Coexisting and modulating factors, and related syndromes

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Chapter 3
Introduction

In this chapter different coexisting and modulating factors will be discussed. Attention will be primarily focused on the coexistence of irritable bowel syndrome, and furthermore on the prevalence of Raynaud's syndrome in fibromyalgia, and also of Sjögren's syndrome. Next the prevalence of sexual abuse in the history of female fibromyalgia patients will be outlined. Weather-dependent complaints in fibromyalgia are addressed in chapter 6.

The second part of this chapter will summarize the related syndromes of fibromyalgia, like chronic fatigue syndrome and myofascial pain syndromes.

Coexisting and modulating factors

In an article by Reilly and Littlejohn (1) they comment on the first presentation of fibromyalgia patients which is in their experience often with peripheral arthralgic complaints. The study included 216 consecutive new referrals to a general rheumatology clinic. 10% of these new referrals were diagnosed as fibromyalgia, of which half presented with pain in hands or wrists. Their message is that joint pain and tenderness do not necessarily mean there is joint pathology and that a mistaken diagnosis of seronegative arthritis or similar should be avoided where there is good evidence of fibromyalgia, so that fruitless and potentially dangerous therapies are withheld. We all know that at the first presentation of what turns out to be a fibromyalgia patient, we have to include rheumatoid arthritis in our differential diagnosis.

Pellegrino (2), in an anecdotal report, mentions atypical chest pain as an initial presentation of fibromyalgia.

Langevitz et al. (3) described the possible link between familial mediterranean fever (FMF) and fibromyalgia symptoms. A subpopulation of patients with FMF experience chronic lower body pain and the authors tried to determine if these chronic musculoskeletal complaints were due to FMF itself or to mechanical problems in the lower body or to other factors operative in fibromyalgia. In 93 consecutive patients with FMF a tender point count was conducted (Smythe 14 tender point count). Patients with 10 or more tender points and widespread pain were considered to have fibromyalgia. The same definition of widespread pain as was defined in the 1990 ACR criteria was used. Furthermore tenderness thresholds at 7 tender points and 5 control points were obtained. Thirty of their patients (35.5%) were found to have fibromyalgia. Dolorimeter thresholds were significantly lower in the female fibromyalgia group, both at the tender points sites and the control sites. The tenderness thresholds at control sites in the fibromyalgia group were also significantly lower than thresholds at the same sites in the patients without fibromyalgic
complaints. The authors conclude that their data suggest that the chronic experienced pain in a subgroup of FMF patients is associated in part with fibromyalgia and likely due to mechanical problems in the lower back rather than to the concomitant FMF itself. Recognition of the fibromyalgic complaints could help the patients to cope with this problem.

This report shows us that fibromyalgic complaints can coexist with other diagnoses, and that we have to be aware of this if a patient experiences widespread pain.

Irritable bowel syndrome

In the criteria published by Yunus (4) the irritable bowel syndrome (IBS) is one of the minor symptoms in fibromyalgia, which may lead to diagnosing fibromyalgia. Campbell (5) also put emphasis on IBS in the diagnostic process. In later criteria sets for diagnosing fibromyalgia, for instance the 1990 criteria, IBS is no longer part of the diagnostic tools.

Fibromyalgia and IBS frequently coexist, and both are common conditions which account for 30% or more of referrals to rheumatology and gastroenterology clinics (6). Veale et al. (6) studied the prevalence of fibromyalgia in IBS patients and that of IBS in fibromyalgia patients, using strict criteria for diagnosis of fibromyalgia and IBS, and compared these to both normal and disease control groups. The authors said that no earlier study examined both patients groups simultaneously to evaluate the frequency with which the conditions coexist. They studied four patient groups, 20 with fibromyalgia, 20 with IBS, 20 with inflammatory arthritis, 20 with inflammatory bowel disease and also 20 normal controls (recruited from patients attending for uncomplicated fractures). Results show that 70% of the fibromyalgia group had IBS and 65% of the IBS patients had fibromyalgia. In the control groups (all patients except fibromyalgia patients) 12% had fibromyalgia and 10% IBS. So these results indicate that fibromyalgia and IBS frequently coexist, and the authors suggest a common pathogenetic mechanism for both conditions may be present. We must realize that the number of patients in this study was not very high. Romano (7) also published about the coexistence of IBS and fibromyalgia. Three hundred patients in a private rheumatology practice were studied prospectively; 100 patients fulfilled the diagnostic criteria of primary fibromyalgia syndrome (a compilation of different diagnostic sets), 100 patients with an arthritis disorder who fulfilled criteria for secondary fibromyalgia syndrome, that is patients with nonrestorative sleep, specific and reproducible tender areas and complaints of musculoskeletal pain and achiness, and a third group of 100 patients who had arthritic diseases but did not have problems with sleep, nor did they have enough myofascial tender areas to fulfil the diagnostic criteria for fibromyalgia. These 300 patients were asked for IBS-symptoms (using a questionnaire). IBS was diagnosed in 49% of primary fibromyalgia syndrome patients, in 19% of patients with secondary fibromyalgia, and in 9% with arthritic
controls. Regarding all fibromyalgia patients together (primary and secondary) IBS coexists in one third of the fibromyalgia group.

