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Original Article

British Journal of Pain
2017, Vol 11(2) 97–101

DOI: 10.1177/2049463717701393
journals.sagepub.com/home/bjp
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Fibromyalgia in Behçet's disease: a narrative review

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Abstract

Introduction: Fibromyalgia is characterised by chronic widespread pain and tenderness. It has often been reported to occur concomitantly with chronic rheumatological conditions. Behçet's disease is a chronic relapsing, multisystem, autoinflammatory disease. There is only limited understanding of a potential relationship between fibromyalgia and Behçet's disease.

Aim: Given the potential detrimental influence of pain on the outcome of chronic disease, the aim of this narrative review is to gain an understanding of the incidence and presentation of fibromyalgia in Behçet's disease.

Methods: Electronic databases Scopus, Medline, PubMed and UpToDate were searched.

Results: A total of 269 studies were identified, and limitations and exclusion/inclusion criteria were applied to ensure accurate and comparable selection of studies; four studies were selected. All cases were assessed for the presence of fibromyalgia according to the 1990 or 2010 diagnostic criteria of the American College of Rheumatology, with Behçet's disease diagnosed according to the International Study Group (ISG) for Behçet's disease criteria. A higher prevalence of fibromyalgia (5.7–37.1%) was reported in Behçet's disease compared to that of the general population (2.9–4.7%).

Discussion: While an increased prevalence of fibromyalgia was found in patients with Behçet's disease, this needs to be considered within the context of limited available evidence. The potential impact of these conditions on the disease activity of each other is not clear and may require a prospective study.

Conclusion: Fibromyalgia appears to be more prevalent in those with Behçet's disease than would be expected in the overall population. Significance: This review provides some evidence that fibromyalgia is more prevalent in those with Behçet's disease. To ensure appropriate patient treatment choices, it is important that both conditions are diagnosed where they co-exist.

Keywords

Fibromyalgia, Behçet's disease, prevalence, narrative review, diagnosis

Background and objective

Fibromyalgia is a non-autoimmune rheumatological disorder characterised by chronic widespread pain, and often tenderness, and may also include additional symptoms.[1] The estimated prevalence of fibromyalgia in the general population is 2.9–4.7%.[2] The diagnosis of fibromyalgia is predominantly based on clinical symptoms.[3] The original, American College of Rheumatology (ACR) criteria for fibromyalgia required that widespread pain is present in the upper and lower

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Table 1. American College of Rheumatology criteria for fibromyalgia.

Criteria:
A patient satisfies diagnostic criteria for fibromyalgia if the following three conditions are met:
- Widespread pain index (WPI) ⩾ 7 and symptom severity (SS) scale score) ⩾ 5 or WPI 3–6 and SS scale score ⩾ 9
- Symptoms present at a similar level for ⩾3 months
- Patient does not have a disorder that would otherwise explain the pain

WPI, in how many areas has the patient had pain in the last week (score between 0 and 19):
- Shoulder girdle (left), shoulder girdle (right), upper arm (left), upper arm (right), lower arm (left), lower arm (right), hip (buttock, trochanter, left), hip (buttock, trochanter, right), upper leg (left), upper leg (right), lower leg (left), lower leg (right), jaw (left), jaw (right), chest, abdomen, upper back, lower back and neck

SS scale score:
- Three symptoms – fatigue, waking unrefreshed and cognitive symptoms.
- For each of the three symptoms, level of severity using the following scale – 0 = no problem; 1 = slight or mild problems, generally mild or intermittent; 2 = moderate, considerable problems, often present and/or at a moderate level; 3 = severe, pervasive, continuous, life-disturbing problems.
- Considering somatic symptoms in general, indicate whether the patient has 0 = no symptoms, 1 = few symptoms, 2 = a moderate number of symptoms, 3 = a great deal of symptoms.
- The SS score is the sum of the severity of the three symptoms plus the extent of somatic symptoms. The final score is between 0 and 12.

Source: Reproduced from Wolfe et al.,[4] with permission.

quadrants and left and right sides of the body, including axial pain, and that the patients indicate tenderness in ⩾11 of 18 defined 'positive', that is, painful to a specified pressure 'tender points'.[4] The 2010 (ACR) classification criteria for fibromyalgia, which are currently valid in parallel to the original criteria, stipulate the diagnosis in patients with >12 weeks symptom duration based on a widespread pain index, and scales, of symptom severity (Table 1);[5] these new criteria do not require the examination of tender points.

Behçet's disease (BD) is a chronic relapsing, inflammatory rheumatological disease with no pathognomonic test.[6] Its course is characterised by unpredictable exacerbations and remissions.[7] BD occurs worldwide, with particular prevalence along the traditional Silk Road trading route from China to Spain.[8] It is rarely diagnosed in northern Europe.[9]

The diagnosis is based predominantly on clinical features. The International Study Group (ISG) diagnostic criteria[10] require the presence of recurrent oral ulcers (⩾3 in 12 months) and any two of recurrent genital ulcers, eye lesions, skin lesions and positive pathergy test (evaluation of the heightened inflammatory response). This has been expanded in the newer International Criteria for Behçet's Disease[6] to include vascular manifestations and adding a weighted points system (Table 2).

