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Review

Clinical and scientific understanding of fibromyalgia

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Abstract: Fibromyalgia is a common chronic pain condition with worldwide prevalence of 2-4%. It is characterised by chronic widespread musculoskeletal pain, fatigue, sleeping disturbances and cognitive dysfunction. It remains a contested illness with some physicians who consider it as a functional somatic disease rather than a "real" specific disease. The ACR diagnostic criteria have provided a powerful endorsement for clinicians and patients who suffer from above symptoms. Fibromyalgia is thought to be a central sensitization syndrome caused by alternated nociceptive processing in the central nervous system. Emerging evidence has suggested that alternative mechanisms such as systemic or neuroinflammation may be important in subgroup of patients. This review will give an overview of pathophysiology and therapies for fibromyalgia.

Keywords: Fibromyalgia, Pain, Mechanism

Fibromyalgia is "new " name for an old condition, characterised by chronic widespread pain, fatigue, sleeping disturbance and cognitive dysfunction [1]. It is often associated with somatic functional diseases such as headache, temporomandibular joint disorder, irritable bowel syndrome, interstitial cystitis (painful bladder syndrome) and dysmenorrhoea. Patients with fibromyalgia frequently report many psychological symptoms such as anxiety and depression. Patients usually present with a cluster of somatic, psychological and cognitive symptoms [2]. The severity and anatomical location of pain often varies from day to day. Due to the lack of specific diagnostic tests and limited awareness of physicians, diagnosis of fibromyalgia is often missed or delayed [3].

Definition and diagnostic criteria

Fibrositis or generalised fibrositis was used as the diagnostic label for the most part of last century [1]. Since the publishing of American College of Rheumatology (ACR) 1990 classification criteria, fibromyalgia as a diagnosis has been widely accepted and used by clinicians and researchers. It was based on consensus of a group of rheumatologists in ACR who have expertise in fibromyalgia. The cardinal symptom is chronic widespread pain for over 3 months and the essential signs are 11 out of 18 tender points, which are identified on palpation with a force of approximately 4 kg at the axial skeleton and muscular tendons [2]. The ACR 2010 diagnostic criteria exclude the tender point examination. It is made by scoring patient-report symptoms in two categories: wide pain index (WPI) and symptom severity (SS). WPI score is correlated with the number of painful body parts (total scores 0-19). Symptom severity range from no problem to severe symptoms (0-3) in 4 domains: fatigue, unrefreshing sleep, cognitive and somatic symptoms. The total score in SS scale is 0-12. The definition of fibromyalgia is WPI $\geq$ 7 and SS $\geq$ 5 or WPI 3-6 and SS $\geq$ 9 [3]. Therefore, fibromyalgia and chronic widespread pain could be considered as the continuum of chronic pain syndromes with fibromyalgia as a diagnostic label for patients who have concomitant psychological and somatic symptoms.

Pathophysiology

Fibromyalgia can be broadly divided into primary and secondary, the latter having an identifiable ongoing nociceptive input such as rheumatoid arthritis or osteoarthrosis [2]. For example, 14% patients with rheumatoid arthritis suffer from generalised pain, which meets the diagnostic criteria of fibromyalgia [4]. Primary fibromyalgia is independent from periph-

eral nociceptive input. Thus, primary and secondary fibromyalgia might have distinct underlying mechanisms. This review uses fibromyalgia to represent primary fibromyalgia, unless stated otherwise.

Various viral and bacterial infection are linked to fibromyalgia. Infection with Epstein-Barr, parvovirus, Borrelia (Lyme disease) and Campylobacter has been found associated with fibromyalgia temporally [2, 5]. The prevalence of fibromyalgia is significantly higher in patients with hepatitis C or HIV infection [6, 7]. Recent studies suggest that viral or bacterial infection regulate pain process through neuronal and non-neuronal mechanism by activating specific receptors and producing pro-inflammatory cytokines [8].

