Original research article

Screening for adult ADHD in patients with fibromyalgia syndrome

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Running title:

Fibromyalgia syndrome and associated adult ADHD

Abstract

Objectives: Fibromyalgia syndrome (FMS) is a common chronic pain disorder associated with altered activity of neurotransmitters involved in pain sensitivity such as dopamine, serotonin and noradrenaline. FMS may impact significantly on an individual's functioning due to the presence of chronic pain, fatigue and cognitive impairment. Dyscognition may be more disabling than the chronic pain but is mostly under-recognized. This study aimed to assess the potential co-occurrence of FMS and adult attention deficit hyperactivity disorder (ADHD), a chronic neurodevelopmental disorder, also associated with impaired cognition and dopaminergic function.

Methods: In a cross sectional observational study, 123 previously confirmed FMS patients were screened for adult ADHD using the World Health Organisation Adult ADHD Self Report scale v1.1 (ASRS-v1.1). The Revised Fibromyalgia Impact Questionnaire (FIQ-R) was used to assess the impact of FMS. Cognitive assessment was based on self-report in accordance with the 2011 modified ACR criteria and the FIQ-R, respectively.

Results: Of the 123 participants, 44.72% (n=55) screened positively for adult ADHD. Participants with both FMS and a positive adult ADHD screening test, scored higher on the FIQ-R score (64.74 [SD-17.66] vs 54.10 [SD-17.10]). Self-reported cognitive impairment was rated higher in the combined group (Odds ratio = 10.61; 95% CI [3.77-29.86], $P<0.01$).

Conclusions: These results indicate that the co-occurrence of adult ADHD in FMS may be highly prevalent and may also impact significantly on the morbidity of FMS. Patients with FMS should be assessed for the presence of adult ADHD.

Key Words: Fibromyalgia syndrome; adult attention deficit hyperactivity disorder; cognitive impairment

Introduction

Fibromyalgia syndrome (FMS) is a common disorder of chronic widespread musculoskeletal pain and associated symptoms such as chronic fatigue, sleep disturbance, and cognitive impairment.[1] The American College of Rheumatology (ACR) first published criteria for FMS in 1990.[2] These criteria emphasized the presence of chronic widespread pain in all four quadrants of the patient's body and the presence of pain on at least 11 of 18 specific tender point sites with digital palpation.

The new diagnostic criteria for FMS published in 2010 do not require a tender point assessment. This two part self-administered questionnaire firstly assesses pain on 19 sites on a pain diagram (widespread pain index) and part two measures the intensity of 3 core symptoms, namely fatigue, insomnia and cognitive impairment, each on a 0-3 score, as well as a single average score (0-3) for any somatic symptoms. The 2010 criteria were modified in 2011 and proposed for use in clinical and epidemiological studies. These modified 2010 criteria include a simplified scoring for only three somatic symptoms namely headaches, abdominal pain/cramps and depression as a single 0-3 score.[3]

In recent population-based studies of FMS using these updated criteria, a prevalence of 6,4% and 5,4% was found respectively in the USA and in Scotland.[4,5] FMS most commonly occurs in the age group 20-55 years with a female to male ratio of 6:1.[6]

Whilst the precise pathophysiology of FMS is not fully understood, a number of studies have suggested involvement of genetic factors. Candidate genes that have been implicated in FMS include several genes involved in pain transmission such as the catechol-O-methyltransferase (COMT), serotonin transporter (5HTT) and the D4 dopamine receptor (DRD4) genes.[7,8] FMS has a strong familial predisposition and is currently viewed as a polygene polymorphism.[9,10,11,12,13] Other studies have implicated the involvement of pain modulating neurotransmitters such as dopamine (DA), noradrenaline (NA), serotonin and others.[14]

Neuroimaging studies,[15,16,17] using positron emission tomography (PET) and radiolabelled dopamine-specific ligands have supported the likelihood of disruption of dopaminergic neurotransmission in FMS patients.

