Identification of subgroups among fibromyalgia patients

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SUMMARY

This paper presents some hypotheses concerning the identification of homogeneous subgroups among fibromyalgia (FM) patients in order to improve the management of the disease. It also reviews the available literature. Three methods for subgrouping are discussed according to clinical features, biomarkers and gait analysis. Clinical subgrouping based on cluster analysis has been used for the identification of homogeneous subgroups of patients and, more recently, homogeneous clinical features. Longitudinal studies using clinical subgroups to direct treatment and predict outcome are still required. Biomarkers in FM, which is a neurobiological disease, are proving to be of interest. Nonetheless, for the moment, none of them can be used to subgroup FM patients. Due to the fact that cortical and subcortical mechanisms of gait control share some cognitive functions which are involved in FM, gait markers have been proposed to evaluate and to subgroup FM patients in clinical settings. Three out of 4 core FM symptoms are linked to gait markers. Kinesia measured by means of cranio-caudal power is correlated to pain and could be proposed to assess pain behavior (kinesiophobia). Stride frequency (SF), which is linked to physical component, allows the identification of a hyperkinetic subgroup. Furthermore, SF has been correlated to fatigue during the 6-minute walking test. Stride regularity, which expresses the unsteadiness of gait, is correlated to cognitive dysfunction in FM. A reduction in stride regularity allows a homogeneous subgroup to be recognized that is characterized by increased anxiety and depression, and decreased cognitive functions. These results need to be validated in further studies before use in daily clinical practice.

Key words: *Fibromyalgia, subgroups, gait analysis.*

Reumatismo, 2012; 64 (4): 250-260

INTRODUCTION

Fibromyalgia (FM) is a disturbing disease the different aspects of which each presents its own challenges: diagnosis, implication of co-morbidities, severity, identification of homogenous subgroups, pathogenesis, and etiology. The 1990 American College of Rheumatology (ACR) classification criteria have been used to identify FM patients for inclusion in clinical trials (1). They included the presence of widespread pain for at least three months, and pressure pain at a minimum of 11 of 18 pre-defined tender points. However, these criteria alone do not encapsulate the complexities of FM that is characterized by many other core symptoms, such as fatigue, sleep disturbance, and cognitive dysfunction (2). In 2010, Wolfe developed new ACR criteria (3), which excluded the tender point examination and included a widespread pain index, and a symptom severity scale taking into account cognitive symptoms, inadequate sleep patterns, fatigue, and a number of somatic symptoms. At the same time, much effort has also been made to better identify disease subgroups, primarily according to their clinical characteristics, and more recently by means of biomarkers. Gait analysis is one of the proposed biomarkers. Interest in gait analysis grew after walking speed had been reported to precede the development of cognitive impairment (4). Subsequently, thanks to gait analysis systems specifically developed for clinical settings, quantitative gait assessments have provided more powerful gait variables than walking velocity, such as stride variability (also termed stride regularity) (5, 6). Stride variability reflects unsteady gait and is useful to identify the risk of falls or/and dementia in elderly people (7, 8). Evidence of the importance of

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cognition for gait was provided by the observation that frail or cognitively impaired elderly people could no longer walk while performing a secondary task such as talking (9). So, gait has to be considered not as an automated motor task but as a cognitive function (10). Gait of healthy older adults is a motor task requiring the involvement of higher-level cognitive input even in steady-state while walking normally (11). Since then, a large number of reports have highlighted the role of cognitive function in healthy walking; however, brain substrates and neural networks underlying gait are still not well understood (12). The relation between cognitive functions and gait depends, in part, on the analytic approach used for cognitive evaluation, the assessed gait parameters, and the walking condition. A cognitive approach usually takes into account executive function, attention, memory, speed processing, and the verbal intelligence questionnaire (13). In 2007, Verghese et al. (7) demonstrated that quantitative measure of gait can be reduced to three domains: walking speed, stride frequency, and stride variability. There is convergent evidence for the important role of attention and executive functions in predicting differences in gait performance, mainly in gait speed and stride variability (13). However, memory and verbal IQ was related to velocity. In addition, memory was also related to stride frequency (14). At the same time, gait analysis shows a growing interest in the neuropsychological domain, in particular, with regard to cognition and dementia (15). Quantitative gait dysfunction predicts risk of cognitive decline in initially non-demented older adults, and also risk of dementia (7) as well as anxiety and depression contribute to altered walking (16). Depression and anxiety have a negative influence on gait, possibly by reducing the attention paid to gait control (17). Given that cognitive impairment in FM is one of the key symptoms, gait analysis has been recently proposed as an objective measurement for quantifying and subgrouping FM patients (18). The aim of the present article is to review and discuss the clinical interest of methods of subgrouping FM patients. Three methods for subgrouping are proposed according to clinical features, biomarkers, and gait analysis.

