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NOVOSTI U DIJAGNOSTICI I LIJEČENJU REUMATSKE POLIMIJALGIJE

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Reumatsku polimijalgiju (PMR) karakteriziraju bolovi, slabost i zakočenost mišića ramenog i zdjeličnog obruča. Pacijenti ne mogu podići ruke iznad glave i ne mogu ustati iz sjedećeg položaja bez pomoći ruku. Dijagnostičke metode kao što su ultrazvuk (UZV), magnetska rezonanca (MR) te 18F fluorodeoxyglukoza (FDG) PET/CT pokazali su da bolest zahvaća periartikularno vezivno tkivo, ponajviše burze i tetive. Patohistološki nalaz ovih mišića potpuno je uredan. PMR može prethoditi gigantocelularnom arteritisu (GCA) ili se javiti paralelno s njim. Žene obolijevaju tri puta češće, a bolest se gotovo uvijek javlja iznad pedesete godine života. Poslije reumatoidnog artritisa PMR je druga najčešća upalna reumatološka bolest. Cjeloživotna šansa za obolijevanje je oko 2%. Uzrok ove bolesti nije poznat. Zabilježena je povezanost s HLA-DR4 alelom. Jedan životinjski model sugerira da i PMR i GCA započinju aktivacijom dendritičnih stanica u stijenci velikih krvnih žila, što rezultira proizvodnjom interleukina 1 (IL-1) i IL-6, uzrokujući supresiju T-regulatornih stanica i povećan Th17 odgovor. Za razliku od GCA, pacijenti s PMR-om ne regrutiraju T stanice koje proizvode interferon-γ (IFN-γ). Bez IFN-γ koji bi stimulirao makrofage, ne razvija se arterijska upala karakteristična za GCA. Prisutnost IL6 u perifernoj krvi vjerojatno je odgovorna za sistemske manifestacije bolesti kao što su umor, subfebrilitet, bol, gubitak težine, depresija i slab apetit. Bolest se klinički prezentira naglim početkom. Slabost i bol mišića ramenog obruča prisutna je u 80-90% pacijenata, a bol u vratu i zdjeličnoj muskulaturi u njih 70%. Jutarnja zakočenost traje duže od 45 minuta. Dijagnoza PMR-a u osoba koji godinama razvijaju bolove ramenog i zdjeličnog obruča nije vjerojatna. Simptomi zahvaćanja distalnih zglobova javljaju se u pola pacijenata, i to u najviše u ručnim i metakarpofalangealnim (MCP) zglobovima, a u 10% pacijenata razvije se i bilateralni sindrom karpalnog tunela. Dvije trećine pacijenata imaju UZV-om dokazan bilateralni subakromijalni/subdeltoidni bursitis i to je jedno od glavnih obilježja PMR-a. Nešto rjeđe nađe se i izljev u sinovijalnoj ovojnici tetive duge bicepsa. Što se tiče zdjeličnog obruča, studije rađene s PET/CT-om našle su nakupljanje FDG-a u području sjednih kvrga, velikih trohantera, a MR je je pokazao interspinozni bursitis u području vratne i lumbalne kralježnice. Čak 99% pacijenata ima povišen C reaktivni protein (CRP), a 94% ima i povišenu sedimentaciju (SE). Tipično je odsustvo reumatoidnog faktora (RF) i anticitrulinskih (anti-CCP) antitijela. Brojne studije su zaključile da je normalan CRP iznimno rijedak i da je osjetljiviji od SE za praćenje uspjeha liječenja. U oko

