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Inflammatory, endocrine and metabolic correlates of fatigue in obese children

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ABSTRACT

Alterations in endocrine functions and low-grade systemic inflammation represent fundamental characteristics of obesity. These biological systems have been repeatedly linked to fatigue symptoms. The aim of the study was to assess the relationship between fatigue dimensions and metabolic/inflammatory markers in a sample of non-diabetic obese children. The possibility that inflammation-induced alterations in tryptophan metabolism relates to specific dimensions of fatigue was also investigated in a subsample of patients.

The study was conducted in 41 obese children, median aged 12 [9–15] years, recruited in a pediatric tertiary center. Three dimensions of fatigue (e.g., general fatigue, sleep/rest, cognitive fatigue) were assessed using the Pediatric Quality of Life Inventory Multidimentional Fatigue Scale. In addition, a principal component analysis was performed to identify fatigue dimensions that were specific to the population under study. This analysis extracted five relevant dimensions corresponding respectively to concentration, energy, self-perceived cognitive efficiency, sleep/rest and motivation/anhedonia. Blood samples were collected for the measurement of inflammatory and metabolic markers, including high sensitivity C-reactive protein (hs-CRP), insulin, uricemia and glycaemia. Tryptophan, kynurenine and neopterin levels were also determined in a subsample of 17 patients.

In the whole population under study, cognitive fatigue and reduced motivation/anhedonia were associated with BMI, independently of sex and age. The dimension of reduced motivation/anhedonia was associated with insulin resistance and inflammatory biomarkers. The association with insulin resistance persisted when the extent of fat mass (BMI-SDS) was taken into account. No association was found between tryptophan metabolism and specific dimensions of fatigue, but kynurenine and the kynurenine/tryptophan ratio correlated with insulin and HOMA-IR.

These data indicate that insulin resistance in non diabetic obese children is associated with both cognitive fatigue and reduced motivation/anhedonia and with alterations in tryptophan metabolism. Further investigations are needed to determine whether inflammation-induced alterations in tryptophan metabolism is directly or indirectly implicated in insulin resistance and related fatigue.

1. Introduction

The prevalence of childhood obesity has substantially increased worldwide in both industrialized and low/middle-income countries (Lobstein et al., 2015), with significant impact on the burden of national health systems (Lobstein et al., 2004). Obesity in childhood and adolescence leads to physical and psychosocial health consequences and is associated with multiple complications, including cardiovascular, endocrine/metabolic and psychological/neuropsychiatric comorbidities (Ebbeling et al., 2002; Lobstein et al., 2004). Insulin-resistance, in particular, is frequent in obesity. Several mechanisms have been suggested to explain this effect, increased plasma-free fatty acid level, low-grade inflamma-

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tion, oxidative stress, altered gene expression and mitochondrial dysfunction (Hirabara et al., 2012). Chronic state of low-grade inflammation in insulin-responsive tissues, mainly muscles, liver and adipose tissue, is a major contributor of insulin resistance (Hirabara et al., 2012), with obesity-induced pro-inflammatory cytokines secretion in adipose tissue disrupting insulin signaling and promoting systemic insulin resistance (Shu et al., 2012). Systemic low-grade inflammation in obesity is susceptible to reach the brain and to promote local inflammation. There is now some evidence suggesting that this process may contribute to the psychological/neuropsychiatric comorbidities of obesity, such as depression, fatigue, sleep alterations and cognitive impairment (Lasselin and Capuron, 2014; Miller and Spencer, 2014).

Obese patients often report fatigue, with a prevalence being close to 60% in adult obese subjects (Impellizzeri et al., 2013; Lasselin and Capuron, 2014). In pediatric obese populations, fatigue was shown to be particularly prevalent and severe, being comparable to fatigue experienced by pediatric patients receiving cancer treatment (Varni et al., 2010). Moreover, together with sleep problems and sadness, fatigue was found to account for a large part of quality of life impairment in obese children and adolescents with nonalcoholic fatty liver disease (Kistler et al., 2010).

