Clinical Nutrition 34 (2015) 1258–1265

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Is glutamine deficiency the link between inflammation, malnutrition, and fatigue in cancer patients?☆

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ARTICLE INFO

Article history:
Received 5 August 2014
Accepted 29 December 2014

Keywords:
Solid tumors
Cancer related fatigue
Inflammation
Malnutrition
Glutamine

SUMMARY

Purpose: Evaluation of potential associations between plasma glutamine levels and the incidence of cancer related fatigue, physical performance, poor nutritional status, and inflammation in patients with solid tumors.
Study design: Mono-center cross-sectional study recruiting 100 (34 women) consecutive patients (September 2009–March 2011; ≥18 y) with solid tumors and causal tumor therapy.
Methodology: Fasting venous blood was harvested for routine clinical chemistry, amino acid (HPLC) and inflammation marker analyses. Clinical assessments included global, physical, affective and cognitive fatigue (questionnaire) and Karnofsky performance status. Nutritional status was evaluated using bioelectrical impedance analysis, the Prognostic Inflammatory and Nutritional Index and plasma protein levels. Regression analyses were performed to correlate continuous variables with plasma glutamine (95% confidence intervals).
Results: Nutritional status was impaired in 19% of the patients. Average plasma glutamine concentration (574.0 ± 189.6 μmol/L) was within normal range but decreased with impaired physical function. Plasma glutamine was linked to the ratio extracellular to body cell mass ($p < 0.044$), CRP ($p < 0.001$), physical ($p = 0.014$), affective ($p = 0.041$), and global fatigue ($p = 0.030$). Markers of inflammation increased with low physical performance.
Conclusions: The data support our working hypothesis that in cancer patients systemic inflammation maintains a catabolic situation leading to malnutrition symptoms and glutamine deprivation, the latter being associated with cancer related fatigue.

1. Introduction

Malnutrition, pro-inflammatory reactions, and fatigue are clinical symptoms often observed in cancer diseases. Cancer-related fatigue (CRF), a subjective feeling of tiredness or weakness, is persistent, not relieved by rest [1], and occurs both during and after anti-cancer therapy [2]. Its prevalence varies between 32% [3] and over 90% [4]. Obviously, age and sex are non-suggestible criteria: younger patients experienced more fatigue than older ones; men reported less fatigue than women [3]. In addition, the location of the tumor, the advancement and severity of the underlying disease, as well as the modalities and lines of treatment may influence fatigue prevalence [3,5]. Malnutrition and weight loss occur with a prevalence of 38% [6,7] ranging from 31% in patients with favorable non-Hodgkin lymphoma to 87% in patients with gastric cancer [8]. Earlier studies showed that weight loss and fatigue are strongly associated [7,8]. The increase in the systemic inflammatory

☆ This work was part of the Master Thesis of U.S.
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http://dx.doi.org/10.1016/j.clnu.2014.12.021
0261-5614/

response (marker: C-reactive protein, CRP) in patients with lung cancer was associated with greater weight loss, higher fatigue score and reduced survival rate [9]. In patients with advanced cancer, higher levels of cytokines were correlated with physical fatigue [10]. In a large study of 1466 cancer patients across eight European countries, the majority of cancer symptoms as well as the occurrence of fatigue, occurred together with increased CRP levels [11].

The underlying mechanism(s) for CRF is still unknown [2]. Several hypotheses are proposed including potential relations to both chronic physical or psychological comorbidities like anemia [12], pain, depression, anxiety, sleep disturbance, and immobility [13]. However, clear evidence to support these hypotheses is not available.

Glutamine is the most abundant amino acid in the body and constitutes 61% of the total pool of amino acids in the human muscle [14]. It is the most important circulating "nitrogen shuttle" accounting for 30%–35% of all amino acid nitrogen transported in the blood [15] and serves as important precursor for the de novo synthesis of nucleotides, nucleic acids, amino sugars, proteins, and glutathione. Glutamine is a preferred respiratory fuel for rapidly proliferating cells such as enterocytes and lymphocytes [15]. Metabolically, glutamine is needed for endogenous citrulline and arginine synthesis [16] and reveals an interdependency with the inflammatory response, e.g. the production of interleukin-6 (IL-6) [17]. Characteristic for hypercatabolic situations during cancer is a hyperinflammatory cytokine release pattern combined with an insufficient endogenous availability of glutamine due to increased consumption. Overall glutamine deprivation is associated with depression, reduced protein synthesis, muscle loss and possibly physical as well as emotional fatigue [18,19]. Consequently, glutamine is considered a "conditionally indispensable amino acid" in hypermetabolic and hypercatabolic situations [19]. Current studies evaluating the effect of radiotherapy on blood chemistry factors as well as urinary and plasma amino acid concentrations in breast cancer patients [20] support the notion that glutamine deprivation may at least be associated with fatigue symptoms. During five weeks of radiotherapy, one third of the patients developed CRF; in these patients, urinary excretion of several amino acids, specifically glutamine, was decreased compared to non-fatigued patients.