FMS is currently categorized as a central sensitivity syndrome associated with abnormalities in pain processing, including increased neuronal activity in the dorsal horn (central sensitization) and decreased functioning of the inhibitory descending pain pathways.[18] FMS is therefore regarded as a “pain amplification syndrome” which has been supported by functional imaging studies.[1,18,19]

In addition to chronic pain, FMS patients often have associated comorbidities such as irritable bowel syndrome, interstitial cystitis and mood disorders.[1,20] Both anxiety and depressive disorders are more prevalent in FMS patients than in healthy controls.[6] Restless legs syndrome, considered a DA dysregulation disorder[21], has also been demonstrated in up to 31% of FMS patients.[22]

A highly prevalent complaint in FMS patients is that of cognitive symptoms, such as difficulty with concentration and attention, forgetfulness, and problems with word-finding and word fluency.[23] Self-reported cognitive impairment (also referred to as “fibro-fog”), can be more disabling to patients than their widespread pain.[24] However, impaired cognition often remains under-recognized and under-treated, partly due to the complexity of the neurophysiological assessment of dyscognition in FMS patients.[25] Possible reasons for the association of cognitive symptoms with FMS include the interference of pain with cognition, the presence of sleep and mood disorders, chronic medication such as antidepressants, anti-epileptics and strong analgesics, and alterations in cerebral blood flow.[26]

Another disorder associated with impaired cognition and considered to be related to dopaminergic function, is attention deficit hyperactivity disorder (ADHD).[27] This chronic neurodevelopmental disorder may occur either as inattentive or hyperactive/impulsive

presentations, or with mixed symptoms. ADHD is mostly diagnosed in childhood, occurring in approximately 3.4-4.4% of children[28], with 30-70% persisting into adulthood.[29] Adult ADHD, occurring in 1-3% of the general population, usually manifests as the inattentive presentation. This condition is also often associated with psychiatric comorbidities such as anxiety and depressive disorders.[30] In addition, it has been suggested in the literature that ADHD may be associated with pain disorders through shared mechanisms such as dopamine dysregulation.[31]

The shared symptoms of impaired cognition experienced by both FMS and ADHD patients could indicate a possible association between these disorders. Two recent studies have indicated a higher frequency of both childhood and adult ADHD in FMS patients.[32,33] In these studies, the diagnosis of FMS was based on the 1990 ACR criteria which do not include a cognitive assessment.

In the light of the high prevalence of self-reported cognitive impairment in FMS patients and its established impact on functioning, this study aimed to investigate the potential co-occurrence of adult ADHD in patients with previously confirmed FMS and who continue to fulfil the modified ACR 2010 criteria in a South African chronic pain practice. This practice manages the full spectrum of chronic pain disorders with a special interest in fibromyalgia and related pain disorders.

Materials and Methods

Study design and participants

A cross sectional observational study design was used. Over a period of five months (December 2015 to April 2016), consecutive adult patients, 18 years and older, attending a chronic pain practice in Pretoria, South Africa, who had been previously diagnosed with FMS,

were screened for eligibility for the study. All patients included in the study had both an original diagnosis of FMS based on a comprehensive clinical assessment and also continued to meet the modified ACR 2010 criteria for FMS.[34] According to these criteria, a widespread pain index (WPI) of ≥7 and symptom severity (SS) scale score of ≥5, or WPI of 3-6 and SS scale score of ≥9, is considered diagnostic of FMS, given that the symptoms have been present at a similar level for at least 3 months, and that another disorder that would otherwise explain the pain has been excluded. All patients were screened by the same clinician, who has extensive experience in managing patients with FMS and other chronic pain disorders.

Procedure

Study participants completed a set of paper-based self-administered questionnaires either at home or at the medical practice. Completion of questionnaires took approximately 25 minutes. Data was collected anonymously, with only the study number assigned to each participant being used on the questionnaires. Each participant received a study information leaflet and gave written informed consent, before completing the study questionnaires. Ethics approval was given by the Research Ethics Committee of the Faculty of Health Sciences of the University of Pretoria, South Africa.

Measurement instruments

The World Health Organisation Adult ADHD Self Report scale-v1.1 (ASRS-v1.1) was used to screen for adult ADHD. This screening tool was developed for the purpose of epidemiological surveys of mental health in the general population and has been recommended for use in primary care screening, as well as clinical studies.[35,36] This concise questionnaire which can be self-administered, is based on current symptoms in contrast to instruments that identify

retrospective childhood ADHD. Each of the six ASRS screener questions asks respondents to indicate how often, during the past six months, have they experienced a particular symptom of ADHD, using a five-point scale of never (0), rarely (1), sometimes (2), often (3) and very often (4). For each five-point scale, responses that are consistent with a diagnosis of adult ADHD are shaded on the screener response form. Participants with four or more responses falling within the shaded section of each questionnaire would be considered to screen positively for adult ADHD.

