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Relationship between fatigue and gait abnormality in Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome Hypermobility type

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ABSTRACT

Ehlers-Danlos syndrome (EDS) is a clinically and genetically heterogeneous group of inherited connective tissue disorders characterised by joint hypermobility, skin hyperextensibility and tissue fragility. It has recently been shown that muscle weakness occurs frequently in EDS, and that fatigue is a common and clinically important symptom. The aim of this study was to investigate the relationship between fatigue severity and the gait pattern using 3D Gait Analysis (GA).

Eleven individuals with Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome Hypermobility type (JHS/EDS-HT) were investigated using muscle strength measured with standardised questionnaire measuring fatigue (Fatigue Severity Scale, FSS) and quantitative 3D GA. Our data showed that FSS value well correlated with the peak of vertical component of ground reaction force ($r = -0.66$, $p < 0.05$). The negative correlation gives evidence that the higher the fatigue is the more reduced force is during gait. Our results showed that the ground reaction force has been applied as a functional evaluation score for detecting pathology in gait of JHS/EDS-HT participants and the found correlation between vertical force and fatigue demonstrated that muscle fatigue may be associated with a loss of proprioceptive acuity in lower limb muscles.

1. Introduction

Joint Hypermobility Syndrome (JHS) is a probably common and largely unrecognised heritable connective tissue disorder mainly characterised by joint hypermobility (JHM), joint instability and chronic pain (Voermans et al., 2010). Recently, the JHS has been considered the same condition, with extreme clinical variability, with the Ehlers-Danlos Syndrome Hypermobility type (EDS-HT) (Tinkle et al., 2009). Actually the JHS/EDS-HT is recognised as a severely and disabling condition with chronic pain and fatigue as major determinants for such severe deterioration of quality of life (Castori, Camerota, Celletti, Grammatico, & Padua, 2010; Voermans et al., 2010).

Fatigue has been described as an associated feature with a positive and direct relationship with muscle weakness; in particular fatigue has a high prevalence among EDS individuals with a most often severely fatigue among the hypermobility

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type (Castori, Celletti, Camerota, & Grammatico, 2011; Voermans & Knoop, 2011; Voermans et al., 2010; Voermans, Knoop, Bleijenberg, & van Engelen, 2011). Fatigue is considered the reduced capacity to sustain force or power output (physiological) reduced capacity to perform multiple tasks over time (psychological) and simply a subjective experiences of feeling exhausted, tired, weak or having lack of energy (Wessely, 1995). The perception of fatigue is subjective and no exact definition exists because of overlap between the lay notion of tiredness and the clinically relevant symptom of fatigue (Chaudhuri & Behan, 2004). Understanding if the main component in perception of fatigue is central (subjective sense of fatigue) of peripheral (objective reduction in motor power in muscle fatigability) may help physician in the EDS-HT/JHS management.

Muscle fatigue in fact adversely affects movement coordination and reaction times (Lin et al., 2009), which are considered important components of gait control. The literature provides some evidence of fatigue-related changes of the biomechanical characteristics of gait even if previous studies were limited in numbers and used widely different protocols to induce fatigue and dependent variables. Strikingly the most commonly studied variables, gait speed, step or stride length and stride time appeared not affected in a majority of studies (Granacher, Wolf, Wehrle, Bridenbaugh, & Kressig, 2010; Helbostad, Leirfall, Moe-Nilsssen, & Sletvold, 2007; Kavanagh, Morrison, & Barrett, 2006; Olson, 2010; Parijat & Lockhart, 2008; Yoshino, Motoshige, Araki, & Matsuoka, 2004). In addition, these studies were conducted on healthy subjects, younger and/older but not in pathological individuals. Fatigue has a positive and direct relationship with muscle weakness and from literature we know that ankle muscle weakness has been suggested as a possible cause of reduced ankle power output in late stance in children with Cerebral Palsy (Gage, 2004) and in elderly gait (Kerrigan, Todd, Della Croce, Lipsitz, & Collins, 1998; Winter, Patla, Frank, & Walt, 1990).