Yunus (8) performed a controlled study of primary fibromyalgia syndrome for clinical features and association with other functional syndromes, among which IBS was one. IBS was significantly more common in primary fibromyalgia syndrome, compared with RA and normal control groups.

Both syndromes occur predominantly in women and the pathogenesis of both syndromes remains obscure.

An other study for bowel dysfunction in fibromyalgia (criteria of Smythe) was undertaken by Triadafilopoulos et al. (9). They used a validated self-administered questionnaire to assess the prevalence of symptoms of bowel dysfunction and IBS in a group of 123 patients with fibromyalgia. These patients were compared with 54 patients with degenerative joint disease and with 46 normal controls. They found a high prevalence (60%) of gastrointestinal symptoms suggestive of IBS in the fibromyalgia patient group, and that these symptoms worsened during stress or disease exacerbations. In contrast, only 13% of degenerative joint disease patients and 0% of normal controls reported any symptoms of bowel dysfunction.

Prescott (10) reported on a study of clinical features of fibromyalgia in the adult Danish population. Study population was based on a national health interview survey. In this study subjective swelling, fatigue and headache were significantly associated with the number of tender points and with the diagnosis of fibromyalgia. However the symptoms like irritable bowels, morning stiffness and sleep disturbances were not related to fibromyalgia. This finding might be explained, according to the authors, by the changing of criteria sets in classifying fibromyalgia. The Yunus criteria included irritable bowel symptoms as one of the minor criteria, thus bringing in a diagnostic bias.

Also addressing the comorbidity of, among other disorders, IBS and fibromyalgia was Hudson in 1992 (11). Doing this they assessed the personal and family histories of a broad range of medical and psychiatric disorders in 33 female fibromyalgia patients. In this patient group there were high rates of migraine, IBS, chronic fatigue syndrome, major depression and panic disorder. There were also high rates of familial major mood disorder. The authors were especially focused on these disorders using a structured clinical interview comprising the symptoms and complaints of these disorders, by standard operational criteria. They found no case of somatization disorder in their patient group. If the symptoms of chronic pain would not have been attributed to the fibromyalgia, the authors mentioned, than 21% would have met criteria for somatization disorder. In most cases the associated disorders began at least 1 year before the onset of the fibromyalgia symptoms, except the chronic fatigue syndrome. The chronic fatigue syndrome almost always preceded the fibromyalgia start within a year. This last finding could suggest, according to the authors, that the current diagnostic criteria do not adequately distinguish these two disorders, or even
that these two are actually the same illness. The authors think their results are consistent with the possibility of a shared, heritable?, abnormality that is necessary, but not sufficient, for these disorders to occur. So other factors, like for instance exposure to certain viral antigens, might be necessary for the development of fibromyalgia. They also stress that their hypothesis does not imply that any of these disorders causes another.

In our study 30% of the fibromyalgia patients said they had symptoms of IBS, and 16% of the RA patients. IBS was present, in our opinion, in the presence of chronic, moderate or severe constipation and/or diarrhoea as well as moderate or severe abdominal pain related to bowel movement in the absence of an underlying organic condition, as assessed by medical history. Yunus in 1989 used the same criteria. Summarizing the results of the different studies mentioned above, there seems to be a high incidence of IBS in patients with fibromyalgia. An explanation for this coexistence can not be found in these articles, but most authors suggest there is a common pathogenetic pathway. Fibromyalgia is not a disorder with solely musculoskeletal complaints; other psychophysiological factors can be involved. Weather-dependent fibromyalgic complaints are often mentioned, see chapter 6 (12). Patients with fibromyalgia frequently report problems associated with cold: worsening symptoms in cold weather, having cold hands, and feeling colder than others. In our study (12), where we examined the subjective complaints of the fibromyalgia patients, compared with objective meteorological factors, we were not able to confirm the hypothesis that weather influences pain and other complaints in fibromyalgia patients. One year later, Hagglund et al. (13) conducted a very similar study like ours. Their study group of fibromyalgia patients reported that weather affected musculoskeletal symptoms predominantly, but they did not find any correlation between meteorological data and disease severity measures. They found a strong association between beliefs about weather and self-reported pain. The authors had to come to the same conclusion like we did: fibromyalgia patients belief that weather affects their symptoms, but is very unlikely that there are physiologic changes associated with actual weather.

