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ESTUDO EPIDEMIOLÓGICO DAS DOENÇAS REUMÁTICAS EM PORTUGAL – EPIREUMAPT

Jaime C. Branco*, Helena Canhão**

As doenças reumáticas (DR) são, nos países desenvolvidos, o grupo de doenças mais frequentes da raça humana e representam um importante problema médico, social e económico.

As DR, no seu conjunto, têm um enorme impacto quer no indivíduo doente e sua família, quer ao nível social e representam uma avultada factura económica para os países.

As DR são o primeiro motivo de consulta nos cuidados de saúde primários e são também a principal causa de incapacidade temporária para o trabalho e de reformas antecipadas por doença/invalidez. Assim, as DR têm um importante impacto negativo em termos de saúde pública, com tendência crescente, tendo em conta os actuais estilos de vida e o aumento de longevidade das populações.

As queixas clínicas referidas ao sistema músculo-esquelético (SM-E) atingem, em média e em cada momento, cerca de 1/3 da população adulta, 1/4 das pessoas maiores de 18 anos padecem de alguma forma de doença M-E que, tem um carácter crónico em 1/5 de todos os indivíduos adultos. As DR constituem entre 70% e 85% de todas estas situações[1].

No 4º Inquérito Nacional de Saúde 2005/06 a prevalência, das DR auto-declaradas, ao longo da vida, foi de 16,3% para a população continental. Este valor só foi ultrapassado pela HTA com 20% de prevalência. A frequência das DR nas Regiões Autónomas (RA) foi menor (6% para a Madeira e 12,9% para os Açores). Quer no Continente quer nas RA, as DR foram mais prevalentes nas idades mais avançadas e nas mulheres, para todos os grupos etários[2].

Num estudo do Observatório Nacional de Saúde, de 2005, a prevalência auto-declarada das DR foi ainda mais elevada (24%) mas continuou a ser mais frequente nas mulheres (29,1%) do que nos homens (18,3%) e também aumentava com a idade[3].

Os estudos realizados em Portugal no início do milénio mostraram números homogéneos e coincidentes, apresentando as DR como a patologia clínica mais prevalente (entre 28% e 37% da população) e principal motivo de consulta de clínica geral/medicina familiar (i.e., 20% do total)[4,5].

O Observatório Nacional das Doenças reumáticas (ONDOR), utilizando a coorte EpiPorto (n=2485 indivíduos) identificou pelo menos um diagnóstico de DR (entre as doenças mais frequentes e/ou mais importantes) em 23% dessa população. De novo, as mulheres (28,7%) apresentavam pelo menos uma destas doenças mais frequentemente do que os homens (13,1%)[6].

As queixas dolorosas músculo-esqueléticas são também muito frequentes nas crianças e adolescentes. Num estudo realizado, em 2002, pelo nosso grupo de trabalho, que incluiu 762 indivíduos entre 6 e 17 anos, a prevalência da dor músculo-esquelética nos 3 meses anteriores à avaliação foi de 28,4%. Estas dores foram muito mais mencionadas pelos indivíduos do sexo feminino (62,8%) e foram sobretudo referidas aos membros inferiores[7].

O programa CINDI *(Countrywide Noncommunicable Disease Intervention),* patrocinado pela Organização Mundial de Saúde, realizado em Portugal, nos anos 80, incluiu a avaliação da prevalência das DR. Neste estudo, efectuado na península de Setúbal, foi observada, por reumatologistas, uma população aleatorizada de 1381 indivíduos de ambos os sexos[8]. A Tabela I resume as prevalências encontradas neste trabalho para algumas DR.

Este trabalho realizado há mais de 20 anos, foi o que, até hoje, envolveu a maior amostra populacional com o objectivo de estudar a prevalência de várias doenças reumáticas no nosso país.

Muitos outros trabalhos de natureza epidemiológica foram efectuados entre nós. Uns destinavam-se a caracterizar apenas uma patologia espe-

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Tabela I. Frequência de algumas (DR)*

DR	Prevalência
Gota úrica	1,5%
Artrite reumatóide	0,36%
Espondilite anquilosante	0,22%
Artrite psoriática	0,14%
Artrite idiopática juvenil	0,07%

*Nesta população de 1.381 indivíduos não foi encontrado qualquer caso de lúpus eritematoso sistémico

cífica; outros, ou foram levados a cabo em áreas geográficas menores, ou não conseguiram reunir populações mais amplas.

Os estudos que foram realizados nos últimos dez anos foram objecto de extensa e profunda revisão. As conclusões deste trabalho apontam para várias e importantes lacunas no conhecimento epidemiológico das DR em Portugal[9].

A falta de dados epidemiológicos nacionais, confiáveis e actualizados sobre as DR em geral e algumas das mais importantes em particular, é uma realidade há muito identificada.

Por isso, o Programa Nacional Contra as Doenças Reumáticas (PNCDR), aprovado por despacho ministerial de 26 de Março de 2004, apontava, como primeiro dos cinco objectivos específicos identificados, a necessidade de «conhecer a prevalência das DR abrangidas pelo presente Programa»[10].

Três dos outros quatro objectivos definiam a precisão de «conhecer a incidência, respectivamente, das doenças reumáticas periarticulares, lombalgias e fracturas osteoporóticas»[10].

Em consequência, o EpiReumaPt começou a ser desenhado e planeado logo no fim de 2004. Contudo, por vicissitudes várias, só a partir de 2010 se foram sucessivamente reunindo os meios materiais, os recursos humanos, a capacidade organizativa e os apoios financeiros para o concretizar.

Neste sentido, foi publicado o protocolo do estudo e foram criadas as condições julgadas necessárias e suficientes para que ele se possa iniciar no último trimestre de 2011[11].

A extensa e árdua recolha de dados (isto é, inquérito do entrevistador e consulta do reumatologista) vão durar, pelos menos, 2 anos. Seguir-se-á a demorada e complexa fase de tratamento estatístico da enorme quantidade de elementos recolhidos.

Assim, será possível que os primeiros resultados possam começar a ser libertados durante a primeira metade do ano de 2014.

Exactamente nesse momento, em que cessa a vigência do PNCDR, estaremos na posse dos resultados necessários para elaborar o próximo Programa, que se espera poder servir como guia para o planeamento e roteiro para a administração dos recursos do Sistema Nacional de Saúde, tendo em vista a resolução das necessidades e carências identificadas, sempre com o intuito de melhorar a assistência médica aos doentes reumáticos no nosso País.

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ACPA [ANTI-CITRULLINATED PROTEIN ANTIBODIES] AND RHEUMATOID ARTHRITIS

Rene E. M. Toes*, Diane van der Woude*

Abstract

It has recently been discovered that anti-citrullinated protein antibodies (ACPA) are present in 50% of patients with early rheumatoid arthritis (RA). Assays for detecting ACPA have been shown to have very good diagnostic and predictive characteristics, and they may facilitate the identification of patients with early arthritis who need aggressive treatment.

In addition to their diagnostic and predictive properties, ACPA have also provided new insights into the pathophysiology of RA. The specific association of certain genetic and environmental risk factors with ACPA-positive but not with ACPA-negative RA, has led to new concepts of the underlying pathogenetic mechanisms. The fact that ACPA--positive patients have a more severe disease course with greater joint destruction has also fueled the hypothesis that ACPA themselves may be pathogenic. Although there is no direct proof for this intriguing theory so far, it is clear that ACPA allow the classification of RA patients into two different disease subsets that are associated with distinct pathophysiological mechanisms and clinical outcomes.

Rheumatoid arthritis (RA) is a chronic, potentially destructive, arthritis which has a large impact on patients' quality of life[1]. It has become clear that in order to be able to prevent disease progression and joint destruction, RA needs to be diagnosed early, which requires diagnostic markers which can reliably predict disease development and progression[2]. Some of the most attractive diagnostic markers are autoantibodies.

Rheumatoid factor (RF) has long been known to be a marker of future RA development[3], but more recently, a better diagnostic and predictive marker has emerged in the form of anti-citrullinated protein antibodies (ACPA).

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Development of anti-citrullinated protein immunity

ACPA were first described as anti-perinuclear factor over 45 years ago, but it was not until several years later that recognition of this antigen was found to be exclusively dependent on the presence of citrulline-residues[4,5]. Based on these findings, several commercial assays that test for the presence of antibodies to cyclic citrullinated proteins (CCP) have been developed and successfully introduced in clinical practice[6].

Several studies have investigated at what point in time individuals develop ACPA. Using pre-disease samples from blood bank donors who later developed RA, it was shown that ACPA can be detected years before disease manifestation[7,8]. Furthermore, ACPA titers were found to increase up to the point of disease onset. However, once present, ACPA almost never disappear, but tend to persist in the vast majority of patients in whom they have developed. Likewise, ACPA-negative RA-patients hardly ever sero-convert, indicating that ACPA are a stable biomarker that does not demand re-testing once ACPA-status is known.

The fact that ACPA appear in the pre-clinical phase of RA, together with the finding that ACPA can exacerbate arthritis in mice, suggest that anti--citrulline immunity may play a role in the pathogenesis of the disease[9]. This notion is further supported by investigations into the risk factors that are associated with RA.

Genetic risk factors for RA

The risk of developing rheumatoid arthritis is known to be influenced by several genetic risk factors, of which the HLA-DRB1 shared epitope (SE) alleles confer the highest risk[10]. After the first descriptions of ACPA, it soon became clear that the SE alleles were only associated with ACPA-positive RA and thus only predisposed to ACPA-positive di-

sease[11]. Intriguingly, no apparent contribution of the SE alleles to the progression towards RA or the progression of RA is found when the analyses are stratified for the presence of ACPA in a patient--population with early arthritis[12,13]. Thus, the SE alleles do not independently contribute to the progression to or of RA, but rather predispose to the development of ACPA. The latter is also reflected by the observation that the presence of HLA-SE-alleles influences the profile of the antigens recognized by ACPA, indicating that they are a risk factor for ACPA-development[14].

Conversely, there are other genetic risk factors, which have been described to be exclusively associated with ACPA-negative RA, such as HLA-DR3[15]. Because there are no markers available that are specific for this disease subset, it is currently not feasible to determine if this genetic risk factor predisposes to specific immunological alterations in these patients.

Not only genetic, but also environmental risk factors are known to contribute to the etiology of RA. Many epidemiological studies have shown an association between cigarette smoking. Smoking was found to interact with the HLA SE alleles in the predisposition for RA[16,17]. Interestingly, this association is also predominantly associated with ACPA--positive RA, mainly in the context of the presence of the HLA-SE-alleles[18,19]. Together, as distinct genetic-and environmental factors associated with ACPA-positive and negative disease, these findings indicate that ACPA-positive- and negative RA are distinct disease entities. Nonetheless, at first clinical presentation, no apparent clinical differences seem to be present, although it is clear that ACPA--positive patients will suffer from a more progressive disease course as compared to ACPA-negative subjects[20].

Conclusion

The discovery of the RA-specific anti-citrullinated protein immune response has had great implications, not only for diagnosis and disease prediction, but also for the way we think about the pathophysiology of the disease. Recognition of the distinct genetic and environmental risk factors involved in ACPA-positive versus ACPA-negative disease, has allowed us to view rheumatoid arthritis in a more differentiated way. Even though there is no conclusive proof as yet that ACPA themselves are pathogenic, they allow a useful distinction of disease subsets, each with associated risk factors and prognosis. For the ability to serologically confirm the diagnosis of RA, as well as with regards to the pathophysiologic understanding of the disease, the identification of ACPA has been a great step forward.

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RANK/RANKL/OPG: LITERATURE REVIEW

Silva I*, Branco JC**,*

Abstract

The discovery of the receptor activator of nuclear factor-kB (RANK)/RANK Ligand (RANKL)/osteoprotegerin (OPG) pathway contributed to the understanding of how bone formation and resorption were processed and regulated. RANKL and OPG are members of the tumor necrosis factor (TNF) and TNF receptor (TNFr) superfamilies, respectively, and binding to receptor activator of NF-kB (RANK) not only regulate osteoclast formation, activation and survival in normal bone modeling and remodeling, but also in several other pathologic conditions characterized by increased bone turnover. There is accumulating evidence of the potential role of OPG and RANKL in other tissues.

Looking beyond the RANK/RANKL/OPG axis, Wingless (Wnt) pathway emerged as the osteoblast differentiation way, and also as a bone mass regulator.

Researchers have been discovering new molecules and cytokines interactions. Altogether, data suggest that RANK/RANKL/OPG system could be targeted as a new treatment strategy in bone conditions. FREEDOM is the more recently published clinical trial about a RANKL-specific recombinant fully human monoclonal antibody (denosumab). OPG is also a potential innovative therapeutic option to be investigated.

Keywords: RANK; RANKL; Osteoprotegerin; Osteoclast; Bone Formation.

Introduction

Bone is a connective tissue made up of specific cells, osteoblasts (bone-forming), osteocytes (osteoblasts entrapped within lacunae) and osteoclasts (bone-reabsorbing), and an extracellular matrix of proteoglycans and collagen mineralized by the deposition of calcium hydroxyapatite[1]. Bone remodeling results from the balance between osteoblast and osteoclast activity, through four phases: activation, resorption, reversal and formation. This includes removal of trenches or tunnels of bone from the surfaces of trabecular and cortical bone, respectively, by osteoclasts, while osteoblasts subsequently fill in these trenches by laying down new bone matrix[2].

Formation matches resorption during normal bone remodeling. This remodeling becomes disturbed in a variety of pathologic conditions that affect the skeleton (osteoporosis, glucocorticoid-induced bone loss, multiple myeloma, and rheumatoid arthritis)[2,3]. Discovery of the receptor activator of nuclear factor-kB (RANK)/RANK ligand (RANKL)/ /osteoprotegerin (OPG) signaling pathway as a major regulatory system for osteoclast formation and action, showed the major role of the tumor necrosis factor (TNF) superfamily in bone metabolism[1,5].

Studies also revealed new functions of this triad in other pathologies and tissues, and suggest that in response to mechanical forces osteocytes regulate the osteoclasts recruitment to sites of bone resorption, by inducing the RANKL expression by osteoblastic cells in the local micro-environment[2-4]. Emerging treatments have been explored according to new molecules and mechanisms discoveries.

Osteoblasts differentiation and proliferation depends on Wingless (Wnt)/β-catenin pathway and mutations on some of their proteins lead to bone diseases (eg. loss-of-function mutation in the Wnt co-receptor low-density lipoprotein receptor-related protein 5 (LRP5) is associated with osteoporosis)[6,7].

In this article, we will review RANK/RANKL/OPG triad, its role in the bone, and recent concepts.

RANK, RANKL and OPG signaling pathway

Ostoblasts are mononuclear cells responsible for

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the deposition of bone matrix and for osteoclasts regulation. They originate from mesenchymal stem cells (MSC) by the action of transcription factors like core binding factor α1 (Cbfa-1) also known as Runx2, osterix (Osx), activating transcription factor 4 (ATF4), and bone morphogenic proteins (BMP) as BMP4[6]. Osteoclasts are derived from mononuclear precursors in the myeloid lineage of hematopoietic cells that also originate macrophages[2]. Macrophage-colony stimulating factor (M--CSF) expression by osteoblastic stromal cells is required for progenitor cells to differentiate into osteoclasts, but is unable to complete this process by its own. In a 1997 publication OPG was identified, and its gene encoded a member of the TNF receptor family. In a 1998 publication RANKL was reported as a new member of the TNF family that could bind to OPG and RANK[8]. RANK/RANKL/ /OPG are closely linked with each other.

RANKL is synthesized in membranous or soluble form by the osteoblastic lineage cells, the immune cells, and some cancer cells. This factor links to the osteoclasts surface receptor, RANK, and stimulates bone resorption through osteoclastogenesis and the activation of multinucleated mature osteoclasts. OPG that is secreted by osteoblasts as a decoy receptor for RANKL, prevents RANKL from binding to RANK and bone resorption[1-6].

In the immune system RANKL in activated T cells binds to RANK expressed by the dendritic cells, regulating the function and survival of those cells. OPG is produced by B-lymphocytes and dendritic cells, maintaining an equilibrium in this system[1].

OPG

OPG belongs to the TNF receptor superfamily (TNFRS), preventing the biological effects of RANKL. Also known as TNFRS member 11B (TNFRS11B), osteoclastogenesis inhibitory factor (OCIF) and tropine reductase 1 (TR1), is highly expressed as a soluble protein, closely related to CD40 and able to bind to CD40 ligand (CD40L). Is produced in the adult lung, heart, kidney, liver, thymus, lymph nodes, bone marrow, osteoblasts, vascular smooth muscle cells, B-lymphocytes, and articular chondrocytes[1-3,6]. Over expression of OPG in the mice resulted in osteopetrosis and its deficiency determined osteoporosis[6]. The osteoprotective role of OPG is supported by the report of homozygous deletions of 100 kilobases of OPG in juvenile Paget's disease, and the inactivating deletion in exon 3 of OPG in idiopathic hyperphosphatasia[3].

When RANKL expression is up-regulated OPG expression is down-regulated or not induced to the same degree as RANKL, and the RANKL/OPG ratio favors osteoclastogenesis[2]. OPG expression in osteoblasts is increased by vitamin D3, interleukin (IL)-1α, IL-1β, TNFα, TNFβ, BMP2, transforming growth factor β (TGFβ) and 17 -estradiol and Wnt signaling pathway. Its expression is decreased by prostaglandin E_2 (PGE_2), parathyroid hormone (PTH), glucocorticoids and insulin-like growth factor-1 (IGF-1) (Figure 1)[4].

Furthermore, the RANKL/OPG ratio expressed by pre-osteoblasts cells is higher than in mature osteoblasts, favoring osteoclasts maturation and action. Jagged1/Notch1 signaling negatively regulates osteoclast formation directly and indirectly by changing RANKL/OPG ratio in stromal cells. So, bone mass is regulated by osteoblasts through three signaling pathways: RANKL/RANK, Wnt/ /β-catenin and Jagged1/Notch1[2]. Jagged 1 is a 180 kDa type I transmembrane glycoprotein with an extracellular DSL (delta, serrate, lag-2 consensus sequence) domain that is necessary for bin-

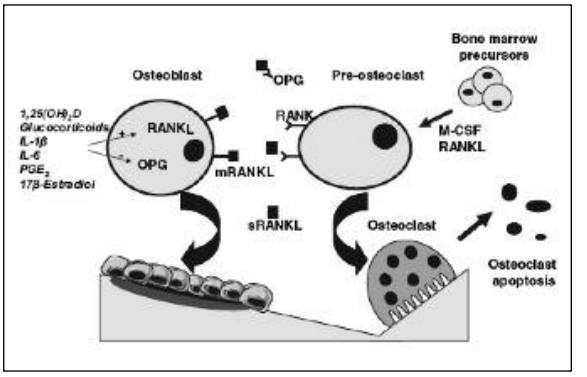

Figure 1. Regulatory mechanisms of bone remodeling: role of RANK, RANKL and OPG in osteoclast activation. OPG expression in osteoblasts is increased by vitamin D3, interleukin (IL) -1α, IL-1β, TNFα, TNFβ, BMP2, transforming growth factor β (TGFβ) and 17β-estradiol, and Wnt signaling pathway. Its expression is decreased by prostaglandin E2 (PGE2), parathyroid hormone (PTH), glucocorticoids and insulin-like growth factor-1 (IGF-1). From: Vega D, Maalouf NM, Sakhaee K. The role of receptor activator of nuclear factor-kB (RANK)/RANK ligand/Osteoprotegerin: clinical implications. The journal of clinical endocrinology and metabolism. 2007; 92: 4514-4521.

ding to Notch receptors. Jagged-Notch signaling specifies cell fate, modulates cell proliferation and differentiation, especially during hematopoiesis, myogenesis, neurogenesis and development of the vasculature. Direct cell-cell interactions are thought to be necessary for functional Notch signaling[2,6].

In mammals there are four Notch receptors (Notch 1-4). The canonical Notch signaling in skeletal biology is evolving while the non-canonical is poorly understood[9]. Suppression of Notch signaling by a selective g-secretase inhibitor or Notch2 short hairpin RNA suppressed RANKL-induced osteoclastogenesis. Induction of Notch signaling by Jagged1 or by ectopic expression of intracellular Notch2 enhanced nuclear factor of activated T cells 1 (NFATc1) promoter activity leading to the increase of osteoclastogenesis[10]. In a pathological context, aberration of Notch signaling is associated with osteosarcoma[9,10].

RANKL

RANKL belongs to the TNF superfamily, is expressed in bone, lung, bone marrow and lymphoid tissues, and exists as 3 isoforms: RANKL 1, 2 and 3. These three isoforms of this type II homotrimeric transmembrane protein can differentially regulate osteoclastogenesis and exists as a soluble and a membranous form. Soluble form has low capacity to generate osteoclasts[11]. Typically is expressed in a membrane-bound form in osteoblasts and activated T cells, and after a proteolytic cleavage by matrix metalloproteases (MMP3 or 7) or a disintegrin and metallopeptidase (ADAM) is secreted. Its expression by synovial cells and activated T cells in patients with rheumatoid arthritis contributes, with TNF, to joint destruction[1,2,8]. RANKL stimulates the release of immature osteoclasts progenitors into the circulation. Analysis of RANKL promoter revealed the presence of binding sites for vitamin D and glucocorticoids (stimulators)[6]. Clinical studies in mice showed RANKL expression in mammary epithelial cells during pregnancy and its effect in lactational hyperplasia of mammary epithelial cells and milk production. RANKL is also expressed by some malignant tumors cells, thus regulating tumor cell proliferation and probably migration[1,2]. Recently, the first report of a mutation in the RANKL gene was described in Canada. The affected individuals had osteopetrosis, without obvious defect in immunologic system[2].

