Smyrna Tıp Dergisi *Derleme*

The clinical approach to the polymyalgia rheumatica
Polimiyalji romatika'ya Klinik Yaklaşım

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Abstract
Polymyalgia rheumatica is a kind of rheumatic disease that causes pain and stiffness in the muscles and joints. It mainly affects the elderly and is seldom diagnosed in patients <50 years of age. In this article; it was tried to give out information about polymyalgia rheumatica
Keywords: Polymyalgia rheumatica, rheumatic disease, clinical approach

Özet
Polimiyalji romatika eklem ve kaslarda ağrı ve tutukluk yapan bir çeşit romatizmal hastalıktır. Özellikle yaşlıları etkiler, 50 yaşın altında nadir görülür. Bu makalede, polimiyalji romatika hakkında bilgi verilmeye çalışılmıştır.
Anahtar kelimeler: Polimiyalji romatika, romatizmal hastalık

Kabul Tarihi: 08.01.2013

Introduction

Polymyalgia rheumatica (PMR) is one of the most common inflammatory rheumatic diseases of the elderly and is characterized clinically by aching and morning stiffness in the shoulders, hip girdle and neck (1). It is characterized by proximal myalgia of the hip and shoulder girdles with accompanying morning stiffness that lasts for more than one hour.

Epidemiology

The prevalence of PMR is approximately 16,8 to 53,7 per 100,000 of the population over 50 years of age (2). The reported annual incidence in Europe and the United States of America varies between 1,3 and 11,3 per 10000 individuals aged over 50 years (3). In Europe, the frequency of decreases from north to south, with a high incidence in Scandinavia and low incidences in Mediterranean countries (1). Its incidence among people over 50 is in the range of 0,1-0,5%. The incidence rate peaks in the age group of 60-70 years. It is also found in younger people, but far less frequently (4). Women are twice as likely to get PMR as men.

Etiology and pathogenesis

The etiology of the disease has not been until now clarified exactly. PMR is characterized by a hyperproduction of interleukin-6 (IL-6) and the role of other circulating cytokines in their pathogenesis remains unclear (5). Increased IL-6 in the serum has been observed in PMR patients, suggesting an inflammatory role for IL-6. IL-6 promoter polymorphisms have been suggested to affect the clinical expression of PMR (6). PMR is a multigenic disease. An autoimmune process mayhap play a role in PMR development and is associated with the HLA-DR4 haplotype (7). Genetic causes and polymorphisms of additional genes involved in the initiation and regulation of inflammatory reaction have been considered to be possible susceptibility factors for PMR. In particular, TNF-α and IL-1 receptor antagonist gene polymorphisms are predisposing factors and may be implicated in the pathogenesis of PMR (26). The pathological findings in PMR patients are, a mild synovitis characterized by macrophages and CD4+ T lymphocytes has been described in synovial membranes from involved joints (1).

Clinical Manifestations

Symptoms and signs of PMR is characterized by the onset of aching and morning stiffness related to synovitis of proximal joints and inflammation of extra-articular synovial structures in the shoulders, torso, neck and hip girdles in patients and are usually symmetric. Symptoms tend to come on quickly, over a few days or weeks, and sometimes even overnight. The onset of the illness can be sudden. The onset of polymyalgia rheumatica is usually rapid but may be insidious. However, symptoms may have been present

for weeks or months before the diagnosis is made (8). The aching and morning stiffness in the neck persists for at least 2 weeks. Shoulder pain and stiffness are the most common symptoms of PMR. Stiffness after periods of rest is typical. Approximately half of patients show with symptoms of distal musculoskeletal manifestations, such as carpal tunnel syndrome and nonerosive, asymmetrical peripheral arthritis (9). Palpable synovitis seems to may in more peripheral joints, such as the knees, wrists, and metacarpophalangeal joints and is usually mild and nonerosive (10). Low-grade fever, fatigue, anorexia, weight loss, and depression occur in in about 40% of patients, indicating systemic inflammation (11).

Laboratory findings and imaging

The characteristic laboratory finding in PMR is an erythrocyte sedimentation rate (ESR) and C- reactive protein (CRP) concentration are highly elevated but are normal in some patients. The ESR value most often used to define this elevation is 40 mm per hour (12), and some patients have values that may exceed 100 mm per hour (13). Nonetheless, some reports, a sizable proportion of patients with PMR, from 7% - 22% had an ESR that was either normal or slightly increased (14). Other laboratory findings (15) include anemia, elevated alkaline phosphatase and gammaglutamyl transpeptidase, thrombocytosis, elevation of creatine kinase and aldolase, and antinuclear antibodies , rheumatoid factor are negative (12). Magnetic resonance imaging (MRI), ultrasonography (US), fluorodeoxyglucose–positron emission tomography, scintigraphy have all been used to detect synovitis in proximal joints and periarticular studies (16). US studies shows shoulder or hip effusions in approximately 68% of patients with PMR (17).