From these considerations and from the clinical need to better analyse the element in JHS/EDS-HT individuals, the aim of this work was to investigate the possible relation between the intensity of fatigue and main gait pattern assessed with quantitative Gait Analysis (GA) in EDS-HT/JHS individuals. Although in fact, the poor postural control and the abnormal gait pattern of these participants have been demonstrated in literature (Cimolin et al., 2011; Galli, Rigoldi, et al., 2011; Galli, Cimolin, et al., 2011; Rigoldi et al., 2012), their relationship with fatigue is still lacking.

2. Materials and methods

2.1. Participant selection

We studied 11 participants (10 female, 1 male; mean age $\pm$ standard deviation: 43.08 $\pm$ 6.78 years), all directly evaluated in a multidisciplinary outpatient clinic dedicated to hypermobility. Subjects were selected on the basis of a clinically confirmed diagnosis of EDS-HT/JHS; diagnosis was established on both the Villefranche and Brighton criteria (Beighton, De Paepe, Steinmann, Tsipouras, & Wenstrup, 1998; Grahame, Bird, & Child, 2000) and participants were considered affected if meeting at least one of the two sets of diagnostic criteria. Additional extra-articular features were also investigated and registered accordingly. A group composed by 20 healthy adults (normal healthy adult: NHA; 10 female, 10 male; mean age $\pm$ standard deviation: 37.23 $\pm$ 8.91 years) was included as control group.

The study was approved by the Ethics Research Committee of the Institute and written informed consent was obtained by the participants.

2.2. Outcome tools

All participants were asked to complete a questionnaire to evaluate the intensity of fatigue. The Fatigue Severity Scale (FSS) is a scale quantifying fatigue intensity, which has been used in different chronic conditions, showing a high internal consistency and validity. The FSS is composed of nine items with a seven-point response format that indicates the degree of agreement with each statement. The score considered is the mean value of the items (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989).

All participants were evaluated instrumentally using an optoelectronic system with passive markers (ELITE2002, BTS, Milan, Italy) with a sampling rate of 100 Hz, two force platforms (Kistler, CH) and 2 TV camera Video system (BTS, Italy) synchronised with the system and the platforms for videorecording. To evaluate the kinematics of each body segment, passive markers were positioned on the participants' body, as described by Davis, Ounpuu, Tyburski, and Gage (1991). Participants were asked to walk barefoot at their own natural pace (self-selected and comfortable speed) along a walkway (10 m long) where the two force platforms were placed. At least six trials were collected for each participant in order to ensure the consistency of the data. All graphs obtained from GA were normalised as % of gait cycle and kinetic data were normalised for individual body weight. In order to define the gait pattern of JHS/EDS-HT participants and to quantify their deviations from normality, some parameters (time/distance parameters, angles joint values in specific gait cycle instant, peak values in ankle moment and power, and in ground reaction force graphs) were identified and analysed (Galli, Cimolin, et al., 2011). As we know from literature that fatigue has a direct relationship with muscle weakness and that ankle muscle weakness has been suggested as a possible cause of reduced ankle power output in late stance, in this analysis we decided to focus our attention on ankle power and on the ground reaction force (Gage, 2004; Kerrigan et al., 1998; Winter et al., 1990).

In particular the analysed parameters were the followings:

Ankle joint power (Fig. 1):

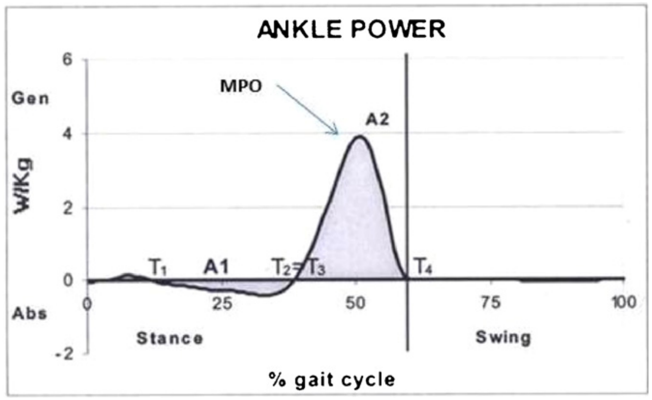

Fig. 1. Ankle power plot for a healthy subject showing A_1, A_2 and MPO indices and T_1, T_2, T_3 and T_4 (A_1: absorbed work in early and midstance; A_2: generated work at push-off during terminal stance; MPO: Max at Push-Off; T_1 and T_2: frames in which the ankle joint power pattern goes through the zero in the first phase of stance; T_3 and T_4: frames in which the ankle joint power pattern goes through the zero at push-off).

