

Polymyalgia Rheumatica - a Disease of the Elderly

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Polymyalgia rheumatica is a disease that occurs mostly in the elderly and is rarely seen in patients less than 50 years of age. Polymyalgia rheumatica is a vasculitis, which manifests itself as an inflammatory disease of the vascular wall that can affect any type of blood vessel, regardless of its size. It has been considered a form of giant cell arteritis, involving primarily large and medium arteries and to a lesser extent the arterioles. Clinical manifestations are caused by the generic pathogenic process and depend on the characteristics of the damaged organ. PMR is a senescence-related immune disorder. It has been defined as a stand-alone condition and a syndrome referred to as rheumatic polyarteritis with manifestations of giant cell arteritis (especially in cases of Horton's disease and temporal arteritis) which are commonly associated with polymyalgia. The clinical presentation is clearly dominated by the painful girdle syndrome, with a feeling of general discomfort. Polymyalgia and temporal arteritis may coexist or be consecutive to each other in the same patient, as in most of our patients. The present study describes 3 cases of polymyalgia rheumatica, admitted to the Clinic of Rheumatology of Sf. Apostol Andrei Hospital, Galati. The cases were compared with the literature. Two clinical aspects (polymyalgia rheumatica and/or Horton's disease) and the relationship between them were also considered. Polymyalgia rheumatica is currently thought to have a multifactorial etiology, in which the following factors play a role: genetic factors or hereditary predisposition (some individuals are more prone to this disease), immune factors and viral infections (triggers of the disease). Other risk factors of polymyalgia rheumatica include age over 50 years and the association with giant cell arteritis. The characteristic feature of the disease is girdle pain, with intense stiffness of at least one hour's duration. Markers of inflammation, erythrocyte sedimentation rate and C-reactive protein are almost always increased at the onset of the disease. Diseases that can mimic the clinical picture of polymyalgia rheumatica are neoplasia, infections, metabolic disorders of the bone and endocrine diseases.

Keywords: polymyalgia rheumatica, inflammation, arthralgia, myalgia

Polymyalgia rheumatica (PMR) is a heterogeneous disease, with a diverse clinical spectrum and a variable disease course. That is why, in 2012, PMR was newly defined by the European League Against Rheumatism and American College of Rheumatology [1].

Current research in polymyalgia rheumatica (PMR), either isolated or complicated with giant cell arteritis, is linked to data available on arteritis damage. Several genetic factors have a major etiopathogenic role, shown by the cases of familial PMR published to date. Histocompatibility antigens are present in both polymyalgia and Horton's disease. Some exogenous (viral, microbial, physical, etc.) factors may also be involved in the etiology [2].

After rheumatoid arthritis (RA), PMR is the second most common chronic inflammatory disorder, with an incidence of 2.43% in women and 1.66% in men. PMR occurs in 50% of patients with giant cell arteritis, whereas 15% of the latter will develop PMR. The two diseases may occur simultaneously or within a longer period of time (for example, some patients may develop giant cell arteritis after the musculoskeletal symptoms of PMR disappear) or at the peak of the inflammatory process [3].

PMR affects predominantly medium and large-sized blood vessels. PMR occurs mostly in the elderly and it may be complicated by neurological, systemic and ophthalmic disorders. Visual loss is one of the most important comorbidities in giant cell arteritis and it may occur in 60%

of patients. The disease can also cause headache, masseter claudication and mandibular pain. These symptoms are caused by the fact that the inflammation dramatically reduces the lumen size, interfering with normal tissue oxygenation resulting from poor blood flow through the blood vessels. Inflammation may also involve the aortic arch and its branches, and in some cases even the venous system [4].

Given the frequency with which PMR is associated with giant cell arteritis, evidence was provided that the pathogenesis of the disease shares a common mechanism with Horton's disease.

The main characteristic of PMR pain is that its highest intensity is in the morning (morning stiffness) or after prolonged rest. It is relieved throughout the day by progressive joint mobilization. Muscle and joint damage can be symmetrical and bilateral, but it may also act asymmetrically, being more severe on one side than the other [5].

According to the literature, disturbances of humoral and cellular immunity are also found in PMR patients. However, it is not yet fully understood which is the main trigger of the disease. It was suggested that circulating immune complexes or autoantibodies may have a pathogenic role. Triggering immune phenomena may occur during the aging process, such as the presence of autoantibodies acting against a component of the arterial wall, which becomes

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antigenic after the loss of T lymphocyte tolerance or viral aggression [6-8].

