Review articles

Fibromyalgia syndrome, a problem of tautology

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Summary

Fibromyalgia syndrome is generally taken to denote a clinical state of widespread musculoskeletal pain, stiffness, and fatigue but its pathophysiology, physical and psychological, is unknown, and the nature of the diagnostically mandatory "tender points" remains obscure. Diagnostic criteria convey no pathophysiological insight and they have been "validated" via a circular argument in which the evidence on which the construct is based is taken as proof of its veracity. The concept of fibromyalgia syndrome is valid only in the sense that it includes all possibilities. An alternative approach to this very real clinical presentation is via secondary hyperalgesia.

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Introduction

According to the "Copenhagen declaration", fibromyalgia syndrome (FS) is now established as a distinctive diagnosis, defined as a "painful, non-articular condition predominantly involving muscles" and as the "commonest cause of chronic, widespread musculoskeletal pain".[1] Thus a pain syndrome is said to define itself. The characteristic features of fibromyalgia are "tender points", the nature of which remains elusive. No distinctive tissue pathology, pathophysiology, or psychopathology has been found.[2-5] The declaration recommends criteria put forward by the American College of Rheumatology in 1990.[6] These criteria are the latest in a series, all suffering from the problem of syndromic diagnosis where variable combinations of features are put forward as an entity, which then implies pathogenetic homogeneity (table 1).[6-8] All rely on tender points, in the absence of their clinicophysiological explanation, a situation which invites circular argument.

The existence of the clinical problem labelled FS is not in dispute but it has become a tautological concept, one that can be shown to be true because it includes all possibilities. We seek a more rational approach to diffuse musculoskeletal pain, concentrating on establishing a clinicopathological basis as a way out of the circularity that characterises this syndrome.

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Tender points

Although tender points are the hallmark of this diagnosis, their number, location, and how to measure the tenderness are contentious. Tenderness (more correctly, hyperalgesia[9]) has been measured by direct digital palpation or by pressure dolorimetry. Both pain threshold (discrimination of nociceptive quality) and pain tolerance, reflecting unwillingness to receive more stimuli, have been used as indices but their underlying mechanisms are very different.[10,11] Pressure algometry is a psychophysical technique in which a varying stimulus is applied until a predetermined pain response by the subject occurs. It is very difficult to offer this mechanical stimulus randomly or to include supramaximal stimuli and a degree of expectancy cannot be avoided. Both the length of the scale and the size of the footplate of the dolorimeter affect threshold responses.[12] Pressure algometry has nonetheless been the major investigative tool used in attempting to validate the construct of FS:

(1) Only one study has found reduced threshold and tolerance for pressure-induced pain in "fibrositis" patients over "tender points" but not over control (non-tender) points.[13]

(2) Lower pain threshold and pain tolerance over one non-tender point at the elbow was found in fibrositis patients compared with conrols.[14]

(3) A third study, looking at pain threshold only, found that patients were more sensitive than controls at both tender and non-tender points and that the difference between patients and controls over non-tender points was the more impressive.[15]

(4) Lower pain tolerance (only) was found in 19 of 75 artibrary anatomical sites in fibromyalgia patients, which included tender and non-tender points.[16]

(5) Using pressure algometry in patients fulfilling older criteria for FS[8] and in control groups with "articular" (rheumatoid arthritis and osteoarthritis) and "generalised non-articular" rheumatism, Quimby et al found that pain tolerance at tender points correlated with tolerance at non-tender points but that the presence of tender points did not correlate with any symptoms.[17] Furthermore about half of the individual variability in pain tolerance at tender points could be accounted for by the patients' general tolerance level for pressure-induced pain.

Dolorimetry thus suggests that fibromyalgia patients are more sensitive than controls, not only at tender points but also at non-tender points, which calls into question the discriminative validity of those points. The tender points seem to reflect either a state of more general somatic awareness or one of hyperalgesia rather than a distinct pathological entity.