(a) A_1: absorbed work in early and midstance (total negative work; J/kg).
(b) A_2: generated work at push-off during terminal stance (positive work; J/kg).
(c) MPO (Max at Push-Off): peak of ankle power at push off (W/kg);

The amount of generated and absorbed work can be calculated by mathematically integrating the power curve over the time period of interest, according to the formula given below:

$$A_1 = \int_{T_1}^{T_2} P dt \qquad A_2 = \int_{T_3}^{T_4} P dt$$

where A_1 is the absorbed work, A_2 is the generated work, P is the ankle joint power, T_1 and T_2 the frames in which the ankle joint power goes through the zero in the first phase of stance and T_3 and T_4 the frames in which the ankle joint power goes through the zero at push off (Fig. 1). Every kinetic index was normalised to subject's body mass.

Vertical GRF (Fig. 2):

(a) Max VGRF (Max of Vertical GRF): peak of vertical GRF at push-off (%BW: %body weight).

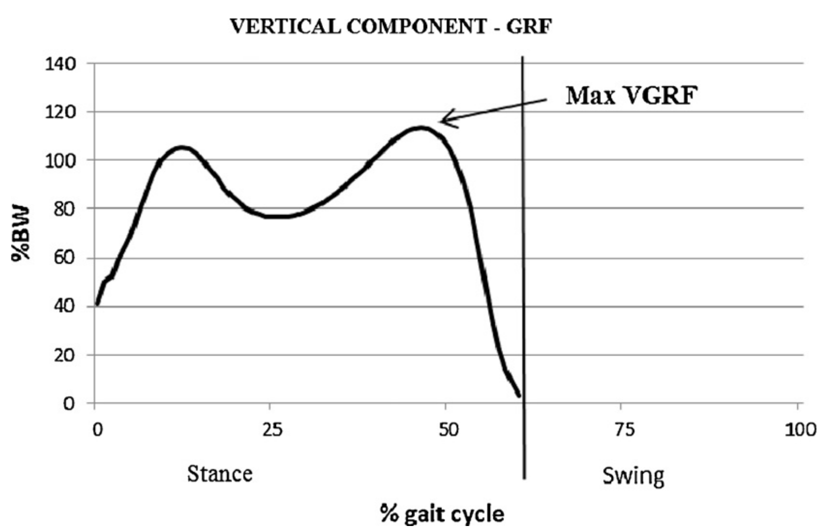

Fig. 2. Vertical component of GRF plot for a healthy subject showing Max VGRF index (Max of Vertical GRF)

2.3. Statistical analysis

All the previously defined parameters were computed for each participant and then the mean values and standard deviations of all indexes were calculated for JHS/EDS-HT group and NHA. Kolomogorov–Smirnov tests were used to verify if the parameters were normally distributed; the parameters were not normally distributed, so we used Mann–Whitney *U*-test to compare the values of JHS/EDS-HT participants versus NHA, and Spearman's correlation (r) was calculated between the FSS mean score and GA parameters. Statistical significance was set at $p < 0.05$.

3. Results

FSS mean score in our population shows a statistically significant difference if compared to those of normal healthy adults (6.2 ± 0.9 versus 2.3 ± 0.7; $p < 0.05$).

The research of correlations between the FSS scores and GA measures revealed that no significant correlation were found with Ankle Power parameters (A_1, A_2 and MPO indices) from a statistical point of view ($r = 0.06$ in FSS and A_1; $r = -0.19$ in A_2 and FFS; $r = -0.20$ in MPO and FSS; $p > 0.05$). On the contrary, the maximum of ground reaction force (GRF) vertical component (Max Vertical GRF index) was well correlated with FSS mean value (Fig. 3). This correlation is negative ($r = 0.66$, $p < 0.05$), representative of an increased fatigue when the GRF is low.