Raynaud's syndrome

Questionnaire-based studies have demonstrated a 30-53% prevalence of symptoms suggestive of Raynaud's syndrome in patients with fibromyalgia. In our study sample this was 23% in the fibromyalgia group. Different authors have studied the relationship between fibromyalgia and symptoms of Raynaud's syndrome, and these studies are discussed in chapter 2 (14-17).

Sjögren's syndrome
Vitalli and other Italian coworkers (18), reported on fibromyalgia features in patients with primary Sjögren's syndrome. Patients with fibromyalgia often describe the presence of dry mouth and dry eyes. They compared three groups of 30 patients, one group with primary Sjögren's syndrome, one group with osteoarthritis and a third group with diabetes mellitus. Fibromyalgia features were found in 47% in the Sjögren's group, in 70% of the osteoarthritis group and only 33% in the diabetes group. In the Sjögren's group there was the highest prevalence of moderate-severe depression (also 47%). The criteria for fibromyalgia were those of Yunus (1981). The fibromyalgic pain in the Sjögren-patients appeared, according to the authors, to be closely correlated with psychopathological changes, and in particular depression. In patients with primary Sjögren's syndrome the neurotic changes might be a consequence of chronic disease state. They suggest that the Sjögren patient suffers more and experiences more impairments and disabilities than is commonly acknowledged and this might induce neurotic changes, like depression, more than is expected. The development of fibromyalgic pain could be the consequence of these psychological changes, more so than related to other disease-specific mechanisms. The association of fibromyalgia with primary Sjögren's syndrome was prospectively studied by Bonafede et al. (19). Seventy-two fibromyalgia patients underwent a Schirmer test and those persons with an abnormal test had a minor salivary gland biopsy. Nearly 40% of a tertiary centre fibromyalgia population had a positive Schirmer test. In total 6.9% of their study sample had probable Sjögren's syndrome, and 11% possible Sjögren's syndrome (established after the biopsy). They followed these patients for a period of over 6 years and none of these patients have developed systemic complications of Sjögren's syndrome.

The relationship between fibromyalgia and Sjögren's syndrome is not clear. There is no evidence for an autoimmune basis in fibromyalgia, and an infectious etiology seems also farfetched. Maybe stress plays an important factor in developing fibromyalgic complaints in patients with Sjögren's syndrome.

Prevalence of sexual abuse in fibromyalgia

In 1995 two studies were published concerning the prevalence of a history of sexual abuse in women with fibromyalgia (20,21), by Taylor et al. and Boisset-Poiro et al. Information was gathered by the use of self-administered questionnaires, and in both studies a control group of women was present. In the study of Taylor the control group consisted of healthy controls, in the study of Boisset-Poiro of rheumatology patients (non-fibromyalgia). In the two fibromyalgia groups, as well as in both control groups the incidence of reported abuse was high (more than 50%), but no statistically significant difference was found between the patient group and control group in both studies. The authors conclude that sexual abuse does not cause fibromyalgia, but their results show that sexual abuse is correlated with the number and severity of associated
symptoms, and furthermore that abuse (not only sexual, but also physical, drug and alcohol, and eating disorders) might have an effect upon the expression and perpetuation of fibromyalgia in adult women. Hudson (22) presses on the fallacy that a found correlation between childhood (sexual) abuse and fibromyalgia does not necessarily mean that there is a causal link between the two. Both may very well be caused by the same (third) factor. Hudson states that the only thing to do to get a definite answer concerning this causality question is a prospective longitudinal study of a group of children that were sexually abused, and another, matched, group that was not, and to see if over the years a medical or psychiatric illness develops. In these studies remarkable high numbers of sexual abuse in fibromyalgia patients came forward. The relationship between the abuse and fibromyalgic complaints could, once again, be the (psychological) stress phenomenon. Stress could represent some etiologic role in the development of the fibromyalgia syndrome.

Fibromyalgia and related syndromes

Fibromyalgia as a separate entity is very often not recognised, but on the other hand fibromyalgia has certainly an overlap with other syndromes. It is very difficult to say if these related syndromes, like chronic fatigue syndrome, myofascial pain syndrome, female urethral syndrome, and fluid retention syndrome are distinguishable other syndromes or if their part of the same spectrum of symptoms. We tend to believe they are overlapping syndromes, especially fibromyalgia, chronic fatigue syndrome and myofascial pain syndrome (figure 1).