Subgrouping FM patients by means of clinical features

As early as 1995, Strazt et al. (19) identified different subgroups of this disease by distinguishing between FM with and without depression. Turk et al., (20) using cluster analyses from the Multidimensional Pain Inventory (MPI), classified FM patients into 3 subgroups based on psychosocial and behavioral characteristics: dysfunctional, interpersonally distressed and adaptative copers. Similarly by using the MPI, Thieme et al. (21) showed that these 3 subgroups were characterized by varying proportions of comorbid anxiety and depression. Giesecke et al. (22) using cluster analysis based on psychosocial domain (depression and anxiety), cognitive domain (catastrophizing, control over pain), and neurobiological domain (tenderness), showed that there may be three different subgroups: one in which patients exhibit extreme tenderness and low levels of distress, an intermediate subgroup with a high level of tenderness and a high level of distress, and a third with low level of tenderness and moderate levels of distress. On the basis of the associated clinical signs and symptoms, Müller et al. (23) found that FM patients can be divided into four subtypes: sensitivity to pain, comorbid pain-related depression, concomitant depression, and FM due to somatization. Their findings have been recently replicated in a highly disabled sample of patients (24). Using the Fibromyalgia Impact Questionnaire (FIQ), De Souza et al. (25) featured two distinct subgroups: one characterized by low anxiety levels, depression and morning tiredness, while the other was characterized by elevated pain levels, fatigue, morning tiredness, stiffness, and depressive symptoms. Similar results have been recently reported in a large sample of FM patients (26). Using the Medical Outcomes study 36-item Short Form Health Survey (SF-36), Oswald et al. (27) identified two subgroups: the first demon-

strated psychological dysfunction, whilst the second achieved normal psychological scores. In a large cohort of FM patients, Wilson et al. (28) established three categories of symptoms (musculoskeletal, non-musculoskeletal, and cognitive/psychological). According to this classification, a cluster analysis identified four subgroups: those scoring high in the three domains, those with moderate scores in both physical domains and high in the cognitive/psychological domain, those with moderate scores in both physical domains and low in the cognitive/psychological domain, and those low in the three symptom domains. More recently, Rehm et al. (29) proposed the identification of FM subgroups on the basis of their sensory symptoms (pressure pain, prickling, burning and thermal hypersensitivity) and comorbidities by the use of a patient-reported questionnaire. Further details of these studies are shown in Table I.

Subgrouping FM patients using biomarkers

A plethora of objective markers has been shown to be abnormal in FM, and some of these may even have characteristics of a biomarker because they are not only abnormal in patients *versus* controls, but also they change along with symptoms. The question is whether there are FM biomarkers that may be useful in FM subgrouping.

Genetics

There is clear evidence of a strong familial association in FM patients. Therefore, the progress being made in FM genetics is likely to lead to better classification of subgroups within the heterogeneous FM syndrome (30).

Table I - Main subgrouping FM patients by means of clinical features.