4. Discussion

In the present study we investigated the possible correlation between gait pattern and intensity of fatigue in EDS-HT/JHS individuals. Fatigue has been recognised as a serious symptom of many chronical illnesses that can significantly impair a person's functioning and negatively impact their quality of life (Chaudhuri & Behan, 2004). Focusing on EDS-HT/JHS individuals, fatigue is considered one of the major determinants for such severe deterioration of quality of life in this individuals (Voermans et al., 2010) and understanding if the main component in perception of fatigue is central (subjective sense of fatigue) of peripheral (objective reduction in motor power in muscle fatigability) may help physician in individuals management.

Our data showed that FSS value well correlated with the peak of vertical component of ground reaction force. The negative correlation gives evidence that the higher the fatigue is the more reduced force is during gait. In literature, fatigue is generally used to describe a number of phenomena with a variety of causes (Egerton, Brauer, & Cresswell, 2009), and more strictly it indicates an inability of muscles to generate or maintain force or power output (Enoka et al., 1992; Gandevia, 2001). No evidence is present on this topic in EDS-HT/JHS individuals and our results confirmed this concept in this pathological state.

These results may be useful from a clinical point of view as GA, in particular, quantitative data related to kinetics (ground reaction force), provided information in order to give a clearer insight into the gait pattern in these individuals. In particular, the ground reaction force has been applied as a functional evaluation score for detecting pathology in human gait and the found correlation between vertical force and fatigue demonstrated that muscle fatigue may be associated with a loss of

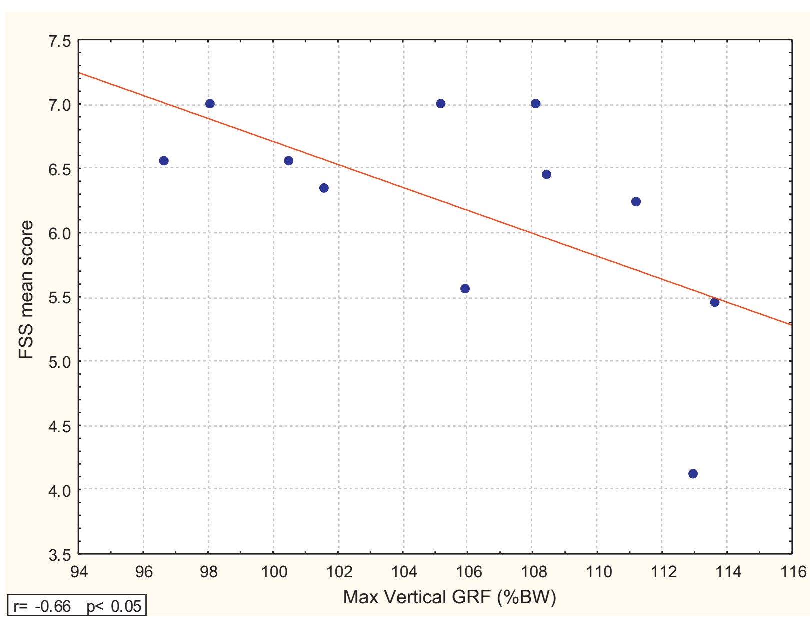

Fig. 3. Correlation between Max of Vertical GRF index and FSS mean score ($r = -0.66$, $p < 0.05$).

proprioceptive acuity in various lower limb muscles. This result was demonstrated in multiple sclerosis where researchers found a decreased median frequency of vertical ground reaction force correlated with an increased muscle fatigue (Wurdeman, Huisinga, Filipi, & Stergiou, 2011). The only study conducted on JHS/EDS-HT by Voermans et al. (2011) suggested a positive and direct relationship between fatigue severity, assessed with a questionnaire, and muscle weakness, measured with and hand-held dynamometry. In this pathology no studies have been previously conducted on the research of a correlation between clinical scales and objective data computed by quantitative GA.

It is important to underline that also other determinant involved in fatigue in JHS/EDS-HT, that are sleep disturbance, concentration problems, social functioning, self-efficacy concerning fatigue and pain severity (Voermans et al., 2010). It should be investigated whether these factors are really the cause or the consequence of fatigue.

The main limitation of this study is the small sample size resulting in limited strength of the clinical and statistical findings; however, it is important to underline that EDS-HT/JHS is a rare syndrome and studies with large sample sizes are difficult to perform. In addition our study represents the first attempt to assess the relationship between standardised questionnaire measuring fatigue and quantitative 3D GA, which is the gold-standard for investigating the gait pattern in humans.

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