American College of Rheumatology study

Semantic issues

The 1990 report of the American College of Rheumatology (ACR) study is the basis for current diagnostic criteria for FS—namely, a history of widespread pain and pain in 11

Smythe and Moldofsky[7]	Yunus et al[8]	Wolfe et al[6]
Widespread aching and stiffness of more than 3 mo duration	Generalised aches and pains (or prominent stiffness) in at least three anatomical sites for at least 3 mo duration	Widespread pain of at least 3 mo duration
Tender points 12 out of 14	Tender points 5 or more	Tender points 11 out of 18
Skin roll tenderness over upper scapular region		
Normal investigations	Absence of traumatic injury, structural rheumatic disease, infectious arthropathy, endocrine-related arthropathy, and abnormal laboratory tests	
Poor sleep	Poor sleep	
Chronic fatigue	General fatigue	
Emotional disturbance	Anxiety	
Morning stiffness	Headache; irritable bowel; subjective swelling; non-radicular numbness; influence of activity, weather, and anxiety	

Table 1: **Comparison of criteria sets for FS**

out of 18 tender point sites on digital palpation. "Widespread pain" was defined as pain on the left and right sides of the body plus pain above and below the waist plus axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back pain). Furthermore shoulder pain and buttock pain were each defined as "involved side" pain whilst low back pain was defined as "below waist" pain. Thus pain in one shoulder, the contralateral buttock and the anterior chest would be "widespread" pain. A response of "tender" was held not to imply pain when grading the severity of tender points; only a specific complaint of "pain" was acceptable. Yet "tenderness" is the synonym for hyperalgesia, which by definition is an increased painful response to a noxious stimulus and includes a painful response to a stimulus not normally noxious.[9] This semantic distinction is clearly artificial with obvious potential for biased interpretation.

Patients and controls

Each investigator used his or her own criteria for diagnosis, thus inviting circular argument. Furthermore, the controls for "primary fibromyalgia" were the "next age- and sex-matched patient with neck pain syndromes, low back pain syndromes, local (regional) tendonitis, trauma-related pain syndromes and possible SLE, RA or other disorders" (emphasis added). Surely this was an exercise in syndrome substitution, not justified on pathophysiological grounds. The controls for "secondary fibromyalgia" were the "next age- and sex-matched patient with the [same diagnosis] but without fibromyalgia". All criteria depended upon tender points yet these points were not sought in people not complaining of widespread pain; so, on the basis of patient selection alone, the study was doomed to being unable to do other than confirm the prejudged features common to all investigators.

Clinical algometry

Digital palpation was performed over, originally, 24 "active" and 6 control sites. A response of "tender" was considered not to denote pain and scored 0 (no pain). 4 was "unbearable" pain where the patient was unable to be touched; 1+ denoted "mild or greater" pain whilst 2+ denoted "moderate or greater" pain. These scores were used to generate "average tenderness" and the prevalence of sites of nominated degrees of tenderness, without evidence that the subjects treated these ordinal categories as equally spaced. The data were subjected to statistical analysis using the t-distribution when non-parametric analysis was more appropriate.[11,18] This procedure not only translated the categorical responses into a framework which implied ratio scale properties but also generated results with no ready clinical meaning. What does an average tenderness of 1·5 mean?

Dolorimetry was done over 6 active and 3 control sites, which generated a mean score expressed in kg per 1·54 cm^2. There was a ceiling of 6·5 kg, which may have biased mean scores towards smaller values. The SEs for scores over control sites were an order of magnitude greater than those over active sites and there was little difference between scores over control sites in FS patients (mean 5·1 [SE 0·79]) and those over active sites in controls (4·9 [SE 0·08])

Conclusions from ACR study

The four main qualitative conclusions were that palpation was more discriminating than dolorimetry in identifying tender points; that tender points were the most powerful discriminators between fibromyalgia patients and controls; that the greatest discriminating power lay in tenderness scores of "mild or greater"; and that the "best separation between patients and controls occurred at about the thirteenth point for mild tenderness and at about the sixth point for moderate or greater tenderness".[6]

The first conclusion is a blow for all who attempt to quantify hyperalgesia by measurement. The second and third simply reiterate the basis on which the FS patients were chosen—indeed any other result would have refuted the basis for selection. The fourth conclusion simply means that the more tender you are the more likely you are to be distinguished from those not so tender.

