAM	756 (99–3264)	82 (69–107)	< 0.001
	SAH	135 (18–591)	19 (10 − 23)	0.002
Pro-inflammatory cytokines (pg/mL)	IL-1α	0.05 (0.01–1.25)	0.24 (0.01–30.77)	0.252
	IL-1β	0.79 (0.39–1.83)	0.57 (0.37–1.05)	0.743
	IL-6	1.03 (0.45–2.05)	1.12 (0.47–11.56)	0.653
	IL-8	2.07 (0.58–15.60)	1.58 (1.12–18.14)	0.624
	IL-17	1.96 (1.04–5.48)	4.09 (1.23–12.94)	0.102
	TNF-α	7.92 (3.62–14.81)	9.17 (3.92–13.67)	0.287
	TNF-β	0.01 (0.00–1.94)	0.02 (0.00–119)	0.617
	MCP-1	254 (185–1014)	267 (216–357)	0.935
	IP-10	277 (170–1855)	489 (264–1764)	0.153
	GRO	829 (197–2473)	704 (303–1014)	0.595
	MDC	554 (299–1288)	527 (295–759)	0.744
	MIP-1α	1.00 (0.54–3.62)	2.24 (0.66–34.89)	0.077
	MIP-Iβ	18.61 (1.01–37.62)	19.57 (1.84–68.80)	0.327
	VEGF	156.71 (0.01–376)	255.33 (1.32–704)	0.102
	GM-CSF	3.62 (1.06–15.20)	3.01 (1.77–13.67)	0.744
	IFN-γ	3.62 (1.67–9.72)	10.92 (4.94–82.04)	0.007
Anti-inflammatory cytokines (pg/mL)	IL-4	0.48 (0.04–2.83)	0.68 (0.16–26.46)	0.327
	IL-10	0.75 (0.27–1.39)	0.79 (0.41–3.29)	0.935
	IL-13	0.11 (0.02–9.17)	0.15 (0.02–78)	0.368
	G-CSF	13.67 (7.69–46.01)	16.83 (7.69–135.66)	0.653

Met: methionine; Hcy: homocysteine; Cys: cysteine; SAM: S-Adenosylmethionine; SAH: S-Adenosylhomocysteine.

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were excluded from data analysis (n = 1).

Hcy-lowering treatment (pyridoxine 7/9, folic acid 8/9, betaine 7/9, methionine-restricted diet 3/9) was prescribed; but only 3/9 patients had tHcy < 100 μmol/L (target level). Most patients (7/9) were pyridoxine nonresponsive. Because of the high concentrations of tHcy with a wide range we consider this an ideal group to explore the potential relation between cytokines and tHcy. Cytokines plasma levels were similar in patients and controls, with the exception of IFN-γ, which was three-fold reduced ($p = .007$) in patients (Table 1). In line an inverse association of Hcy and SAM with IFN-γ was found (r − 0.487 and r − 0.537; $p < .05$).

To our knowledge, only one study had previously evaluated cytokines in HCU patients. Keating et al. measured 16 cytokines in plasma of HCU patients, and found that patients with tHcy > 150 μM, ($n = 5$) had increased levels of several pro-inflammatory cytokines (IL-1a, IL-6, TNF-α, IL-17 and IL-12), while well controlled patients (Hcy < 86.1 μM, n = 5) had not [4]. The authors provided no information about which patients received treatment. IFN-γ was not evaluated in this study. In previous studies, reduced IFN-γ levels have shown anti-inflammatory properties [5,6].

In summary, our study provides no evidence of increased inflammatory cytokines in HCU patients on treatment, despite poor metabolic control. Hcy may even show anti-inflammatory properties like glutathione [7], what could explain the finding of lowered IFN-γ. The potential impact of Hcy-lowering treatment on cytokines requires further study.

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