MicroRNAs (miRs) are small non-coding RNAs that function in the spatiotemporal regulation of protein translation in animal cells. MiR-21 was identified as a miR expression signature of RANKL--induced osteoclastogenesis that down-regulates programmed cell death 4 (PDCD4) protein level, and RANKL-induced c-Fos up-regulates miR-21 gene expression[12].

RANK

RANK belongs to the TNFR superfamily, is synthesized as a type I homotrimeric transmembrane protein, and is expressed by different tissues such as skeletal muscle, thymus, liver, colon, mammary glands, prostate, pancreas, and cells of the monocyte/macrophage lineage (precursors and mature osteoclasts, B and T cells, dendritic cells, fibroblasts, and articular chondrocytes). RANKL produced by osteoblasts binds to RANK in the surface of osteoclasts, recruits the tumor necrosis factor receptor associated factor (TRAF) 2,5 and 6 that bind to RANK cytoplasmic domain (only TRAF6 seems to be essential in osteoclasts), leading to NF-kB activation and translocation to the nucleus. NF-kB increases c-Fos expression and c-Fos interacts with NFATc1 to trigger the osteoclastogenic genes transcription (Figure 2). At least seven signaling pathways are activated by RANK-mediated protein kinase signaling: four mediate osteoclastogenesis (inhibitor of NF-kB kinase/NF-kB, c-Jun amino-terminal kinase/activator protein-1, c-myc, and calcineurin/NFATc1) and three mediate osteoclast activation [Rous sarcoma oncogene (src) and mitogen-activated protein kinase kinase 6 (MKK6)/p38/microphthalmia-associated transcription factor (MITF)] and survival (src and extracellular signal-regulated kinase)[1,2,6,8].

On the basis of mice studies, NFATc1 was described as the master regulator of osteoclastogenesis (Figure 3). It is activated by a calcium-dependent calcineurin dephosphorylation. However some patients treated with cyclosporine A (NFATc1 inhibition) presented bone loss, what brought another explanation: NFATc1 also positively regulates expression of osterix, an essential transcription factor in osteoblast function, and the result of this net effect is reduced bone formation and osteoporosis[3].

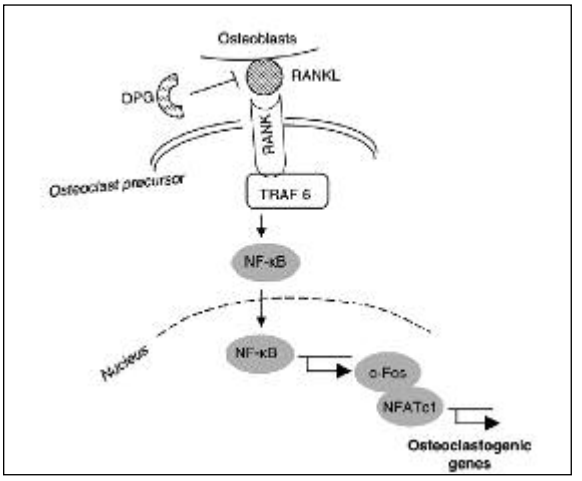

Figure 2. The essential signaling pathway for normal osteoclastogenesis. RANKL produced by osteoblasts binds to RANK in the surface of osteoclasts, recruits the tumor necrosis factor receptor associated factor (TRAF) 2,5 and 6 that bind to RANK cytoplasmic domain (only TRAF6 seems to be essential in osteoclasts), leading to NF-kB activation and translocation to the nucleus. NF-kB increases c-Fos expression and c-Fos interacts with FATc1 to trigger the osteoclastogenic genes transcription. From: Boyce BF, Xing L. Biology of RANK, RANKL, an osteoprotegerin. Arthritis research and therapy. 2007;9:1-7.

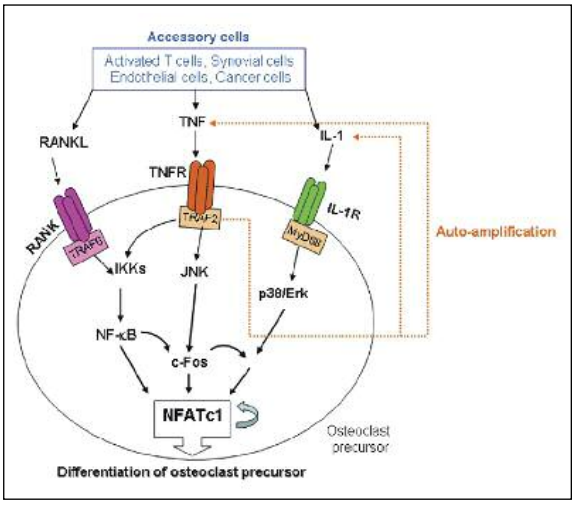

Figure 3. Signaling pathways involved osteoclastogenesis in diseases states with the activation of NFATc1. On the basis of mice studies, NFATc1 was described as the master regulator of osteoclastogenesis. From: Boyce BF, Xing L. Functions of RANKL/RANK/OPG in bone modeling and remodeling. Archives of biochemistry and biophysics. 2008; 473:139-146.

OPG/RANKL complex

The OPG/RANKL ratio is considered to better reflect the bone remodeling environment signs. A high ratio represents bone formation while a low ratio favors bone resorptio[1,4].

After OPG/RANKL complex formation, its internalization can be either through lipid rafts by membranous syndecan-1 or by the clathrin coat formation pathway. These two mechanisms control the bioavailability of extracellular OPG. In addition, glycosaminoglycans (GAGs) such as heparin, heparin sulfate, chondroitin sulfate and dermatan sulfate binds OPG via the heparin binding domains and compete with OPG/RANKL interaction, thus preventing OPG internalization through membranous RANKL. This internalization process is of particular importance for future therapeutic involvement of OPG[1].

The anti-resorptive effect of OPG can be explained by its properties of a decoy receptor and as a modulator of RANKL half-life. As RANKL and OPG controls each other bioavailability, the balance between RANKL and soluble OPG will be important for a curative application of OPG[1].

RANK/RANKL/OPG pathway in rheumatological conditions

Bone diseases are related to increased bone resorption, disturbed coupling between bone formation and resorption, and bone destruction[2].

GENETIC DISORDERS: *familiar expansile osteolysis* [activating 18-bp tandem duplication in the gene coding RANK (TNFRSF11A)]; *familiar form of early-onset Paget disease of bone* (similar 27-bp duplication of the previous gene); *expansile skeletal hyperphosphatasia* (15-bp tandem duplication in RANK); *idiopathic hyperphosphatasia* or *juvenile Paget disease* [homozygous complete deletion of OPG gene (TNFRSF11B)][5]. Sabacchi et al[13], reported mutations in the gene encoding RANKL in 6 patients with autossomal recessive osteopetrosis.

RHEUMATOID ARTHRITIS (RA): RANKL has been implicated as an important mediator of bone erosion[14]. Synovial T cells express RANKL and there is an over expression of RANKL messenger RNA (mRNA) and OPG in the RA patients synovium at the site of bone resorption, which contributes to osteoclast differentiation and activity[14-16]. OPG binding to soluble RANKL can better prevent osteoclast activation in non erosive arthritis than in RA[17]. Elevated serum levels of soluble RANKL normalize after anti-TNF therapy[4,8,14]. Assmann et al,

studied genetic variations of this pathway in the susceptibility to RA and showed the minor allele of the RANK SNP rs35211496 might be protective against RA[18]. Haynes et al, confirmed the hypothesis that successful treatment with modifying anti-rheumatic drugs (DMARDs) reduce RANKL/OPG ratio, suppressing osteoclast formation in the RA synovial tissue[19,20].

Spondyloarthropathies (SpA): the pattern of paraarticular bone tissue damage is different between different forms of peripheral arthritis. In SpA there is limited degradation of the paraarticular bone with new bone formation that can result in ankylosis[21]. In human SpA are described osteoclastic foci in the subchondral bone marrow of hip joints, which suggests a relation with cartilage-induced inflammation (the osteoclasts number is not increased at axial inflammation sites). The RANK/RANKL/OPG pathway contribute to bone erosions was demonstrated in RA, and also psoriatic arthritis (PsA), but only scarcely in peripheral joint inflammation in SpA[21]. Vandooren et al[22], demonstrated that both RANKL (mostly by cadherin 11-expressing synovial fibroblasts and CD3 T cells) and OPG were expressed in the inflamed synovium; the presence of osteoclasts precursors in the inflamed synovial tissue and that the factors needed to local osteoclastogenesis are present in the SpA synovium. There were no qualitative or quantitative differences in the expression of RANKL, OPG, and RANK between nonpsoriatic SpA, psoriatic SpA and RA synovium with the same degree of inflammation. They conclude that the relative protection against bone erosion in SpA cannot be explained by differences of RANK/RANKL/OPG synovial expression, and that these factors expression is disconnected from systemic and local inflammation[22].

Osteoporosis: in human osteoblastic cell lines have been shown a dose and time-dependent increase in OPG mRNA in response to 17-estradiol, which probably decreases the RANK-RANKL binding and osteoclastic bone resorption. Human bone marrow cells from untreated early postmenopausal women showed a greater expression of RANKL compared to the estrogen-treated group[4,8]. Ominsky et al, showed that ovariectomy in rats was associated with high levels of serum RANKL and osteoclast surface and reduced areal and volumetric BMD[23]. It was also showed that OPG reduced osteoclast surface and prevented ovariectomy-associated bone loss in the lumbar vertebrae, distal femur and femur neck[23]. In the glucocorticoid-induced osteoporosis the RANK/RANKL/OPG role was described: glucocorticoids stimulate RANKL expression by osteoclasts and inhibit OPG synthesis, favoring osteoclasts differentiation and proliferation (increased RANKL/OPG ratio and urinary and serum markers of bone resorption)[4,8].

Osteoarthritis (OA): OPG and RANKL have been found to be expressed and modulated in human OA subchondral bone, and by other articular chondrocytes. The OPG/RANKL ratio in the synovial fluid is greater in OA compared to RA. There are two different phenotypes of subchondral bone osteoblasts, L-OA (low endogenous levels of PGE_2) and H-OA (high endogenous levels of PGE_2). L-OA presents low PGE_2 level, low OPG/RANKL ratio, high osteoclastogenesis and a decreased subchondral bone thickness; while H-OA shows high PGE_2 level, high OPG/RANKL ratio, low osteoclastogenesis, and an increased subchondral bone thickness[1,24]. A recent *in vitro* study with human L-OA subchondral bone osteoblasts showed that the combination of glucosamine and chondroitin sulfate modulated OPG/RANKL ratio, decreasing bone resorption[25]. The addition of OPG or the inhibition of RANKL would be beneficial on the subchondral bone of the L-OA (resorptive phase), while in the H-OA patients the anti-resorptive agents are less effective as the subchondral bone seems to be in a formation phase[1]. Moreno-Rubio et al[24], showed that in patients with OA celecoxib decreased RANKL synthesis in the cartilage by increasing the OPG:RANKL ratio; in vitro, PGE2 regulated the expression and release of the mediators of bone metabolism by articular chondrocytes.

Polymialgia rheumatic (PMR): Pusatelli et al[26], found no significant differences in circulating OPG levels in PMR patients in the active phase of the disease or the follow-up compared to normal controls; the systemic RANKL (sRANKL) production is increased, is not modulated by corticosteroid treatment, and can be related to bone osteoporosis.

Systemic sclerosis (SS): microvascular damage is an early pathogenetic event in SS and RANK/RANKL/OPG system is involved in vascular biology. Dovio et al[27], showed that higher sRANKL levels and sRANKL/OPG ratio in patients with SS are a consequence of altered bone microenvironment, and showed dissociation between the well established activation/injury endothelial marker, soluble vascular cell adhesion molecule (sVAM), and OPG, as another vascular damage marker.

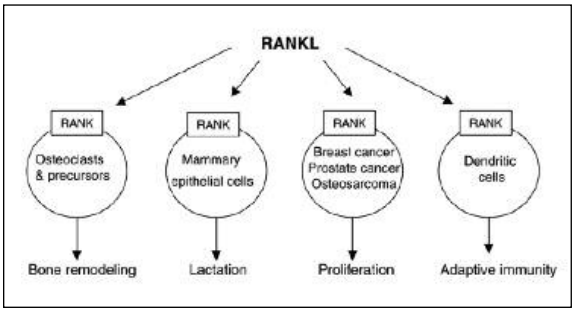

Figure 4. The role of the RANKL/RANK system in bone and other tissues. From: Boyce BF, Xing L. Biology of RANK, RANKL, an osteoprotegerin. Arthritis research and therapy. 2007;9:1-7.

JUVENILE DERMATOMYOSITIS (JDM): Rouster-Stevens et al[28], documented that at the time of diagnosis of JDM untreated patients have an elevated RANKL/OPG ratio compared to normal controls, and this ratio is related to lower bone mineral density (BMD)[29,30].

RANK/RANKL/OPG pathway in non-rheumatologic conditions

There is accumulating evidence of the potential role of OPG and RANKL in other tissues (Figure 4)[1].

BONE TUMORS: osteoclastic activating factors are produced by myeloma cells in response to IL-1, IL-6 and TNF-α. IL-7 may increase RANKL production in T cells, and there is also an increased lysosomal degradation of OPG. Although serum OPG levels correlated with World Health Organization multiple myeloma performance status, it have not be found to be associated with clinical stage or survival[4,29]. Myeloma cells release not only RANKL, but also dickkopff-1 (DKK-1), which suppresses bone formation, enhancing tumor growth. In metastatic bone diseases, tumor cells increase RANKL:OPG ratio directly and by T cells, osteoblast/stromal cells and endothelial cells, together with PTH related peptide, increasing bone removal and tumor growth[8].

VASCULAR CALCIFICATION: there are two main types of vascular calcification, depending if the calcium deposits are located in the intima (intimal calcification, related to atherosclerotic plaques) or in the medial layer (medial calcification, related to chronic kidney disease). An imbalance in the RANK/RANKL/OPG system was suggested as responsible for the calcification process of atherosclerotic plaques[4]. The identification of tissue-specific isoforms could increase the importance of sRANKL and OPG in predicting calcified plaque rupture[31,32]. However, direct evidence of a role of RANKL on vascular calcification is missing[33]. Panizo et al[33], showed that RANKL is able to induce vascular smooth muscle cells (VSMCs) calcification in vitro by binding to RANK; RANK activation will increase BMP4 expression by stimulating alternative NF-kB pathway. The inhibition of RANKL maybe is a possible target to treat vascular calcification[33,34].

INFLAMMATORY BOWEL DISEASE (IBD): Moschen et al[35], demonstrated that IBD is related to alterations in the RANKL/OPG system, and elevated RANKL/OPG ratio is associated to bone loss.

DIABETES MELLITUS (DM): Secchiero et al[36], showed that OPG but not the RANKL is significantly increased in type 2 DM patients compared to controls; serum OPG increases early after DM induction in mice, and showed a positive correlation with blood glucose levels and inverse correlation with free RANKL levels. Thus, increased OPG production represents an early event in DM and possibly is related to endothelial cell dysfunction.

CHRONIC ALCOHOLIC LIVER DISEASE: OPG is raised in alcoholics, especially in cirrhotics without relation with decreased BMD. Raised TNF and IL-6 levels were related with increased OPG levels, which support the protective effect of OPG in bone loss[37].

THYROID TUMORS: the role of RANK/RANKL/OPG in thyroid pathophysiology remains unclear. Heymann et al[38], showed that RANK/RANKL/OPG is expressed in the pathological thyroid gland by follicular cells, by malignant parafollicular cells, and in metastatic lymph node microenvironment. Thus this system might have a role in the pathogenesis of these tumors.

CHRONIC RENAL FAILURE: Fahrleitner-Pammer et al[39], demonstrated that RANK/RANKL/OPG system is associated with BMD in predialysis chronic renal failure. Serum OPG concentrations are lower in patients with adynamic bone disease, in contrast to those with increased bone turnover due to secondary hyperparathyroidism. It is possible that increased serum OPG in chronic kidney disease patients is an adaptative mechanism to attenuate PTH-induced bone loss[4].

BREAST AND PROSTATE CANCER: OPG production by breast cancer cells is a possible survival mechanism of the tumoral cells, because OPG inhibits TNF-related apoptosis-inducing ligand (TRAIL).

OPG is also a potential indicator for the diagnosis and early progression of prostate cancer (elevated levels)[4].

Wnt signaling pathway: interaction with RANK/RANKL/OPG

The Wnt proteins are a family of secreted growth factors found in all animal species that bind to cell--surface receptors and regulate cellular activities like cell fate, determination, proliferation, migration, polarity, and gene expression[6]. Genes encoding for Wnt proteins are highly conserved. At least four signaling pathways are described: Wnt/β-catenin; planar cell polarity; Wnt/Ca^{2+}; and protein kinase A.

The main biologic functions of the Wnt pathway in bone metabolism are: mesenchymal cell differentiation, implications in multiple myeloma and metastatic bone disease, bone mass regulation and bone response to mechanical loading.

The Wnt/β-catenin pathway involves the binding of Wnt proteins to LRP5 or 6 and a member of frizzled (Fz) family of proteins, increasing intracellular β-catenin levels which promote the transcription of target genes inside the nucleus. Its role in bone biology, RA and OA, has been highlighted. Wnt/receptor Fz is inhibited by members of the secreted frizzled-related protein family (sFRP) and Wnt inhibitory factor (WIF-1). Sclerostin (encoded by *SOST* gene) blocks LRP5 activity[6]. Inactivating mutation of Wnt co-receptor LRP5 and the lack of β-catenin, blocks the expression of transcription factors that determine osteoblastic phenotype and the mesenchymal cell achieves another phenotype (chondrocyte or adipocyte)[6,8], which results in reduced OPG expression and bone loss.

The Wnt signaling in osteoprogenitors promotes new bone formation by functioning as a positive regulator and upregulating OPG and down-regulating RANKL. Kamiya et al[7], found that osteoblasts respond to BMP signaling to support differentiation of osteoclasts through RANKL/OPG pathway, possibly by downregulating *Opg* gene and upregulating *Rankl*. It was also showed in mice that BMP signaling via BMP1A receptor directs osteoblasts to reduce bone mass by upregulating sclerostin expression as a Wnt inhibitor, and supporting osteoclastogenesis through the RANKL/OPG pathway.

Dkk-1 is a soluble inhibitor of Wnt pathway and a negative regulator of osteoblastogenesis in vivo (in mice)[40]. Diarra et al[41], proposed that Dkk-1 is a master regulator of joint remodeling, shifting the balance from bone resorption (increased Dkk-1 expression) to bone formation (decreased Dkk-1 expression). Wnt inhibitors Dkk-1 and 2 can induce osteoclastogenesis by changing the RANKL/OPG pathway in vitro[42] (Figure 5).

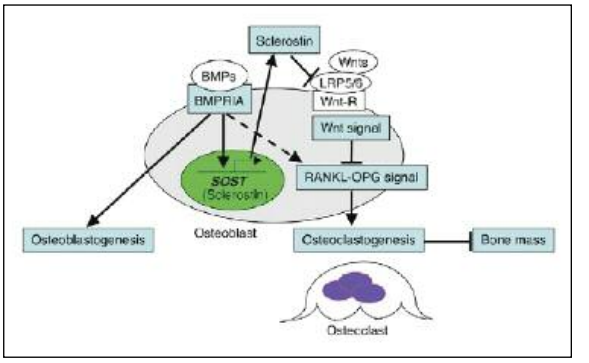

Figure 5. A model of the relationship between BMPR1A and canonical Wnt signaling in mouse bone. Wnt inhibitors Dkk-1 and 2 can induce osteoclastogenesis by changing the RANKL/OPG pathway in vitro.
From: Kamiya N, Ye L, Kobayashi T, Mochida Y, Yamauchi M, e tal. BMP signaling negatively regulates bone mass through sclerostin by inhibiting the canonical Wnt pathway. Development 2008;135:3801-3811.

Wnt system activation seems to be responsible for syndesmophyts growth in SpA.

New hypothesis

IL-6 is a mechano-sensitive cytocine and probably a key factor to the biomechanical control of bone remodeling in OA, possibly decreasing OPG/RANKL ratio[43,44].

TGFβ inducible early gene-1 (TIEG) directly binds to and inhibits OPG promoter activity in osteoblasts, explaining the possible inability of TIEG knockout osteoblasts to support osteoclast differentiation[45].

Leukotriene B4 is capable of inducing osteoclast differentiation by a RANKL-dependent mechanism[46].

Pigment epithelium-derived factor (PEDF), the most potent inhibitor of angiogenesis, up-regulates OPG and thus inhibits osteoclast function by regulating OPG expression[47].