trećine pacijenata PET/CT često pokazuje i upalu blažeg intenziteta u velikim arterijama, ali značajno manjeg intenziteta u odnosu na GCA. Najčešće su zahvaćene arterije subklavije, ali mogu biti zahvaćene i velike krvne žile vrata. Ta upala ne zahtijeva izmjenu terapije (npr. povećanje doze glukokortikoidne (GK) terapije ili korištenje IL-6 blokatora) jer ona ne dovodi do teških komplikacija GCA, poput sljepila ili moždanog udara. Ponekad osoba koja se u početku prezentira samo kao PMR razvije GCA te je uvijek potrebno tražiti znakove ove bolesti (bol vilice, smetnje vida, temporalnu glavobolju ili druge simptome). Ako se postavi sumnja na GCA, potrebna je daljnja obrada, odnosno UZV i biopsija temporalnih arterija, MR angiografija i PET/CT prema odluci liječnika. Na prisustvo GCA potrebno je uvijek posumnjati u slučajevima kada imamo remitirajući oblik bolesti, stalno povišene reaktante akutne upale, febrilitet i nedovoljnu učinkovitost male doze GK. Osim GCA, u tim slučajevima potrebno je isključiti i malignu bolest i infekciju. Što se tiče pacijenata s nekompliciranim tijekom PMR-a, osim standardne laboratorijske obrade i UZV-a nije potrebna daljnja dijagnostička obrada. Premda je bilo pretpostavki o povezanosti PMR-a i malignih bolesti, istraživanja to nisu potvrdila. Diferencijalno dijagnostički, PMR je najsličniji seronegativnom artritisu te se u oko 20% pacijenata dijagnoza PMR-a vremenom promijeni u seronegativni RA. U novije vrijeme PMR i GCA viđeni su tijeku liječenja inhibitorima kontrolnih točaka u terapiji malignih bolesti, kao i kod ipilimumaba u terapiji malignog melanoma. Mialgije i miozitisi mogu se javiti i kod terapije statinima, ali onda je povišena vrijednost kreatin kinaze u serumu. Kod hipotireoze također imamo artralgije, bolove i ukočenost mišića. Liječenje uključuje srednje ili male oralne doze GK, s tim da nije bilo studija koje bi pokazale je li učinkovitiji metilprednizolon ili prednizon. Uobičajena doza je 15 mg prednizona dnevno u jutarnjim satima. Kod blage prezentacije bolesti i kod pacijenata asteničke konstitucije može se započeti liječenje i sa 7,5 ili 10 mg dnevno, dok se kod pacijenata s većim BMI-jem i/ili težom prezentacijom bolesti može započeti i sa 20 mg dnevno. Najveća preporučena doza je 25 mg prednizona dnevno. Pacijentima s naglašenim noćnim bolovima i zakočenošću, doza GK bi se mogla podijeliti na jutarnju i večernju, premda ovakav pristup nije znanstveno utemeljen. Smanjenje doze GK treba početi dva do četiri tjedna nakon povlačenja simptoma. Uobičajeno, doza se smanjuje svaki mjesec za 2,5 mg za vrijednosti iznad 10 mg prednizona, a za 1 mg doze ispod 10 mg. Intramuskularne injekcije i aplikacije GK u ramena ispitivani su u randomiziranim studijama kao alternativa liječenju oralnim dnevnim dozama, ali takva liječenja nisu zaživjela u svakodnevnoj praksi. Nesteroidni protuupalni lijekovi nemaju učinka u ovoj bolesti. Fizikalna terapija bez medikamentne terapije nema nikakav učinak. Kod liječenja GK veliku važnost treba pridati evaluaciji komorbiditeta. Kod nereguliranog dijabetesa, značajne arterijske hipertenzije, zatajenja srca i teške osteoporoze koriste se niže doze GK i dodaje se metotreksat kao „GK sparing agent". Odnedavno, u ovim slučajevima, ili u situacijama kada nije moguće adekvatno kontrolirati bolest navedenom terapijom, odobreno je i korištenje blokatora IL-6 receptor sarilumaba. Premda se drugi inhibitor IL-6, tocilizumab, pokazao učinkovit za liječenje PMR-a, za sada nije odobreno liječenje u toj indikaciji. Za inhibitore

janus kinaze i rituksimab ne postoje velike randomizirane studije, dok su veće studije za anti-TNF pokazale da nema učinka u PMR-u. I naša grupa autora je opisala pacijenticu kojoj je dijagnosticiran ankilozantni spondilitis i teži oblik PMR-a, te je liječena adalimumabom i GK. Pacijentica je ušla u remisiju obje bolesti pa je svojevoljno ukinula GK, što je uzrokovalo relaps PMR-a, dok je AS bio i dalje u remisiji. Liječenje PMR-a obično traje godinu ili dvije, ali nije neobično da traje i tri do šest godina.

Ključne riječi

bol, rame, kuk, upala, onesposobljenost

WHAT IS OLD AND WHAT IS NEW IN THE DIAGNOSTICS AND TREATMENT OF POLYMYALGIA RHEUMATICA?