Reference	Methods	Subgroups (SG)
Turk et al. (20)	Descriptive classification based on the Multidimentional Pain Inventory (MPI)	SG 1: adaptive copers with low perceived disability and depression SG 2: interpersonally distressed: i.e., having high pain or pain interference, high disability, and depression SG 3: dysfunctional due to intermediate pain levels and less substantial psychosocial impairment
Giesecke et al. (22)	Cluster analysis based on 3 different domains features: mood (anxiety, depression), cognition (catastrophizing, control of pain), and hyperalgesia/ tenderness.	SG 1: low hyperalgesia/sensitivity to pain moderate levels of anxiety and depression moderate levels of catastrophism and pain control SG 2: high levels of hyperalgesia/sensitivity to pain elevated levels in anxiety and depression highest levels of catastrophism and lowest levels of pain contol SG 3: highest levels of hyperalgesia and sensitivity to the pain normal levels of anxiety and depression very low levels of catastrophism and the highest levels of pain control
Müller et al. (23)	Descriptive classification based on associated clinical signs and symptoms	SG 1: FM with extreme sensitivity to pain, but not associated to psychiatric conditions SG 2: FM and depression related with comorbid pain SG 3: depression with concomitant fibromyalgia syndrome SG 4: fibromyalgia due to somatisation
Oswald et al. (27)	Descriptive classification based on the Short-Form-36 Health Survey	SG 1: demonstrated psychological dysfunction SG 2: showed normal psychological scores
De Souza et al. (25)	Cluster analysis based on the VAS subscales of the Fibromyalgia Impact Questionnaire (FIQ).	SG 1: the lowest level of pain, fatigue, morning tiredness, stiffness, anxiety, and depressive symptoms SG 2: elevated levels of pain, fatigue, morning tiredness, stiffness, anxiety and depressive symptoms
Wilson et al. (28)	Cluster analysis from 3 symptom factor scores based on a set of 18 physical, psychological, and cognitive symptoms.	SG1: high on all 3 symptom domains, musculoskeletal, non-musculoskeletal, and cognitive/psychological SG 2: moderate on the 2 physical symptom domains and high on cognitive/ psychological symptoms SG 3: moderate on the 2 physical symptom domains and low on cognitive/ psychological symptoms SG 4: low on all symptom domains

Measurements of pain and tenderness
The tender point count included in the 1990 ACR criteria is not considered to be a biomarker due to the frequent discrepancies of this outcome in longitudinal studies. The increased painful perception of other stimuli applied to the skin (decreased threshold to heat, cold and electrical stimuli) measured at random have been shown to be suitable in the follow up of FM patients, suggesting that this type of measurement could become a FM biomarker. However, no subgrouping has been carried out using measurements of pain and tenderness except in the study by Giesecke et al. in which pain and tenderness measurement was used together with clinical evaluations (22).

Functional imaging of the central nervous system
These methods allow the way in which the brain processes the sensory experience of pain to be visualized. Thanks to the growing literature on neuroimaging in FM, we can expect this promising technique to be be used as a biomarker in FM patients, and possibly in the near future as a method of FM subgrouping (31).

Heart rate variability measurements (HRV)
Given the role attributed to altered function of the autonomic nervous system in FM, heart rate variability has been suggested to be a biomarker (32). Recently, in a pilot study, Lerma et al. (33) found that HRV parameters were correlated to pain intensity and so nocturnal HRV can differentiate between patients and controls (odds ratio 13.6). This biomarker could, therefore, help to subgroup FM patients.
Many others markers have been tested (event-related potential, sleep and activity, stress-response systems, neurotransmitter levels, sex hormones, autoantibodies and immunological markers); however, none of them has acquired the status of being useful biomarkers for subgrouping FM patients (34).