One main quantitative conclusion concerned the number of tender points required for diagnosis (whilst not stating which ones were important): the ACR committee "reduced the number of tender points required for examination from 24 to 18" before determining that any 11 of these 18 provided the best diagnostic criterion for FS.[6] This conclusion recalls the point made by Quimby et al[17] that if the degree of tenderness itself fails to be a criterion, the only distinction of FS from non-FS is the number of tender points.

Sensitivity and specificity figures were also generated. Table 2 adds to table 6 in the ACR study the false positive rate and the likelihood ratio (the odds that, given the stated feature, the patient has the disease), both calculated from data in the paper. Widespread pain, as defined, generated a likelihood ratio of only 1·4; 22% of those considered not to have FS had the number of tender points required for that diagnosis; sensitivity for tender points in FS was less than 100%, despite the fact that these were the basis for the diagnosis; the ACR criteria themselves had 90% sensitivity

	Sensitivity	Specificity	False positive	Likelihood ratio
Tenderness				
11 of 18 tender points (*a*)	90	78	22	4·1
12 of 14 tender points[7]	65	89	11	5·9
Dolorimetry (6 sites)	69	76	24	2·9
Pain				
Widespread (*b*)	98	31	69	1·4
"All over"	67	81	19	3·5
Neck	85	50	50	1·7
Post thorax	72	76	24	3·0
Low back	79	54	46	1·7
Combination				
ACR criteria (*a*) + (*b*)[6]	88	81	19	4·6

Sensitivity and specificity values (%) taken from table 6 of ACR report;[6] false positive rates (%) and likelihood ratios calculated from these values.

Table 2: **In search of gold standard for FS**

and 20% false-positivity rates; and the best likelihood ratio still depends on the number of tender points, in which context previous criteria[7] perform better. What condition did the 19% false-positives have? And what is the diagnosis in the "variable proportion of otherwise typical patients"[1] who have less than 11 tender points? Quimby et al[17] found that no symptoms or combination of symptoms correlated with the presence, frequency, or sensitivity of tender points.

What then is the "gold standard" for the diagnosis of FS? It cannot be "widespread pain"; "pain all over" is more likely but is not well defined. The only possibility is a number of tender points, the major contributor to the combination criteria. However, it is a fallacy to have a gold standard which incorporates the diagnostic feature of interest.[19]

FS as tautology

"Tender points are inherently more tender than non-tender points, whether one is dealing with normal or fibromyalgia patients."[15] Selecting on the basis of pain and hyperalgesia must generate a high degree of accuracy if those criteria are then used to justify the selection. It is therefore a major concern if the sensitivity and specificity figures thereby generated fail to reflect that accuracy. The evidence which leads one to a proposition cannot then be used to justify the validity of that proposition.[20]

Thus FS is a tautology as the proposed criterion of a specified number of "tender points" can be violated too easily, thus blurring any distinction between it and "non-fibromyalgia". Furthermore, how can 20% of subjects satisfy the criteria and not be said to have fibromyalgia, especially when it is claimed that fibromyalgia can coexist with "any other condition"?[6] The argument remains hopelessly circular.

Resolution

We suggest that there has been a conceptual jump from "tender points" to "FS" without pathophysiological explication. The central problem of the pain itself is ignored and attention is focused away from understanding the hyperalgesia towards "making a diagnosis".

The key to resolving the problem of the external validity of FS may be found in the phenomenon of secondary hyperalgesia. Whilst primary hyperalgesia is localised to the site of injury and persists until the injury is healed, secondary hyperalgesia occurs in undamaged tissues, the innervation of which is in the same or adjacent segments to that of the noxious stimulus. Cutaneous secondary hyperalgesia may be associated with noxious stimulation of either deep or superficial tissues. Furthermore whilst primary hyperalgesia is characterised by lowering of both threshold and tolerance to thermal and mechanical stimulation, in secondary hyperalgesia these thresholds are normal whilst tolerance is again lowered.[21,22] FS can thus be appreciated clinically as a syndrome featuring secondary hyperalgesia.