The mechanisms underlying the development of fatigue in obese children may, non-exclusively, involve endocrine/metabolic and inflammatory related processes. In support of this notion, alterations in endocrine functions and low-grade systemic inflammation represent fundamental characteristics of obesity (Pasquali et al., 2006; Castanon et al., 2014). These biological systems have been repeatedly linked to fatigue symptoms (Kaltsas et al., 2010; Dantzer et al., 2014). Moreover, inflammation is known to induce substantial alterations in the biosynthesis of monoamines such as dopamine, noradrenalin and serotonin, which are notorious for playing a major role in the pathophysiology of fatigue symptoms. These alterations include inflammation-mediated effects of the enzyme indoleamine-2,3-dioxygenase (IDO-1). IDO-1 is the first and rate-limiting enzyme responsible for the degradation of tryptophan along the kynurenine pathway, a pathway leading ultimately to the production of neuroactive metabolites. *In vivo*, the ratio of kynurenine/tryptophan (Kyn/Trp) represents a reliable estimate of IDO-1 activity (Widner et al., 1997) and is associated with depression (Miura et al., 2008). Recent report suggests that inflammation-induced alterations in tryptophan metabolism play a role in the development of neuropsychiatric symptoms, including fatigue symptoms in cancer patients (Kim et al., 2015) and in the healthy elderly (Capuron et al., 2011b). It is thus highly possible that this process also contributes to obesity-related fatigue. The aim of the present study was to assess the relationship between fatigue symptoms and metabolic/inflammatory markers in a sample of non-diabetic obese children. We also investigate in a subsample of these patients the possibility that alterations in tryptophan metabolism relate to specific fatigue dimensions.

2. Materiel and methods

2.1. Patients

The study was conducted in a sample of 41 children aged 7 to 16 years old, recruited from the healthcare program for children with obesity as defined by the International Obesity Task Force (Cole et al., 2000) in a pediatric tertiary center (Aquitaine Specialized Centre of Obesity, CHU Bordeaux). This program contains anthropometric and metabolic measurements as routine evaluations. Subjects with known or suspected genetic or syndromic obesity, known or acute signs of inflammatory or infectious disease, and/or any psychiatric disorder were excluded. Informed consents were obtained from children and their parents.

2.2. Clinical/medical assessments

Children were admitted at the hospital during the evening of day 0, and submitted to a physical examination in order to confirm that they exhibited normal physical examination results apart from obesity. Clinical assessments (body weight, height, waist circumference (WC) and blood pressure) were repeated on day 1 between 8 am and 9 am. Clinical assessment of body mass index (BMI), WC, systolic and diastolic blood pressure were transformed in standard deviation score (SDS) for age and sex based on references in a French population (Rolland-Cachera et al., 1991; Mellerio et al., 2012).

2.3. Fatigue measurement

Fatigue was assessed on day 0 using the Peds-QL® (Pediatric Quality of Life Inventory) Multidimensional Fatigue Scale (PedsQL™, Mapi Research Trust, Lyon, France; www.pedsql.org). This scale contains 18 items, each scored from 0 to 4, assessing three dimensions of fatigue corresponding respectively to general fatigue (6 items), sleep/rest fatigue (6 items) and cognitive fatigue (6 items) (Varni et al., 2002, 2004, 2010). Relevant to the present study, the Peds-QL® Multidimensional Fatigue Scale has been validated in a standard population of children with obesity (Varni et al., 2010). The same interviewer administered the scale during the entire study. According to the manual scoring instructions, raw scores for each item were transformed on a 0–100 scale, and a mean score was calculated for each dimension with higher scores indicating lower/fewer fatigue symptoms.

2.4. Biological samples

Fasting blood samples were collected between 8 am and 9 am on day 1 for routine biological measurements as planed in the healthcare program and for the assessment of biomarkers including tryptophan, kynurenine and neopterin, high sensitivity C-reactive protein (hs-CRP), insulin, uricemia and glycaemia.

Serum samples were stored at −80 °C until thawed for biological assays. Insulin was assayed with the automated analyzer Liaison (Diasorin, France); inter-assay CV were 4.6, 4.6, 4.7% at 13.7, 43.3, 135.6 mU/L.hs-CRP, uricemia and glycaemia were determined by a routine AU analyzer (Beckman Coulter, France). Total tryptophan and kynurenine serum concentrations were determined by high-performance liquid chromatography as described elsewhere (Widner et al., 1997). Neopterin concentrations were determined by enzyme-linked immunosorbant assay (BRAHMS Diagnostica, Hennigsdorf, Germany).

2.5. Data analyses and statistics

Extreme values for hs-CRP (>2 standard deviation (SD) above the mean) were observed in 3 participants (hs-CRP: 36, 37 and 39 mg/l). Similarly, extremes values for HOMA-IR (>2SD above the mean) were observed in 2 participants (HOMA-IR: 11 and 16). Data for these subjects were considered as outliers and were not considered for data analysis. Anthropometric data and biological parameters were mean ± standard deviation.

Markers of IDO-1 activity and neopterin were measured in a subgroup of patients (N = 17). Since these measurements were not forecasted in the initial research program but were implemented in the context of an ancillary study, they were performed only in those 17 patients who had additional samples available for the assays. In order to confirm that this subgroup was not different from the