The BD pathophysiology is complex. There is a combination of both autoimmune and autoinflammatory features.[11] Familial occurrence of BD is known, and an association has been identified with HLA-B51/B5.[9,12]

Both fibromyalgia and BD can impact considerably on the quality of life of those with the conditions.[13] Clinical observations at the UK National Centre for Behçet's disease have suggested that there may be a high prevalence of fibromyalgia among UK Behçet patients. Higher prevalence of fibromyalgia than in the general population has been well established for other rheumatological conditions, such as rheumatoid arthritis (RA);[2,14,15] however, there has been limited consideration of the relationship between fibromyalgia and BD.[16] We set out to review the evidence in this area and to consider what evidence is available on the prevalence of fibromyalgia in BD.

Databases and data treatment

To identify relevant studies, the electronic databases Scopus, Medline, PubMed, and UpToDate were searched in April 2016. BD and alternative search terms, Behçet's syndrome, Silk road disease, Behçet–Adamantiades and Morbus Behçet were entered in combination with AND chronic widespread pain, fibromyalgia or chronic pain. All titles and abstracts were screened using the inclusion criteria and potentially relevant full-text papers ordered. Reasons for exclusion included unclear whether BD had been diagnosed using established criteria, only study abstract available, pain in BD that was unspecified or was related to inflammatory processes of BD.

No date limitations were applied to the search; all study types were included and only papers written in English were included. Only full-text papers were included. Clinical signs form the basis of diagnosis in all of the included conditions; therefore, participants with BD had to have been diagnosed using criteria that were established at the time the study was undertaken; similarly, the process used to diagnose fibromyalgia

had to have been described. Where the patients with BD were a subset but the data relating to BD could be extracted, these data were included.

Results

There were four papers that included patients with BD, reported on cross-sectional studies and met the inclusion criteria for this review (Table 3). All used the ISG criteria to diagnose BD[9] and the ACR 1990 classification criteria to diagnose fibromyalgia.[5] All were small, single-centre studies. None reported any conflicts of interest.

Prevalence of fibromyalgia

A prevalence of fibromyalgia in those with BD in these studies was 5.7%,[17] 8.9%,[19] 18%[16] and 37.1%.[18] All of the studies identified a higher proportion of females in those with fibromyalgia and BD than in those without fibromyalgia and with BD, with females representing from 66.7% to 100% of those with both conditions.

Table 2. International Criteria for Behçet's disease – point score system: scoring ⩾4 indicates Behçet's disease.

Sign/symptom	Score
Oral aphthosis	2
Genital aphthosis	2
Ocular manifestations	2
Skin manifestations	1
Vascular manifestations	1
Central nervous system involvement	1
Positive pathergy test[a]	1

Source: Reproduced from International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD) 2014, with permission.
[a]Pathergy testing optional; where conducted, 1 extra point may be assigned for a positive result (a positive pathergy test indicates that the immune system is overreacting to a minor injury).

Disease activity

Three of the four included studies considered BD activity in those with and without fibromyalgia. This was using the Behçet's Disease Current Activity Form (BDCAF) overall[17] or BDCAF clinical features,[16] or using clinical manifestations for BD, via a clinical interview and summation of current clinical disease manifestations and those over the previous month.[18]

In the one study using the BDCAF overall form, the three participants with concomitant BD and fibromyalgia had BDCAF activity scores of 3.03 (standard deviation (SD) ± 0.05); the 50 participants without fibromyalgia had BDCAF scores of 1.98 (SD ± 0.65), $p = 0.008$.[17]

Where the comparison of BDCAF scores on the clinical features of the scale were considered,[16] differences were found in

- Fatigue in those with fibromyalgia (N = 18, 3.5 ± 0.5) compared with those without (N = 82, 1.7 ± 0.3), $p = 0.000$;
- Headache in those with fibromyalgia (N = 18, 3.1 ± 0.9) compared with those without (N = 82, 1.2 ± 0.4), $p = 0.01$;
- Arthralgia in those with fibromyalgia (N = 18, 1.9 ± 1.5) compared with those without (N = 82, 1.2 ± 0.7), $p = 0.01$.

No differences were found in oral ulceration, genital ulceration, skin lesions, arthritis, gastrointestinal involvement, eye involvement, central nervous system involvement or major vessel involvement.[16] Correlations were found between BD activity and total Fibromyalgia Impact Questionnaire (FIQ) scores in those with

Table 3. Characteristics of included studies.