Diagnosis of PMR

The disease first described by Bruce as "senile rheumatic gout" and known since 1957 as PMR. The name has changed several times over the years (18) (Rhizomelic pseudoarthrosis, humeroscapular periarthrosis, and anarthritic rheumatoid syndrome, etc.). The diagnosis of PMR is based primarily on clinical features, elevated acute phase reactants provide secondary support for the diagnosis, and exclusion of other causes. There have been a large number of initiatives to construct diagnostic criteria for PMR. The most commonly cited criteria sets are presented in Table 1 (12,19,20,21). The first evaluation of criteria for PMR was suggested by Bird in 1979 (19). In 1982, Chuang and colleagues (22) defined new clinical criteria and have changed the age of onset to 50 years. Two years later, Healey added the evaluation of the rapidity of response to prednisone to Chuang's criteria, as previously established by Jones and Hazleman (23).

Table 1. *Diagnostic Criteria for Polymyalgia Rheumatic*

Bird et al.	Morning stiffness >1 hr Bilateral shoulder pain and/or stiffness Age ≥65 year Depression and/or weight loss Time from onset to maximal symptoms <2 week ESR >40 mm/hr	3 or more of the following, or at least 1 plus positive result of temporal artery biopsy
Healey	Bilateral upper arm tenderness Morning stiffness >1 hr Elevated ESR (≤40 mm/hr) >1 mo of neck, shoulder, or pelvic girdle pain (any two areas) Exclusion of other diagnoses	All criteria should be met
Jones and Hazleman	Rapid response to daily prednisolone ≤20 mg Morning stiffness >1 hr Shoulder and pelvic girdle pain ESR >30 mm/hr or CRP >6 mg/L No rheumatoid or inflammatory arthritis or malignant neoplasm; no objective signs of muscle disease	All criteria should be met
Chuang et al.	Prompt and dramatic response to systemic corticosteroids >1 mo bilateral aching and stiffness of at least two of the following areas ESR >40 mm/hr Age ≥50 Exclusion of other causes	All criteria should be met

Differential Diagnosis of PMR

It is important to rule out conditions that can present with features similar to those of PMR. See table 2 for examples of disorders that can cause similar symptoms (1,24).

Table 2. *Examples of diseases that can cause similar symptoms to PMR*

Differential Diagnosis	Examples of diseases
Rheumatic diseases	Remitting seronegative symmetric synovitis with pitting oedema (RS3PE syndrome)
Infection	Late onset Rheumatoid arthritis, often seronegative for rheumatoid factor
Degenerative disorders	(common)
Giant cell arteritis	Late onset spondyloarthopathy
Muscle diseases	Spondyloarthritis
Malignancy	Polymyositis/dermatomyositis
Chronic pain syndrome	Systemic lupus erythematosus
Neurological disorders	Pseudogout
	Fibromiyalgia
	Other connective tissue disorders
	Viral or bacterial illness
	Chronic osteomyelitis
	Tuberculosis
	Infective endocarditis
	Cervical and lumbar spondylosis
	Bilateral adhesive capsulitis
	Rotator cuff syndrome
	Osteoarthritis
	Osteoporosis
	Drug induced
	Muscular dystrophy
	Multiple myeloma
	Leukaemia
	Lymphoma
	Lung carcinoma
	Other occult carcinomas
	Parkinson's disease
	Myasthenic syndromes

Many features of PMR may cause to diagnostic fault. Any one of three patients with PMR have systemic symptoms such as fever, anorexia and weight loss. A considerable number of patients may have additional musculoskeletal manifestations (25). The differential diagnosis of PMR includes multiple rheumatologic and nonrheumatologic disorders. PMR and some forms of rheumatoid arthritis (RA) are difficult to distinguish (26). It is well known that a usually seronegative subset of elderly onset RA mayhap show a PMR-like onset with prevalent involvement of the girdles, high ESR values and good response to low dose steroid treatment (27). Swelling of the metacarpophalangeal joints, ankles and elbows and loss of passive range of motion of the wrists, glenohumeral joints and hips, point to RA rather than PMR. Any evidence of erosive arthropathy suggests an alternative diagnosis than PMR (28)**.**

Giant cell arteritis (GCA) is an inflammatory disease of blood vessels, most commonly involving large and medium arteries, and the etiology of disease is unknown (29). PMR and GCA are closely related inflammatory conditions that affect different cellular targets in genetically predisposed persons. The two disorders may represent different manifestations of a shared disease process. These overlapping pathologies often ocur together and are defined by similar and often vague nonspecific symptoms, elevated acute-phase reactants and a predictable response to corticosteroids. Clinical manifestations may vary from the classic constellation of temporal headache in the elderly accompanied by constitutional signs, jaw claudication and visual symptoms; therefore, a high index of clinical suspicion may be necessary to identify the disorder (30).