MSCs can differentiate into adipocytes, osteoblasts, and other cells. There are a reciprocal relation between adipogenesis and osteogenesis. Der-Chih et al[48], identified cAMP/PKA signaling, that

regulates bone homeostasis, as a via controlling cyto-differentiation of MSCs (adipocytogenesis, osteogenesis, osteoclastogenesis) by controlling the release of leptin and altering RANKL/OPG gene expression.

The leucine-rich repeat-containing 17 (LRRc17) is a member of the LRR superfamily that acts as a negative regulator of RANKL-induced osteoclast differentiation (by decreasing NFATc1 expression depending on phospholipase C signaling), and thus, is a specific inhibitory molecule for osteoclastogenesis. Recombinant LRRc17 did not affect the differentiation of other myeloid precursors. The regulation of LRRc17 expression in oteoblasts by $1,25(OH)_2D_3$ suggests that this molecule is produced by osteoblasts and regulates its interaction with osteoclasts[49].

Emerging treatments

RANKL-SPECIFIC RECOMBINANT FULLY HUMAN MONOCLONAL ANTIBODY (DENOSUMAB): clinical trials showed its effectiveness in suppressing bone resorption, with an increase in BMD in postmenopausal women with osteoporotic low BMD[50], and have the potential to prevent progression of erosions in RA and metastatic bone disease. The recently published FREEDOM study[51] assessed the effects on fracture reduction in postmenopausal osteoporosis, and achieved a reduction of vertebral and hip fractures to 2,3% and 0,7% respectively, compared to 7,2% and 1,2% in the placebo group. As in the other trials, adverse events (infections or neoplasm) were similar to placebo[4,8].

OPG: beside its ability to inhibit osteoclastic activity, OPG can promote cell survival by inhibiting TRAIL-induced apoptosis[52]. A randomized controlled trial was conducted in postmenopausal women to determine the effect of a single subcutaneous dose of OPG on bone resorption (by urinary N-telopeptide and seric alkaline phosphatase). It concluded that OPG acted primarily on osteoclasts to decrease bone resorption and that a single OPG subcutaneous dose (3mg/Kg) was effective to reduce the bone turnover for a sustained period[52,53]. However, OPG has also been reported as a potential survival factor for several different cell types, through the TRAIL activity inhibition. Breast cancer cells produce OPG in order to be protected from the TRAIL effects in vitro[54]. Holen et al, demonstrated that OPG can act as an endocrine survival factor for breast cancer cells[55]. This new unexpected role of OPG discouraged investigators to further studies of the OPG administration bone effects. OPG might be a therapeutic option for bone lysis in metastatic breast cancer and in multiple myeloma. OPG is a potential marker of prostate cancer progression or relapse, and a potential marker of bone disease in renal osteodystrophy[52].

Conclusion

The RANK/RANKL/OPG pathway mediates the effects of the calciotropic hormones in different tissues and their imbalance contribute to several clinical rheumatologic and non-rheumatologic conditions. Multiple molecular discoveries gave rise to different mechanisms of interaction between signaling pathways that tried to explain bone formation/resorption. According to this development, new emerging treatments have been studied, like denosumab already approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of postmenopausal osteoporosis and the potential role of OPG as an osteoclastic inhibitor and a cell survival promoter.

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BIOLOGIC THERAPY AND PREGNANCY. A SYSTEMATIC LITERATURE REVIEW

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Abstract

Aim: To review available data regarding the safety of biological therapies during pregnancy, focusing on agents used in rheumatology.
Methods: A systematic literature search was carried out to identify all studies with human data on fetal and/or child outcomes following exposure to biologic agents during pregnancy.
Results: A total of 65 publications out of 745 identified references were included in the review.
Conclusions: Experience with pregnancy exposure to anti-TNF agents has been slowly accumulating. Although the numbers are small and with few controlled studies the reviewed data suggest that the overall risk of TNF antagonists is relatively low and benefits may outweigh the risks of drug exposure to the fetus. Information on other biologic agents is still very limited. Large controlled studies with longer follow-up periods will be necessary before firm conclusions about the safety of biologics during conception and pregnancy can be drawn.

Keywords: Biologics; anti-TNF; Pregnancy; Systematic literature review

Introduction

The use of medications during the conception period or throughout pregnancy is a cause of great concern and anxiety for patients and the physicians caring for them.

In the past 15 years, several biologic therapeutic agents have been approved for the treatment and have significantly improved outcomes among patients with various immune-mediated inflammatory disorders such as rheumatic and inflammatory bowel diseases which disproportionately affect females during reproductive years. Choosing appropriate treatment for pregnant patients may be challenging and important issues emerge addressing the risk of adverse fetal outcomes or adverse pregnancy.

All biological manufacturers recommend that these drugs should be avoided during pregnancy and lactation. Indeed, none of the biologic therapies are described as safe to use during human pregnancy either by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA)[1-3]. All approved anti-tumor necrosis factor (anti-TNF) agents and anakinra are classified as Pregnancy FDA Category B. This category indicates that although no risk is apparent from animal studies, there are no controlled studies of women receiving these agents during pregnancy, and therefore, it is not known if they can cause fetal harm. Rituximab, abatacept and tocilizumab are classified as Pregnancy FDA Category C, which means that no controlled studies in humans have been performed and that animal studies have either shown adverse events or are not available. For ethical reasons, randomized trials cannot be designed to evaluate the safety of these drugs during pregnancy. It is nearly inevitable though that there will be some patients exposed to these drugs during pregnancy, typically during the early stages of an unplanned or unknown pregnancy and that difficult decisions will have to be made in the individual clinical settings.

To provide further information on this topic and because biological agents may represent an important therapeutic alternative in pregnant women experiencing persistent or increased disease activity, we decided to perform a systematic literature review of the relevant data available focusing on agents used in rheumatology.

Methods

A systematic literature search for articles published

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up to October 20th of 2010 was carried out to identify all studies with human data on fetal and/or child outcomes following exposure to biologic agents during pregnancy. The search strategy for PubMed was restricted to articles published in English, French, German, Portuguese or Spanish and included the following medical subject headings (MeSH) terms: "infliximab", "adalimumab", "abatacept", "rituximab", "tocilizumab", "golimumab", "certolizumab", "pregnancy", and the non-MeSH terms "etanercept", "anakinra" and "teratogenicity". A hand-search of relevant references not captured by the electronic searches was also made looking for the reference lists of the retrieved articles. Other references, including the product monographs, data provided by the Organization of Teratology Information Specialists (OTIS) studies and the European League Against Rheumatism (EULAR), American College of Rheumatology (ACR) and the European Crohn's and Colitis Organisation (ECCO) congress abstracts were also reviewed.

Articles were selected in a systematic two-step approach. First, titles and abstracts of all identified references were screened, excluding articles that clearly did not address the topic of interest. Second, retrieved articles, including case reports, case series, letters, registries reports, and narrative reviews, were selected for full paper review, applying the following inclusion criteria: 1) data on women with any disease exposed to infliximab (INF), etanercept (ETA), adalimumab (ADA), rituximab (RTX), anakinra (ANAk), abatacept (ABAt), tocilizumab (TCZ), golimumab (GOL) and certolizumab (CTZ) during pregnancy; 2) reported outcome on pregnancy length, health condition of live births, neonatal complications, fetal development, congenital defects/malformations, miscarriages or elective terminations. Papers were included only if related to patients exposed to the biologic during pregnancy. Reports of patients exposed to treatment before conception were excluded, except for rituximab for which data will be presented separately.

Results

The systematic review search identified a total of 745 references, of which 65 met the inclusion criteria and were selected for detailed analysis. Data retrieved will be presented the most accurately possible avoiding duplication of reported cases. Nevertheless, it is difficult to be sure that individual cases were not reported in the registries. For studies with more than one publication describing results among overlapping groups of participants and with the same outcome measure, we considered only the dataset with the largest number of patients and the longest follow-up. In a first section, we will present the number of pregnancies and outcomes definitely known for each biologic. Afterwards and separately, we will show data describing the number of pregnancies and/or the number of live births and/or their outcomes for a whole group of patients where results cannot be individualized by anti-TNF agent or other biologic. As it is understandable, the exact number of pregnancies exposed to each biologic is therefore difficult to assess.

Additional information on reports of pregnancies exposed to biologic therapies may be seen in Table I.

TNF antagonists

Infliximab – FDA Pregnancy category B

Infliximab is a chimaeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNF. It's approved for the treatment of severe rheumatoid arthritis, ankylosing spondylitis, adult and paediatric Crohn's disease, ulcerative colitis, psoriatic arthritis and adult plaque psoriasis, when the response to conventional treatment has been inadequate.

Advised period of discontinuation of infliximab before conception based on the summary of the product characteristics (SPC) is 6 months[4]. However, according to other recommendations a pregnancy appears acceptable 2 months after interrupting infliximab, respecting a time interval of five half-lives and using the highest half-life values reported[5,6].

Experience with pregnancy exposure to infliximab has been slowly accumulating and this is reflected in the number of reports found in the literature search. Twenty-four references where the safety of infliximab during pregnancy was evaluated were selected for detailed analysis: data from four registries, three case series and individual case reports[7-30].

According to information from the selected articles, there were 156 patients treated with inflixi-

Table I. Summary of pregnancies exposed to anti-TNF therapies

Author, year	Study info	Biologic	Other drugs	Pregnancies, no.	Live births, no.	Exposition	Spont. Abortions, no.	Therap. Abortion, no.	Birth defects/ Complications	Comment	Other	Disease
Gracia, 2006	BIOBADASER	INF	yes	4	3	T1		1	0			RheumDis
Katz, 2004	INF Safety Database	INF	some: MTX 8%; AZA 33%, MTNZ 14%	96	64	32bC; 58T1; 6 ND	14	18	5 (all in patients exp. to INF during pregnancy)	1 premat with intracerebral and intrapulmonary bleeding died; 1IRDS; 1 intestinal malrotation (exp. LFN); 1 Tetralogy Fallot; delayed development and hypothyroidism		8RA, 82 CD, 2JIA, 1 UC; 3NR
Mahadevan, 2005	Intentional Tx	INF	some	10	10	2T1; 8T2-3	0	0	1	1 respiratory distress (ICU)	3 premat	CD
Schnitzler, 2007	Intentional Tx	INF		12	10	T1T2	1		0		2 premat	IBD
Berthelot, 2009	CRI	INF		3	3	1T1; 2T1-2	0	0	0			1JIA, 1RA, 1SpA
Chambers, 2004	OTIS	INF	no	4	3	T1	1		0		2 premat	RA
Tursi, 2006		INF	yes	1	1	T1-3	0	0	0			CD
Angelucci, 2008		INF	yes	1	1	T1	0	0	0			CD
Burt, 2003		INF	no	1	1	T1	0	0	0			CD
Kinder, 2004		INF	MTX	1	0	T1	1 (MTX)	0	0			RA
Vasiliauskas, 2006		INF	no	1	1	T1	0	0	0			CD
Stengel, 2008		INF	mesalazine	1	1	T1-3	0	0	0			CD
Chaparro, 2010		INF	ND	1	1	T1-3	0	0	0			CD
Akinci, 2008		INF	ND	1	1	T2-3	0	0	0			SpA
Palmer, 2008		INF	no	1	0	T1	1		1		delayed development	UC
Antoni, 2002		INF		1	1	T1			0			PsA
Srinivasan, 2001		INF		1	1	T1			0		death on day 3	CD
James, 2001		INF		1	1	T2 (single dose)			0			CD
Nerome, 2008		INF	MTX	1	1	T1-2			0		premat	JIA
Correia, 2010		INF		2	2	T3			0			IBD
Puig, 2009		INF		1	1	T1			0			Psoriasis
Ostensen, 2008		INF		5	1	T1			4			RA, PsA, Oligoart
Rosner, 2007		INF	AZA	3	3	T1-3	0	0	0		1 premat	1JIA and 2RA
Kane, 2009		INF		3	3	T1-2	0	0	0			CD

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Table I. Summary of pregnancies exposed to anti-TNF therapies *(continuation)*

Author, year	Study info	Biologic	Other drugs	Pregnancies, no.	Live births, no.	Exposition	Spont. Abortions, no.	Therap. Abortion, no.	Birth defects/ Complications	Comment	Other	Disease
Berthelot, 2009	CRI	ETA	1MTX	10	7	6T1; 2T1-2	2	1 (MTX)	0			2RA; 6SpA; 1PsA; 1JIA
García, 2006	BIOBADASER	ETA	NR	8	4	T1		2				RheumDis
Chakravarty, 2003		ETA	some	7	6	"during pregnancy"	1	0	0			RA
Kosvik, 2005		ETA	no	5	3	T1	2	0	0			IJA and RA
Roux, 2007		ETA	yes	3	2	T1	0	1	1	UTI + CAH		RA
Rump, 2004		ETA	no	1	1	T1	0	0	0			RA
Feyertag, 2004		ETA	no	1	1	T1-3	0	0	0			RA
Carter, 2006		ETA	no	1	1	T1-3 (high dose)	0	0	1	VACTERL assoc		PsA
Sinha, 2006		ETA	no	1	1		0	0	0			RA
Micheloud, 2006		ETA	no	1	1	T2-3	0	0	0			SLE (LN)
Otermin, 2007		ETA	no	1	1	T1-3	0	0	0			JIA
Rosner, 2007		ETA	MFM	1	1	T1-3	0	0	0			SLE
Umeda, 2010		ETA		1	1	T1, T2 and T3	0	0	0			RA
Murashima, 2009		ETA	PDN	1	1	T1-T3	0	0	0		premat	RA
Rump, 2010		ETA		8	6	C and "during pregnancy"	1		1	Megacolon congenitum		RA and AS
Borrego, 2010		ETA	NSAIDs	1	1	T1	0	0	0			PsA
Ostensen, 2008		ETA		9	5	6T1; 3T3		1	3 outcome unkown			RA and AS
Johnson, 2008	OTIS	ETA	yes	139	130	T1	6 (1 Trissomy 18)	2 (1 unspecified heart defect)	11	1 atrial septal defect + patent ductus arteriosus, esotropia, and inguinal hernia; 1 transverse stomach with epispadias + congenital eye defect in a twin whose co-twin had displaced stomach; 1 ventricular septal defect + patent foramen ovale + patent ductus arteriosus; 1 ventricular septal defect + pulmonic stenosis; 1 pyloric stenosis; 1 cystic adenomatoid malformation; 1 hypospadias + inguinal hernia; 1 volvulus; 1 microcephaly; 1 congenital hypothyroidism; 1 Trissomy 21		RheumDis

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Table I. Summary of pregnancies exposed to anti-TNF therapies *(continuation)*

Author, year	Study info	Biologic	Other drugs	Pregnancies, no.	Live births, no.	Exposition	Spont. Abortions, no.	Therap. Abortion, no.	Birth defects/ Complications	Comment	Other	Disease
Johnson, 2009	OTIS	ADA		94	80	T1	13	1	7	1 undescended testicle, 1 microcephaly, 1 ventricular septal defect, 1 congenital hip dysplasia, 1 congenital hypothyroid, 1 bicuspid aortic valve and agenesis of the corpus callosum, 1 congenital hydronephrosis		CD and RA
García, 2006	BIOBADASER	ADA		2	?	T1		1	0			RheumDis
Berthelot, 2009	CRI	ADA		2	2	1T1; 1 T1-3			0			1RA; 1 SpA
Vesga, 2005		ADA	no	1	1	T1-3	0	0	0			CD
Sanchez, 2005		ADA		1	1	T1		0	0			CD
Kraemer, 2008		ADA	LFN until W8	1	1	T1-3	0	0	0			Takayasu
Mishkin, 2006		ADA	no	1	1	T1-3	0	0	0			CD
Coburn, 2006		ADA	yes	1	1	T2T3	0	0	0			CD
Carter, 2007		ADA		1	1	T1	0	0	1	VACTERL assoc		?
Jurgens, 2009		ADA		1	1	T1	0	0	0			CD
Dessinioti, 2010		ADA		1	1	T1			0		low weight	Psoriasis
King, 2008	BSRBR	7INF+ 40ETA+ 11ADA	29MTX	58	30	55T1; 3T1-3 (3ETA:T1-T3 "all healthy")	18	6	4 + 2	3 intrauterine death and 1 neonatal death; 1 congenital hip dysplasia and 1 pyloric stenosis		RheumDis (mostly RA)
Strangfeld, 2007	RABBIT	INF+ETA +ADA	2 MTX/LFN	22	20	mostly T1; 3T2 /T3	2	0	0			RheumDis
Cush, 2005	On-line query (USA)	INF+ETA +ADA		454	378	"during pregnancy"	25	5	0		9 premat	RA
Oussalah, 2009		CTZ		1	1	T1 and T3				0		CD

NF - infliximab, ETA - etanercept, ADA - adalimumab, RTX - rituximab, ANAk - anakinra, ABAt - abatacept, TCZ- tocilizumab, CTZ - certolizumab, MTX - methotrexate, AZA - azathioprine, MFM - mycophenolate mofetil, MTNZ - metronidazole, PDN - prednisolone, ND - not described, T1 - 1st trimester, T2 - 2nd trimester, T3 - 3rd trimester, RA - rheumatoid arthritis, PsA - psoriathic arthritis, JIA - juvenile idiophatic arthritis, AS - ankylosing spondylitis, RheumDis - rheumatic diseases, CD - Crohn's disease, IBD - inflammatory bowel disease, UC - ulcerative colitis, SLE (LN) - systemic lupus erythematosus (lupus nephritis); for other acronyms please see text.

mab during pregnancy. Of these women, about 70% were exposed in the first trimester, around 5 to 10% throughout pregnancy and the remaining on the first two trimesters or punctually to control flares.

Congenital malformations and other complications occurred in 8 infants one intestinal malrotation (concomitant leflunomide), one tetralogy of Fallot, one child experienced intracerebral and intrapulmonary hemorrhage and died at 24 weeks, another died on day 3 (reason not known), 2 had respiratory distress (1 in an infant with seizures) and 2 delayed development (1 with hypothyroidism)[9,10,20,22].

Etanercept – FDA Pregnancy category B

Etanercept is a TNF receptor-IgG fusion protein that binds TNF molecules preventing these from binding TNF receptors on the cell surface. It is approved for the treatment of severe rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult and paediatric plaque psoriasis, in patients who failed to respond to conventional therapies.

In the SPC, the safety interval between the last treatment and conception is not referred[31]. Recommendations vary advocating different safety intervals from 3 weeks to 2 months[5,6].

Eighteen papers were selected for their report of etanercept exposure in pregnant women: data from three registries, five small case series and individual case reports[7,8,27,28,32-45]. Overall, taking into account the included studies, exposure to etanercept was reported in 199 pregnancies. Exposure occurred in the first trimester in about 70% of the patients and in other trimesters or throughout pregnancy in the remainder.

Congenital malformations or other complications in confirmed pregnancies exposed to etanercept were noticed in 14 cases: 1 VACTERL syndrome (Vertebral defects [V], Anal atresia [A], Cardiac abnormalities [C], Tracheoesophageal fistula or tracheal atresia/stenosis [T], Esophageal atresia [E], Renal and/or Radial abnormalities [R], and pre-axial Limb abnormalities [L]), 1 megacolon congenitum, 1 atrial septal defect with patent ductus arteriosus, esotropia and inguinal hernia, 1 transverse stomach with epispadias and congenital eye defect in a twin whose co-twin had displaced stomach, 1 ventricular septal defect with patent foramen ovale and patent ductus arteriosus, 1 ventricular septal defect with pulmonary stenosis, 1 pyloric stenosis, 1 cystic adenomatoid malformation, 1 hypospadias with inguinal hernia, 1 volvulus, 1 microcephaly, 1 congenital hypothyroidism and 1 Trissomy 21. Another case with trissomy 18 resulted in abortion[37,38,44]. There was another case described as a congenital abnormality but that might be interpreted as hereditary adrenal hyperplasia with 21 hydroxilase inheritated from the father [34].

Adalimumab – FDA Pregnancy category B

Adalimumab is a fully human monoclonal antibody that binds to TNF±, preventing it from activating TNF receptors. It is approved for the treatment of severe rheumatoid arthritis, ankylosing spondylitis, idiopathic juvenile arthritis, adult and paediatric Crohn's disease, ulcerative colitis, psoriatic arthritis and adult plaque psoriasis, when the response to conventional treatment has been inadequate.

The SPC advises a safety interval between the last treatment of adalimumab and the conception of 5 months[46]. Again, other recommendations exist based on half-lives of the product, stating shorter periods of 8 weeks and 3 months as possibly safe[5,6].

Existing data on adalimumab use during pregnancy is more limited than for the previous agents and based on the information from three registries and individual case reports. Overall, eleven papers were selected for the information on adalimumab exposure during pregnancy[7,27,47-55]. According to information from the selected articles, exposure to adalimumab during pregnancy occurred in 106 patients. Exposure occurred in the first trimester in approximately 90% and throughout pregnancy in just about 10% of patients.

Overall there were 8 reported malformations: 1 VACTERL syndrome, 1 undescended testicle, 1 microcephaly, 1 ventricular septal defect, 1 congenital hip dysplasia with inguinal hernia, 1 congenital hypothyroidism, 1 bicuspid aortic valve and agenesis of the corpus callosum (twin pregnancy in which 2nd twin had patent ductus arteriosus) and 1 congenital hydronephrosis (twin pregnancy in which 2nd twin was spontaneously aborted)[51,52].