Figure 1
Fibromyalgia and Chronic Fatigue Syndrome

Fibromyalgia and chronic fatigue syndrome are conditions which are both controversial. Both syndromes go by different names. Fibromyalgia has been known as soft tissue rheumatism, psychogenic rheumatism, fibrositis, myofascial pain syndrome etc. Chronic fatigue syndrome is known as chronic Epstein-Barr Virus syndrome, postviral fatigue syndrome, postviral exhaustion, neurasthenia, myalgic encephalomyelitis etc, and a more popular namegiving "yuppy plague".

Chronic fatigue syndrome is characterized by chronic, debilitating fatigue lasting longer than 6 months, with exclusion of other conditions that may cause similar symptoms. Nonspecific neurological symptoms like poor concentration, visual blurring and vertigo are often mentioned by patients with chronic fatigue syndrome. It happens that the fibromyalgia patient, with complaints of widespread pain, consults a rheumatologist, and that a chronic fatigue patient is more often seen by a neurologist. Specific musculoskeletal symptoms and signs are required for the diagnosis of fibromyalgia and severe debilitating fatigue is required for the diagnosis chronic fatigue syndrome. But actually most patients with fibromyalgia also complain about fatigue, and on the other hand patients with chronic fatigue often have musculoskeletal complaints.

Interest in a viral genesis of the fibromyalgia syndrome came along with the interest in the chronic fatigue syndrome, surely because of the many similarities between the two syndromes.

In an editorial (23) Wessely addresses the chronic fatigue syndrome and refers to neurologists. In the editorial he discusses the supposed relations between the chronic fatigue syndrome and neuromuscular disorders, and psychiatry, infection, and the immune system. Finally Wessely puts forward his idea of the concept of the chronic fatigue syndrome, in which he sees chronic fatigue as a dimensional in stead of a categorical variable. Fatigue can be seen anywhere on a spectrum from no fatigue to worst possible fatigue and there is no clear boundary to separate the normal from the abnormal. Being on the end of the spectrum could mean severe morbidity which in itself needs treatment. In the treatment of chronic fatigue Wessely sees a crucial role for rehabilitation, where a physical and psychological approach are combined. As in the fibromyalgia syndrome recognition of the complaints is very important and over investigation should be avoided. The patients with these complaints should be taken for real and the patient presenting with a psychosocial disability needs our attention and care as any other patient. This again shows the similarities between the patients with fibromyalgia and chronic fatigue syndrome.

David et al. (24) stressed as well on the possible interactions between psychological and physical influences on health, and this should be given much more attention. Both conditions are controversial, because of lack of objective evidence for structural pathology or disease. So it is often said that psychogenic factors play the most
important role in the etiology of these syndromes. A lot of work has been done in investigating psychological backgrounds of fibromyalgia patients, see chapter 10. The results were contradictory, but most investigators found elevated psychological test scores in patients with primary fibromyalgia syndrome. The question which came first, the psychological symptoms or the physical symptoms, is of course not answered. Altogether should the dichotomy of organic versus functional be replaced by a multifactorial approach, as well in fibromyalgia as in chronic fatigue syndrome.

Ideas on viral etiology of chronic fatigue syndrome and fibromyalgia syndrome
Several studies have been published on the search for a viral etiology (25-29). An anecdotal report on parvovirus B19 infections in fibromyalgia (25), and Buchwald published a study (26), in which he described the antibody titers to Epstein-Barr virus in patients with fibromyalgia. He found that these titers were not significantly different from those in age- and sex-matched healthy and unhealthy controls. Later studies did actually not find higher titers of the antibody against the Epstein-Barr virus in patients with the chronic fatigue syndrome. The association between Coxsackie B virus infection and the postviral fatigue syndrome and the assessment of immunological abnormalities associated with this syndrome, were studied by Nash et al. (27) and Miller et al. (28). Miller found no significant differences between different categories of patients according to clinical likelihood of the syndrome nor any predictive value in a fourfold rise or fall in the Coxsackie B virus IgG titre in patients between entry and review at six months. Nash et al. reported in a case report the history of a patient who met the fibromyalgia criteria according to Smythe and who had evidence of chronic infection with Coxsackie virus over a 4-year period of follow-up.

