According to the classification criteria proposed by the American College of Rheumatology, fibromyalgia is a long-standing multifocal pain condition combined with generalised allodynia/hyperalgesia. It is the generalised allodynia/hyperalgesia that distinguishes fibromyalgia from other conditions with chronic musculoskeletal pain. Central sensitisation of nociceptive neurons in the dorsal horn due to activation of N-methyl-D-aspartic acid receptors and disinhibition of pain due to deficient function of the descending inhibitory system are probable pathogenic factors for allodynia/hyperalgesia. Furthermore, chronic pain is a chronic emotional and physical stressor. Chronic stress and chronic sleep disturbance are not specific for fibromyalgia but could be the causes of symptoms like fatigue, cognitive difficulties and other stress-related symptoms. They may also cause neuroendocrinological and immunological aberrations.

Key words: fibromyalgia, muscle pain, allodynia, hyperalgesia.

This overview will deal with FM as a disease of the nociceptive system. A similar overview entitled “Is fibromyalgia a central pain state?” has recently been published in the Journal of Musculoskeletal Pain (1). Two books published in 2002 deal with the pathogenesis and treatment of symptoms in FM (2, 3).

DEFINITIONS AND DIAGNOSTIC CRITERIA

The classification criteria of the FM syndrome proposed and accepted by the American College of Rheumatology (ACR) in 1990 are often in practice also used as diagnostic criteria (4). The criteria consist of one symptom and one sign. The symptom is multifocal musculoskeletal pain; the sign is generalised allodynia/hyperalgesia. The pain in FM is usually not pain all over, and the pain sites are not strictly symmetrical. The pain is, however, multifocal and is experienced in both the upper and lower half of the body and on both sides. Axial pain is also a symptom. The pain is more or less continuous. Only about 30% of the patients have shorter pain-free periods or episodes. The pain intensity is usually moderate or high, and varies from time to time also during the same day (5). The pain locations may also change from one time to another.

The generalised allodynia/hyperalgesia is the sign that distinguishes FM from other conditions with widespread musculoskeletal pain. Allodynia is pain elicited by non-noxious stimuli that are not normally painful. Hyperalgesia is increased intensity and prolonged duration of pain caused by noxious stimuli. In the clinical setting, pressure allodynia is tested by determining whether moderate pressure from the tip of the thumb (around 4 kg) evokes pain. If it does, this is a tender point. The ACR criteria for FM require that allodynia should be tested at 18 specified locations and that there should be tender points at no fewer than 11 of these sites.

As will be discussed below FM should be suspected in any chronic musculoskeletal pain condition when localised or regional pain spreads to several sites, when temporary or intermittent pain becomes more or less continuous, when pain on movement becomes pain at rest, or when segmental allodynia/hyperalgesia becomes generalised. FM may be the end stage in a continuum that starts with chronic localised musculoskeletal pain. This in turn means that a pain drawing and a tender point examination ought to be performed in all patients with long-standing muscu-
losskeletal pain. Such an examination does not take long to perform.

**PATHOGENESIS OF GENERALISED ALLODYNIA/HYPERALGESIA**

Nociceptive signals from peripheral tissues can be modulated at several levels of the CNS, from the dorsal horn to the cortex. It is the balance between facilitation and inhibition that determines the pain sensitivity. In the spinal cord the focus of interest is on the Wide Dynamic Range (WDR) neurons in lamina V in the dorsal horn. These neurons receive input both from C fibres (pain) and A-beta fibres (touch) from peripheral tissues and input from descending inhibitory tracts from the brainstem. The descending tracts are in turn controlled by connections with the hypothalamus and cortex. In the WDR neurons, neuronal activity from the periphery and the brain is integrated. Long-standing bombardment of nociceptive neurons in the CNS by impulses in primary afferent nociceptive neurons induces neuronal plasticity changes.

The studies of FM that show that there is a changed function of the nociceptive system in patients with FM can be divided into studies showing ongoing activity in afferent nerves in FM, studies showing central sensitisation of nociceptive neurons, studies showing deficient function in the descending inhibitory system and, finally, studies that show changes in peripheral tissues like muscles. Examples will be given below.