Other data on pregnancy exposure to anti-TNF

As referred before, further data come from studies describing the number of pregnancies and/or the number of live births and/or their outcomes for a whole group of patients that cannot be individualized by anti-TNF or other biologic. These data is discussed here, separately.

One of the largest descriptions on anti-TNF ex-

posure during pregnancy comes from an internet survey based on practicing US rheumatologists recall on the use of biological agents published by Cush in 2005[56]. This study describes 454 pregnancies exposed to anti-TNF agents (81% to etanercept) with 378 normal deliveries, 9 premature babies, 5 therapeutic abortions, and 25 miscarriages in this group. TNF antagonists were used throughout the pregnancy in 31.3% of the patients. There were no birth defects, fetal malformations, or neonatal deaths reported. However, detailed information could only be retrieved on part of the patients and therefore, there is some uncertainty as to the exactitude of the data[57].

In 2006, Hyrich et al published the outcomes of 23 pregnant patients exposed to anti-TNF treatment (ETA, n=17; INF, n=3; ADA, n=3) at the time of conception and/or during pregnancy identified from the British Society for Rheumatology Biologics Registry (BSRBR) database[58]. In 2008, the BSRBR updated the previous publication and reported 58 women directly exposed (DE) to an anti-TNF drug (INF, n=7; ETA, n=40; ADA, n=11; and MTX, n=29), during pregnancy[59]. Data from the BSRBR were described in patients receiving anti-TNF therapy for rheumatic diseases alongside a parallel DMARD control group: 41 women previously exposed (PE) to anti-TNF therapy (INF, n=14; ETA, n=21; ADA, n=6; MTX, n=1 at conception) and 6 pregnancies in the DMARD only control group. Anti-TNF therapy was discontinued in all but 2 pregnancies in the DE group (3 babies - 1 twin pregnancy). A trend towards a higher miscarriage rate was seen in the DE group compared to the PE group and DMARD group: 18/58 (31%) versus 7/41(17%) and 1/6 (16%). There were 30/58, 32/41, and 5/6 live births in the DE group, PE group, and DMARD control group, respectively. Two congenital abnormalities were reported in each DE (1 congenital hip dysplasia and 1 pyloric stenosis) and PE (1 strawberry naevus and 1 "winking jaw syndrome") groups. Additionally, 3 intrauterine deaths, 1 neonatal death, and 6 elective terminations were reported in the DE group. One intrauterine death and one elective termination were reported in the PE group.

Strangfeld et al collected data from the German biologics register (RABBIT), a study evaluating patients with Rheumatoid Arthritis (RA) who initiated therapy with a biologic agent[60]. Analysis was performed of 37 pregnancies in 29 women who were exposed to anti-TNF agents during conception or at least the first trimester of pregnancy: INF (n=2), ADA (n=5), ETA (n=20), DMARDs (n=8). Comparison was made to those who stopped either biologic and/or other DMARDs before conception. Mean birth weight was similar in infants exposed to biologic therapy (3.1 kg) compared to infants exposed to non-biologic therapy (3.1 kg). There were no congenital malformations reported. Three patients re-initiated treatment with the biologic after week 20 and continued the therapy until delivery. Mothers and newborns were reported to be well post-partum (ETA, n=2; INF, n=1).

See additional information on Table I.

Golimumab and Certolizumab – FDA Pregnancy category B

Golimumab (a human monoclonal anti-TNF-α antibody) and certolizumab (a PEGylated Fab fragment of humanized monoclonal TNF-α antibody) are the two latest anti-TNF biologics. Golimumab is indicated for the treatment of severe rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis and certolizumab is indicated for rheumatoid arthritis, in both cases, in patients who have responded inadequately to conventional therapy.

According to the SPC, women of childbearing potential should use adequate contraception to prevent pregnancy and continue its use for at least 5 and 6 months after the last certolizumab and golimumab administration, respectively[61,62].

As both of these therapies are relatively new, there are no published data regarding their use in human pregnancy apart from a report in abstract form of a woman treated with certolizumab during the first and third trimesters delivering a normal baby[63].

Rituximab – FDA Pregnancy category C

Rituximab is a monoclonal chimaeric human-mouse antibody that binding specifically to a transmembrane antigen, CD20, located on pre-B and mature B lymphocytes, mediates B cell death. This drug is indicated for the treatment of non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukaemia (CLL) in combination with chemotherapy, and for severe, refractory rheumatoid arthritis.

Since rituximab is an IgG-based antibody, it is likely to cross the placental barrier and interfere with fetal and neonatal B-cell development and given its pharmacokinetic properties and its long-term effects it may cause some concern even when

the mother is exposed to treatment before conception[64,65]. Due to the long retention time of rituximab in B-cell-depleted patients, the SPC mentions that women of child-bearing potential should use effective contraceptive methods for 12 months following the last infusion before conception[65]. However, the elimination half-life of rituximab suggests that a 6-month wait may be adequate, as stated by some published recommendations[5,6].

Published experiences on the use of rituximab during pregnancy consist of a limited number of case reports. Our literature search found 16 women exposed to rituximab at least 6 months before conception, at conception or during pregnancy[28,64,66-76]. Some of them were also exposed to other treatments, potentially harmful, for life threatening situations as lymphomas[69,71,74-76]. Treatment with rituximab was administered in the first trimester in three, in the second and/or third in eight pregnancies. There were 15 live healthy neonates and 1 elective termination. There were no serious infectious complications documented. Additional information on reports of pregnancies exposed to rituximab may be seen in Table II.

Anakinra – FDA Pregnancy category B

Anakinra is a human interleukin-1 receptor antagonist approved for the treatment of severe rheumatoid arthritis in patients who have not responded adequately to convencional therapy. Although without a formal indication it has also been used to treat the systemic form of juvenile idiopathic arthritis.

The safety interval between the last administered dose and conception is not referred in the SPC[77].

Information regarding ANAk during pregnancy is limited to data from the German Register[60]. Two pregnancies exposed to ANAk during the conception/first trimester have had good outcome with no malformations described.

Abatacept – FDA Pregnancy category C

Abatacept is a fusion protein that selectively modulates a key costimulatory signal required for full activation of T lymphocytes. It is approved for the treatment of refractory rheumatoid arthritis and polyarticular juvenile idiopathic arthritis.

The elimination half-life of abatacept suggests that an 18 week wait between the last abatacept infusion and conception may be adequate[5]. The SPC advises effective contraceptive methods for at least 14 weeks following the last infusion until attempts to conceive[78].

In the double blind and open-label periods of the 5 core studies and in another phase II trial, 10 pregnancies that involved women treated with abatacept were reported[79].

Of these 8 women, 7 received MTX and 1 leflunomide as concomitant medication. Three subjects experienced a spontaneous abortion during the first trimester (two had a history of previous spontaneous abortions). Two subjects had their pregnancy terminated. Three pregnancies were ongoing at the time of the report.

In a phase II trial of abatacept for multiple sclerosis (IM101200), 2 women became pregnant. One subject delivered a healthy baby 10 months after discontinuation from the study (was not exposed during pregnancy) and the other subject had an elective abortion at 4 weeks gestation[79].

Tocilizumab – FDA Pregnancy category C

Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors. It is indicated for the treatment of refractory rheumatoid arthritis. According to SPC, pregnancy appears acceptable 3 months after stopping tocilizumab[80].

No data on exposure to tocilizumab during human pregnancy have been published.

Discussion

Although currently available data are sparse and limited in number, experience with pregnancy exposure to biological therapies is slowly accumulating. Interpretation of the results must be cautious and some important issues need to be considered:

Many women had active disease and were concomitantly exposed to potential teratogenic drugs such as MTX, leflunomide and metronidazole.

Exposure may be divided into two groups: a) unplanned pregnancies – exposure occurred at the time of conception and 1st trimester; b) pregnant women who were treated intentionally because of active refractory disease. The duration and time of exposure during pregnancy to these agents may lead to different outcomes; in most of the reports, women have suspended the biologic treatment as soon as the pregnancy was confirmed, usually in the first trimester.

Doses of anti-TNF vary depending on the di-

Table II. Summary of pregnancies exposed to other biologics (non-anti-TNF)

Author, year	Study info	Biologic	Other drugs	Pregnancies, no.	Live births, no.	Exposition	Spont. Abortions, no.	Therap. Abortion, no.	Birth defects/ Complications	Comment	Other	Disease
Ng, 2009		RTX	AAS+Igs+ PDN	1	1	>=6months befC	0	0	0			APPS
Ponte, 2010		RTX		2	2	T1	0	0				Atopic Dermatitis
Pellkofer, 2009		RTX		1	1	C	0		0			Optic Neuromyelitis
Ostensen, 2008		RTX		3	2	3 mo bC e T1-T2	0	1	0			SLE
Herold, 2001		RTX	HOP	1	1	T2 e T3	0	0	0		premat	Lymphoma
Kimby, 2004		RTX		1	1	T1	0		0			Lymphoma
Friedrichs, 2006		RTX	CHOP	1	1	T2 e T3	0	0	0			Lymphoma
Scully, 2006		RTX		1	1	T2 e T3	0	0	0		premat	TTP
Ojeda-Uribe, 2006		RTX		1	1	T1	0		0			AI HemolAn
Maglorie, 2006		RTX	CHOP	1	1	T2	0	0	0			Lymphoma
Decker, 2006		RTX	CHOP	1	1	T2	0	0	0		premat	Lymphoma
Klink, 2008		RTX	Igs	1	1	T3	0	0	0			ITP
Rey, 2009		RTX	CHOP	1	1	T2 e T3	0	0	0		premat	Lymphoma
Strengfeld, 2007	RABBIT	ANAk		2	2	>T1; 2 T2-3			0			RheumDis
Abatacept_EMA 2007		ABAt	MTX or LFN	8	3?		T1 (3 ongoing pregnancies when reported)	3	2 (MTX or LFN)	?	RA	
Abatacept_EMA 2007		ABAt		1	0	T1		1				Multiple Sclerosis

sease being treated; in some reports a high dose was used to obtain disease control (ex. the patient who delivered a baby diagnosed with a VACTERL association was being treated with 100 mg weekly of etanercept for severe psoriatic arthritis).

The outcome of each pregnancy may be dependent on several other factors including the individual women herself, the disease, the activity state and the presence of other co-morbidities[81]. This information is lacking in most of the reports.

Congenital anomalies are seen in 3 to 5% of live births and some are relatively more common like those that involve the nervous system, the heart, the limbs and the urinary system (with a prevalence of more than 20 cases per 10,000 births)[82]. VACTERL is a nonrandom association of birth defects that occurs in 1.6/10,000 live births[83]. The frequency of preterm births varies from 5 to 13% in most of developed countries[84]. The risk for congenital anomalies or prematurity is described to be higher in RA when compared to women without RA[81]. It is obvious that the lack of a nontreated control group in most of the reports included in this systematic review may lead to some bias but, importantly, no specific pattern of congenital defects has been noted in infants prenatally exposed to biologics.

The Otis (Organization of Teratology Information Specialists) Collaborative Research Group, a not-for-profit organization in United States and Canada, has been prospectively following pregnant women exposed to anti-TNF during pregnancy. They provide the some of the few controlled information included in this systematic review based on data from pregnancy outcomes in exposed group compared with those in a disease-matched non-treated control and healthy control groups[29,37,52]. The preliminary data of the information published suggest that the rate of major structural defects in the TNF treated group is similar to the general population rates[52]. Preterm delivery and poor growth are increased in the exposed group and diseased non exposed group suggesting that it might be attributable to the underlying maternal disease[37,52].

Aside from the current systematic review, three other publications have to be mentioned and introduced in the discussion. A recently published paper raised concerns of a possible causative effect of the TNF antagonists in some congenital anomalies that are part of the VACTERL spectrum[51]. This study based on a voluntary post-marketing adverse event database of FDA was not included in the systematic review because it is not possible to know the total number of pregnant women exposed to TNF-antagonists and it reports only those with bad pregnancy outcomes. The information provided may still, nevertheless, be important. The review reported 41 children with 61 congenital anomalies born to 40 mothers receiving a TNF antagonist. The TNF antagonist was considered the "primary suspect" as the cause of the birth defect in all cases (22 ETA and 19 INF). The most commonly reported anomaly was a form of heart defect. A total of 24 children (59%) had ≥1 congenital anomaly considered part of VACTERL association.

Conversely, Snoeckx et al conducted a search of the Benefit Risk Management Worldwide Safety Database (SCEPTRE) of Johnson & Johnson for all medically confirmed cases of pregnancy reported in patients who have ever received INF (before or after conception) in order to identify any cases of VACTERL association[85]. Pregnancy outcome data were available for 627 cases. The number of patients directly exposed to INF during pregnancy is not specified and the report included women that had been treated with INF years before conception. There were 14 cases with ≥1 congenital anomalies/malformations but none of the reported cases met the criteria for VACTERL association.

Also the TREAT registry was designed to assess the long-term safety of infliximab in patients with Crohn's disease. A total of 114 pregnancy known outcome reports in patients treated with infliximab have been collected as of June 2008[86]. Again, the number of patients directly exposed to INF during pregnancy is not known and many women treated with INF years before conception were included. A total of 9 neonatal problems were reported (5 premature infants, 1 jaundice, 1 hypoxia, 1 ventricular defect and 1 with congenital ectrodactyly). None of the reports with neonatal problems met the criteria for VACTERL association.

As it is the predominant route of communication between the mother and the fetus, understanding the process of placental transfer of some drugs would help us to better evaluate the risk of their exposure during pregnancy. Theoretically, the structure of several of the molecules, which contain a human immunoglobulin G1 (IgG1) constant region, allows little placental transfer of the molecule during the first trimester[87]. However, IgG subclasses are readily passed into the foetus during the second and third trimesters, which specifical-

ly raises questions regarding safety of administration of these drugs beyond the 2nd trimester of pregnancy. There are studies that prospectively analyzed INF serum levels in newborns exposed in utero to INF during 2nd and/or 3rd trimesters[15,30,88]. Data is somewhat contradictory. In one study, levels of INF were not detectable in the newborn, suggesting that INF was not transferred from mother to child[30]. In the other studies, the authors found detectable levels of INF in the newborn and until 2 to 6 months of age[15,88].

Rituximab was also evaluated in similar studies describing women treated with the drug during the 2nd and 3rd trimester of pregnancy. Serum levels of the drug and B lymphocytes in the neonate and in the mother were measured[64,71,75]. At birth, RTX serum levels were detectable and neonates had very low or no detectable B-cells. Time of rituximab administration during gestation did not appear to influence this outcome. A decline in RTX levels seemed consistent with the known half-life of rituximab and at the age of 6 months, the number of B-cells was in the normal range. In addition, normal immunoglobulin levels and normal vaccination responses could be demonstrated.

Despite the persistence of some doubts and the insufficient data on the safety of these agents, some important organizations have already stated their position on the use of biologics during pregnancy. The official recommendations of the American Society of Gastroenterology published in 2006 declared that "there is growing body of evidence suggesting low risk of infliximab during pregnancy"[89]. The reference centre for teratogenicity of France (CRAT) has implied that infliximab might be used for the treatment of a refractory disease if this is the only way for controlling active disease, warning however to avoid the final weeks of the third trimester[5].

We may conclude that the true implications of biologic exposure during pregnancy are yet unknown. The existing evidence suggests that the overall risk of TNF antagonists is relatively low and benefits may outweigh the risks of drug exposure to the fetus. At least we may say that although the numbers are small and there is little information from controlled studies the reviewed data suggest that women who inadvertently become pregnant while taking anti-TNF agents may be reassured that stopping the treatment and continuation of pregnancy does not appear to hold a real increased risk of congenital malformations. Information on other biologic agents (not TNF blockers) is still very limited. The decision to treat with a biologic agent in pregnancy should be made on a case-by-case basis. What remains for the patient, the rheumatologist and the obstetrician to do is to balance the risk between the importance of remaining in remission or with partial control of the disease with the potential risk of these drugs to cause any harm.

Patients with inflammatory rheumatic disorders and the physicians caring for them should keep in mind that disease activity at the time of conception or during the course of pregnancy may be associated with a risk of low birth weight, premature births and spontaneous abortions. In women with a severe, refractory disease course, in whom biological therapies have been the only agents to induce and maintain remission, therapy may probably be continued at least until conception.

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BIOLOGICALS AND SWITCH IN RHEUMATOID ARTHRITIS THROUGHOUT TIME – ARE WE BEING MORE AGGRESSIVE?

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Abstract

Objectives: To investigate the switches performed in patients with rheumatoid arthritis under biological therapy and specifically comparing the switches from earlier days with more recent switches.
Patients and methods: Patients with rheumatoid arthritis under biological therapy followed at Hospital Garcia de Orta, Almada, and included in the Rheumatic Diseases Portuguese Register (Reuma.Pt) were included in this study. Switches occurring before and after January 2007 were compared with respect to patients' demographic and clinical characteristics, such as disease activity and duration of biological therapy. The survival of the first biological agent was compared between patients starting biological therapy before and after 2007. EULAR response and remission rate at the last evaluation were calculated. Comparisons between groups were established using a t-test or chi-square, as appropriate. Survival curves of the first biological were compared through the logrank test.
Results: In total, 123 patients were included in the analysis (mean age 57.0 ± 13.1 years and mean disease duration 11.7 ± 8.0 years). A total of 85 switches were documented, 20% of which took place before 2007. Comparing the switches before and after 2007, the latter were registered among older patients (recent switches 56.2 ± 12.9 years *vs* older switches 48.9 ± 11.0 years, p=0.04) and with a shorter duration of the first biological agent (recent switches 461.9 ± 293.2 days *vs* older switches 773.7 ± 475.8 days, p=0.03). No further significant differences were found, including the disease activity. The survival of the first biological was shorter in patients starting biological therapy after 2007 (2949 days for biological onset before 2007 and 818 days for onset after 2007, p <0.001). A good EULAR response was achieved by 19% and 30% of the patients, before and after 2007, respectively (p = 0.23). Remission was achieved by 14% and 22% of the patients, before and after 2007, respectively (p = 0.30).
Conclusions: Switches were more frequently performed in more recent years, in older patients and with a shorter duration of biological therapy. A trend towards a better and more targeted control of the disease could be discussed in light of our results. Although switches were more frequently performed in more recent years, in older patients and with a shorter duration of biological therapy, there is still room for improvement when aiming at remission, for example by applying a tighter therapy strategy like the "treat to target model".

Keywords: Rheumatoid Arthritis; Biological Therapy; Drug Switching; Registries; Portugal.

Introduction

In the last decade, biological therapies have dramatically changed the treatment of rheumatoid arthritis (RA) in such a way that remission is currently an achievable goal. This goal has been advocated by recent initiatives, namely the *Treat to Target*[1] and the EULAR recommendations for the management of RA[2], as attaining a state of remission or low disease activity leads to better structural and functional outcomes than allowing residual disease activity[3,4], and the earlier the remission state is achieved the better it is[1]. Both initiatives recom-

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mend that patients should be followed meticulously and existing therapy should be intensified or ultimately changed for another one until the target is achieved: remission[1,2]. With respect to biological therapy in RA, a "cycling for remission" approach has recently been proposed: start with an effective agent; move to another effective agent unless persistent remission is achieved with acceptable toxicity; consider going back to the most effective agent if none of the biological disease modifying anti-rheumatic drugs (DMARDs) results in remission[5]. This proposal is presented in light of the evidence reflected in the EULAR recommendations for the management of RA[2], and the process can develop at a relatively fast pace, as a patient's response to treatment during the first 3 months of biological therapy is known to determine the level of disease activity at 1 year[6].

For several years, inhibitors of TNF (etanercept, infliximab, and adalimumab) and anakinra have been the only option available for patients failing synthetic DMARDs. Recently, biological agents with novel mechanisms of action (rituximab, abatacept, and tocilizumab) have been approved for use in patients with RA and, even more recently, the armamentarium of biological agents has been enriched through the approval of new TNF inhibitors, golimumab and certolizumab pegol. The diversity of biological agents increases the possibilities of switching therapies and consequently of achieving successful treatment response. Patients may fail to achieve the target with one medication, for instance, a TNF inhibitor, but then may respond very well to another medication with an identical[7, 8] or different mechanism of action[9-11]. Consequently, rheumatologists' clinical practice is expected to have been adapted, throughout this decade, to a more intensified treatment strategy and to a better and more targeted control of the disease. A more aggressive attitude towards RA therapy, more specifically involving biological therapy, is therefore expected. Hence, it is interesting to reflect upon our daily clinical practice and to analyze how we are dealing with switches. The aims of the present study were to investigate the switches performed in patients with RA under biological therapy and to compare older switches (i.e. performed in earlier days) versus more recent switches and the circumstances in which these took place, as well as to evaluate the survival of the first biological. Aiming at higher response levels as we currently do, we would expect to identify, comparing to earlier days, a higher number of switches currently being performed, a lower disease activity value before a switch and a shorter survival of the first biological agent.