The presence of parvovirus B19 infection in chronic fatigue was subject of study by Ilaria et al. (29). Parvovirus B19 had been identified in some fibromyalgia patients, see above and chapter 2, and because the considerable overlap between chronic fatigue syndrome and fibromyalgia the authors were interested if this same virus could be involved in chronic fatigue syndrome. Bone marrow and serum samples of a selected group of chronic fatigue patients most likely to have parvoviral infection were obtained. However no evidence of clinically important parvoviral infection was found. Altogether no substantial evidence have been put forward for a viral etiology in the chronic fatigue syndrome (nor in the fibromyalgia syndrome).
Chapter 3

Hormonal disturbances in chronic fatigue syndrome

Sternberg (1993) (30) subscribes the importance of a variety of neuroendocrine abnormalities in rheumatologic disease and associated fatigue syndromes including the chronic fatigue syndrome. She states that now researchers have proven the interactions between the immune system and central nervous system, and vice versa. As an example of this she says that products of the immune system, such as cytokines, stimulate parts of the central nervous system (CNS), such as the hypothalamus, and thus initiate a cascade of hormonal events which results in suppression of the immune/inflammatory response through the potent anti-inflammatory/immunosuppressive effects of the glucocorticoids. And next that an interruption of this feedback loop by any means and at any point may result in susceptibility to or enhancement of inflammatory disease. Special interest is laid on abnormalities in hypothalamic-pituitary-adrenal function in which case lethargy and fatigue states can occur. This could be explained by a central adrenal insufficiency, by means of a deficiency of cortico releasing hormone (CRH) and/or cortisol, or by means of a primary adrenal insufficiency, in which there is glucocorticoid deficiency on the whole. Enhanced immune responsiveness is associated with both lethargy and fatigue states, regardless of the etiology of the hypocortisolism. Furthermore Sternberg suggests that a hyporesponsive adrenal cortex can result in increased susceptibility to disordered states of immunity, manifesting either as chronic fatigue or fibromyalgia. This theory is gaining more and more support, where an abnormal reaction to stress plays an important role. Stress influences the central nervous system and immune system.

Trace elements in chronic fatigue syndrome

Cox et al. (31) tested the hypotheses that patients with chronic fatigue syndrome have low red blood cell magnesium and that magnesium treatment would improve the wellbeing of such patients. They did this in a case-control study and a randomized, double-blind, placebo-controlled trial. They found that patients with chronic fatigue syndrome had lower red cell magnesium concentrations than healthy controls, and in the clinical trial patients treated with magnesium claimed to have improved energy levels, better emotional state and less pain. In the control group the results were far less. Red cell magnesium returned to normal in all patients on magnesium, but in only 1 (of 17) patient on placebo. The authors suggest that these findings show that magnesium may play a role in chronic fatigue syndrome.

Lund-Olesen and Lund-Olesen (32) hypothesized in a case report, that a virus injury to the calcium channels could be a causative factor in the pathogenesis of the chronic fatigue syndrome/fibromyalgia. The authors suggest that an injury to the calcium channels will lead to larger quantities of calcium ions entering the striated muscle cells and this would result in increased muscle tone, and the cells and whole muscle,
will develop a state comparable to that following static muscular work. The authors suggest placebo-controlled studies with calcium antagonists in patients with chronic fatigue syndrome.

The study on the low red blood cell magnesium is interesting, also while it is performed in a well-designed way. The study on calcium is speculative and can not lead to any conclusions, being just one case report.

**Depression and chronic fatigue syndrome**

Kendell (33) made a statement about his viewpoint of chronic fatigue, viruses and depression. According to Kendell the description of a depressive episode begins with the statement that the subject suffers from lowering of mood, reduction of energy, and decrease in activity. Capacity for enjoyment, interest, and concentration are impaired, and marked tiredness after even minimum effort is common (10 revision of International Classification of Disease). Apart from the absence of any reference to previous viral infection, this description is almost the same as the one for the postviral fatigue syndrome. Depressive illness are also twice as common in women as in men and are uncommon in children; both features of postviral fatigue syndrome as well. When patients with chronic fatigue are assessed psychiatrically more than half of them are found to fulfil operational criteria for psychiatric disorder.

**Sleep problems in chronic fatigue syndrome**

Whelton in 1992 (34) compared sleep physiology, viral serology and symptoms in 14 chronic fatigue patients and 12 healthy controls. All patients had unrefreshing sleep and α-intrusion in nREM sleep. They found no difference in Epstein-Barr virus serology. The chronic fatigue patients had significantly more tender points than the control group, and had also more somatic complaints and depressive symptoms. The chronic fatigue patients did not have irresistible daytime sleepiness, although they complain of daytime exhaustion. These findings are very similar to those published on the fibromyalgia syndrome.

**Treatment modalities in chronic fatigue syndrome**

Treatment for the chronic fatigue syndrome has consisted intravenous immunoglobulin treatment, as a trial. The result of this study (35) indicated that intravenous IgG is unlikely to be of clinical benefit in chronic fatigue syndrome. However, Llyod et al. (36) published a study in which they suggested that immunomodulatory treatment with immunoglobulin is effective in a significant number of patients with chronic fatigue syndrome. According to the authors this should be a support to the concept that an immunologic disturbance may be important
in the pathogenesis of this disorder. Straus (37) commented on these two studies, which have opposite conclusions. With regard to sample size and immunoglobulin dosage there were differences in these two studies, and also the study cohorts may not have been comparable.