**Substance P in the cerebrospinal fluid (CSF)**

The neuropeptide substance P is produced mainly in the cell bodies of primary afferent C fibres. It can also be produced in neurons in the CNS. In FM around 80% of patients have increased levels of substance P in CSF (7, 8). In the literature the origin of increased substance P in CSF in patients with FM has been attributed to release from neurons in the CNS. One can, however, not exclude that the increased content of substance P in CSF could be caused at least partly by release from primary afferent neurons. The substance P levels in CSF can, for example, increase in nociceptive pain due to arthrosis (6). The levels decrease after operation, concomitant to pain relief.

In FM findings in skin biopsies indicating neurogenic inflammation have been detected (9). Neurogenic inflammation is caused by release of neuropeptides, including substance P, from the peripheral endings of primary afferent nociceptive nerves.

**Studies that show amplification of pain sensitivity**

In a recent study published in Arthritis & Rheumatism, Gracely et al. (10) used functional magnetic resonance imaging to study the pattern of cerebral activation during application of painful pressure in patients with FM and healthy controls. The same pattern of brain activation was found in patients with FM and in healthy controls. The difference was that this pattern was elicited in the patients with FM by pressure that was about three times less than in healthy controls. Crofford & Clauw (11) commented on the results in an editorial from which I quote: ‘Taken together the data on pain processing in FM demonstrate that the central representation of pain correlates with the patients’ report on pain and that purely behavioural or psychological factors are not primarily responsible for the pain and tenderness in FM’.

Using single-photon emission computed tomography, Mountz et al. (12) found that regional cerebral blood flow in the left and right hemispheres and left and right heads of the caudate nucleus were lower in patients with FM than in healthy controls. Bradley et al. (13), discussing these findings in an overview of results obtained by brain imaging in patients with FM, maintained that the reduced blood flow is secondary to hypersensitivity in spinal and peripheral nociceptive neurons. Blood flow in these structures is increased in acute pain, whereas in chronic pain, such as cancer pain, neuropathic pain and FM, the blood flow is reduced.

Two studies (14, 15) show an increased amplitude of the cerebral somatosensory potentials evoked by laser heat stimuli to the dorsal surface of the hand in patients with FM compared with controls. Lorenz et al. (15) concluded that the effect on one component (N170) of the laser-evoked potential can best be explained by ‘exogenous factors like peripheral and spinal sensitisation or reduced cortical or subcortical inhibition of nociception’. Abnormal responses to electrocutaneous stimulation in patients with FM have been reported by Arroyo & Cohen (16) and Vecchiet et al. (17).

**Stimulus (pressure)-response (pain) function**

When noxious stimuli activate high-threshold mechanosensitive neurons, the stimulus-response function is a power function. Activation by non-noxious stimuli gives a linear function. Bendtsen et al. (18) found that patients with FM display a linear stimulus (pressure)-response (pain) function in contrast to normal controls, who showed a power function. The authors interpret their findings as support for the notion that there are ‘aberrant central pain mechanisms’ in FM.

**Decreased inhibition of pain**

Tonic inhibition of pain caused by activity in the descending inhibitory tracts is an important part of our pain defence system, especially for the inhibition of musculoskeletal pain (19). The origin of these tracts is in the periaqueductal grey in the mesencephalon and the raphe magnus nucleus in the medulla. The end station is dorsal horn neurons. The degree of activity in the descending inhibitory tracts depends both on nociceptive input from the periphery and influences from the cortex and hypothalamus. One way of testing the descending inhibitory system is to test...
diffuse noxious inhibitory control (DNIC). Kosek & Hansson (20) have used the DNIC test in patients with FM. A blood pressure cuff was placed around the left upper arm and inflated to 200 mmHg. The test subject then performed submaximal muscle contractions by the wrist extensors. The ischaemic pain was the heterotopic noxious conditioning stimulus. Quantitative sensory testing was performed in the right thigh. In the controls the pressure pain threshold increased. No increase was seen in patients with FM. This indicates a disturbance in the function of the descending inhibitory tracts.

Kosek et al. (21) have also studied pressure pain thresholds during isometric muscle contractions. In healthy controls, the thresholds increased in the contracting muscles. In FM patients, the thresholds decreased.