In the general population, the WHO ASRS has been shown to have a sensitivity of 68.70%, a specificity of 99.50%, and a total classification accuracy of 97.90% in identifying persons with adult ADHD.[35]

The impact of FMS on individual subjects was measured using the Revised Fibromyalgia Impact Questionnaire (FIQR).[37] This instrument is self-administered and easy to complete. Three domains, namely the severity of FMS symptoms, daily functioning, and the overall impact of FMS are evaluated using 11-point Likert scales, where higher scores indicate more severe symptoms (total combined score 0-100).

The Hospital Anxiety and Depression Scale (HADS) was used to screen for the presence of current anxiety and depression in all participants.[38] This scale uses 14 items (7 each for anxiety and depression), with the total score for each domain ranging from 0-21. A score of 8 or more per domain is suggestive of the relevant mood disorder.

Cognitive function was assessed using participants' self-report of cognitive symptoms as in the modified ACR 2010 criteria and the FIQR, respectively. These questions were as follows: "Do you experience any trouble with thinking or remembering?", which is rated as none, mild, moderate and severe, and "Please rate your level of memory problems", to be rated on a scale of 0-10, where 0 was "Good memory" and 10 was "Very poor memory".

Statistical analysis

Data was analysed using STATA package release 14. The primary outcome (co-occurrence of adult ADHD and FMS) has been presented as a percentage. Analyses used to compare FMS participants with and without adult ADHD included Chi-square test for categorical variables, Student's t-tests for continuous data and Mann Whitney for non-parametric data. Statistical analysis was conducted at the 95% confidence level and a *P* value < 0.05 was considered statistically significant.

Results

The sample included 123 participants with confirmed FMS as described above, of whom 87.80% were female, with a mean age of 49.89 years (standard deviation [SD]–12.08). Most participants were in a stable relationship, had a tertiary education, and were formally employed (Table I). The mean duration of FMS diagnosis was 12.34 years (SD–8.19), with 50.82% of participants indicating an emotional factor as precipitant for their FMS. A physical triggering event was noted in 44.26% of participants.

Using the WHO ASRS questionnaire, 44.72**%** (*n*=55) of participants screened positively for associated adult ADHD. Of these, 7.27% indicated a previous diagnosis of adult ADHD, with a median (IQR) duration of ADHD diagnosis of 7 (2-10) years. Neither age (*P*=0.28) nor gender (*P*=0.45) were found to be associated with a positive screening test for adult ADHD.

In the group of FMS patients who screened positively for concomitant adult ADHD, the mean FIQR score was substantially higher than in the FMS alone group (Table II).

Table I Demographic characteristics of sample

Characteristic	
Age in years, mean (SD)	49.89 (12.08)
Sex, n (%)	
Female	108 (87.80)
Male	15 (12.20)
Marital status, n (%)	
Married/domestic partnership	79 (64.23)
Single/never married	25 (20.33)
Divorced/separated	14 (11.38)
Widowed	5 (4.07)
Highest educational level, n (%)	
High school	26 (21.14)
Tertiary	97 (78.86)
Employment, n (%)	
Employed/self employed	81 (65.85)
Retired	19 (15.45)
Home maker	14 (11.38)
Unemployed	7 (5.69)
Student	2 (1.63)

Based on the HADS scores, there were higher frequencies of positive screening for anxiety (OR=4.17; 95% CI [1.45–11.99]) and depression (OR=2.37; 95% CI [1.14–4.91]) in the combined FMS and ADHD group as compared to the FMS alone group. In the combined group 90.91% screened positively for anxiety, markedly more than in the FMS alone group (*P*=0.005). (Table II)

Mean self-reported scores for memory impairment (measured as part of the FIQR questionnaire) were significantly higher in the combined FMS and ADHD group as compared to the FMS alone group (*P*<0.0001). In addition, the combined group reported "moderate or severe" trouble with thinking or remembering in the memory sub question in the modified ACR 2010 criteria significantly more often than subjects in the FMS alone group (*P*=0.0001; OR=10.61; 95% CI [3.77-29.86]). (Table II)

Table II Fibromyalgia impact, mood disorders and cognitive impairment

	Total*	FMS alone	FMS and Adult ADHD	P-value†
Participants screened, n (%)	123 (100)	68 (63.28)	55 (44.72)	-
Positive screen depression, n (%)	55 (44.72)	24/68 (35.29)	31/55 (56.36)	0.019
Positive screen anxiety, n (%)	98 (79.68)		50/55 (90.91)	0.005
ACR cognitive impairment positive screen‡, n (%)	83 (67.48)	48/68 (70.59)	50/55 (90.91)	0.0001
FIQR score, mean (SD)	58.85 (±18.07)	33/68 (48.53)	64.74 (±17.66)	0.001
		54.10 (±17.10)		

ACR= American College of Rheumatology; ADHD= attention deficit hyperactivity disorder; FIQR= Revised Fibromyalgia Impact Questionnaire; FMS= fibromyalgia syndrome

*Variables in the total group are not mutually exclusive.