Patients and methods

Study population

Data from the Rheumatic Diseases Portuguese Register, Reuma.pt, more specifically the register of patients with RA receiving biological therapies (BioRePortAR) and the subset from Hospital Garcia de Orta, Almada, has been used. Reuma.pt has been described in detail elsewhere[12]. In summary, this electronic register was launched in 2008 and continuously includes patients from several Portuguese Rheumatology departments. Inclusion criteria are RA, diagnosed according to the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) criteria[13] and start of biological therapy. Data from the previous years, from the introduction of biologicals in 2000 until 2008, have been collected on paper and later were entered into the electronic register; these data have been systematically collected according to a standardized, published protocol, which contained the same items as the ones included in the electronic register[14]. Reuma.pt is also used as an electronic patient chart and, therefore, the frequency of observations of the patients is not pre-determined. Assessments are made by rheumatologists, in general every 3-4 months, and include clinical information, such as the monitoring of disease activity (Disease Activity Score with 28-joint assessment – DAS28[15]), medication, adverse events, and comorbidities. Function is monitored through the Health Assessment Questionnaire (HAQ) once a year[16]. Demographic and other clinical characteristics, including health habits and previous medication, are collected at the onset of biological therapy. Data from all patients exposed to biologicals from 2001 to 2011 were used. Data refer to usual clinical practice, without any intervention on the decisions of the rheumatologists. Patients with missing information at baseline, i.e. evaluation corresponding to the start of the first biological, were not included in the analysis, in order to require all the patients to have a complete follow-up while on biological therapy and to assure completeness of the information on switches.

Switch assessment and subcohorts

A switch of biologicals was defined as the start of a subsequent biological, independently of the reason of discontinuation of the previous one. In order to investigate the current practice with respect to switches and to compare our earlier practice in terms of switches with our more recent clinical practice, a time cut-off was necessary. We decided to establish the cut-off as of January 1st 2007, with the following reasoning: 1) it divided the total period (2001-2011) in approximately balanced parts in terms of number of patients starting a first biological therapy in each of them; 2) in 2007, the Portuguese guidelines for the use of biologicals in RA were updated by the RA Study Group (GEAR) of the Portuguese Society of Rheumatology[17]. In these guidelines, the criteria for introduction and maintenance of biologicals were discussed, as well as the contraindications and procedures in case of inadequate response.

Taking the cutoff of 2007 into account, three subcohorts of patients could be identified: subcohort 1 – patients starting the first biological in the period of 2001-2006 and being followed-up during the same period (2001-2006); subcohort 2 – patients starting the first biological in the period of 2001-2006 and being followed-up in the period of 2007-2011, actually including the same patients as subcohort 1, but in a later follow-up period, and only excluding patients with a definitive discontinuation of biological therapy in the follow-up period of 2001-2006; subcohort 3 – patients starting the first biological in the period of 2007-2011 and being followed-up in this period. Each of these subcohorts was analyzed in terms of demographic and clinical characteristics of the patients, including initial and final levels of DAS28 (calculated with the erythrocyte sedimentation rate) and HAQ, number of switches, ratio of switches per number of patients on biologicals, number of first switches, disease duration and time under biological exposition.

Switches before 2007 were designated as older switches and switches after 2007 as recent switches. Older and recent switches were compared with respect to demographic and clinical characteristics of the patients at the evaluation immediately before the switch, as this was considered the evaluation where the rheumatologist actually made the decision about the switch. Clinical characteristics compared were disease duration, time under biological exposition, disease activity (as measured by the DAS28), function (as measured by the HAQ), concomitant therapy with corticosteroids, concomitant therapy with methotrexate, and duration of first biological at first switch. Because recent switches included both switches in patients who started biological therapy before and after 2007, a more pure comparison between older and recent switches was also performed, in which only the recent switches of patients who had started their first biological after 2007 (i.e. belonging to the subcohort 3) where compared to older switches (subcohort 1).

Furthermore, the survival of the first biological was evaluated through means of assessing its survival time for half of the patients and comparing the survival between patients starting their first biological before and after 2007.

Disease activity control

A possible way to assess the effectiveness of optimal and targeted disease activity control and of the approach to switches throughout time is to evaluate its effect, more specifically the disease activity control achieved at the last evaluation of the total population and stratified by each subcohort. Disease activity control was considered to be evaluable when the DAS28 was available at the last evaluation of each subcohort. For the purpose of this assessment, patients starting a new biological or awaiting a switch at their last evaluation, or who had discontinued biological therapy permanently were not included, as the disease activity control could not be properly evaluated in these cases. Remission achieved at the last assessment, as defined by a DAS28<2.6[18], was also determined.

For all the patients with an available DAS28 both at baseline and at the last evaluation, the EULAR response was calculated[19], both for the total population and also split by each subcohort.

Statistical analysis

Continuous variables are presented as means ± standard deviations, and categorical variables as frequencies.

Comparisons were established between different groups. Continuous variables were compared using an independent two-samples *t*-test adjusted for heterogeneity of variances, as appropriate. Categorical variables were compared using the chi-square test.

The survival of the first biological was assessed through means of a survival analysis and the sur-

vival curves for patients starting their first biological before and after 2007 were compared by a log-rank test.

Statistical analysis was performed assuming a 5% significance level and using STATA SE 10.

Results

A total of 123 out of 159 patients with RA who have been treated with biological therapy at the Hospital Garcia de Orta were included in this analysis. Eight patients were not included because information was only available from recent evaluations and not from the first years of follow-up. The remaining 28 patients have been on biological therapy at some point throughout the follow-up period (16 pertaining to the 1st subcohort, 5 to the 2nd, and 7 to the 3rd subcohort), but have been definitely discontinued, mainly due to adverse events, others due to loss to follow-up or transfer to another hospital, and their information was no longer available.

The demographic and clinical characteristics of the included population are summarized in Table I. The majority of the patients were on a TNF inhibitor as a first biological (33% infliximab, 32% etanercept, 20% adalimumab), followed by tocilizumab (7%) and anakinra (2%).

Table II shows the characteristics of each of the subcohorts stratified according to the date of onset of biological therapy and the follow-up period. A total of 56 patients started their first biological in the period of 2001-2006 and the same patients were followed-up in both periods (2001-2006 and 2007--2011). A total of 67 patients were started on a biological in the period 2007-2011. Patients from the subcohorts 1 and 3, starting a biological before and after 2007, respectively, had similar demographic and clinical characteristics, except for the age at onset of first biological, which was higher in the group of patients who started their first biological in the period of 2007-2011 (55 years old *vs* 50 years old).

With respect to the switches, fifty-eight patients (47%) had their biological therapy switched at least once (Table I). A total of 85 switches were registered, of which 17 (20%) in the 1st subcohort (Table II). In total, 68 switches were of recent onset (i.e. taking place after January 2007), of which 32 (47%) in patients who had started their first biological before 2007. Comparing subcohorts 1 and 3 (i.e. starting their first biological before and after 2007),

Table I. Demographic and clinical characteristics of the population

	Mean ± SD or n (%) (N = 123)
Current age (years)	57.0 ± 13.1
Female gender (%)	106 (86%)
Disease duration (years)	11.7 ± 8.0
Time under biological exposition (years)	4.4 ± 2.8
Rheumatoid factor positivity (%)	81 (66%)
ACPA positivity (%)	86 (70%)
Number of patients with at least one switch (%)	58 (47%)
Number of biologicals per patient	1.72 ± 0.95
Frequency of number of biologicals per patient (%):	
• 1	63 (51%)
• 2	40 (33%)
• 3	15 (12%)
• 4	4 (3%)
• 7	1 (1%)

there was an increase in the number of switches, with a ratio of switches per number of patients under biologicals of 30% in subcohort 1 and of 54% in subcohort 3 ($p = 0.02$). A tendency towards a lower disease activity level at baseline and at the final evaluation was found throughout time, but the difference between subcohorts 1 and 3 was not statistically significant.

Table III shows the comparison between switches of older and recent onset. Patients with recent switches were found to be statistically significantly older. This difference was also found when the comparison was refined to patients from subcohort 3 only (i.e. starting their first biological in the period of 2007-2011) compared with subcohort 1. Comparing all the recent and older switches, a longer time under biological exposition was found in patients with a recent switch (3.0 years in recent switches *vs* 1.6 in older switches, $p < 0.01$). In patients from subcohort 3, a trend towards shorter biological exposition was found compared with subcohort 1 (1.2 years *vs* 3.0, $p = 0.16$). Patients with a recent switch and who had started the first biological in the period 2007-2011 had a shorter duration on their first biological at the time of their first switch (461.9 ± 293.2 in recent switches

Table II. Demographic and clinical characteristics of the subcohorts stratified by onset of biological therapy and follow-up period

	Cohort 2001-2006	Cohort 2007-2011		
	Follow-up period 2001-2006	Follow-up period 2007 – March 2011		
	Subcohort 1 Mean ± SD or n (%) N = 56	Subcohort 2 Mean ± SD or n (%) N = 56	Subcohort 3 Mean ± SD or n (%) N = 67	p value §
Age at onset of 1st biologic (years)	49.8 ± 12.3		54.7 ± 13.7	0.04*
Female gender (%)	50 (89%)		56 (84%)	0.36
Rheumatoid factor positivity (%)	35 (64%)		46 (69%)	0.10
Disease duration at onset of 1st biologic (years)	6.6 ± 7.2		7.6 ± 8.0	0.46
Number of switches	17	32	36	–
Ratio number of switches/number of patients under biologic (%)	17/56 (30%)	32/56 (57%)	36/67 (54%)	0.02*
Number of first switches	15 (15/17 = 88%)	14 (14/32 = 44%)	28 (28/36 = 78%)	0.08
Ratio number of first switches/ /number of patients under first biologic	15/56 (27%)	14/56 (25%)	28/67 (42%)	0.12
Initial DAS28	5.8 ± 1.2 (n = 50)	4.0 ± 1.4 (n = 48)	5.7 ± 1.2 (n = 66)	0.67
Final DAS28	4.0 ± 1.4 (n = 48)	3.7 ± 1.2 (n = 52)	3.7 ± 1.3 (n = 62)	0.07
Initial HAQ (0-3)	1.6 ± 0.7 (n = 41)	1.0 ± 0.7 (n = 47)	1.5 ± 0.6 (n = 52)	0.67
Final HAQ (0-3)	1.0 ± 0.7 (n = 47)	1.0 ± 0.8 (n = 42)	1.0 ± 0.6 (n = 48)	0.70
Time under biological exposition (years)	2.9 ± 1.8 (n = 56)	4.2 ± 0.3 (n = 56)	4.2 ± 0.1 (n = 67)	<0.01*
Definitive discontinuation of biologics	0	3 (5%)	2 (3%)	–

§Comparison between subcohort 3 and subcohort 1
*Statistically significant difference (*p*-value <0.05)

vs 773.7 ± 475.8 days in older switches, $p = 0.03$). No further significant differences were found between older and recent switches. Interestingly, a slight tendency towards a lower level of DAS28 was noted in recent switches.

The survival of the first biological was shorter in patients who started biological therapy in the period of 2007-2011. The time to 50% discontinuation of the first biological was 2949 days when the first biological was started before 2007, compared to 818 days when the first biological was started in the period of 2007-2011 ($p < 0.001$) (Figure 1).

One hundred and eleven patients were considered evaluable for analysis of disease control, as assessed at the last observation (Table IV). Only patients that had not recently started a new biological, had not been proposed for a switch and had not definitely discontinued biological therapy were included for this analysis. In terms of EULAR response, 53% had a moderate response, 35% a good response and 12% none. A total of 24 patients (22%) were in remission (DAS28 < 2.6).

Dividing the population in the three subcohorts and considering the last evaluation of each of

Table III. Comparison of the disease activity between older and recent switches

	Older switch (before 2007) N = 17+ Mean ± SD or n (%)	Recent switch, all considered (after 2007) N = 68 Mean ± SD or n (%)	p value§	Recent switch only from subcohort 3¶ (after 2007) N = 36 Mean ± SD or n (%)	p value¤
Age (years)	48.9 ± 11.0 (n = 17)	56.2 ± 12.9 (n = 68)	0.04*	56.6 ± 14.1 (n = 36)	0.049*
Disease duration (years)	7.4 ± 4.5 (n = 17)	9.2 ± 7.5 (n = 66)	0.22	7.5 ± 8.6 (n = 34)	0.98
Time under biological exposition (years)	1.6 ± 1.3 (n = 17)	3.0 ± 2.7 (n = 68)	<0.01*	1.2 ± 0.9 (n = 36)	0.16
Duration of first biological at first switch (days)	773.7 ± 475.8 (n = 15)	918.6 ± 932.0 (n = 42)	0.45	461.9 ± 293.2 (n = 28)	0.03*
DAS28 before the switch	5.7 ± 1.3 (n = 14)	5.2 ± 1.6 (n = 64)	0.28	5.7 ± 1.8 (n = 34)	0.91
HAQ (0-3)	1.3 ± 0.5 (n = 8)	1.1 ± 0.8 (n = 26)	0.53	1.2 ± 0.8 (n = 14)	0.65
Corticosteroids (%)	15 (88.2%)	46 (67.7%)	0.09	28 (77.8%)	0.36
Methotrexate (%)	15 (88.2%)	56 (82.4%)	0.60	29 (80.6%)	0.49

+n refers to number of observations/switches; some patients had more than one switch
§Comparison of older *vs* recent switches, all considered
¤Comparison of older *vs* recent switches in subcohort 3 (i.e. patients started on biological in the period of 2007-2011)
¶Subcohort 3 means that patients were started on a first biologic in the period of 2007-2011
*Statistically significant ($p < 0.05$)

them, a trend towards a higher achievement of remission and a better profile of EULAR responses was found in subcohort 2 (i.e. patients starting biological therapy in the period of 2001-2006 and being followed--up in the period of 2007-2011) and subcohort 3 (i.e. patients starting biological therapy in the period of 2007-2011).

Discussion

This study showed a clear increase in the number of switches in patients with RA under biological therapy throughout time, specifically when comparing patients who started biological therapy before and after 2007. Patients with a recent switch were found to be older and had a shorter duration of the first biological compared with patients with a switch before 2007. No significant differences with respect to disease activity before the switch could be demonstrated. The survival of the first biological was shorter in patients who started biological therapy in the period of 2007-2011. A trend towards a better disease activity control, as assessed by the mean final DAS28 score and the EULAR response, was also manifest in the more recent follow-up period (i.e. 2007-2011), when compared to the earlier follow-up period of 2001-2006.

These results suggest a trend towards a better and more targeted disease control of patients with RA under biological therapy throughout time. This goes along with what we expected, with the improvements we have witnessed in RA during the last decade and with the consequent increasing level of demand we have with respect to the disease control. In more recent years, switches were performed at an earlier stage, in terms of the duration of biological therapy, suggesting that rheumatologists were reducing the time to evaluate the effectiveness of a therapy before switching if they were not satisfied with the results. This is also in line with the larger availability of biologicals in recent years, including drugs with a different mode of action. However, disease activity was still considerably high before a switch, and has not decreased significantly throughout time, as one may have expected. One potential

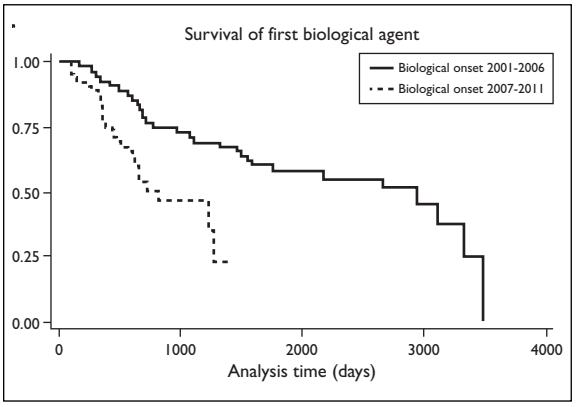

Figure 1. Time to discontinuation of the first biologic agent, stratified by the period for onset of biological therapy

explanation for this is that rheumatologists may be reluctant to switch and still wait a long period before actually changing the biological. This period was on average of 467 days in more recent years, which is around 15 months. There seems to be room for improvement in this aspect.

Another finding was that recent switches were performed in older patients. We would instead expect that patients were started on biological therapy earlier in their disease course and, consequently, in their life. However, this would also be dependent on an earlier referral of patients from their general practitioners to rheumatologists, and actually no difference was demonstrated in the disease duration before a switch. The fact that switches were performed in older patients potentially reflects the increased occurrence of switches that can take place and to a less restrictive group of patients, being in fact generalizable to older patients as well. Remission was achieved in approximately one fifth of the patients. This number is in line with remission achievements in other observational studies. The German registry, RABBIT, showed a remission rate achieved in 16% of the patients under biological therapy[20]. In the Italian registry, MonitorNet, 36% of the patients were reported to be in remission[21]. The data from the German registry are from a publication from 2006, which can justify a lower value. The data from the Italian registry are from 2009 and only included patients who were started on biological therapy after 2007, which can partially explain the higher achievement of remission. Interpreting our findings in light of these other publications, we can conclude that our patients' disease activity control was in line with other observational studies and potentially with some room for improvement in this aspect. To our knowledge, no previous studies focused on the same aspect as we did, meaning that no studies specifically addressed the circumstances in which

Table IV. Comparison of the disease activity between older and recent switches

	n (%)	Subcohort 1§ (n = 56)	Subcohort 2¶ (n = 56)	Subcohort 3¤ (n = 67)	p value subcohort 3 *vs* subcohort 1
Disease activity control evaluable at last observation*	111 (90%)	56 (100%)	51 (91%)	60 (90%)	–
EULAR response evaluable	99 (89%)	43 (77%)	41 (80%)	56 (84%)	–
• Good	35 (35%)	8 (19%)	18 (42%)	17 (30%)	
• Moderate	52 (53%)	25 (58%)	20 (46%)	32 (57%)	0.23
• None	12 (12%)	10 (23%)	5 (12%)	7 (13%)	
Remission	24 (22%)	8 (14%)	11 (22%)	13 (22%)	0.30

§Subcohort 1: start of first biologic before 2007, follow-up period before 2007. For this cohort, the last observation is the first observation in the next follow-up period (beginning of 2007)
¶Subcohort 2: start of first biologic before 2007, follow-up period after 2007
¤Subcohort 3: start of first biologic after 2007, follow-up period after 2007
*By disease activity control evaluable at last observation is meant that the patient did not start a new biologic at the last evaluation, was not proposed to switch at the last evaluation and did not discontinue a biologic definitely, as these cases compromise the evaluation of disease activity control

switches take place or compared switches from earlier years with switches from more recent years.

The main limitation of the present study is the relatively small population. Some of the differences between the groups did not reach statistical significance and only remained as a trend. A second potential limitation is that not all patients that started biological therapy were included in the dataset, and therefore selection bias may have occurred. Nevertheless, all the efforts were done to include the maximum number of patients possible and we are confident that they are a good representation of the total population.

We strongly believe that this type of analyses provides clinicians with insight to their behavior in clinical practice. Clinicians might have the slightly deviated perception they are being interventive enough in their medical decisions, for instance of keeping or changing a therapy, and only when the reality is put into numbers can the misperceptions be understood. A parallelism can probably be established with situations when a tight control of RA is compared to routine clinical care, just as for example was illustrated in the TICORA trial, where it was demonstrated that a tight control led to significantly better outcomes[22]. This parallelism can at the moment only remain as an image to better illustrate the idea and, if deemed to be true, then a scientific demonstration will be required.

Conclusion

In summary, this study demonstrated that switches in biological therapy were more frequently performed in more recent years, compared to the period before 2007. Patients with switches in biological therapy performed in more recent years were older and had a shorter duration of biological therapy compared to switches in biological therapy before 2007. A trend could be shown towards a better and more targeted control of the disease. Nevertheless, there is still room for improvement, especially when aiming at remission and following the current EULAR recommendations for the treatment of RA[2], for example, applying a tighter therapy strategy, like the "treat to target model"[1].

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INTEROBSERVER RELIABILITY IN ULTRASOUND ASSESSMENT OF RHEUMATOID WRIST JOINTS

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Abstract

Objective: To evaluate interobserver reliability in the ultrasound assessment of synovitis in the radiocarpal (RC), midcarpal (MC) and ulnocarpal (UC) joints in RA.

Methods: Ultrasound examinations of 295 rheumatoid wrist joints were performed over a three month period. The RC, MC and UC joints were examined using dorsal longitudinal ultrasound scans. Synovial thickening was assessed by quantitative measurement and a previously established semi-quantitative scoring system (Grades 0 to 3). Interobserver reliability was determined by the comparing the findings of two radiologists who were unaware of each other findings.

Results: The intraclass correlation coefficient (ICC) between examiners for the quantitative measurement of synovitis in the RC, MC and UC recesses were 0.508, 0.346 and 0.240 ($p<0.001$), respectively. Weighted kappa values using the semi-quantitative scoring system were 0.308, 0.312 and 0.153 for the RC, MC and UC joints, respectively.

Conclusion: Interobserver reliability of the ultrasound assessment in rheumatoid wrists proved good for the quantitative measurement of synovitis in the RC joint, but poor agreement was found for the MC and UC joints. Using the semi-quantitative scoring system, interobserver agreement was poor for all three joints (RC, MC and UC).

Keywords: Ultrasonography; Reliability; Wrist; Rheumatoid Arthritis.