Central sensitisation

Besides depression of tonic inhibition, a central sensitisation due to activation of N-methyl-D-aspartic acid (NMDA) receptors on nociceptive neurons in the dorsal horn may be a pathogenetic factor for the generalised allodynia/hyperalgesia in FM. This statement is based on results from pharmacological pain analyses, determination of degree of temporal summation, and response to experimentally induced muscle pain.

Pharmacological pain analysis refers to the effect on pain of infusion of placebo, morphine, lidocaine or ketamine. Pain is estimated by a visual analogue scale (VAS). The test subject is considered responsive if the pain is reduced by 50% or more. With respect to activation of NMDA receptors, the response to ketamine, which is a non-competitive NMDA-receptor antagonist, is particularly of interest. In our studies, a total of 58 patients with FM were tested. Thirty-three (57%) were ketamine responders (22, 23, 24), experiencing decreased resting pain.

In collaboration with the Institute for Sensory-Motor Interaction at Aalborg University, Denmark, we performed studies in patients with FM where intramuscular pain was induced by infusion of hypertonic saline (25). The infusion was computerised to keep the amount of saline infused and the rate of infusion constant. The test subject recorded the experimental pain intensity continuously on an electronic VAS scale. The test muscle was the anterior tibialis muscle where neither the patients nor the healthy controls had ongoing pain. Pain intensity, pain duration and area of referred pain were recorded. Pain duration was longer and the area of referred pain was larger in patients compared with controls. The degree of temporal summation of electrical stimuli of the same intensity was tested. The summation pain threshold was defined as the stimulus intensity causing the 5th stimulus in a train of stimuli (2Hz) to be painful. In the controls the summation pain threshold was 89% of the threshold for a single stimulus. In patients with FM, the corresponding figure was 72%. Staud et al. (26) found that temporal summation was greater in patients with FM than in controls. They used repetitive thermal stimulation to induce temporal summation, which is equivalent to the ‘wind up’ phenomenon. Temporal summation, which is not the same as central sensitisation but may initiate it, is caused by activation of NMDA receptors.

In one study we tested the effect of placebo and ketamine on the pain induced by intramuscular infusion of hypertonic saline (24). The test subjects were patients with FM who had previously been labelled as ketamine responders. In comparison with the placebo, ketamine reduced pain intensity, allodynia and the area of referred pain.

From the above studies it can be concluded that central sensitisation of nociceptive neurons due to activation of NMDA receptors, probably on WDR neurons in the dorsal horn, is part of the pathophysiology of allodynia/hyperalgesia in a majority of patients with FM.

Musculoskeletal pain generators (for overview, see 27)

Localised musculoskeletal pain often precedes the multifocal pain in FM. It is possible that muscle pain of different origins initiates neuroplastic changes in nociceptive neurons in the CNS. It is also possible that minor pathological changes in muscles can maintain pain when generalised allodynia is established. The pain-provoking factors in the muscle may not be the same at all pain sites, and at the same site the cause of pain may differ from one time to another. In patients with FM the tissue oxygen pressure, measured with an oxygen electrode directly on the muscle surface of the trapezius muscle, showed changes that indicated a disturbed regulation of intramuscular microcirculation (28). In another study it has been shown that in a subgroup of patients with FM there was insufficient relaxation between contractions, which means that there could also be hypoxia during dynamic muscle work (29). Hypoxia may sensitize intramuscular nociceptors.

A reduced amount of energy-rich phosphates has been found in the muscles of patients with FM (30, 31).

In a study of 10 patients with FM, pain and allodynia were recorded during lumbar epidural blockade by lidocaine (32). Pain and allodynia vanished completely in the lower extremities during the blockade, indicating that the prerequisite for pain in these particular patients, at least, was ongoing impulse traffic in primary afferent nociceptive and or non-nociceptive neurons. In patients with FM where allodynia/hyperalgesia has already been established, it is possible that activity in afferent nerves during normal muscle contractions or tension could be enough to elicit pain.

WHAT CAN CAUSE OR INCREASE THE DEGREE OF ALLODYNIA/HYPERALGESIA?

All the above-mentioned studies taken together not only indicate, but also confirm, that there is a long-standing or permanent hypersensitivity in FM to pain that has a biological cause. How-
ever, it is possible that several different factors contribute to the development of generalised allodynia/hyperalgesia. These factors will be discussed below.