Also other treatment modalities in the chronic fatigue syndrome are suggested, like for instance cognitive behavior therapy (38). 50 patients enrolled an open trial, in which the rationale was that a distinction could be drawn between factors that precipitate the illness and those that perpetuate it. Similarities can be seen here with the fibromyalgia syndrome. Perpetuating factors can be cognitive factors like the belief that physical symptoms would mean tissue damage, but also behavioral factors such as persistent avoidance of activities associated with an increase in symptoms. The authors warn not to avoid physical and mental activity, because in their opinion this only works counterproductive. The authors have an interesting theory on the etiology of chronic fatigue syndrome: "..it is plausible that an initial ineffective trigger may begin a cycle in which both attributional and cognitive factors fuel avoidant behaviour. The initial symptoms, in particular fatigue and myalgia, engender a state of "learned helplessness" being potent, aversive and uncontrollable, and may also trigger or exacerbate the mood disorder that is found in many patients. Continuing attribution of all symptoms to a persistent, untreatable "virus", continues to increase helplessness, although preserves self esteem. Avoidant behavior, which is reinforced by the advice currently offered to patients, sustains symptoms, by decreasing activity tolerance and increasing sensitivity to any stimulation, as does associated mood disorder. Re-exposure to activity causes more symptoms, and more fear. The result is a vicious circle of symptoms, avoidance, fatigue, demoralisations and depression..". Therefore they see a chance for success when the avoidance behavior could be reduced and the perception of helplessness could be decreased and improvement of mood could be achieved.

This theory also would fit the fibromyalgia syndrome perfectly.

Comparison between fibromyalgia syndrome and chronic fatigue syndrome

The relationship between fibromyalgia and chronic fatigue syndrome has been studied by several investigators.

Moldofsky et al. (39) have noted similar sleep disturbances in fibromyalgia and chronic fatigue syndrome. In 1989 Moldofsky (40) wrote about non-restorative sleep and symptoms after a febrile illness in patients with fibromyalgia and chronic fatigue syndromes. A febrile illness may trigger alteration in sleep-wake brain and immune functions in patients with fibrositis or chronic fatigue syndromes. In this article Moldofsky tried to find connections between sleep disturbances, immune functions, chronic fatigue and myalgia. The author stated that earlier experimental data and
clinical observations suggested a connection between the sleep-waking brain and immune system, but the contribution of disturbances in the sleep-waking brain and immune system to chronic fatigue and myalgia is as yet not clear. In 1988 Goldenberg (41) looked for evidence for chronic viral disease in fibromyalgia and other chronic fatigue syndromes. Goldenberg gave a summary of the literature of the different syndromes and reviewed the last studies concerning the two syndromes, including their own study (42,43). Goldenberg (42) stated that the two syndromes have similar clinical and demographic features. He found that most patients with chronic fatigue syndrome have a tender point examination similar to patients with fibromyalgia. Another point he makes is that similar pathophysiologic changes have been described in both syndromes. Single fiber electromyographic changes and reduced high energy phosphate levels in muscle have been reported in both conditions, suggesting that muscle alterations may be important. Depression is also common in both syndromes. In another publication of Goldenberg (43) he reported a high frequency of fibromyalgia in patients with chronic fatigue in an academic primary care practice. Of 27 chronic fatigue patients 19 (70%) had a tender point examination similar to those of patients with fibromyalgia, and these patients had persistent diffuse musculoskeletal pain. The other 8 patients did not have musculoskeletal pain and the tender point examination in those patients was similar to those in healthy controls.

Wysenbeek et al. (44) investigated fibromyalgia patients for chronic fatigue syndrome symptoms. This study was conducted in Israel. Only 21% (7 of 33) of the fibromyalgia patients fulfilled criteria for the chronic fatigue syndrome, which is a lower number than other authors reported. They asked however if painful glands were present, while in other studies the authors asked for swollen glands. This could explain the differences in study outcome. In conclusion Wysenbeek stated that there is a limited relationship between the two syndromes and that they do not seem to represent the same condition.

Goldenberg (45) tried to bring a synthesis between fibromyalgia, chronic fatigue and myofascial pain syndromes, for which syndromes there is an overlapping area. A Danish group performed a 4-year follow-up study in fibromyalgia and looked closer into the relationship with the chronic fatigue syndrome (46). They wanted to investigate the common existence or later appearance of other diseases in patients that were diagnosed as fibromyalgia, and to describe the overlap between fibromyalgia and chronic fatigue syndrome. Their patients attended the department of rheumatology. In their follow-up period only 2 of 91 patients developed another somatic disease that could explain the muscle pains. The pain was generally reported to be aggravated. There was no notable decrease in muscle strength. Only one fifth of their fibromyalgia patient group fulfilled all the criteria of the chronic fatigue syndrome, including sudden onset of symptoms, fever, lymphadenitis, or pharyngitis.