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Introduction

In recent years, musculoskeletal ultrasound has become an important diagnostic tool for rheumatic disease, as it allows the detection of the inflammatory process in intra-articular and periarticular structures as well as the identification of bone erosion[1,2]. This exam has a number of advantages over other imaging methods, including its non-invasive nature, good visualization of the joint cavity, absence of radiation, and wide acceptance by patients. The exam's dynamic and rapid execution enables it to assess multiple joints at low cost, thereby making it is a "bedside exam"[3,4]. Despite these significant advantages, ultrasound findings remain highly dependent on the individual examiner's findings. This occurs partially due to the subjective assessment of the images and the low degree of standardization of the technique due to the small number of multi-center studies involving the method[5-9].

In cases of rheumatoid arthritis (RA), the wrist is affected in 90% of patients in the first 10 years of the disease[10]. The wrist is an anatomical complex made up of various articular recesses and inter-bone ligaments. The three main recesses in the wrist are the radiocarpal (RC), midcarpal (MC) and ulnocarpal (UC)[11,12]. Ultrasound has proven useful in the assessment of these articular recesses as well as in the distinction between healthy individuals and patients with chronic inflammatory arthropathy of the wrist[13-16]. It is a helpful tool for guiding procedures, assessing sub-clinical findings and monitoring treatment[16,17].

There are few studies investigating interobserver reliability in the ultrasound assessment of musculoskeletal conditions[6-9,18-21]. The majority of these studies have analyzed ultrasound reliability for the joints of the hands and feet, knees and periarticular structures, such as in cases of rotary cuff injury[7-9,14-16]. The reliability of ultrasound assessment of

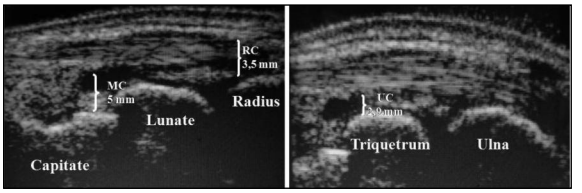

Figure 1. B-mode US synovial thickness measurements in the wrist joint, scanned in a longitudinal plane of the dorsal central and ulnar surface of radiocarpal (RC), midcarpal (MC) and ulnocarpal (UC) recess. Synovial measurements were performed perpendicular to the great axis and at the point of greatest thickness

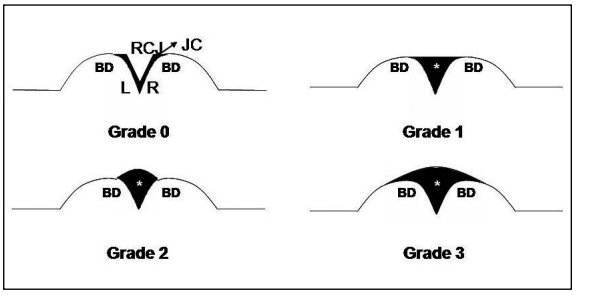

Figure 2. Illustration of semi-quantitative scoring system at radiocarpal joint: L – lunate; R- radius; RCJ – radiocarpal joint; JC – joint capsule; BD – bone diaphysis; * – synovial thickening

the wrist has only been evaluated regarding the presence or absence of synovitis in a small number of patients with different chronic inflammatory conditions[8-9,22]. There is no evidence of any study investigating interobserver reliability in the ultrasound assessment of the synovium in different articular recesses of the wrist.

The aim of the present study was to determine interobserver reliability in the ultrasound assessment of the radiocarpal (RC), midcarpal (MC) and ulnocarpal (UC) recesses of the wrist in patients with RA and clinical synovitis.

Methods

A cross-sectional study was carried out involving patients with RA based on the classification criteria of the American College of Rheumatology[23] presenting clinical synovitis in at least one of the wrists. The patients included had no diagnostic criteria for any other collagen disease

Ultrasound Assessment

Assessments were carried out by two radiologists with experience in musculoskeletal ultrasound. Two hundred and ninety five wrists of RA patients with clinical synovitis were examined by ultrasound over a three-month period. The ultrasound examinations were performed using a Sonosite 180 Plus (SonoSite. Inc – United States) device equipped with a linear probe (5 to 10 MHz).

All patients were instructed to stay seated in a comfortable position in front of the examiner with their hand in a pronated position on top of the desk to take dorsal scans in neutral position of the wrist.

The ultrasound examinations were performed from the dorsal aspect of the wrist with the transducer in a longitudinal position. The examinations were performed from the radial and ulnar sides as well as midline to assess the RC, MC and UC recesses in accordance with the standards established by the European League Against Rheumatology[24].

Both quantitative and semi-quantitative measurements were performed in each recess for synovial thickening[13,19]. The quantitative measurement was obtained from the distance between the joint capsule and subchondral bone (Figure 1). For the semi-quantitative assessment, a modified version of a previously established semi-quantitative scoring system to evaluate metacarpophalangeal (MCP), proximal interphalangeal and metatarsophalangeal joints were used[19]. A single score was used for effusion and synovitis, ranging from 0 to 3: 0- no synovial thickening; 1- minimal synovial thickening up to the joint capsule; 2- synovial thickening causing curvature of the joint capsule, but without extending to the bone diaphysis; 3- synovial thickening with curvature of the joint capsule and extending to at least one bone diaphysis. Figure 2 displays the semi-quantitative measurement at radiocarpal joint and respective scores.

Interobserver Reliability

Interobserver reliability was determined by comparing the mean quantitative and semi-quantitative scores obtained by two radiologists who were unaware of clinical assessments. Each operator performed the ultrasound exams sequentially and independently. The assessments were performed in different rooms, using the same machine and settings, and the measurements were recorded on separate charts. Therefore, each evaluator was blinded to the measurements of the other.

Table I. Demographic parameters, disease related variables in 59 RA patients

Age, years (Mean ± SD)	48.7 (± 9.25)
Gender (Women/ Men)	55/4
Race (White/ Black)	52/7
Disease Duration, years	11.33 (± 9.61)
Functional Class	II (46)
	III (13)
Rheumatoid Factor (positive) (%)	59
Prednisone, mg/day (Mean ± SD)	6.65 (± 5.22)
Diphosphate Cloroquine (%)	7
Methotrexate (%)	89
Sulfassalazine (%)	13
Leflunomide (%)	42

SD – standard desviation

Table II. The mean quantitative measurement (mm) of synovial in the RC, MC and UC recess according to Operator A and Operator B

Recesses (Mean ± SD)	Operator A (n-295)	Operator B (n-295)	ICC (R)
RC recess (Mean ± SD)	5.09 mm (± 1.83)	4.82 mm (± 1.41)	0.482
MC recess (Mean ± SD)	4.53 mm (±1.83)	4.40 mm (±1.34)	0.509
UC recess (Mean ± SD)	5.34 mm (± 1.68)	7.03 mm (± 1.74)	0.240

RC – radiocarpal; MC – mediocarpal; UC – ulnocarpal; SD – standard desviation; ICC – intra-class correlation coefficient

Statistical Analysis

The intra-class correlation coefficient (ICC) was used for the quantitative measurements and weighted Kappa test (κ) was used for the semi-quantitative measurements. For the ICC, interobserver reliability was considered excellent if $R > 0.75$, good to optimal if R was 0.4 to 0.75 and poor if $R < 0.4$[25]. With the Kappa test, interobserver reliability was considered excellent if $\kappa > 0.81$, substantial when values were 0.61 to 0.80, moderate when values were 0.41 to 0.60, good when values were 0.21 to 0.40, minimal when values were 0.20 to 0 and poor when the value was 0[26].

Results

Fifty-nine patients with RA were analyzed. Table I displays the demographic data and clinical parameters.

Ultrasound Assessment

A total of 295 assessments were performed on the rheumatoid wrists over a three-month period. The mean quantitative measurement of synovium in the RC, MC and UC recesses according to Operator A was 5.09 ± 1.83 (1.2 – 10.12) mm, 4.82 ±1.83 (0 –11.66) mm and 5.34 ± 1.68 (1.16 – 12.23) mm, respectively. According to Operator B, these measurements were 4.53 ± 1.41 (1.7 – 9.9) mm, 4.40 ±1.34 (0.66 – 8.3) mm and 7.03 ± 1.74 (1.16 – 11.56) mm, respectively (Table II).

In the semi-quantitative measurements of the RC recess, Operators A and B determined a score of 1 in 147 and 164 assessments, a score of 2 in 121 and 115 measurements, and a score of 3 in 27 and 16 measurements. In the semi-quantitative measurements of the MC recess, Operators A and B determined a score of 1 in 28 and 103 assessments, respectively; a score of 2 in 164 and 126 measurements, respectively; and a score of 3 in 27 and 16 measurements, respectively. In the semi-quantitative measurements of the UC recess, Operators A and B determined a score of 1 in 97 and 118 assessments, respectively; a score of 2 in 152 and 117 measurements, respectively; and a score of 3 in 46 and 60 measurements, respectively (Table III).

The absolute agreement for semiquantitative scoring for both observers was 58,3% for RC, 47,5% for MC and 46,4% for UC recess.

Interobserver reliability

The ICC between the two evaluators for the quantitative measurements of the RC, MC and UC recesses was 0.508, 0.3463 and 0.240 ($p<0.001$), respectively. Weighted Weighed kappa values for semi-quantitative assessments of the RC, MC and UC recesses were 0.308, 0.312 and 0.153, respectively (Tables II and III).

Discussion

The present study assessed the interobserver reliability ultrasonography for quantitative and semi-quantitative measurements of wrist in patients with long-standing RA. The wrist is one of the most affected joints in RA and is a complex anatomical structure made up of various joint recesses and pe-

Table III. Interobserver agreement for the semi-quantitative scores of the RC, MC and UC recesses according to Operator A and Operator B

Recess (n = 295)	Operator	Semi-quantitative scores (N)			kappa
		1	2	3	k
RC recess	A	147	121	27	0.308
	B	164	115	16	
MC recess	A	103	164	28	0.312
	B	66	126	103	
UC recess	A	97	152	46	0.153
	B	118	117	60	

RC – radiocarpal; MC – mediocarpal; UC – ulnocarpal; A – operator A; B – operator B

riarticular structures, which makes the physical exam of this joint a difficult task that requires the use of imaging methods[11,14,15]. A number of studies have demonstrated the ultrasound is capable of revealing inflammatory alterations in this joint. However, there are no previous studies that have evaluated the interobserver reliability of this method for joint recesses of the wrist[1-4].

In the present study, good reliability (ICC = 0.5081) was found for the RC recess, whereas poor correlations were found for the MC (ICC = 0.3463) and UC (ICC = 0.240) recesses. Likewise, poor interobserver reliability was found for the semi-quantitative assessment for all three recesses analyzed (RC, MC and UC), with Kappa values of k = 0.308, k = 0.312 and k = 0.153, respectively. Two previous studies involving experts in musculoskeletal ultrasound and the assessment of different joints found moderate interobserver reliability (k = 0.59 to 0.61) regarding the presence or absence of synovitis in the wrist; these studies report interobserver reliability similar to that found in the present study in the quantitative measurement of synovia in the RC recess[8,9]. Unlike the present study, however, these studies only performed a qualitative assessment (presence or absence of synovitis) and did not perform a quantitative measurement of synovitis. Moreover, no systematic examinations of rheumatoid wrists were carried out, but rather the evaluation of different joints and degenerative inflammatory conditions[8,9].

Iagnocco *et al.*, investigated the presence or absence of synovitis in the wrists of patients with systemic lupus erythematosus and found optimal interobserver reliability for the RC recess (k = 0.73 to 0.89)[22]. A recent study investigated interobserver reliability in the ultrasound assessment of synovitis in 28 joints in patients with RA and found moderate reliability (k = 0.49) for the presence of synovitis in the RC recess of the wrist[27].

Few studies on ultrasound have employed a quantitative measurement of the synovia as an assessment instrument. Schmidt *et al.*, determined reference values for the measurement of the synovium in different joints in healthy individuals; in the wrist, the mean distance between the joint capsule and scaphoid bone profile was < 1.5 mm[28]. Koski (2003) established the measurement of the synovium in the recesses of rheumatoid joints and considered unequivocal synovitis to be a measurement greater than 2 mm in the RC recess and the presence of any area of synovial proliferation in the MC recess[13]. However, interobserver reliability was not determined in either of these studies.

The poor interobserver reliability (ICC = 0.346) for the quantitative measurement of synovitis in the MC recess in the present study may have occurred due to the fact that the patients had long-standing RA, in which erosion is common and the possible destruction of the carpal bones, such as the lunate and capitate, has occurred, which would hamper the visualization of the subchondral bone profile for the quantitative measurement. In the UC recess, there is a presence of the triangular fibrocartilage and the styloid process, which may have impaired the exact positioning of the transducer, thereby causing an anisotropic effect and leading to the poor reliability in the measurement of the synovium in this recess. Moreover, a portable ultrasound device of lesser resolution was used in the present study, which may have compromised the adequate localization of the joint capsule and hampered the quantitative measurement.

A semi-qualitative assessment of synovitis in the

RC, MC and UC recesses was employed in the present study, as this method is the most common form of measuring synovial thickening. For this assessment, a semi-quantitative scoring system which was previously estabilished by Szkularek *et al.*, for small joints of the hand and feet (proximal metacarpophalangeal, interphalangeal and metatarsophalangeal) was used[19]. In this study the scoring system for synovitis and joint effusion showed moderate to optimal interobserver reliability (ICC of 0.61 and 0.78, respectively) for all evaluations[19]. In the present study, the scoring system was modified to determine the presence of synovitis and joint effusion in the same assessment. This decision was made due to the fact that both alterations occur simultaneously in the chronic inflammatory process. However, there was poor interobserver reliability in the assessment of the recesses. The MCP joints used by Skzudlarek *et al.*, are considered joints with a simple anatomical model, in which the subchondral bone and cartilage may be assessed and detection of synovitis is easy[26]. An explanation for different levels of agreement between studies may be that the wrist is a more elaborate joint with diverse recesses and multiple ligament structures[11,12].

The assessment of synovial proliferation in the present study was not carried out with the aid of a power Doppler signal. This decision was made due to the low resolution of the ultrasound device in the assessment of a power Doppler, which could have compromised the results.

In conclusion, there was moderate interobserver reliability for the quantitative measurement of the synovium in the RC recess and poor reliability regarding the MC and UC recesses. The semi-quantitative assessment of the synovium using a previously established scoring system for small joints demonstrated poor interobserver correlations for the RC, MC and UC recesses of rheumatoid wrists. Further studies are needed for the standardization of a quantitative measurement of the synovium in joint recesses of the wrist as well as the validation of semi-quantitative scoring systems for this frequently affected joint in patients with RA.

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MUSCULAR KINETICS AND FATIGUE EVALUATION OF KNEE USING BY ISOKINETIC DYNAMOMETER IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Abstract

Objective: Ankylosing Spondylitis (AS) is an inflammatory disease that is observed with arthritis, sacroiliitis and disability. The aim of the study was to compare the strength and fatigue of knee extensor/flexor muscle group usage by isokinetic in patients with AS with controls.
Methods: Twenty-six AS diagnosed patients and twenty-six healthy volunteers with similar age, height, body weight and gender were included in this study. In both groups the isokinetic tests are conducted by isokinetic dynamometer for every subject. Knee extension/flexion patterns;peak torque, agonist/antagonist ratio and work fatigue isokinetic parameters were evaluated during the knee 60º/s,180º/s and 240º/s angular velocities.
Results: Knee extension/flexion muscle strength in patient group was significantly lower compared to the control group in all angular velocities ($p< 0.05$).
Conclusions: The study showed knee muscle weakness and fatigue in patients with AS compared to the control group.

Keywords: Muscle strength; Dynamometer; Knee; Ankylosing spondylitis; fatigue

Introduction

Ankylosing Spondylitis (AS) is an inflammatory disease of unknown etiology. Inflammation primarily affects the joints and causes secondary changes in these regions. The spine is the fundamentally affected region in AS[1]. In most of the patients, the peripheral joints are mildly affected without showing any deformity. In time, impaired spinal mobility may cause articular instability and force the patients to use their knee muscles more for postural control and for activities of daily living[2,3]. Furthermore, changes in spine give rise to deformities in peripheral joints. Peripheral joint involvement may also affect posture and thus cause disability[3]. Patients suffering from hip joint involvement rarely develop mild knee flexion pattern in knees during walking in order to make the walk more comfortable[2]. Peripheral joint involvement can be present in about 25% of patients as an asymmetrical oligoarthritis predominantly in lower extremities, particularly affecting the knees[4]. On the other hand, systemic inflammation may also affect the knee muscles. Marcora *et al.*, found reduced appendicular muscle mass in patients with long-standing AS compared to healthy controls. This muscle wasting is significantly associated with reduced knee extensors muscle strength and grip strength of the dominant hand[5]. Local inflammation (achilles tendon enthesitis), frequently seen in seronegative spondyloarthritis patients, may affect the knee muscle[6]. Consequently, strength of knee muscles may be affected due to some reasons in AS patients who have a long-standing disease and impaired posture of spine. However, it is not yet clear whether strength of knee muscles may have an effect on AS patients who have no postural disorders.

In addition, for the chance of success it can be important to know which muscle group is mostly affected during the rehabilitation of AS patient. When weakness is suspected in a muscle group, it is useful to evaluate the isokinetic performance in increasing speed in every angle of that muscle[7]. Although isokinetic testing was used to different

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joints in rheumatoid arthritis, fibromyalgia syndrome and in some other rheumatologic based diseases as well, there is few knowledge about peripheral weakness in patients with AS[8-10]. A study detected muscle weakness and fatigue in ankle plantarflexor muscle groups in AS patients compared to the control group[11].

The objective of this study was to measure the strength and fatigue of the knee extensor/flexor muscle group using by isokinetic in AS patients, who do not have postural disorders or peripheral joint involvement; to compare with healthy controls, and to determine the relation of these values with the functional situation.

Material and Methods

Twenty-six male patients between 18-54 years of age diagnosed with AS and referred to Physical Medicine and Rehabilitation division AS unit, and a control group consisting of 26 healthy males between 20-56 ages were enrolled for this study. The patient group was chosen according to Modified New York diagnosing criteria, diagnosed with AS but not in active period. Patients having serious knee injury, having serious lumbar pain, hip pain or knee pain, having some other systemic diseases, limitations in hip and knee joints, and having surgery in lower extremities were not included in this study group. The control group was selected from the hospital staff with similar age and gender. The control group with serious knee trauma, hip, knee and hip osteoarthritis demonstrated by X--rays, other comorbidities and ligament injury were excluded from the study. Informed consent of the subjects was sought and the ethical committee approval was obtained prior to the initiation of the study.

Evaluation parameters

Knee extensor/flexor muscle group isokinetic muscle strength (peak torque) of both groups was evaluated by Biodex System 3PRO Multijoint System isokinetic dynamometer. Before testing AS patients the following evaluations were performed: Body weight-height, visual analog scale (VAS), modified lumbar Schober (MLS), lower extremity range of motion (ROM) as measured by goniometry, presence of enthesitis as determined by Berlin Enthesitis Index (BEI), the activity of the disease as measured by C-reactive protein (CRP), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score and functional status as determined by Bath Ankyolosing Spondylitis Functional Index (BASFI)[12].

Pain

Pain was evaluated by VAS score between 0-10. No pain corresponded to (0), whereas intolerable pain was expressed with (10) points. The severity of the pain was investigated separately if it occurred at night and during resting. The higher points show the severity of the pain[13].

Enthesitis

According to BEI, the patient is asked to evaluate presence of pain during palpation to 12 enthesis areas in the lower extremities. The patient replies with "yes" or "no" and score is determined between 0-12. The score gives an idea about the activity of the disease[12].

Activity of the Disease

BASDAI gives information about the activity of the disease. The evaluated activity is mostly about the presence of inflammation in peripheral joints. Fatigue, axial pain, peripheral pain, morning stiffness and the presence of enthesopathy is evaluated by VAS between 0-10 points. It is accepted as the activity period of the disease, when BASDAI is >4[12,14].

Functional Status

In BASFI scale, 10 daily activities are evaluated. The patient is asked to evaluate each activity by VAS between 0 and 10 according to the difficulty experienced during each activity. The scores show 0= no difficulty, 5= moderate difficulty, 10= maximum difficulty, the total maximum score is determined as 10[15].

Muscle Testing

Isokinetic tests with Biodex System 3PRO Multijoint System isokinetic dynamometer were applied to both groups The reliability of the dynamometer was determined both in healthy group and the AS patient group[16-18]. The tests were performed according to standardizations developed by Wilk *et al*[10]. Warm-up was accomplished on ergonomic bicycle for 10 min. at 60 rpm.

For knee extension/flexion pattern measurement the arms of the dynamometer were held parallel to the leg of the patient having pads fixed dis-

tally. Distal resistance pad was fixed. The stability of the patient on the dynamometer chair was achieved by putting a belt covering the thorax, hip and thigh regions, and the procedure was explained to the patient to ensure good cooperation[10].