Subgrouping FM patients by means of Gait analysis
Walking speed, the primary gait measure, is of clinical interest in FM during both fast and comfortable walking. Pankoff demonstrated that the 6-minute walk test (6MWT) (35), a well-known test for the evaluation of cardiorespiratory aptitude, is reliable in FM patients, and significantly correlated to FIQ total score. This result was replicated by Homann (36), who found in addition a negative correlation between the 6MWT and the functional capacity of FM measured by means of the Health Assessment Questionnaire. Comfortable walking speed decreases significantly in FM patients, in relation to a shortness of stride length and a reduction in cycle frequency (37). Jimenez *et al.* replicated this result and found in addition a negative correlation between comfortable walking speed and FIQ (38).
More results concerning gait variables and psycho-characteristics of FM patients have been recently found through a multicenter case-control observational study carried out on the interaction between FM and gait in FM patients (18). This study aimed to characterize gait disorders in primary FM patients, looking for correlations between gait markers and main FM features, and subgrouping FM patients according to gait markers. The population included 52 patients each matched to an individual control. Patients with primary FM were recruited according to ACR criteria. All of them had achieved an average pain visual analog score (VAS) of at least 40 on a scale of 0-100 mm. Clinical assessments included pain during the previous week and this was measured by means of the 100-mm VAS pain score, according to the Short Form McGill Pain Questionnaire (SF-MPQ) (39). The Coping Strategies Questionnaire (CSQ) was used to assess patient's strategies to cope with chronic pain, and the efficacy of these strategies in controlling pain (40). The CSQ assessed the use of 6 cognitive coping strategies (diverting attention, reinterpreting pain sensations, coping self-statements, ignoring pain sensations, praying or hoping, catastrophizing) and one behavioral coping strategy (increasing activity level). Fatigue intensity was measured by the Chalder Fatigue Scale (CFS) (41). Sleep quality and disturbances

were assessed by the Pittsburg Sleep Quality Index (PSQI) (42). The SF-36, including both physical component summary (PCS) and mental component summary (MCS), was used for the assessment of health status, functional status and quality of life (43). The FIQ was used to assess the overall symptomatology of FM patients (44).

Gait analysis was carried out on patient and controls according to a validated gait test and a reliable and suitable accelerometric method (Locometrix™). A gait test was performed during a stabilized walk at a self-selected speed that provided stabilized gait measurements. The duration of gait analysis was long enough to include 19-21 gait cycles and to provide reliable gait measurements (45). Five main gait markers were selected: walking speed (m/s), stride length, stride frequency (SF), *i.e.* the number of gait cycles per second [Hertz (Hz)]. Stride regularity quantifies the spatial-temporal similarity between successive gait cycles, which is a measure of stride-to-stride variability (dimensionless). Cranio-caudal power (CCP), W/kg) measures the amount of movement (magnitude and frequency) in the cranio-caudal axis, which measure the kinesia (46).

Statistical analysis were carried out according in three successive steps. A preliminary single blind analysis was performed as an initial validation of gait markers. The statistician had to cluster all participants (patients and controls, identities were coded) into FM patients and control subjects using k-means cluster analysis limited to two clusters. The blind cluster analysis showed that SF was the most discriminating marker among patients and controls (38 of 52, 73%). ROC curves confirmed the utility of gait markers in the identification of FM patients [area under the curve for SF, SR and CCP were 0.740 (0.044), 0.678 (0.052) and 0.690 (0.053), respectively]. An area under the curve of 0.7 or above is acceptable for predictive ability (47).

A second step, in an open statistical analysis, made comparisons between FM patients and control subjects. The aim was to quantify FM patients according to psychometric, self-questionnaire assessment