A new syndrome is introduced by Buchwald and Garrity (47), in their comparison
study of patients with chronic fatigue, fibromyalgia and multiple chemical sensitivities (MCS). The authors themselves state that there are no generally agreed-on criteria for MCS, but it could be summarized as an acquired disorder triggered by exposure to diverse chemicals at doses far below those documented to cause adverse effects in humans. The demographic characteristics and specific symptoms were very similar. Seventy percent of the fibromyalgia group met the criteria for chronic fatigue and 30% of the MCS group met criteria for chronic fatigue. Health care use was highest in the fibromyalgia group (39.7 contacts in the previous year), but also high in the other two groups (MCS 23.3 contacts, chronic fatigue 22.1 contacts). The authors found no difference in health locus of control between the three groups. Regarding all the different studies on chronic fatigue syndrome in relation with fibromyalgia syndrome, we belief these two are overlapping syndromes. How many patients fulfil both criteria sets depends on what particular criteria sets were used in the different studies.

Fibromyalgia and myofascial pain syndromes

A clear distinction between fibromyalgia and myofascial pain syndrome was not made in the earlier days. Simons and Travell (48) were the pioneers in the field of myofascial pain syndromes, but in the beginning and middle of the eighties there still was a lot of confusion on the terminology, for instance "Fibrositis/fibromyalgia; A form of myofascial trigger point.", by Simons in 1986 (49), and even in 1989 in a publication by Fishbain (50) "DSM-III diagnoses of patients with myofascial pain syndromes (fibrositis)." Simons puts the question forward whether patients diagnosed as having fibromyalgia are only having extensive multiple myofascial trigger points aggravated by severe perpetuating factors or that fibromyalgia is a separate systemic disorder that is responsible for the symptoms or, thirdly, there could be a combination of fibromyalgia and myofascial trigger points. The different features of fibromyalgia and myofascial pain syndrome are compared with one another and the difference between tender points and trigger points is elucidated (see also chapter 7). A trigger point is always a tender spot and a tender point may, or may not, be a trigger point. This is of importance, according to Simons, because trigger points are responsive to specific treatment. Simons states that fibromyalgia and myofascial pain syndromes are almost certainly separate entities, but a considerable number of patients could have both conditions. This leaves the reader a little in the dark. There have been a number of investigators who looked into the different aspects of each of the syndromes, for instance Sheon (51). He emphasizes the distinction between tender and trigger points. At one point Sheon asks a very interesting question, if these two disorders are really different entities or part of a spectrum of a muscular rheumatic disorder. Unfortunately this question stays unanswered. It is basically the same question that Simons in 1986 addressed. Myofascial pain syndrome can be seen
as a local form of fibromyalgia. Myofascial pain syndromes are characterized by trigger points and there is no need to have generalized pain complaints. Durette et al. (52) evaluated needle electromyographic activity in patients with myofascial pain syndrome and in patients with fibromyalgia. They selected tender points in fibromyalgia patients, similar tender areas with pain referral, so called trigger points, and associated muscle bands and adjacent uninvolved musculature. Not in any of the muscles of the participating subjects there were spontaneous fibrillatory or positive sharp wave potentials found. Neither was their evidence of focal motorunit activity in the tender points, trigger points or associated muscle bands in either group. There were no differences found in motor unit recruitment in the sampled areas. Following these findings the authors say that no electrodiagnostic evidence of ongoing denervation or focal muscle spasm is found in association with focal myofascial pain or fibromyalgia.

Yunus et al. (53) outlined clinical features and muscle pathology in fibromyalgia syndrome and myofascial pain syndrome. Stress was laid on the pathologic changes in muscle in the fibromyalgia syndrome, namely moth-eaten appearance of type I fiber and myofibrillar lysis with glycogen and mitochondria deposition. Pathologic changes in muscle in myofascial pain syndromes are not further discussed. Yunus, however, recommended strongly further controlled studies to establish meaningful pathologic changes in muscle in fibromyalgia.

Scudds et al. (54) conducted a comparative study of pain, sleep quality and pain responsiveness in 20 patients with fibromyalgia and 18 with myofascial pain syndrome. The authors found substantial differences in overall pain and pain responsiveness between the two groups. The myofascial pain group was significantly younger than the fibromyalgia group, but there was no difference in duration of the pain complaints between the two groups. They also looked for differences in anxiety and depression on VAS-ratings, but no differences were found. The fibromyalgia group had lower generalized pain thresholds, meaning that they were more responsive to pain, and they also scored higher on mean VAS scores concerning pain intensity. No differences were found in sleep quality, measured with VAS as well. These findings still could mean that the two syndromes are part of a continuum; fibromyalgia being the more severe in experiencing pain complaints.