Neuroinflammation occurs in the peripheral (PNS) and central nervous system (CNS) in response to viral and bacterial infection [8]. Approximately a quarter of fibromyalgia patients have an identifiable history of infection or trauma [5]. Bacterial infection could directly and indirectly regulate primary sensory neurons through the activation of toll-like receptors expressed on neurons and glial cells [8]. Activation of non-neuronal cells such as macrophages or Schwann cells in the PNS and glial cells including astrocytes and microglia in the CNS produce various pro-inflammatory mediators. Evidence of systemic inflammation and neuroinflammation has been found in patients with fibromyalgia [8, 9, 10]. For example, the level of interleukin (IL)-8 is raised in plasma and cerebrospinal fluid (CSF) in fibromyalgia patients [11, 12, 13]. Bäckryd and colleagues also found raised CSF chemokine called fractalkine, which is released by microglia [13]. The growing appreciation of role of glial cells in the development and maintenance of neuropathic, inflammatory and postoperative pain [9]. It remains to be investigated whether glial cells activation is an underlying cause of fibromyalgia. Subtypes of fibromyalgia such as inflammatory fibromyalgia have been proposed to reflect a distinct pathogenesis of systemic and neuroinflammation [10, 14].

Fibromyalgia shows significant familial aggregation. Studies on genetic predisposition have revealed a possible link between specific genetic polymorphisms and the development of fibromyalgia. For example, polymorphisms in the serotonergic, dopaminergic and catecholaminergic pathways convey the genetic susceptibility [15, 16] and additional candidate genes continue to emerge. The association and linkage studies have expanded our knowledge of genetic basis of fibromyalgia. Further studies are required to evaluate these findings.

Sleep disturbance including insomnia, nocturnal restlessness, frequent awakenings and unrefreshed sleep occurs in 90% patients with fibromyalgia [17]. It is commonly thought to be the result of severe pain. Increasing evidence suggests a causative relationship between poor sleep and chronic pain. Sleep deprivation impairs descending pain inhibitory pathway. Epidemiological study has showed that insomnia is a risk factor of developing chronic widespread pain in otherwise healthy adult population. It remains unclear how sleep disturbance contributes the development of fibromyalgia. Trauma, either physical such as whiplash or psychological such as childhood adversities, serves as a stressor [2, 18]. Certain personality traits including catastrophizing also predispose patients to fibromyalgia. It is a general notion that fibromyalgia is caused by a combination of genetic susceptibility and environment exposure such as infection or psychological stress [2].

Medication therapies

The social and economic burdens for these patients are high, rivalling other major healthcare condition [19]. Pain relief is one of the main reasons why people with fibromyalgia seek medical care. Three drugs have been proved by FDA to treat pain in fibromyalgia: pregabalin, duloxetine and milnacipran [18]. Pregabalin, an anti-epileptic medication, binds to the α2δ subunit of voltage-gated presynaptic calcium channels. Duloxetine and milnacipran selectively inhibit reuptake of serotonin and noradrenaline. To date, milnacipran is not licenced in the UK market. A recent Cochrane review has shown that pregabalin at a dose of 300 to 600 mg produces significant pain reduction in fibromyalgia patients with moderate to severe pain, with an efficacy similar to that of duloxetine [20]. Low dose amitriptyline at 10-50 mg is often prescribed to fibromyalgia patients, particular those with sleep disturbance. Amitriptyline is found to reduce pain and fatigue, and to improve quality of life [21]. Nevertheless, fewer

than half of patients report significant improvement in pain with current medications and intolerable adverse effects are remarkably common. Therefore, most patients will discontinue therapy because of the lack of efficacy or intolerable side effects [19].

Treatment guidelines

Several international evidence -based guidelines in treating fibromyalgia are available [22]. This includes the American guideline published by American Pain Society (APS) in 2005, German guideline published by the Association of the Scientific medical Societies (AWMF) in 2012, Canadian guideline published by Canadian Pain Society (CPS) in 2013 and recently updated European guideline published by European League Against Rheumatism (EULAR) in 2016. Increasing evidence shows that combining patient education with exercise and cognitive behaviour therapy (CBT) provides long-lasting improvement in pain control, functionality and quality of life [18, 23]. Therefore, optimal treatment requires a multi-disciplinary approach with a combination of pharmacological and non-pharmacological options.

Key points

Cardinal symptoms of fibromyalgia are chronic widespread pain, fatigue, sleep disturbance and cognitive dysfunction.

Fibromyalgia has a worldwide prevalence of 2-4%.

ACR 2010 diagnostic criteria are based on patient-reported symptoms after excluding other possible diagnosis. The presence of tender points is no longer required.

Several risk factors including genetic polymorphisms, sleep disturbance, psychological stress and somatic disorders (secondary fibromyalgia) have been identified.

Fibromyalgia is thought to be caused by central sensitization with enhanced ascending pain pathway and reduced descending inhibitory pathway. Emerging evidence suggests systemic and neuroinflammation might play an important role in pathogenesis.

Treatment involves pharmacological and non-pharmacological therapies.

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