Muscle strength is measured better with tests performed with low angular velocities, while high angular velocities are useful for the detection of functional status and endurance of the muscle[7,18,19]. For this reason, slow, moderate and high angular velocities such as 60º/s,180º/s, 240º/s were preferred for the knee extension/flexion pattern[19,21]. The test was performed bilaterally, starting with the dominant side first. Four repetitions were performed at the first two angular velocities in extension/flexion and at the third angular velocity, 20 repetitions were performed. Peak torque (Newtonmetre-Nm) (PT), peak torque/body weight (%) (PT/BW), maximal repetition total work (Joule-J) (MRTW), work/body weight (%) (W/BW), agonist/antagonist ratio (%) (Ag/An) and work fatigue (%) (WF) isokinetic parameters were evaluated at all angular velocities. In order to decrease the occurrence of strain in the muscles, 60 sec. resting period was maintained between each angular velocity[22]. In order to motivate the patients during the test maximal, strength was maintained by verbal instructions. The test was carried out in a quiet and appropriate physical environment with air conditioner.

PT is the highest torque value measured with all velocities in one angular velocity and is expressed in terms of newtonmeter. PT is the most convenient and the most used parameter in isometric test parameters[20]. PT/BW ratio is used to personalize, standardize and interpret isokinetic scores[23]. MRTW is one of the parameters where the relationship between flexion and extension is interpreted and is expressed as Joules[21,24,25]. W/BW is the maximum work (force x distance) produced in a single repetition. This could be a better representation of the functional ability (over PT), because the muscle must maintain the force throughout the range of motion, as opposed to the force at one instant[24]. Ag/An ratio evaluates the balance between the knee extensor/flexor muscles. With this ratio, the weakest muscle in the muscle group can be determined. The ag/an ratio is calculated as the ratio between the peak values of the concentric torque of the flexor muscles, and the concentric peak torque of the extensor of the knee. The hamstring action as antagonist is directly proportional to its ability to generate concentric strength[26-28]. WF test measures the weariness of the muscle after an excess number of repetitions. This is calculated as the percentage of the difference between the production of work between the first 1/3 and the last 1/3 repetitions at the 240º/sec. velocity. There is no standardized test to evaluate fatigue. The number of trials to evaluate fatigue is between 20-100. In this study, we used 20 trials. This parameter acts as a dependent variable used to evaluate the strength of the muscle and shows the endurance capacity of the muscle[29,30].

Statistical Analysis

The comparison demographic data of both groups were assessed using Mann–Whitney U tests. Two way ANOVA was used in the group evaluations for comparisons between the groups for PT, PT/BW, MRTW, W/BW, AG/AN and dominant versus non-dominant leg isokinetic parameters. The comparison WF of both groups was assessed using Mann–Whitney U tests. The correlation between PT parameter and BASFI, VAS and ROM was assessed by Pearson correlation test. $p<0.05$ values were accepted as statistically significant.

Results

Age, gender, height, weight, MLS, VAS, CRP, BASFI, BASDAI, and BEI values are presented in Table I. There was no statistically significant difference between the two groups for age, gender, height and weight. The test group was not in the active stage; BASDAI values were <4, BEI 0-2 and CRP was <5[11]. Resting and night VAS values were below 5. Hip flexion and knee extension and flexion ROM measurements for isokinetic tests performed with the goniometer's dynamometer revealed no statistically significant difference between the two groups. In both groups, the right side was the dominant side.

Significantly lower values than the healthy control group were observed in AS patients for the knee PT, PT/BW, MRTW and W/BW parameters evaluated with bilateral extension and flexion performed at the angular velocities of 60º/s, 180º/s and 240º/s ($p<0.001$) (Tables II, III). There was no significant difference between the groups in dominant versus non-dominant leg for bilateral knee movement tested at 60º/s, 180º/s and 240º/s. Statistical eva-

Table I. Characteristics of patients with ankyolosing spondylitis (AS) and the control group (CG)

	AS (n:26)	CG (n:26)	p
Age/mean	37.04±8.85	38.46±10.35	0.464
Height	172	174.31	0.139
Weight	75.19	73.42	0.288
Modified lumbar Schober	18.72±2.62		
BASFI	3.12±2.20		
BASDAI	2.28±1.41		

luation for the Ag/An parameter revealed a significant difference in AS patients compared to the healthy controls for bilateral knee movements tested at 60º/s ($p<0.05$). There was no statistically significant difference in Ag/An scores for bilateral knee movement tested at 180º/s and 240º/s. There was no significant difference for Ag/An values between the dominant and non-dominant side in AS patients (Table IV).

A significant decrease of work fatigue in AS patients was determined for knee extensors at 240º/s after 20 repetitions ($P<0.05$) (Table V).

There was no statistical correlation between muscle strength measurements and BASFI, VAS and ROM ($p>0.05$).

Discussion

Isokinetic dynamometer is an instrument which helps us to measure the joint movements in all angles, in constant angle speed, allowing maximal muscle contraction along with the measurement of the contraction and muscle capacity objectively[8]. In isokinetic measurements for painful chronic diseases like osteoarthritis, rheumatoid arthritis, fibromyalgia syndrome and chronic low back pain angular velocities such as 60º/s 180º/s, 240º/s and 300º/s angular velocities were used and many repetitions were employed[8,9,18-22,25,31]. There is no standardized model for isokinetic measurement in AS patients, so we have used 60º/s 180º/s, 240º/s angular velocities in our study. The most valid parameter in isokinetic evaluation is the PT which may be affected by body mass index and the PT/BW value is important in this issue as well as the MRTW value that reflects the balance between flexor and extensor muscle groups. The W/BW as one of the best indicator of PT values is also important[20,21,23-25]. The parameters above at all angular velocities showed significant lower scores for knee extensor and flexor muscles on both sides in AS patients as compared to the controls in this study. Although 60º/s Ag/An ratio was significantly decreased on both sides in the AS group, there was no significant difference between the Ag/An ratio for bilateral knee obtained at the angular velocities of 180º/s and 240º/s in the AS and the healthy control groups. Also, higher velocities reflect the Ag/An ratio better than lower velocities[8]. Since the extension and flexion losses for the knee joint are seen together in AS patients, there was no statistically significant difference in Ag/An scores. The low level of the work fatigue showed that the work of knee extensor is decreased in the first third and the last third period of the work thus indicating a decrease in endurance capacity of the muscles. The main finding of this study indicates that in AS patients the tested knee muscles were significantly weaker and the muscle endurance capacity decreases compared to apparently healthy controls. Interestingly, the results of this study show that the forces at different angles and endurance of the tested muscles related to non-involvement joints in patients with AS are lower than those of control subjects.

The reason of the decrease in muscle strength in AS patients is complicated[32]. The decreased muscle strength in inflammatory diseases is related to inflammation, pain, stiffness, inactivity, degeneration at the joints, fatigue and the primary symptoms of AS patients are also pain, enthesis and stiffness[1,33,34]. Inactivity that is related to pain, inflammation and stiffness has a great role in the weakness of muscles in AS patients. Muscle weakness develops in the first week of inactivation. After that, weakness increases rapidly. Decreased physical activity or inactivation results with atrophy in the muscles, which further leads to weakness in the muscles, causes a decrease in neuromuscular performance and thus a decrease in the functional capacity ensues. But, this process does not have to be similar for all muscle groups[1,32,35]. In a study on inflammatory disease, the decrease in dynamic and isometric muscle strength was shown in early stages[36]. Inflammation raises catabolic stimulations including IL-6, IL-1 and TNF alpha cytokine, each case causes muscle protein catabolism. Consequently, inflammatory conditions

Table II. Means of parameters evaluated by the isokinetic test for the knee

Group	AS				CG			
M	Extensors		Flexors		Extensors		Flexors	
S	R	L	R	L	R	L	R	L
PT (Nm)								
60°/s	139.56±28.21	139.67±24.99	61.63±13.52	60.20±10.74	174.29±36.09	171.82±33.97	83.92±22.78	83.27±18.18
180°/s	105.43±21.64	104.90±16.91	58.19±12.72	63.00±14.87	122.78±25.37	125.29±27.36	75.55±19.59	79.16±16.06
240°/s	96.61±16.52	95.52±12.40	67.25±13.11	74.79±15.46	110.62±23.21	111.62±25.31	82.21±18.68	89.35±17.73
PT/BW (%)								
60°/s	187.48±42.10	187.96±38.37	82.50±18.27	81.05±16.97	235.89±36.53	233.25±36.07	114.30±29.67	113.55±24.33
180°/s	141.29±29.45	141.06±25.38	78.33±19.08	85.00±22.34	166.09±24.19	170.13±29.12	103.32±27.44	108.43±23.23
240°/s	129.58±23.97	127.96±17.16	90.70±19.97	101.08±25.27	147.80±22.45	149.88±30.49	110.54±24.98	120.35±23.56
MRTW (J)								
60°/s	147.21±30.92	147.34±25.53	65.29±18.09	64.79±15.48	187.88±40.05	183.04±38.45	98.94±29.30	97.61±24.44
180°/s	117.61±27.48	117.19±17.70	49.42±18.42	47.22±15.21	141.06±30.09	141.47±32.17	73.95±23.29	70.15±19.99
240°/s	100.84±21.67	100.61±15.39	40.20±15.90	38.78±14.09	119.89±24.68	121.56±28.13	59.78±18.78	56.88±19.76
W/BW(%)								
60°/s	191.60±57.17	198.19±38.32	91.77±30.08	94.00±43.17	254.58±43.06	248.01±37.12	134.72±38.06	132.98±31.10
180°/s	157.56±36.71	157.45±26.62	66.22±24.23	63.75±21.74	190.51±26.60	191.65±30.90	100.63±29.83	95.69±25.01
240°/s	135.28±30.17	135.90±22.30	54.27±21.31	52.43±20.09	162.02±21.66	164.65±28.71	81.02±22.51	78.15±23.49

R: right, L: left. AS: ankylosing spondylitis, CG: control group. M: muscle, S: side.

may affect muscle mass and cause loss of strength[37,38]. The chronic inflammatory response is likely to be a major cause of muscle wasting in AS patients. Marcoro *et al.*, showed that patients with long-standing AS have significant losses of lean mass in arms and legs. This muscle wasting is significantly associated with reduced knee extensor muscle strength and grip strength of the dominant hand[5]. The other reason of the decrease in muscle strength is fatigue in AS patients. There are a lot of mechanisms responsible for the development of muscle fatigue[19]. An exceeding fatigue in AS patients is acquainted with activity of the disease, functional disability, and global wellness[34]. The fatigue in muscles is responsible in motor control deficit and in posture and balance changes[1,12,24,34]. Considering the relationship between the postural changes and fatigue, fatigue may play an important role in postural changes in AS patients. In this study, we determined that the muscle endurance capacity decreases in the patient group, even though we used the least number of trials recommended in the literature. According to this result, the muscle weakness can be the cause of fatigue in AS patients, or fatigue seen in most of the AS patients can be one of the causes of muscle weakness.

The other possible reasons for muscle strength decrease mechanism are local inflammation (enthesitis) and proprioception deterioration, which is related to it. Enthesitis, which is the basic mechanism of pathogenesis in AS patients, is an inflammation of enthesis, the location where the point at which a tendon or ligament or muscle inserts into bone. Enthesitis leads to instable joint structure and these changes apparently cause muscle weakness in AS patients. Furthermore, the attachment sites of the ligamentous formations harbor the afferent nerve endings, which regulate the information about posture and are responsible for joint motion; therefore, a pathology at this site results with changes in proprioception in AS patients. Insufficiency of proprioception may a cause to decrease in muscle strength[32,35,39-41]. Consequently, the muscle weakness detected in our study may have correlation with the disorders in proprioceptors that is related to enthesitis.

Table III. p values of isokinetic testing in AS versus CG

	Knee			
	AS-CG		ND-D leg	
	Extensor	Flexor	Extensor	Flexor
PT (Nm)				
60°/s	<0.001	<0.001	0.603	0.755
180°/s	<0.001	<0.001	0.829	0.183
240°/s	<0.001	<0.001	0.990	0.055
PT/BW (%)				
60°/s	<0.001	<0.001	0.635	0.803
180°/s	<0.001	<0.001	0.723	0.215
240°/s	<0.001	<0.001	0.954	0.071
MRTW (J)				
60°/s	<0.001	<0.001	0.727	0.836
180°/s	<0.001	<0.001	0.723	0.215
240°/s	<0.001	<0.001	0.873	0.525
W/BW (%)				
60°/s	<0.001	<0.001	0.724	0.867
180°/s	<0.001	<0.001	0.930	0.484
240°/s	<0.001	<0.001	0.830	0.563

AS: ankylosing spondylitis, CG: control group.
ND: nondominant, D: dominant.

Conclusions

In this study, we detected fatigue and muscle weakness in knee extensor and flexor muscle groups in AS patients compared to the control group. Rehabilitation of the muscle weakness and fatigue is important to delay the development of the posture disorder and thus prevent the development of balance problems in AS patients. More studies are needed to be done on this subject, in order to detect the effect of exercises especially on the lower extremities, on the activity of the disease, on the posture of the patient and on the functional status in early stages of the disease before any postural change occurs in AS patients. The results of this study showed us how important the effect of muscle weakness in maintaining posture in AS patients is. As a conclusion, functional disability in patients with AS is not only developed by axial deformities, but may also by muscular weakness and fatigue affect. Based on this knowledge, it should be reminded that

Table IV. Means of agonist/antagonist parameters evaluated by isokinetic test (%)

	AS		CG		
Group	R (F/E)	L (F/E)	R (F/E)	L (F/E)	p
Knee-AV 60°/s	45.30±12.32	43.50± 6.56	48.28±8.77	48.68± 7.43	0.001
180°/s	56.55±14.32	61.00±16.84	61.84±11.35	80.40±16.22	0.116
240°/s	72.37±18.91	80.05±17.49	75.31±14.65	82.01±17.28	0.312

R: right, L: left. AS: ankyolsing spondylitis, CG: control group. E:extensor, F: flexor.

Table V. Means of work fatique parameters evaluated by the isokinetic test (%)

	Group		AS	CG	p
Knee 240°/s	Extensor	R	35.35 (2.7-64.0)	27.50 (-9.0-47.8)	0.034
		L	35.90 (3.2-65.2)	23.50 (-7.6-45.3)	0.030
	Flexor	R	38.75 (10.2-69.4)	24.30 (-8.3-79.7)	0.253
		L	41.10 (16.6-68.8)	30.70 (-6.0-71.0)	0.249

R: right, L: left. AS: ankyolsing spondylitis, CG: control group. p<0.05

isokinetic evaluation is also important in the follow up of the efficacy of the scheduled effective rehabilitation in patients with AS.

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PSYCHOMETRIC PROPERTIES OF THE PORTUGUESE VERSION OF THE PAIN SELF-EFFICACY QUESTIONNAIRE

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Abstract

Aims: This study sought to translate and evaluate the psychometric properties of a European Portuguese version of the Pain Self-Efficacy Questionnaire (P-PSEQ), in order to enable its use in clinical and cross-cultural studies.

Material and Methods: The Pain Self-Efficacy Questionnaire was translated into European Portuguese and then back-translated into English. A consensus version of the translated version was pre-tested with a pilot sample, followed by cognitive debriefing, resulting in a final version of the measure.

A convenience sample of 174 Portuguese adults with chronic musculoskeletal pain completed the Portuguese Pain Self-Efficacy Questionnaire (P-PSEQ) and criterion measures of pain intensity (Numerical Ratings Scale), pain interference (Portuguese Brief Pain Inventory Interference Scale), quality of life and general health (SF-12), and psychological functioning (Hospital Anxiety and Depression Scale). Cronbach's alpha and composite reliability coefficients were computed as measures of reliability, and confirmatory factor analysis was performed. Pearson correlation coefficients between the P-PSEQ score and the criterion measures were computed to evaluate the construct validity of the scale.

Results: The P-PSEQ demonstrated good to excellent reliability (Cronbach's alpha = 0.88 and Composite reliability = 0.92), and showed moderately strong associations with the criterion measures in the hypothesized directions, supporting its construct validity. Additionally, the confirmatory factor analysis supported a single factor solution, as hypothesized.

Conclusions: The findings provide strong support for the reliability and validity of the P-PSEQ. Research is needed to determine the responsivity of the P-PSEQ and to establish the generalizability of the results in other samples of Portuguese patients with chronic pain.

Keywords: Pain; Pain Assessment; Intractable Pain; Self-Efficacy.

Introduction

Biopsychosocial models of chronic pain hypothesize that psychological and social factors play a key role in the adjustment to chronic pain. Pain self--efficacy – that is, the belief or confidence in one's ability to engage in a specific behaviour or other action to achieve desired goals despite pain[1-4] – has been one of the factors thought to mediate the impact of pain on disability and depression[1,5-7]. There is strong support for the importance of pain self-efficacy across a broad range of pain populations and conditions, with patients endorsing higher levels of self-efficacy reporting lower levels of pain intensity, disability, depression and anxiety[1,4,5,8-14], and higher quality of life and general health[12,15]. Furthermore, self-efficacy is thought to influence thoughts and feelings, which in turn can affect functioning[2,4,16-18]. Self-efficacy may also influence the use of pain coping strategies via its effects on readiness to engage in those coping responses[4,11,19-21], with patients endorsing lower levels of self-efficacy being more likely to use passive coping responses and to catastrophize in response to pain[4,19]. On the other hand, patients endorsing higher levels of self-efficacy have been shown to

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use more adaptive coping responses[2,11,19,22], even after controlling for demographic and medical status variables[11]. Given the importance of self-efficacy in the adaptive management of chronic pain, multidisciplinary treatment programs often aim to increase pain self-efficacy as a way to increase patients' quality of life and enhance positive physical and psychological outcomes in response to treatment.

In order to determine the effects of treatment on pain self-efficacy as well as evaluate its potential role in adjustment to pain, a valid and reliable measure of pain self-efficacy is needed. Moreover, translated measures of the construct are needed for cross-cultural research to determine if the same treatments have similar effects on outcomes across cultures. The Pain Self-Efficacy Questionnaire (PSEQ)[4], which was developed from Bandura's Social Learning theory[2], is the only pain self-efficacy measure developed specifically to assess confidence of patients to engage in a number of activities of daily living, despite pain. The PSEQ was developed to be applicable to patients with all chronic pain conditions and to be easy to understand. It assesses self-efficacy regarding a wide range of functions such as household chores, social activities, work, and coping with pain without medication, yet takes less than two minutes to complete. Previous research shows the PSEQ to be reliable and to have both factorial and predictive validity across a number of languages, cultures, and clinical settings[4,9,12,14,23-33].

Although a Portuguese version of the PSEQ has been developed, it was translated and validated to be used in Brazilian populations[14]. However, a European Portuguese version of the PSEQ has not yet been translated and validated. A European Portuguese version of the PSEQ that is distinct from the Brazilian Portuguese version is needed because of the cultural and language differences between European Portuguese (as spoken in Portugal) and Brazilian Portuguese.

The purpose of this study is to translate and evaluate the psychometric properties of a European Portuguese version of the Pain Self-Efficacy Questionnaire (P-PSEQ), to enable its use in clinical and cross-cultural studies. Based on previous research with the PSEQ in other samples, we hypothesized that: (1) the internal consistency (Cronbach's alpha) of the P-PSEQ would be good to excellent (above 0.80)[34]; (2) the predictive validity of the P-PSEQ would be supported via a pattern of significant negative associations with pain intensity (*r* between -0.12 and -0.39)[4,5,9,12,14,30] and pain interference (*r* between -0.31 and -0.70)[5,9,12,14,30], anxiety (*r* between -0.49 and -0.56)[4,12] and depression (*r* between -0.48 and -0.66)[4,9,12,30] and moderate to strong correlations (i.e., 0.30 or larger) with measures of global physical functioning and psychological functioning[12]; and (3) a factor analysis of the P-PSEQ items would yield one factor that explains a substantial portion of the variance in the items.

Materials and Methods

Subjects

One-hundred and seventy four patients, all over 18 years old, with chronic musculoskeletal pain from seven health care institutions in northern and central Portugal completed the study protocol. Inclusion criteria included: (1) experiencing pain due to a diagnosed musculoskeletal condition for at least 3 months; (2) being at least 18 years old; (3) and being willing to participate in a research. Exclusion criteria included: (1) having a physical or cognitive disability which prevented participation, (2) known/diagnosed severe depression or other severe mental health condition, and (3) pain due to fibromyalgia. As can be seen in Table I, the participants' ages ranged from 23 to 90 years (M = 59.18, SD = 16.11), 60.2% were married or living with a significant other, 26.3% were either single or divorced/separate and 8.8% of the participants were widowed. The majority of the participants were female (60.2%). Most participants had a history of chronic pain for at least two years (65.3%), and 38.8% reported having had pain for more than 10 years.

Measures

All participants were asked to provide basic demographic and pain history information (e.g. age, sex, marital status, level of education, professional status, duration of pain, pain location and cause of pain). They were also asked to rate their pain intensity at its maximum, minimum and on average during the previous 24hours on a 0 to 10 Numerical Rating Scale (NRS). Research supports the validity of the NRS as a measure of pain intensity[35].