†Difference between FMS alone, and FMS and adult ADHD.

‡As measured using a question in the modified 2010 College of Rheumatology criteria to assess cognitive impairment: "Do you have moderate or severe trouble with thinking or remembering?"

Discussion

FMS remains a complex pain disorder associated with multiple co-morbidities. It is also often associated with self-reported impairment of cognition which is mostly neither assessed nor appropriately managed.[24]

Although some observations[32,33,39] have previously been made regarding the association of adult ADHD with FMS, based on shared cognitive impairment, the limited research to date has not used the modified ACR 2010 criteria for FMS. The potential overlap has therefore probably been underestimated and consequently the presence of ADHD and other cognitive symptoms in FMS patients may have been under-reported. A previous study by Derksen et al[32] using the 1990 ACR criteria for FMS found that 25% of patients had a dual diagnosis of FMS and adult

ADHD. Stickley et al[40] have recently also reported that patients with higher ADHD symptom scores (on the WHO ASRS) were found to have an increased risk of experiencing pain. Our finding of the co-occurrence of FMS with a positive screening for adult ADHD of 44.72% is suggestive of a strong association between these disorders. With the validated high specificity of the WHO ASRS screening questionnaire (99.5%) the probability of significant over-diagnosis of adult ADHD in this study is regarded as limited.

The high percentage of FMS patients who screened positive for either anxiety or depression or both is in keeping with previous studies. Thieme et al found co-morbid anxiety and depression in 32.30% and 34.80% of FMS patients, respectively.[41]

Co-morbid mood disorders are also highly prevalent in adult ADHD. When comparing individuals with and without adult ADHD, Kessler et al demonstrated a significantly greater prevalence of both anxiety and depressive disorders (OR=3.7; 95% CI [2.4-5.5] and OR=5.0; 95% CI [3.0-8.2], respectively).[28]

The mean FIQR score in the FMS only group was 54.10 ± 17.10. This is similar to the findings of Bennett et al,[37] which demonstrated a FIQR score of 56.6 ± 19.9 in a FMS population vs healthy controls (12.1 ± 11.6) or patients with rheumatoid arthritis or systemic lupus erythematosus (28.6 ± 21.2). It should be noted that all the patients in our study were on an active and comprehensive management programme for FMS yet continued to score high on the FIQR. Furthermore, the impact of FMS was significantly higher in patients with a positive screening test for adult ADHD (64.74 ± 17.66, P=0.001). The higher FIQR score in the combined group could possibly be attributed to both the impact of dyscognition, as well as the higher frequencies of anxiety and/or depression in patients with unrecognized adult ADHD.

The probable comorbidity of adult ADHD with FMS as illustrated in this study could also have pharmaco-therapeutic implications. Cognitive impairment in ADHD patients has been shown to improve with dopaminergic stimulants, such as methylphenidate.[42] Patients with chronic

pain have also been shown to have lower D2-receptor binding and presynaptic dopamine activity.[43] This may represent an additional therapeutic approach. Evidence that supports dopaminergic dysfunction in FMS patients has led to a randomized controlled trial with pramipexole (a dopamine D2/D3 agonist) which has been shown to significantly improve the pain and other symptoms of FMS in this 14 week study.[44] Furthermore, in a study of 48 FMS patients who received methylphenidate 10-60 mg daily, concentration, energy, and mood improved significantly over the 30 day treatment period.[45] The possible sharing of underlying central neurotransmitter mechanisms in patients with FMS and ADHD needs further investigation.

The main limitation of this study was that a screening questionnaire was used to identify adult ADHD, and future studies should include a comprehensive clinical assessment by an expert clinician for confirmation of the presence of ADHD.

In conclusion, the finding of a potential association between adult ADHD and FMS in this study could have significant assessment and therapeutic implications.

The significant impact of probable adult ADHD on the symptomatology of FMS patients as shown in this study indicates that all patients with FMS should be screened for comorbid adult ADHD. Current international guidelines[46] for FMS assessment and management emphasize the role of the primary health care provider, and therefore the ideal adult ADHD screening tool should be concise and accessible for use in the primary health care setting. The WHO ASRS-v1.1 probably meets this need.

Future studies should assess the response of FMS patients with comorbid adult ADHD to appropriate therapy with regards to their cognitive and other symptoms.

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