The American College of Rheumatology has developed diagnostic criteria for giant cell arteritis; including, patient age of 50 years or older, ESR of 50 mm per hour or greater, new onset of localized headache, temporal artery tenderness or decreased temporal artery pulse, abnormal temporal artery biopsy (31). The diagnosis requires the presence of at least three criteria. Complications are much less likely to occur if treatment is started soon after symptoms begin. Possible complications include blindness in one or both eyes and other serious complications sometimes develop if the inflammation occurs in other arteries; for example, an aneurysm, a stroke, damage to nerves, or deafness (32).

Remitting seronegative symmetric synovitis with pitting oedema (RS3PE syndrome) syndrome is similar to PMR in that it shows arthralgia attributable to tenosynovitis and muscle pain, occurring most commonly in the elderly and shows a good response to corticosteroid treatment (33). The etiology of RS3PE syndrome is stil unknown and some patients have a paraneoplastic disorder that is associated with solid tumors and hematologic disorders (34). RS3PE syndrome occurred especially in men older than 60, and the onset of the disease was sudden and characterized by a symmetrical polyarthritis associated with pitting edema of the extremities of the upper and lower limbs. The following diagnostic criteria include the following; over 50 years of age, sudden onset of polyarthritis, bilateral pitting edema of both hands, and seronegative rheumatoid factor (35). The symptoms and signs of the RS3PE syndrome may be mistaken for those of PMR. Symptoms are usually more prominent distally, unlike PMR.

Treatment of PMR

Treatment with glucocorticoids is the preferred therapy for PMR (1). Once the diagnosis has been made, PMR is an indication for long-term oral glucocorticoid therapy. For more patients, the starting dose of prednisone should be 15–20 mg per day in a single morning dose with food for 3 weeks, tapering to 12.5 mg for 3 weeks, 10 mg for 4-6 weeks, followed by a reduction by 1 mg (4-8 weeks) or else alternate day reductions (36). Usually, patients experience almost complete resolution of symptoms within 2 to 3 days, but clinical responses to lower prednisone doses can be delayed. Monitoring ESR and CRP helps to assess the inflammatory burden. Especially, muscle aches and fatique are used as the main indicators for goals of treatment. Patients with PMR may experience increased bone turnover, even before corticosteroid therapy. As osteoporosis is the second major complication during glucocorticoid treatment, the American College of Rheumatology 2010 recommendations underlined that calcium and a vitamin D supplement (at a dosage of 800–1000 IU day) should be administered in all patients beginning glucocorticoid therapy (37). It has been estimated that steroid-related side effects occur in 65% of patients, and they have been associated with the duration of treatment and the cumulative dose of steroids, and most frequently observed adverse event is type-2 diabetes (39). If there is not a contrendication, non-steroidal anti-inflammatory drugs (NSAIDs) mayhap ensure that supplemental pain relief. However, per a study of 232 patients with PMR by Gabriel and colleagues, NSAIDs are associated with considerable drug-related morbidity and thus should be used with caution (39).

Methotrexate has been investigated in randomized studies in newly diagnosed PMR. One study used methotrexate at 7.5 mg/week plus 20 mg/day of prednisone and found no benefit in outcomes after 2 years of follow-up (40). Another study used oral and intramuscular methotrexate at a higher dose of 10 mg/week added to the prednisone regimen versus prednisone regimen alone. Overall, the patients receiving methotrexate 10 mg/week plus prednisone experienced corticosteroid-sparing effects compared with patients receiving prednisone alone (41). Antitumor necrosis factor alpha agents have also been investigated as corticosteroid-sparing agents in PMR. A randomized study with infliximab revealed no benefit (42). The only randomized trial using azathioprine (150 mg/day) during the maintenance phase of PMR showed a high frequency of adverse drug effects, a high number of patient withdrawal from the study, although a lower cumulative dose of corticosteroid at 52 weeks. At this time, the small number of completers and the high number of giant cell arteritis patients in the study make the study results difficult to interpret (43).

Conclusion

PMR is common and is usually diagnosed and managed in primary care. PMR is relatively common in older people, and so is likely to become more common as the population ages. Diagnostic criteria of PMR are not universally defined. Despite the progress of imaging techniques, a careful clinical examination remains the gold standard for the diagnosis of PMR. It responds quickly to treatment.

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