**Long-standing musculoskeletal localised pain**

In one of our studies (33), 87% of the patients with FM reported initial localised pain. For example, 55% had low back pain before they developed widespread pain. In another study (34), comprising 191 patients with FM, more than 80% reported that localised pain had gradually developed into widespread pain. Lapossy and co-workers (35) found that 25% of women with chronic low back pain developed FM. Around 20% of patients with inflammatory joint diseases also fulfil the criteria for FM (11). All these studies were retrospective. In a prospective study Buskila and co-workers (36) followed 102 persons who had been subjected to a neck injury. They found that no less than 21% met criteria for FM three months after the trauma. In a follow-up study three years later, 50% of the patients who contracted FM after injury still had FM (37). All the patients were still employed.

In summary, it can be stated that patients with long-standing localised musculoskeletal pain, be it myofascial pain, osteoarthritis, painful inflammatory joint disease or pain due to malignancy, risk developing generalised allodynia and widespread pain. Genetic factors, stress-related factors and female gender may increase the vulnerability for acquiring generalised allodynia/hyperalgesia.

**Female sex and oestrogen**

The majority of patients with FM are women. The cause or causes of the predominance of women is not fully known. Factors that have been discussed as possibly contributing to more muscle pain in women than in men are lower muscle strength and greater exposure to static muscle work. Moreover, women have lower pain thresholds than men (38). Animal experiments have shown that there are oestrogen receptors in enkephalinergic neurons in the spinal cord (39). Oestrogen is one factor that regulates pain sensitivity. Low oestrogen levels could be a factor that contributes to allodynia/hyperalgesia.

**Stress**

In the literature, several articles examine neuroendocrinological aberrations in FM. These aberrations are similar to those observed in chronic stress (40, 41). The changes are not found in all patients with FM and are not, as a rule, pronounced (41). A disturbance in serotonin metabolism has been described (42, 43). The clinical impression is that pain and allodynia can be exacerbated by a temporary increase in stress.

**Disturbed sleep**

Sleep in patients with FM is non-restorative (40). Patients rarely feel refreshed when they wake up in the morning. Deep sleep is affected (40). Disturbed deep sleep can cause low levels of growth hormone, which has been found in FM (44).

**Immunological changes**

Chronic stress and disturbed sleep can affect the function of the immune system (41). Recently the importance of the release of proinflammatory cytokines both in peripheral tissues and in the CNS has been discussed as a factor that can cause or contribute to allodynia/hyperalgesia (45, 46). Wallace et al. (47) found increased levels in serum of IL-6 and IL-8 in patients with FM. Zachrisson et al. (48) found that a treatment program aiming at immune stimulation in patients, who met criteria for both FM and Chronic Fatigue Syndrome, gave reduced fatigue and better sleep. The treatment consisted of repeated injections of staphylococcus toxoid.

**Autonomic nervous system**

Symptoms indicating dysautonomia are reported by patients with FM. Studies show that sympathetic hyperactivity and hypo-reactivity in response to stress are found in patients with FM (49).

**Glial activation**

Not only activation of neurons but also activation of microglia and astrocytes may lead to allodynia/hyperalgesia. Watkins et al. (50) presented results from animal experiments that support this statement. Whether these results have any bearing on pain conditions like FM is presently not known.

**Psycho-social factors**

FM is not a psychiatric disease, but psychological distress and depressive symptoms are common. These symptoms are most likely secondary to continuous pain, stress, fatigue and sleep disturbances. Henriksson & Liedberg (51) have studied the factors that are of importance for work disability in women with FM. The study comprised 176 patients with FM, half of whom were employed. Fifteen percent worked full time. In the non-working group 47% considered FM as the main cause for not being able to work.

**CONCLUSION**

For the majority of patients the development of FM is preceded by localised long-standing muscle pain that gradually spreads to
multiple sites and becomes continuous. Segmental allodynia becomes generalised. It is then that the diagnosis of FM can be made. There is strong support for the notion that generalised allodynia/hyperalgesia in FM is due to a possibly permanently disturbed function in the nociceptive system, especially in the CNS. Consequently FM is a disease. The many symptoms besides pain in FM are probably due to changes that are secondary to chronic pain.

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