The cross-sectional relation between medically unexplained physical symptoms (MUPS) and the Cortisol Awakening Response

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ABSTRACT

Objectives: We aimed to assess the cross-sectional relation between levels of cortisol and specific symptom clusters, symptom severity and duration of symptoms in patients with medically unexplained physical symptoms (MUPS).

Methods: Baseline data of a cohort of MUPS patients were used. We chose the Cortisol Awakening Response (CAR) as a cortisol parameter, using saliva samples. We used confirmatory factor analysis for the identification of 4 specific symptom clusters: (1) gastrointestinal symptoms; (2) pain; (3) cardio-pulmonary symptoms; and (4) fatigue. For this factor analysis we used the Physical Symptom Questionnaire (PSQ), which assesses the occurrence and frequency of 51 physical symptoms. Symptom severity was measured with the Patient Health Questionnaire-15 (PHQ-15). Duration of symptoms was based on self-reported duration of top 3 symptoms. We performed multiple linear regression to assess relations between CAR and individual factor scores on symptom clusters, symptom severity and duration of symptoms.

Results: Data from 296 patients (76% female) were included in the analyses. The majority of patients suffered from symptoms in multiple organ systems. Factor analysis confirmed that the model with 4 symptom clusters fitted our data. For the total study population, we found no significant relation between CAR and participants' factor scores on any of the symptom clusters. We also found no significant relations between CAR and severity or duration of symptoms.

Conclusion: Our results suggest that within a heterogeneous MUPS population there is no relation between CAR and symptom severity and duration. However, more studies are needed to confirm our findings.

1. Introduction

In all health care settings many patients present with persistent physical symptoms for which no sufficient somatic explanation is found after proper medical examination. Such symptoms are called persistent medically unexplained physical symptoms (MUPS). In some cases persistent MUPS fit criteria of specific functional somatic syndromes such as Fibromyalgia (FM), Irritable Bowel Syndrome (IBS) or Chronic Fatigue Syndrome (CFS). However, the existence of these syndromes as distinct entities (instead of being an artefact of medical specialization) has been up to debate [1,2]. Patients with persistent MUPS have a greater risk of psychosocial disability and experience more psychological distress than patients with explained physical symptoms [3].

Apart from psychological and social mechanisms, physiological mechanisms are thought to play a role in the development and persistence of MUPS. One of these mechanisms is a disturbed hypothalamic pituitary adrenal axis (HPA axis). It has been firmly established that stress (physical or psychological) influences the bodily hormonal stress system. When exposed to stress the HPA axis is initially up regulated resulting in higher levels of the stress hormone cortisol. However, prolonged stress may lead to a “burnout” response, resulting in HPA axis down regulation and reduced cortisol production [4]. As a result of the reduced cortisol production stress sensitivity increases, which is thought to contribute to the development and persistence of MUPS such as pain or fatigue [5–8].

The cross-sectional relation between cortisol levels and several...
functional somatic syndromes has been studied before. A meta-analysis of 85 studies showed that hypocortisolism was found in CFS and possibly in FM, but not in IBS [9], indicating that the presence and extent of cortisol disturbances within MUPS populations may vary between different symptom clusters. However, results were heterogeneous and the review also included studies in which normal or high cortisol concentrations were found. Furthermore, a limitation of this meta-analysis is that only studies concerning three specific functional somatic syndromes were included (CFS, IBS and FM).

As most studies in this field of research evaluated cortisol levels within populations suffering from specific functional somatic syndromes, knowledge about cortisol levels within heterogeneous MUPS populations (that do not necessarily fit criteria of specific functional syndromes) is scarce. In addition, it is unclear whether severity and duration of symptoms play a role in the relation between MUPS and cortisol levels.

It is important to increase our knowledge about the relation between cortisol levels and all sorts of MUPS, as this may shed light on the issue whether cortisol disturbances are symptom specific or whether they exist in all MUPS patients. This knowledge would provide guidance in the unravelling of the (general or symptom specific) pathophysiology of MUPS. Given the described gaps in current knowledge, we formulated the following research question:

What is the cross-sectional relation between cortisol levels and (1) the presence of symptoms from specific symptom clusters, (2) symptom severity and (3) duration of symptoms in a heterogeneous population of MUPS patients?

Based on the results of earlier studies among patients with functional somatic syndromes, we hypothesized that reduced cortisol levels (as a marker for HPA axis down regulation) are symptom specific and will only be seen in patients with certain specific symptoms (e.g. patients with fatigue). We also hypothesized that reduced cortisol levels are more prevalent among patients with severe symptoms and a long duration of symptoms.