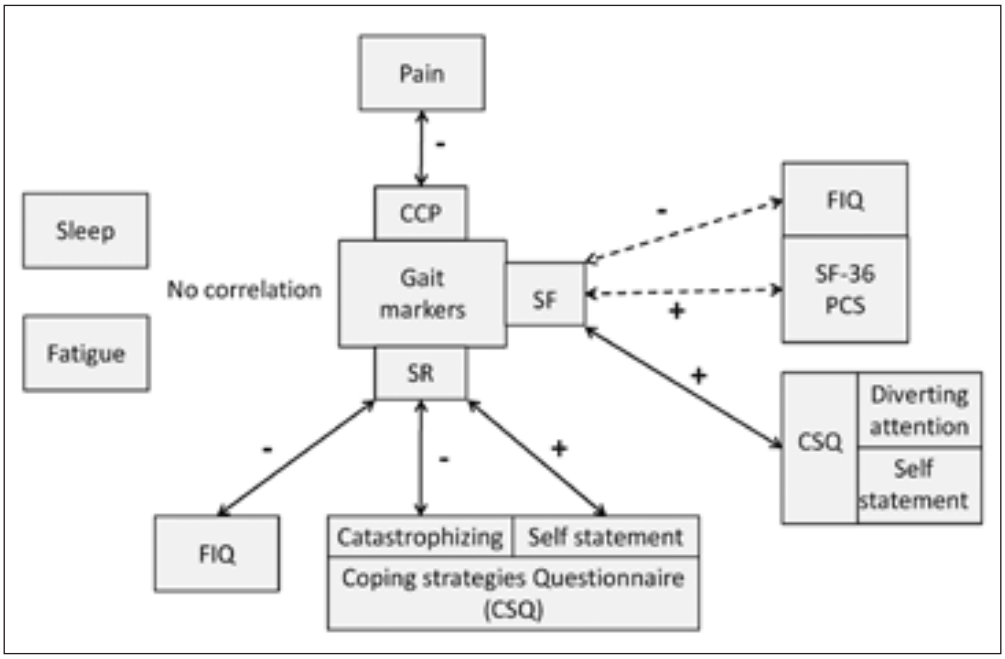

Figure 1 - Correlations between gait markers and main outcomes measurements.
CCP: Cranio-caudal power (kinesia); SF: stride frequency; SR: stride regularity; solid line: significative correlation ($p<0.05$); dotted line: tendency ($p=0.06$); +: positive tendency or significant correlation; -: negative tendency or significant correlation.

and gait markers. Main outcomes were obtained using all items, which differed significantly between patients and controls but there was no center effect. Correlations between gait markers and main outcomes are summarized in Figure 1. Interestingly, FIQ score, taking into account both physical and depression items in FM, was found to be linked to SF and SR. Furthermore, two major items from CSQ were correlated to gait markers: self statement was positively correlated to SF and SR; catastrophizing was negatively correlated to SR. Finally, pain was negatively correlated to cranio-caudal power, which could relate to fear of movement in FM patients.

According to the fact that the main gait markers (SF and SR) do not express the same significance in their relation to cognitive function (mainly executive function and episodic memory) (7), cluster analysis was carried out separately for each gait variable: SF, SR and CCP.

The cluster analysis of SF (Table II) allowed 3 distinct subgroups to be identified. The VAS score was significantly lower in subgroup I than in subgroup II (p=0.01). The FIQ score was significantly lower in subgroup I compared to subgroups II and III (p=0.004). The PCS subscore of SF-36 was significantly higher in subgroup I than subgroup III (p=0.04), and CCP score was significantly higher in subgroup I than the other two subgroups (p=0.0002). The cluster analysis of SR (Table III) allowed 2 distinct subgroups to be identified, the first was characterized by a decrease in SR and the other with a normal SR. No difference was observed for SF and CCP between these two subgroups. Patients with decreased SR had more depression (p=0.03) and showed more anxiety traits (p=0.03) than patients with normal SR. Furthermore, patients with decreased SR had reduced coping strategies such as self-statement (p=0.003) as well as greater tendency towards catatrophizing (p=0.002). Finally, decreased SR was associated with higher FIQ score (p=0.02).

Table II - Classification of fibromyalgia subgroups according to Stride Frequency (SF).

Subgroup 1 normal SF	Lower values of pain Higher physical activity Absence of kinesiophobia
Subgroup 2 moderate decreasing of SF	Higher values of pain Moderate physical activity Moderate value of kinesiophobia
Subgroup 3 High decreasing of SF	Moderate values of pain Lower physical activity Higher values of kinesiophobia

Table III - Classification of fibromyalgia subgroups according to Stride Regularity (SR).