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Polymyalgia rheumatica (PMR) is characterized by the pain, weakness, and stiffness of the shoulder and pelvic girdle muscles. Patients are unable to raise their arms above their head and cannot rise from a sitting position without the help of their hands. Diagnostic methods such as ultrasound (US), magnetic resonance imaging (MRI), and 18F fluorodeoxyglucose (FDG) PET/CT have shown that the disease affects the periarticular connective tissue, mainly bursae and tendons. The pathohistological findings of these muscles are completely normal. PMR can precede or occur in parallel with giant cell arteritis (GCA). Women are affected three times more often and the disease almost always occurs in patients over the age of 50. After rheumatoid arthritis, PMR is the second most common inflammatory rheumatological disease. The lifetime risk of developing the disease is about 2%. The cause of this disease is unknown. The presence of IL6 in the peripheral blood is probably responsible for the systemic manifestations of the disease such as fatigue, low fever, pain, weight loss, depression, and poor appetite. The disease is clinically presented with a sudden onset. Weakness and pain in the muscles of the shoulder girdle is present in 80-90% of patients, and pain in the neck and pelvic muscles in 70% of them. Morning stiffness lasts longer than 45 minutes. Distal joint involvement occurs in half of patients, mosty in the wrist and metacarpophalangeal joints. Bilateral carpal tunnel syndrome develops in 10% of patients. Two-thirds of patients have US-proven bilateral subacromial/subdeltoid bursitis, which is one of the main features of PMR. Less commonly, effusion is found in the synovial sheath of the biceps longus tendon. Regarding the pelvic girdle, PET/CT studies have found FDG accumulation in the ischial tuberosity and greater trochanter, and MRI has shown interspinous bursitis in the cervical and lumbar spine. Almost 99% of patients have elevated C-reactive protein (CRP), and 94% have elevated erythrocyte sedimentation rate (ESR). The absence of rheumatoid factor (RF) and anti-citrullinated protein (anti-CCP) antibodies is typical. Numerous studies have concluded that normal CRP is extremely rare and is more sensitive than ESR for monitoring the success of treatment.

In about a third of patients, PET/CT often shows milder inflammation in large arteries, but significantly less intense than in GCA. The subclavian arteries are most commonly affected, but large blood vessels in the neck can also be affected. This inflammation does not require a change in therapy because it does not lead to serious complications of GCA (such as blindness, a stroke, etc.). Sometimes a person who initially presents only with PMR develops GCA, and therefore it is necessary to look for signs of this disease (jaw pain, visual disturbances, temporal headache, or other symptoms). If GCA is suspected, further workup is required, i.e., ultrasound and biopsy of the temporal arteries, MR angiography, and PET/CT at the discretion of the physician. The presence of GCA should always be suspected in cases where there is a remitting form of the disease, persistently elevated acute inflammatory reactants, fever and insufficient efficacy of low-dose GC. In addition to GCA, in these cases it is necessary to exclude malignant disease and infection. As for patients with an uncomplicated course of PMR, no further diagnostic work-up is required, except for the standard laboratory work-up. Although there were assumptions about a connection between PMR and malignant diseases, studies have not confirmed this. In terms of a differential diagnosis, PMR is most similar to seronegative arthritis, and in about 20% of patients the diagnosis of PMR changes to seronegative RA over time. More recently, PMR and GCA have been seen during treatment with checkpoint inhibitors in the treatment of malignant diseases, as well as with ipilimumab in the treatment of malignant melanoma. Myalgias and myositis can also occur with statin therapy. Arthralgias, pain and muscle stiffness also occur in hypothyroidism. Treatment involves medium or low oral doses of GC, although there have been no studies to show whether methylprednisolone or prednisone is more effective. The usual dose is 15 mg of prednisone daily, in the morning. In mild disease presentation and in patients with asthenic constitution, treatment can be started with 7.5 or 10 mg daily, while in patients with higher BMI and/or more severe disease presentation, treatment can be started with 20 mg daily. The highest recommended dose is 25 mg of prednisone daily. For patients with severe nighttime pain and stiffness, the GK dose could be divided into morning and evening doses. GK dose reduction should begin two to four weeks after symptoms resolve. Typically, the dose is reduced every month by 2.5 mg for values above 10 mg of prednisone, and by 1 mg for doses below 10 mg. Intramuscular injections and GK applications to the shoulders have been investigated in randomized studies as an alternative to treatment with oral daily doses, but such treatments have not become established in everyday practice. Nonsteroidal anti-inflammatory drugs are ineffective in this disease. Physical therapy without drug therapy has no effect. In the treatment of GK, great importance should be given to the evaluation of comorbidities. In uncontrolled diabetes, significant arterial hypertension, heart failure and severe osteoporosis, lower doses of GK are used and methotrexate is added as a "GK sparing agent". Recently, in these cases, or in situations where it is not possible to adequately control the disease with the above therapy, the use of the IL-6 receptor blocker sarilumab has also been approved. Although another IL-6 inhibitor, tocilizumab,

has been shown to be effective, it has not been approved for this indication. Janus kinase inhibitors and rituximab have no large randomized studies, while larger studies for anti-TNF have shown no effect in PMR. Our group of authors also described a patient who was diagnosed with ankylosing spondylitis and a severe form of PMR, and was treated with adalimumab and GK. The patient went into remission of both diseases and voluntarily discontinued GK, which caused a relapse of PMR while AS was still in remission. The treatment for PMR usually lasts a year or two, but it is not unusual for it to last three to six years.

Keywords

pain, shoulder, hip, inflammation, disability

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