Jacobsen et al. (55) compared dynamic muscular endurance (DME) in fibromyalgia (36 patients) and myofascial pain syndrome (18 patients). Patient's groups were matched for sex, age, height and weight, peak torque and contractionsal work of the right quadriceps muscle. A Cybex II dynamometer was used to determine the DME of the right quadriceps muscle. Subjects were asked to perform repeated knee extensions with maximal strength each time (with a constant angular velocity). The DME was defined as the number of repeated knee extensions needed for the contractionsal work in two successive knee extensions to be equal to or below 70% of the initial value. They found a significantly lower voluntary muscular endurance in the fibromyalgia
group. In the myofascial pain group however almost none of the patients had their symptoms in the lower extremities. And how can one be sure that a patient really showed his maximal strength at the initial contraction and during the endurance test? The DME was not related to the number of subjective symptoms of the patients in this study. The patients with a lower muscular endurance, however, also had lower levels of physical activity, which may not come as a surprise. These results are hard to interpret. The impact of experiencing pain on the maximal muscle endurance can not be reliable established, and therefore these results are not very worthful. Smythe (56) addresses the links between fibromyalgia and myofascial pain syndromes too. He urges that more attention should be given to the examination of specific sites of deep tenderness, e.g. tender points and trigger points. He clearly sees two different areas, the widespread pain syndromes and regional pain syndromes. He recommends the study of Wolfe et al. (57) (see chapter 7).

Fibromyalgia and female urethral syndrome

A relationship between fibromyalgia and the female urethral syndrome was suggested by Wallace (58) and Paira (59). The female urethral syndrome is characterized by the presence of urinary frequency, dysuria, suprapubic discomfort and urethral pain. The urine however should be sterile. Wallace and Paira found in respectively 12 and 18% of a group of fibromyalgia patients (respectively 50 and 212 patients) also the presence of the female urethral syndrome. In a control group of patients (same number of patients) with other rheumatic conditions their were none with the female urethral syndrome. Both authors suggest that the female urethral syndrome should be taken into account in the evaluation of every patient with fibromyalgia. But what to do with the male fibromyalgia patients? Wallace remarks that the personality profiles of patients with the female urethral syndrome and patients with fibromyalgia are similar, but no direct comparisons are made. Both authors believe that the urethral syndrome might represent a form of fibromyalgia, or are overlapping syndromes. Both syndromes are said to respond to similar therapies, like cyclobenzaprine, NSAID's, aerobic exercises and swimming.

The authors hypothesize that the urethral musculature is affected in fibromyalgia and that this could explain the combination of the two syndromes. This assumption seems highly speculative, more so while the general opinion moves away from the peripheral (pathogenetic) theory.
Fibromyalgia and fluid retention syndrome

Deodhar (60) draws attention to the fluid retention syndrome in relation to fibromyalgia. Although this fluid retention syndrome is not well known, Deodhar thinks it is important enough that physicians are aware of the symptoms of this syndrome. Another synonym of this syndrome is idiopathic oedema and is said to be seen almost only in women. A diversity of accompanying symptoms are reported, among which fatigue, generalized weakness and bloating. This makes the possible overlap between the fluid retention syndrome and fibromyalgia clear. Fibromyalgia patients often complain of subjective swelling, but this is not seen at the physical examination. The pathogenesis of the fluid retention syndrome is thought to be an unidentified defect in the capillary walls, which makes them more permeable especially when the patient is in the upright position. Management of the fluid retention syndrome leans, as in the fibromyalgia syndrome, on careful explanation of the syndrome and acceptance of the patient's complaints. Furthermore a low carbohydrate and low salt diet. Only 4 patients are described in this study, so we have to wait for the results of a larger, controlled study before this topic can be analyzed in a proper fashion. Interesting in the light of the fluid retention syndrome, with a suspected defect in the capillary walls, is the article by Grassi et al. (61). In their study they found indications for a lowered transcapillary diffusion and an earlier and more rapid interstitial clearance of Na-fluorescein, that was earlier on injected. So they conclude there is a lowered transcapillary permeability in fibromyalgia patients, and this seems contrary to the findings mentioned above in the fluid retention syndrome.

Overlooking the studies on fibromyalgia and related syndromes the conclusion can be drawn that all these syndromes belong to the same spectrum, where different symptoms are more prominent existent in the one syndrome than in the other. It might very well be true that the effort of the physician by asking all the right questions brings forward a wide variety of symptoms that would make the patient fit in more syndromes at one time.
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