As people become more susceptible to PMR with senescence, special attention is paid to the immune changes driven by the aging process, which may confirm possible correlations with the pathogenesis of the disease. PMR patients exhibit mostly symptoms of peri-articular, not intra-articular inflammation, in the form of bursitis, synovitis and vasculitis.

PMR onset and evolution, alone or in association with *temporal arteritis* [9], have been thoroughly researched. Clinically, giant cell arteritis is predominantly characterized by vascular damage, which is generally seen in the cephalic region (temporal arteritis). PMR symptoms include the algic syndrome and other systemic manifestations, such as fever and sweating. Prolonged high fever occurs mostly in patients with PMR associated with giant cell arteritis.

Histopathological findings are similar to those found in giant cell arteritis, where mononuclear infiltrates with giant cells and changes in the inner elastic membrane occur. The arterial vascularisation of upper and lower limbs is particularly affected in PMR patients. Large and medium arteries are mostly involved [10].

Clinical manifestations derive from lowering blood flow to a certain level. *Myalgias* are present and they are more intense in the morning and diminishing throughout the day. There is also a decrease in muscle strength and the patient cannot lift his arms or stand up from bed. These clinical manifestations also occur in polymyositis. General clinical signs of inflammatory disease include inappetence, asthenia, weight loss, low-grade fever. Functional disorders of the liver occur frequently in PMR, mostly in the form of anicteric intrahepatic cholestasis [11,12].

In PMR patients, laboratory investigations show the presence of inflammatory process, characterized by increased acute phase reactants (especially erythrocyte sedimentation rate and *C-reactive protein*) [13] or increased gamma globulins, and some changes in humoral or cellular immunity (particularly qualitative changes of T lymphocytes) and other changes in haematological and serum parameters. Diagnosis is based on the histopathological features [14, 15].

Radiological, scintigraphic or arthroscopic exams can help identify articular changes. Ophthalmologic examination may reveal early signs of temporal arteritis, ocular manifestations of PMR and possible complications of *cortisone therapy*. Angiographic studies and temporal artery biopsies are also used [16-18].

Differential diagnosis involves collagenosis, infective endocarditis, neoplasia with bone metastasis and paraneoplastic syndromes. A special case is rheumatoid arthritis, which has various forms in elderly patients.

Early treatment with corticosteroids significantly ameliorates the symptoms and prevents ophthalmic complications. Cortisone treatment should involve loading doses fitted to the various clinical forms, followed by maintenance doses with dose tapering that can prevent the risk of side effects, especially eye-related adverse reactions. Glucocorticoids in the form of prednisolone (≤ 20 mg) should be administered only after the suspicion of other diseases was eliminated [19].

Nonsteroidal anti-inflammatory drugs may be administered in patients with PMR, idiopathic or associated with Horton's disease, if cortisone therapy with prednisone or methylprednisolone has been discontinued. Moreover, immunosuppressants and plasmapheresis are recommended in patients with absolute contraindications to cortisone [20-22].

Physical therapy should involve an individualized exercise program adapted for older people, which can maintain the mass and function of muscles and reduce the risk of falling.

Experimental part

Material and methods

In the Clinic of Rheumatology of Sf. Apostol Andrei Hospital, Galati 3 PMR patients (2 female and 1 male) were diagnosed and followed between January 2010 and October 2017. The 2 female patients were aged 72, and 76, respectively and the male patient was aged 69. Diagnosis difficulties, laboratory results, therapeutic methods, drug prescriptions, patient- and physician-reported outcomes related to disease activity, physical function and pain were analyzed in order to achieve a better management of this disease.

Results and discussions

PMR occurs mostly in septuagenarians, but it remains a rare disease in Romania, being most common in Scandinavian countries [23,24]. This can be explained by the shorter life expectancy in Romania (almost 75 years), by a less common presence of HLA-DRB1*04 antigens in the Southern European population and also by false or ignored diagnoses which have delayed adequate therapy in our cases. PMR morbidity in Romania could be higher than the officially reported cases.

The onset of the disease, the presence of inflammation and the progress during treatment were followed in our PMR patients. Bilateral shoulder pain with sudden onset was reported by all our patients and it was accompanied by prolonged morning stiffness. The disease was characterized by arthralgia and moderate to severe myalgia, accompanied by muscle stiffness, neck and shoulder stiffness and poor hip mobility. Joint stiffness was more intense in the morning, on waking, or after long periods of inactivity, and it typically lasted for more than 30 minutes. Daily life activities triggered bilateral pain, mostly in the shoulders, in all patients.