A recent study using non-noxious electrocutaneous stimulation in patients fulfilling criteria for FS found little change in perception threshold but marked reduction in pain tolerance in comparison with controls. These findings were considered to be a psychophysical demonstration of secondary hyperalgesia.[23]

The physiology of secondary hyperalgesia itself may be approached as a perturbation of nociception,[24,25] as a problem of somatic preoccupation ("hypervigilance"),[17,26,27] or as a combination of the two. These processes may well converge on the central pathways involved in nociception. Pursuit of the proposal that secondary hyperalgesia is the relevant mechanism underlying FS will need to focus on nociceptive mechanisms and on the identification of the initiating factors, to which the observed phenomena are secondary. Recent work has suggested that the altered central processing considered to be responsible for secondary hyperalgesia depends on continuing peripheral input, especially from nociceptors.[25,28,29]

Medical classifications are not meant to establish absolute truths, being attempts to provide practical ways of grouping phenomena to allow comparisons and to promote understanding.[3] However, the construct of FS is tautologous and lacks both explanatory power and therapeutic implications. The clinical challenge of musculoskeletal pain and tenderness in the absence of defined disease can be better addressed through the pathophysiological perspective of secondary hyperalgesia.

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Non-compliance—or how many aunts has Matilda?

E C Wright

Summary

The compliance of patients with medication prescribed for them is a challenge. It seems that one-third of patients comply adequately, one-third more-or-less, and one-third are non-compliant, so that compliance rates hover around 50%. This can be improved upon, but not by treating failure to comply as a deplorably aberrant behaviour. First we need to know more about compliance and non-compliance, and that means standardising methods of study and measuring, by questioning the patient, counting tablets, or looking at drug metabolites or markers in faeces, blood or urine. Doctors' prejudices and patients' perceptions alike have to be taken into account since strategies for improvement must include both educating the prescriber and counselling the patient.

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Introduction

The seriousness of non-compliance is well recognised in the USA, where it has been designated "America's other drug problem".[1] It is equally important in the UK. In 1957 *The Lancet* published an article that began with one of Hilaire Belloc's *Cautionary Tales:*

Matilda told such Dreadful Lies,
It made one Gasp and Stretch one's Eyes;
Her Aunt, who, from her Earliest Youth
Had kept a Strict Regard for Truth,
Attempted to Believe Matilda:
The effort very nearly killed her.

The article then demonstrated that only 50% of outpatients given drug treatment for tuberculosis had positive urine tests.[2] Investigations into non-compliance multiplied and by 1988 the *Index Medicus* had included more than 4000 articles on the subject, confirming that of patients on long-term medication about half take it in ways that differ from what the doctor prescribed.[3]

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For the biblically minded, the story begins, as an excellent book on compliance[4] shows, in *Genesis* with Eve taking more "medicine" than she was prescribed in the Garden of Eden. For the historically minded, the story begins with an aphorism of Hippocrates: "keep watch also on the faults of the patients, which often make them lie about the taking of things prescribed".

Definitions of compliance

Compliance with what? Medication taking, alterations in diet, advice on exercise or smoking, keeping appointments, and attendance for further investigations are some of the aspects that have been studied. The definition can become elaborated to the point of absurdity, as in an early paper[5] striving for an index of the potential threat of the disease as "the square root of the product of the susceptibility score for each respondent times the severity score for each respondent". Attempts to classify non-compliance may likewise fog the issue. One classification suggested five groups—namely errors of omission, of purpose (taking medication for the wrong reason), of dosage (more, less), of timing or sequence, and of taking potentially interactive medications not prescribed by the doctor.[6] This is all negative, yet can be considered positively, as in another early paper[7] on "patient acceptance of recommended health behaviors".

Studying compliance

It is because compliance involves such a complex set of behaviours that many doctors ignore it completely. Research workers who have taken up the challenge do not get full marks either. In 1979 Sackett and Snow[8] reviewed 537 investigations and found no more than 40 that satisfied their criteria: design, sample selection and specification, description of illness, description of therapeutic requirements, definitions of compliance, and measures for assessing non-compliance. The anticipated length of the treatment and duration of follow-up must also be spelled out.