2. Methods

2.1. Study design and subjects

For this study data of the PROSPECTS study were used. This is an on-going prospective cohort study, following patients with MUPS in multiple healthcare settings. Participants were included between September 2013 and March 2015. They were recruited in general practices and in specialized MUPS programmes of secondary and tertiary care organizations across the Netherlands. Participating MUPS patients were between 18 and 70 years old. For this analysis we only used baseline data.

We have defined MUPS as the presence of physical symptoms, which have lasted at least several weeks and for which no sufficient explanation is found after proper medical examination by a physician.

In primary care, electronic medical records were searched to select patients who visited their general practitioner (GP) twice or more in the last 3 months with one or more physical symptoms without a matching diagnosis. The list of selected patients was checked for exclusion criteria by the GP. In secondary and tertiary care all newly referred patients with MUPS as the reason for referral were screened for exclusion criteria by the physician performing the intake consultation.

Exclusion criteria were a sufficient medical explanation for the symptoms or incomplete diagnostic evaluation, according to the physician, insufficient command of the Dutch language, a cognitive or visual impairment that prohibits participating in a questionnaire survey, severe psychopathology (e.g. psychotic disorder, bipolar disorder), pregnancy, cancer diagnosed in 5 years prior to inclusion, or another life threatening condition or a short life expectancy.

In all setting, patients who did not meet exclusion criteria received by mail the Patient Health Questionnaire 15 (PHQ-15 [10,11]), which is considered an adequate measure for somatic symptom severity, as it assesses somatic symptoms regardless of their aetiology. Patients who returned the questionnaire and had a score of 2 for at least one symptom (indicating that the symptom was bothering a lot) were considered eligible and were approached for informed consent and inclusion.

Further details about the study design have been published elsewhere [12]. The Medical Ethics Committee of VU University Medical Center Amsterdam approved the study protocol and we obtained written informed consent from all participants.

2.2. Measures

2.2.1. Salivary cortisol samples

Cortisol levels vary greatly during the day: they are lowest at the beginning of the night and then increase, reaching a peak level during the first 30–45 min after the awakening (a natural stressor) in the morning [13,14]. This peak is called the Cortisol Awakening Response (CAR). The steepness of this response is thought to be related to stress reactions [15]. We used the Cortisol Awakening Response as a parameter for measuring cortisol levels, as it forms a discrete entity superimposed on the circadian cycle and therefore shows higher intra-personal stability than solitary measurements [16]. The CAR does not seem to be significantly influenced by age, duration of sleep, time of awakening or the use of an alarm and seems to be stable over time [13].

We measured the CAR using saliva samples. This method is commonly used, because of the non-invasiveness and the ability to sample in patients’ natural environment. Salivary cortisol levels correspond well with cortisol levels in plasma [17]. Participants collected saliva samples at awakening time (T0), and 30 (T1) and 60 min (T2) afterwards [18,19]. They collected saliva at home using Salivettes® (Sarstedt, Etten-Leur, The Netherlands). We provided a comprehensive written sampling manual, according to the guideline of the manufacturer. Samples were stored in home refrigerators and returned by mail as quickly as possible (mostly within 1 day). Returned swabs were stored at −20 °C and centrifuged and analysed with all samples in one batch using liquid chromatographic methods coupled with mass spectrometry (LC-MS/MS, using the Acquity UPLC system and the Quattro Premier XE tandem mass spectrometer (Waters Corp., Milford, MA) [20]).

2.2.2. Questionnaires

At baseline, patients answered questions about personal characteristics (general, socioeconomic and medical characteristics) and a subset of validated and widely used questionnaires concerning outcome measures and relevant covariates.

Outcome measures included the presence of symptoms from specific symptom clusters, symptom severity and duration of symptoms. We measured the presence of symptoms from specific symptom clusters with the Physical Symptom Questionnaire (PSQ [21]), which assesses the occurrence and frequency of 51 physical symptoms that are described in the DSM-III classification [22]. For each symptom, participants scored the occurrence in the past week (never/sometimes/often/most of the time, scoring respectively 0/1/2/3 points). The PSQ covers most organ systems and has been used in earlier MUPS studies [3,23]. Symptom severity was assessed using the PHQ-15 questionnaire. Finally, participants reported a top 3 list of their most prominent symptoms, including the duration of these symptoms. The self-reported duration of the most long-lasting top 3 symptom was used to assess the duration of MUPS.

Based on earlier research, we selected potential confounders of the relation between cortisol levels and MUPS [24,25]. These included characteristics (sex, alcohol use, smoking and obesity), but also relevant medication use and received treatments, which were assessed with the Trimbos/IMTA questionnaire for Costs associated with Psychiatric Illness (TIC-P, [26]). Relevant medication use was defined as the use of
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