Subgroup 1 normal SR	Lower values of depression and anxiety Lower values of catastrophism and higher values of self statement
Subgroup 2 decreased SR	Higher values of depression and anxiety Higher values of catastrophism and lower values of self statement

DISCUSSION

Cluster analysis is a multivariate statistical technique that can be used to evaluate the degree of similarity among apparently heterogeneous variables, and to identify related groups of variables based on these similarities. Cluster analysis is regularly used in FM patients. It has been used primarily to identify homogeneous patients and more recently to identify homogeneous clinical features (48, 49). These methods of subgrouping according to clinical subgroups and symptoms aim to improve clinical decision making and, ultimately, to provide more individualized treatment with better results and fewer adverse results. However, longitudinal studies using subgrouping according to clinical features to guide treatments are still needed (50).

Gait analysis in FM

The study reported by Auvinet was a multi center project with a center effect, so some interesting data were excluded, involving gait markers (walking speed and stride length), and psychometric characteristics (physical functions in FIQ, reinterpreting pain sensations in CSQ). These missing data could provide additional information; in particular, physical functions measured

by FIQ, which could be correlated with walking speed and/or SF. Therefore, further studies are needed to investigate walking speed and stride length in FM.

Co-morbidities in gait analysis

In the same study, major depression was one of the exclusion criteria, so the study did not include FM patients with major depression according to the Mini-International Neuropsychiatric Interview (MINI) (51). Depression may be considered a possible confounding factor. On the one hand, depression is linked to FM severity (52). On the other hand, increased level of depression is known to be associated with decreased velocity and increased stride variability (53). So, both FM severity and depression will lead to the same gait abnormality: decreased gait regularity. SR reflects the severity of the illness whatever the cause. Given this, SR cluster analysis showed an increased level of depression in the subgroup with a decreased regularity.

Obesity is sometimes considered a comorbidity due to its high prevalence (32-50%) among FM patients (54). It contributes to the severity of FM as it reduces physical functioning and increases fatigue (55). Obesity has been associated with significant gait abnormalities such as lower SF, decreased SR, and reduced CCP, in comparison with controls (Auvinet, *unpublished data*). Nevertheless, as far as depressed symptoms are concerned, increased obesity or a more severe FM will have similar effects on gait analysis, *i.e.* a decreased SR, so we can assume that obesity is not a confounding factor for gait analysis in FM patients.

Clinical signification of gait markers in FM

Stride frequency was shown to be the best gait marker for the differentiation of FM patients from controls allowing the identification of 3 out of 4 subjects in each group. This raises the question of the importance of SF in FM and its significance in terms of underlying mechanisms. In addition, SF was correlated to diverting attention and coping self-assessment which are associated with high physical and low psychosocial disability levels (56). Finally, there is a weak correlation between SF, FIQ and physical component of SF-36. These results suggest that SF may be of interest in assessing the physical component of FM. Cluster analysis of SF reinforced this view point identifying an interesting subgroup characterized by a normal SF associated with low pain level (VAS), reduced overall symptomatology (FIQ), high physical activity (PCS) and hyperkinesia. The two other subgroups with reduced SF were characterized by high pain level, low physical activity and hypokinesia. Stride frequency could be also of interest in the measurement of fatigue in FM. In a study conducted by Dumolard et al. (57), the decrease in SF during a 6MWT was correlated to the increasing fatigue measured by the Borg scale.