The clinical presentation was clearly dominated by the painful girdle syndrome, with a feeling of general discomfort. Polymyalgia and temporal arteritis coexisted in 2 patients, both female, and were consecutive to each other in the male patient. In all patients, there was no visible joint swelling of the shoulder girdle on physical examination, but the active motion of shoulders, neck and hips was restricted by diffuse pain.

The 3 cases have shown the importance of immune processes, which are weaker than in other collagenoses. PMR is influenced by genetic factors (HLA-DRB1*04 antigen), immune factors (a cellular immune mechanism directed against an antigen in the elastic fiber of the vascular wall). It is generally acknowledged that PMR patients exhibit high levels of IL-1 and IL-6, activated macrophages and dendritic cells, infectious triggers (parvovirus B19, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*).

Constitutional symptoms, such as fatigability, inappetence, weight loss and low-grade fever, were found in all three patients. *The markers of inflammation*, high ESR and CRP values, were also present. The onset of algic symptomatology was acute or subacute. Arthralgia affected the scapular belt, bilaterally, and also the pelvic girdle. Myalgias were present in arms and in the cervical axial segment.

Ultrasonography, a useful diagnostic method in PMR, shows characteristic changes in shoulders and hips. Subdeltoid bursitis and bicipital tenosynovitis in the

scapulohumeral joint and glenohumeral synovitis were present in our study group. Synovitis and trochanteric bursitis in the coxofemoral joint were also detected by ultrasonography.

PMR is currently thought to have a multifactorial etiology, in which the following factors play a role: genetic factors or hereditary predisposition (some individuals are more prone to this disease) and as triggers of the disease, immune factors and viral infections. Other risk factors of PMR include age over 50 years and the association with giant cell arteritis. Environmental and genetic factors correlate with the susceptibility to disease and contribute to its severity. Family aggregation is related to the HLA-DR4 allele; inflammatory cytokines are responsible for the phenotypic independent variables of the disease.

Shoulder pain, both in joints and muscles, with bilateral involvement, is associated with intense stiffness and sensitivity in the arms. Pain and stiffness occurs in cervical muscles. Muscle strength is low. Over time, this can lead to muscle atrophy.

A mild form of synovitis may be present in the fist joint and in the joints of the hand and of the knee. Synovial fluid is moderately inflammatory.

Corticosteroid treatment was the treatment of choice in all cases. There was an improvement both in clinical symptoms and biological constants after about 4 weeks of treatment. Prednisolone (15 mg /day for 3 weeks) was administered to all our PMR patients. Afterwards, the dose was lowered to 12.5 mg /day for another 3 weeks and to 10 mg /day for 4 weeks, being gradually further reduced in the next months. There were no relapses and no glucocorticoid-induced complications. High doses and prolonged corticotherapy (for a year) were needed in 1 case (female) of associated cranial arteritis. When the treatment fails, more aggressive therapies may be tested. For instance, methotrexate, which is already used as an effective therapy in rheumatoid arthritis, may be used also in PMR patients. A combination of methotrexate with prednisone / methylprednisolone is beneficial for reducing the cortisone dose. Methotrexate significantly improves the signs and symptoms of inflammation. It was recently suggested that azathioprine combined with lower doses of cortisone may be efficient in the treatment of giant cell arteritis.

Long-term evolution was good in all three patients, even if the literature suggests that men have a better prognosis than women [19]. The prognosis of PMR is usually favorable, with a small risk of recurrence with giant cell arteritis and no PMR. PMR patients have an increased risk of cardiovascular and metabolic disease associated with long-term therapy. Recommended preventive measures include regular blood pressure and glucose measurements, bone mineral density tests and assessment of 25-dihydroxy vitamin D concentration, based on regional guidelines, quantiferon tests, with or without chest radiographs, cholesterol and triglyceride tests, age-appropriate immunization.

Conclusions

Due to the fact that PMR is associated with senescence, immune changes in the elderly could help us identify possible correlations with the pathogenesis of the disease. Clinically, giant cell arteritis is predominantly characterized by vascular damage, which is generally seen in the cephalic region (temporal arteritis). PMR symptoms are dominated by rhizomelic pain and other systemic manifestations, fever, sweating and weight loss. In all cases, corticotherapy was

the main treatment. If cranial arthritis occurs, higher prolonged doses are required.

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