Reference, country	Patient characteristics, country	Duration of Behçet's disease	Assessment of fibromyalgia
Melikoglu and Melikoglu,[16] Turkey	N = 100, 19–51 years, 60% female, duration of BD	With fibromyalgia (months ± SD) 100.2 ± 64.3, without fibromyalgia 81.9 ± 44.36	FIQ and clinical examination
Haliloglu et al.,[17] Turkey	N = 53, 19–53 years, 41.5% female	Not reported	FIQ and clinical examination
Lee et al.,[18] South Korea	N = 70, mean age 39.0 years (SD 9.4 years), 64% female	With fibromyalgia (mean ± SEM) 3.76 ± 0.72, without fibromyalgia 3.76 ± 0.72	FIQ
Al-Izzi et al.,[19] Iraq	N = 90, 17–62 years, 46% female	Mean 6.5 years	Diffuse pain questionnaire, clinical examination

SD: standard deviation; FIQ: Fibromyalgia Impact Questionnaire; SEM: standard error of mean.

concomitant fibromyalgia ($p < 0.05$)[17] and between BDCAF and FIQ items that refer pain and fatigue.[16]

Where the clinical manifestations were considered, there were no differences found in those with fibromyalgia (N = 26) compared with those without (N = 44) in general manifestations (oral ulcer, genital ulcer, erythema nodosum (EN)-like lesion, pseudofolliculitis, ocular lesion, pathergy test, arthritis, gastrointestinal ulcerations, vascular lesions) or severe manifestations (post-uveitis or retinal vasculitis, gastrointestinal bleeding or perforation, major organ involvement, major vessel involvement, presence of $\geqslant 1$ of severe manifestation).[18]

Discussion

The limited evidence uncovered in this review suggests an increased prevalence of fibromyalgia in people with BD. Based on this evidence, the range of this prevalence appears to be quite wide (5.7–37.1%), although even the lowest prevalence is higher than what is reported in the general population (2.9–4.7%).[3] Previous studies in general population groups have reported fibromyalgia to be more common in females.[20,21] Consistent with this, all the included studies found that BD patients with fibromyalgia were more frequently female, when compared to patients with BD without fibromyalgia.

One study included in this review considered the BDCAF activity scores in those with fibromyalgia and BD and those with BD disease without fibromyalgia. The BDCAF assesses disease activity based on history of clinical features.[22] This study found an association between concomitant fibromyalgia and a higher degree of disease activity, although it should be noted that there were only three participants with both conditions. The review found limited evidence; therefore, it is not possible to identify whether there is any effect of fibromyalgia on BD or BD on fibromyalgia. Patients with fibromyalgia report a high impact on their quality of life, and they experience a lower quality of life than the general population.[23] Similarly, those with BD have reported significantly lower quality of life scores than healthy controls.[24] Both fibromyalgia and BD have had evolving diagnostic criteria reflecting the challenges in providing a clear diagnosis. Considering the impact of each condition on quality of life and the increased prevalence of fibromyalgia in those with BD, there should be further consideration of disease activity scores where patients have both conditions.

There are some important limitations. This review was developed from an expert clinical suspicion and aimed to providing a scoping overview of the area. This narrative review will add to the discussion of this area and provide useful background for future study in this area. These were small localised studies, and none were based in Europe. These studies were based in Turkey, South Korea and Iraq, and the relevance of our findings for other populations is unknown. A consideration of five nationwide surveys (Iran, Korea, Germany, Japan and China) of BD concluded that important clinical manifestations of BD were similar across the surveys.[25] In addition to regional factors, variability in the fibromyalgia in BD incidence may also be related to BD disease parameters in the studied populations. It has been noted previously that variation of BD, including the prevalence of HLA B51 or positive pathergy reactions, may cause differences in prevalence of fibromyalgia, although the numbers studied have been too small to draw firm conclusions.[18] An additional variability may be related to BD disease duration.

The outcomes of this review should be considered in the context of the limited quality of the evidence available which consisted of small, single-centred cross-sectional studies.

All identified studies used the 1990 ACR criteria for diagnosing fibromyalgia. However, outcomes may differ when using the 2010 criteria (Table 1). For example, critics of the original criteria suggest that the tender points required for fibromyalgia diagnosis do not accurately assess tenderness alone;[26] distressed or anxious patients, who may be expectant of pain, might pre-empt and fear it, and thus have a subconsciously heightened response. Conversely, a brief study report compared the 2010 ACR questionnaire with the 1990 ACR tender point examination and found a greater prevalence of fibromyalgia in BD patients.[27] It is reasonable to argue that additional studies are needed to understand the prevalence of fibromyalgia, when diagnosed with the most current ACR criteria in BD. We speculate that a study employing the 2010 criteria, and particularly investigating patients with longstanding BD, might have an outcome that more closely reflects the clinical impression at our centre, namely, a high prevalence of fibromyalgia in BD.

Conclusion

Similar to what has been identified with other rheumatological conditions, such as RA, fibromyalgia appears to be more prevalent in those with BD, than in the general population. Due to the limited evidence, the rare and heterogeneous nature of BD, and the multidimensional presentation of coexisting fibromyalgia, it is not appropriate to translate these associations to a population level. To offer effective treatment choices for those with these conditions, and to potentially minimise the impact on quality of life, it is important to appropriately diagnose both conditions where they co-exist.

Acknowledgements

C.J. and R.H.R. are co-authors.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

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