Stride regularity proved to be of great interest in FM patients: SR was strongly correlated to FIQ and to catastrophizing, a major CSQ item. In FM, catastrophizing is a main cognitive factor, and can prospectively predict high level of pain and depression, and low quality of life (56). SR measures the unsteadiness of gait, and it has been linked to many neurological diseases such as Parkinson's disease (46), Alzheimer's disease (58), and pre-clinical stages of dementia (7). Stride time variability has been shown to be related to specific cognitive processes, namely executive function and attention (59). Recent advances showed that in FM patients there is a reduction in working memory, executive function (60), and attention (61) independently of concomitant psychiatric conditions such as depression and poor sleep (62). Therefore, SR could be suggested as a measurement of cognitive reserve in FM. Cluster analysis confirms the correlations observed in the subgroup with low SR, characterized by reduced self-statement, increasing catastrophizing, and high FIQ. This subgroup was also distinguished by more anxiety and depression. Therefore, one may raise the question as to whether there is a possible overlap between the subgroup with low SR, identified on the basis of gait analysis, and other subgroups distinguished by means of different cluster

methods based on anxiety, depression and cognitive features. Consequently, considering the important role of affect and cognition in FM patients, SR measurement could be suggested before initiating cognitive-behavioral therapies in order to adapt treatment approaches to patients' characteristics (63, 64).

Cranio-caudal power that measures kinesia was found to be the only correlation between pain and gait analysis. Cluster analysis of CCP enabled the identification of a subgroup with low pain level and hyperkinesias In fact, CCP measurement reflected the fear of pain (kinesiophobia), which is a classic behavior feature in FM patients leading to a reduction in their movements (65). This highlights the significance of gait analysis and pain behavior assessment in chronic painful conditions previously described in patients with lower back pain (66). In addition, there is growing evidence that fear of movement plays an important role in the development of chronic pain in musculoskeletal disorders such as low back pain and fibromyalgia (67). Kinesia evaluation by means of CCP measurement could be a promising area of research in the field of pain behavior management.

Clinical value of Gait analysis

The three main gait markers (SF, SR, CCP) were correlated to some major clinical characteristics of patients (VAS, FIQ score, Coping self statement, Catastrophizing, PCF from SF-36). Although these statistical results are important, they are not sufficient for clinical applications. This point received a first answer in a preliminary study which showed that the improvement of gait markers is of clinical significance in FM patients after a 12-week rehabilitation and exercise training program (68).

Future direction

The "stops walking while talking" phenomenon, identified by Lundin-Olsson in older persons prone to falls revealed that cognition takes part in controlling gait, and reinforced the suggestion that gait should also be tested by adding one or more secondary task while walking. Changes in gait performance while performing an attention-demanding task (counting backward…) are compared to walking alone. Dual task (DT) gait analysis under pathological conditions leads to a decrease of walking speed, and an increase of stride variability. Furthermore, it has been shown that DT gait analysis is reliable (69) and consistent (without significant variation over a period of time) (70). Such condition is becoming the classic way to assess the interaction between gait and cognition (16), there is also increasing evidence that FM patients have deficits in attention and working memory, which become more prominent when patients have to cope with an additional source of distraction (61). So, we can assume that DT gait analysis in FM could be of interest in quantifying the patients' cognitive resources.

CONCLUSION

Identifying subgroups in FM remains a challenging goal. Subgrouping according to clinical features is still ongoing from 15 years. Gait analysis was recently considered as an objective method to grade and to subgroup FM patients. In clinical settings, this method appears to be promising and of great practical interest. Three out of 4 core FM symptoms are linked to gait markers. Cranio-caudal power that is correlated to pain could be proposed to assess pain behaviour (kinesiophobia). Stride frequency that is linked to physical component could be suggested as an index to walking training rehabilitation program as well as a gait marker for the occurrence of fatigue during a 6MWT. Stride regularity is linked to cognition in FM and shares some common domains between FM and gait control (attention and executive function), so it could be useful for the measurement of cognitive reserve. Furthermore, gait markers are able to identify homogeneous subgroups. Normal SF is associated with low pain level, reduced overall symptomatology, and high physical activity. A decreased SR allows the recognition of a homogeneous subgroup characterized by an increased anxie-

ty and depression, and decreased cognitive functions. These results need further studies to be validated and so used in the daily clinical practice.

ACKNOWLEDGMENTS

The authors sincerely thank Doctor Alaa Ghali for his valuable assistance in the revision of the manuscript, and Prof. Serge Perrot for his advice and valuable comments on this article.

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