The aim of this cross-sectional study was to elucidate the associations between plasma glutamine levels and the occurrence and severity of CRF, poor nutritional status and inflammation in cancer patients with solid tumors.

2. Materials and methods

The study protocol was approved by the ethics committee of the Faculty of Medicine, Ludwig-Maximilians-University Munich.

2.1. Study participants

Cancer patients with a solid tumor admitted to the Departments of Internal Medicine II and III of the Ludwig-Maximilians-University-Großhadern, Munich, were included. All participants underwent systemic cancer therapy, chemotherapy, tyrosine kinase inhibition or radiation. Inclusion criteria were: 18 years or older, ability to speak and understand German, hemoglobin concentration $\geq$9 g/dl, no transfusions of red blood cell concentrates, no administration of erythropoietin or any glutamine supplements 4 weeks before study entry. Exclusion criteria were as follows: pregnancy/lactation or postpartum period, diagnosis of psychiatric disease, periods of parenteral nutrition, acute infection, and hematological diseases (eg, leukemia). All patients were aware of the purpose of the study and provided written informed consent. A number of 100 patients was considered as adequate to generate a hypothesis (glutamine deprivation is linked to CRF, poor immune status, and malnutrition) for a subsequent clinical trial. Consecutive recruitment was started in September 2009; the target number of subjects was reached in March 2011.

2.2. Study design

On admittance to the hospital, the patients were physically examined. Venous blood was obtained in the morning for routine clinical chemistry, inflammation marker and amino acid analyses. Global, physical, affective and cognitive fatigue symptoms were determined using the German cancer fatigue scale, a questionnaire filled out by the patients. Nutritional status was evaluated using bioelectrical impedance analysis (BIA) and the Prognostic Inflammatory and Nutritional Index (PINI). The Karnofsky Performance Status (KPS) was calculated to judge functional impairment and need for assistance.

2.3. Clinical chemistry and inflammatory markers

Routine clinical chemistry (albumin, prealbumin, complete blood count) was performed in the Institute for Laboratory Medicine/Clinical Chemistry of the Ludwig-Maximilians-University. Inflammatory markers (α-1-acid glycoprotein [α1-AG], CRP, Interleukin-6 [IL-6], Interleukin-10 [IL-10], tumor necrosis factor α [TNFα]) were determined using standard methodology (Future Lab, Munich).

2.4. Amino acid analysis

Heparinized blood samples (5 ml of venous blood) were centrifuged for 10 min at 4 °C in order to obtain plasma which was then deproteinized with sulphosalicylic acid (30 mg/ml plasma) and centrifuged. The supernatant was stored at −70 °C and transferred to the Department of Nutrition and Food Sciences, University of Bonn, Germany, for analysis. Amino acids were determined by reverse-phase high-performance liquid chromatography and fluorescence detection (precolumn derivatization with orthophthaldialdehyde). The coefficient of variation was in the range between 0.4 and 2.2% [28]. The concentration of glutamine and glutamic acid in the plasma of healthy persons has been determined to be 579 ± 9 μmol/l and 58 ± 5 μmol/l, respectively [29,30].

2.5. Cancer-related fatigue

To evaluate the global fatigue score, patients completed the questionnaire of the German version of the Cancer Fatigue Scale (CFS-D) originally developed and validated in Japan [21] asking for signs of physical (6 questions), affective (4 questions), and cognitive (5 questions) fatigue. High scores represent high levels of fatigue. Twenty-four points can be achieved for the answers on physical fatigue, 16 points for affective, and 20 points for cognitive fatigue; the maximum total score is, thus, 60 [21].

2.6. Nutritional status

Bioimpedance analysis (BIA) (BIACORPUS RX 4000, software BodyComp V 8.4; MEDI Cal HealthCare GmbH, Karlsruhe, Germany) was performed (50 kHz, 800 μA) while the patients were lying in a supine position with legs apart and arms not touching the torso. The four surface standard electrodes (tetrapolar technique) were placed on the right hand and foot. Based on the three-compartment model, fat-free mass (FFM) and fat mass (FM) were calculated using resistance (R) and reactance (Xc) measurements [22,23]. FFM was