The Portuguese BPI Pain Interference subscale was used to assess pain interference across seven daily life activities (general activity, mood, walking

Table I. Demographic Information

	Portuguese sample	
	Frequency (%)	Mean (SD)
Age	–	59.18 (16.11)
Sex (female participants)	103 (60.2)	–
Education Level		
Primary education	76 (44.7)	–
Incomplete High School	35 (20.6)	–
High School	27 (15.9)	–
College	32 (18.9)	–
Marital Status		
Single	31 (18.1)	–
Married/Living with other	103 (60.2)	–
Divorced	15 (8.8)	–
Widow	22 (12.9)	–
Professional Status		
Employed	68 (39.8)	–
Unemployed	19 (11.1)	–
Retired (due to disability)	47 (27.5)	–
Retired (normal age)	37 (21.6)	–
Duration of Pain		
3 months to 1 year	36 (21.2)	–
1 to 2 years	23 (13.5)	–
2 to 10 years	45 (26.5)	–
More than 10 years	66 (38.8)	–

ability, normal work, relations with other people, sleep, and enjoyment of life) on 0 to 10 numerical rating scales. Research supports the validity and reliability of BPI in several samples, cultures and languages, including European Portuguese[36-38]. The Portuguese SF-12[39] was used as a measure of perceived Physical (Physical Component Summary, PCS) and Mental (Mental Component Summary, MCS) health status, with higher scores (ranging from 0 to 100) indicating better health. The Portuguese version has evidence supporting its reliability and validity[39]. The Portuguese version of the Hospital Anxiety and Depression Scale (HADS)[40] was used to assess psychological functioning. It asks respondents to rate the severity of 14 depressive or anxiety symptoms on 4-point Likert scales, and has shown good reliability and validity[40]. The possible scores range from 0 to 21. Higher scores reflect higher anxiety or depressive symptomatology. The Portuguese Pain Self-Efficacy Questionnaire (P-PSEQ)[4] was used to assess pain-related self-efficacy beliefs. The 10-item scale assesses confidence of patients to engage in a number of activities of daily living despite pain on 0 - 6 numerical rating scales, where 0 = "not at all confident" and 6 = "completely confident". Higher scores (ranging from 0 to 60) reflect stronger self-efficacy beliefs.

Procedure

The initial phase of the study involved translating and back-translating the instructions and items of the PSEQ. Through expert discussion, we arrived at a consensus version, and verified that its content assessed the same construct as the original. To ensure that the individuals in our population understood the instructions and scale items, we then performed a pre-test of the P-PSEQ in a pilot sample of 15 patients, followed by a cognitive debriefing. After making final modifications based on the results of the cognitive testing, we invited a sample of patients with chronic musculoskeletal pain to complete all of the study measures. All patients who agreed then signed an informed consent form and were administered the 0-10 NRS, P-BPI Interference Scale, SF-12, HADS and P-PSEQ questionnaires.

Data Analysis

Means and standard deviations of the study variables were computed for descriptive purposes. Internal consistency of the P-PSEQ was assessed by computing a Cronbach's alpha. Composite reliability was also computed[41,42]. Then, to test a hypothesized one-factor model for the P-PSEQ items, we performed a confirmatory factor analysis (CFA). Model quality of fitness was evaluated using the Chi Square (χ^2/df), Comparative Fit Index (CFI), Parsimony Comparative Fit Index (PCFI), Goodness of Fit Index (GFI), Parsimony Goodness of Fit Index (PGFI), and Root Mean Square Error of Approximation (RMSEA). The model was considered to have acceptable fit if χ^2/df was less than 5 [42-44], CFI and GFI higher than 0.8[42], the PCFI and PGFI were both higher than 0.6[42,45,46], the RMSEA was lower than 0.10[42,43]. The model was considered to have a good fit it χ^2/df was less than 2[42-44], the CFI and GFI were higher than 0.9[42], PCFI and PGFI higher than 0.8[42,45], and the RMSEA was lower than 0.08[43]. Model adjustment was performed, step-by-step, via Modification Indices analysis (higher than 11; $p<0.001$)[42,43] and based on theory. We also used the Expected Cross-Validation Index (ECVI), to compare fit after models' adjustment, with lower ECVI

Table II. Descriptive Statistics Study Variables

	Mean	(SD)	Min-Max
Pain Intensity (NRS)			
Maximum (last 24 hours)	5.70	(2.49)	0-10
Minimum (last 24 hours)	2.97	(2.25)	0-9
Average Pain	4.59	(2.18)	0-10
Pain Interference (P-BPI)	4.03	(2.44)	0-9
Physical Component Summary (SF-12)	39.07	(23.51)	0-100
Mental Component Summary (SF-12)	57.02	(20.39)	10-100
Anxiety (HADS-A)	7.58	(3.91)	1-20
Depression (HADS-D)	6.07	(3.87)	0-17
Self Efficacy (P-PSEQ)	40.83	(11.31)	6-60

Note: NRS = Numerical Rating Scale of pain intensity; P-BPI = Portuguese Brief Pain Inventory – Interference scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety scale; HADS-D = Hospital Anxiety and Depression Scale – Depression scale; P-PSEQ = Portuguese Pain Self-Efficacy Questionnaire.

reflecting better fit. Finally, Pearson correlation coefficients between the P-PSEQ score (or scores) and the criterion measures were computed to evaluate the construct validity of the scale. Statistical analyses were performed using software PASW Statistics (v.18, SPSS Inc. Chicago, IL) and AMOS (v.18, SPSS Inc. Chicago, IL).

Results

Descriptive information

As can be seen in Table II, the study participants reported mild to moderate levels of pain severity (NRS) and pain-related disability (BPI Pain Interference). Mean scores of SF-12 Physical Component Summary and SF-12 Mental Component Summary indicate significant dysfunction in these areas, relative to published norms for healthy individuals[39]. Overall, the mean scores on the HADS suggested mild levels of anxiety, similar to individuals with a variety of medical disorders, and normal ratings of depressive symptoms[40]. Finally, the sample was characterized by relatively high levels of self-efficacy, on average, according to the cut offs suggested by Tonkin[47] (mean > 40), and when compared to normative datasets for patients with chronic pain, as reported by Nicholas and colleagues[48] in a study of 6124 patients from across the Australian state of New South Wales.

Reliability

The P-PSEQ's internal consistencies (Cronbach's alphas) in our sample and in previous samples are listed in Table III. The scale shows a very good level of internal consistency in our sample that is consistent with other samples, with an alpha coefficient of 0.88[34]. Values for alpha if single items are deleted are comparable to the overall alpha, sug-

Table III. Reliability Analyses of Brief Pain Inventory Interference Scale

P-PSEQ Total scale or item	Our sample	Australia[4]	Brazil[14]	China[12]	Iran[9]
Cronbach's Alpha					
P-PSEQ Total scale	**0.88**	**0.92**	**0.90**	**0.93**	**0.92**
Cronbach's Alpha if item deleted (Item Total Correlation)					
P-PSEQ Items					
Item 1	0.87 (0.48)	- (0.70)	- (0.79)	0.92 (0.72)	–
Item 2	0.86 (0.56)	- (0.72)	- (0.73)	0.92 (0.71)	–
Item 3	0.86 (0.61)	- (0.71)	- (0.67)	0.92 (0.66)	–
Item 4	0.85 (0.70)	- (0.83)	- (0.71)	0.92 (0.66)	–
Item 5	0.86 (0.61)	- (0.74)	- (0.76)	0.92 (0.71)	–
Item 6	0.85 (0.67)	- (0.79)	- (0.77)	0.92 (0.81)	–
Item 7	0.88 (0.43)	- (0.67)	- (0.50)	0.93 (0.62)	–
Item 8	0.86 (0.62)	- (0.79)	- (0.82)	0.92 (0.80)	–
Item 9	0.85 (0.72)	- (0.84)	- (0.80)	0.92 (0.78)	–
Item 10	0.86 (0.63)	- (0.84)	- (0.79)	0.92 (0.75)	–

Note: P-PSEQ = Portuguese Pain Self-Efficacy Questionnaire

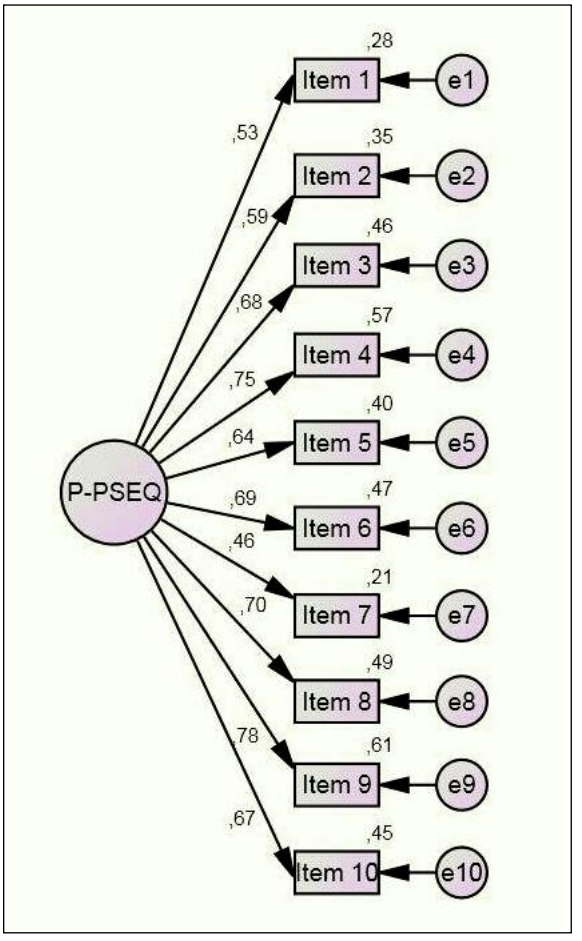

Figure 1. Confirmatory Factor Analysis: Initial Model $\chi^2(35) = 155.58$ ($p<0.001$); $\chi^2/df = 4.44$; CFI = 0.83; PCFI = 0.65; GFI = 0.84; PGFI = 0.54; RMSEA = 0.14 ($p<0.001$); ECVI = 1.15

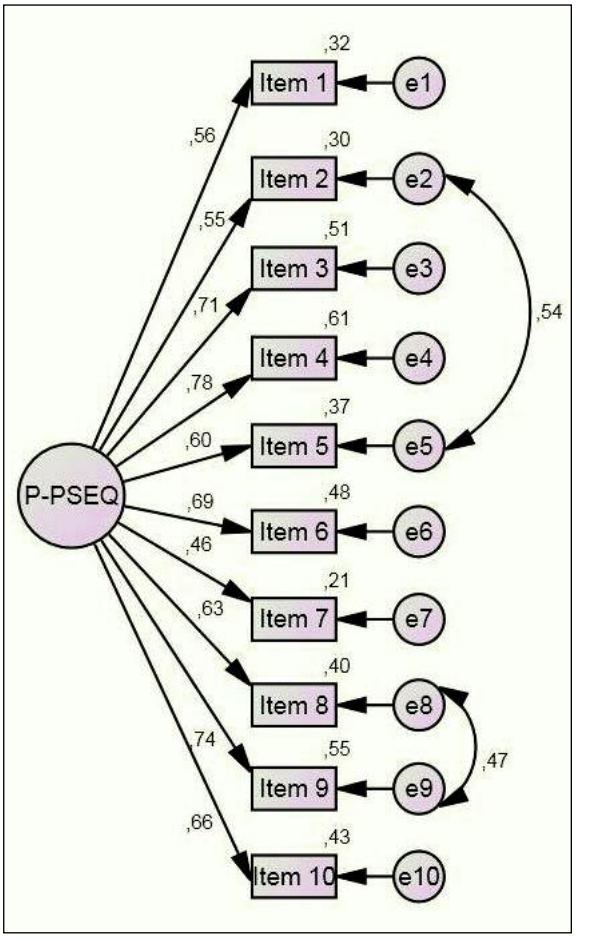

Figure 2. Confirmatory Factor Analysis: Final Model $\chi^2(33) = 66.95$ ($p<0.001$); $\chi^2/df = 2.03$; CFI = 0.95; PCFI = 0.70; GFI = 0.93; PGFI = 0.56; RMSEA = 0.08 ($p=0.05$); ECVI = 0.65

gesting that no item detracts from the reliability of the measure. Additionally, the Composite Reliability coefficient[41,42] of 0.92 indicates excellent reliability[34,41,42,49].

Factor Analysis

A factor analysis of the PSEQ in the original scale development sample resulted in a single factor that accounted for 59% of the variance. This result has been replicated in other samples of patients from Brazil[14] and China[12]. We used a confirmatory factor analysis, using maximum likelihood to estimate model parameters, to determine the fit of a single factor model. Four of the seven combined fit indices for the CFA supported a one-factor solution with acceptable fit. However, the fitness quality of the one-factor solution appeared somewhat limited in our sample [$\chi^2(35) = 155.58$ ($p<0.001$); $\chi^2/df = 4.44$; CFI = 0.83; PCFI = 0.65; GFI = 0.84; PGFI = 0.54; RMSEA = 0.14 ($p<0.001$); ECVI = 1.15] (Figure 1).

Inspection of P-PSEQ items suggests that some items have very similar content, which could potentially explain the reduced fitness levels for the one-factor solution. For example, Item 2 ("I can do most household chores (e.g. tidying-up, washing dishes, etc.), despite the pain") and Item 5 ("I can do some form of work, despite the pain. ("work" includes housework, paid and unpaid work)") appear to assess a very similar domain, as do Item 8 ("I can still accomplish most of my goals in life, despite the pain") and Item 9 ("I can live a normal lifestyle, despite the pain"). Based on an inspection of the modification indexes, specific error terms

Table IV. Correlations with Measures of Pain Intensity, Physical Dysfunction and Psychological Functioning

Scale	Self-Efficacy (P-PSEQ)
Pain Intensity (NRS)	
Maximum (last 24 hours)	-0.27**
Minimum (last 24 hours)	-0.32**
Average Pain	-0.28**
Pain Interference (P-BPI)	-0.41**
Physical Functioning (SF-12, PCS)	0.51**
Mental Health (SF-12, MCS)	0.46**
Anxiety (HADS-A)	-0.39**
Depression (HADS-D)	-0.55**

**p < 0.01
Note: P-PSEQ = Portuguese Pain Self-Efficacy Questionnaire; NRS = Numerical Rating Scale of pain intensity; P-BPI = Portuguese Brief Pain Inventory – Interference scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety scale; HADS-D = Hospital Anxiety and Depression Scale – Depression scale

were correlated sequentially, which resulted in a new model (Figure 2) that maintained all the items of the original P-PSEQ.

After taking into account the error term correlations, the combined fit indices for the CFA, support the one factor solution hypothesized [$\chi^2(33) = 66.95$ ($p<0.001$); $\chi^2/df = 2.03$; CFI = 0.95; PCFI = 0.70; GFI = 0.93; PGFI = 0.56; RMSEA = 0.08 (p=0.05); ECVI = 0.65], with six of the seven combined fit indices for the CFA supporting this solutions, with acceptable to good fit. This new model revealed a goodness of fit significantly higher than the initial model [$\chi^2(33) = 66.95$ ($p < 0.001$), and ECVI considerably different: 1.15 *vs.* 0.65].

Correlational Analysis

Table IV presents the Pearson correlation coefficients computed between the P-PSEQ score and the criterion variables. As hypothesized, statistically significant negative associations were found between the self-efficacy score and pain intensity [ranging between -0.27 and -0.32, $p < 0.01$], pain interference [$r = -0.41$, $p < 0.01$], anxiety [$r = -0.39$, $p < 0.01$] and depression [$r = -0.55$, $p < 0.01$]. Moreover, a statistically significant positive association was found between the P-PSEQ score and the SF-12 Physical Health score [$r = 0.51$, $p < 0.01$] and SF-12 Mental Health score [$r = 0.46$, $p < 0.01$]. All of the significant associations were in the hypothesized directions and showed magnitudes that were within the anticipated ranges, with the exception of anxiety, which was slightly lower than expected, although even for this criterion a moderate association with self-efficacy in the hypothesized direction was found.

Discussion

Consistent with previous findings for other versions of the PSEQ, our results provide strong support for the reliability and validity of the Portuguese PSEQ. Its internal consistency (Cronbach's alpha) is greater than 0.80, indicating good reliability. Moreover, its Composite Reliability coefficient of 0.92 indicates excellent reliability[34,41,42,49]. These values are similar to those found in the original scale development sample and other translated versions of the measure[4,9,12,14]. In addition, the results of a confirmatory factor analysis support a one factor solution[41-46,50] and provides further support for a high level of internal consistency. The correlation coefficients between P-PSEQ scale score and criterion measures are consistent with those found in previous studies[4,9,12,14,30], and support the validity of the P-PSEQ.

Consistent with previous research[1,4,5,8-14], our findings support the importance of self-efficacy as a predictor of adjustment to chronic pain, given its significant associations with pain intensity, physical and psychological functioning (pain interference, anxiety and depression), as well as with global quality of life and general health[12,15]. As a group, the findings from the current and previous studies suggest that the concept and effects of pain self-efficacy are similar across cultures, in line with the findings available for the effects of self-efficacy beliefs on performance[17,51].

There are a number of study limitations that should be considered when interpreting the findings. First, we employed a cross-sectional correlational design. As a result, we were unable to examine the test-retest stability of the P-PSEQ. Also, such a design does not allow for an evaluation of the causal effects of self-efficacy on functioning. Further research is needed to study the stability of P-PSEQ score over time, as well as to determine the potential beneficial effects of interventions that increase pain self-efficacy beliefs. Second, the study sample was one of convenience. We were not able to determine how representative the sample is of

the population of patients in Portugal with chronic musculoskeletal pain. Research is therefore needed to help establish the generalizability of the findings. Third, we did not administer other measures of self-efficacy to help establish the convergent validity of the P-PSEQ. Additional research is needed to help determine the extent of overlap between the P-PSEQ and other pain self-efficacy measures.

Nevertheless, our findings provide support for the reliability and validity of the Portuguese PSEQ, and suggest that the measure may be useful for understanding the importance of the self-efficacy concept to pain and adjustment to pain in Portuguese patients with chronic pain, as well as for cross-cultural research examining similarities and differences in the role that self-efficacy plays in patients from Portugal and patients from other countries and cultures.

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PHYSIOTHERAPY IN HIP AND KNEE OSTEOARTHRITIS: DEVELOPMENT OF A PRACTICE GUIDELINE CONCERNING INITIAL ASSESSMENT, TREATMENT AND EVALUATION

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Abstract

Background: An update of a Dutch physiotherapy practice guideline in Hip and Knee Osteoarthritis (HKOA) was made, based on current evidence and best practice.

Methods: A guideline steering committee, comprising 10 expert physiotherapists, selected topics concerning the guideline chapters: initial assessment, treatment and evaluation. With respect to treatment a systematic literature search was performed using various databases, and the evidence was graded (1-4). For the initial assessment and evaluation mainly review papers and textbooks were used. Based on evidence and expert opinion, recommendations were formulated. A first draft of the guideline was reviewed by 17 experts from different professional backgrounds. A second draft was field-tested by 45 physiotherapists.

Results: In total 11 topics were selected. For the initial assessment, three recommendations were formulated, pertaining to history taking, red flags, and formulating treatment goals. Concerning treatment, 7 recommendations were formulated; (supervised) exercise therapy, education and self management interventions, a combination of exercise and manual therapy, postoperative exercise therapy and taping of the patella were recommended. Balneotherapy and hydrotherapy in HKOA, and thermotherapy, TENS, and Continuous Passive Motion in knee OA were neither recommended nor discouraged. Massage therapy, ultrasound, electrotherapy, electromagnetic field, Low Level Laser Therapy, preoperative physiotherapy and education could not be recommended. For the evaluation of treatment goals the following measurement instruments were recommended: Lequesne index, Western Ontario and McMaster Universities osteoarthritis index, Hip disability and Osteoarthritis Outcome Score and Knee injury and Osteoarthritis Outcome Score, 6-minute walktest, Timed Up and Go test, Patient Specific Complaint list, Visual Analoge Scale for pain, Intermittent and Constant OsteoArthritis Pain Questionnaire, goniometry, Medical Research Council for strength, handheld dynamometer.

Conclusions: This update of a Dutch physiotherapy practice guideline on HKOA included 11 recommendations on the initial assessment, treatment and evaluation. The implementation of the guideline in clinical practice needs further evaluation.

Keywords: Guideline; Osteoarthritis; Physiotherapy; ICF.

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Introduction

The physiotherapist plays an important role in the health care process of the patients with hip and

knee osteoarthritis and could be recommended, based on evidence in literature.

In 2001 the *KNGF Guideline for physiotherapy in patients with Hip and Knee Osteoarthritis (HKOA)* of the *Royal Dutch Society for Physiotherapy* was developed.

A revision was desirable, as since 2001 there has been a substantial increase of publications regarding clinical studies and national[1;2] and international guidelines[3-7] on HKOA. Moreover, the existing Dutch physiotherapy guideline did not include recommendations on outcome measures, and did not provide recommendations on the pre- and postoperative management of patients undergoing hip or knee joint replacement. In addition, the existing Dutch physiotherapy guideline was not using the International Classification of Functioning, Disability and Health (ICF)[8] as a framework to systematically examine a patient's health status and to plan intervention strategies and their evaluation by standardized outcome measures.

The aim of the current revision was to describe evidence-based physiotherapy for HKOA, including initial assessment, interventions, and assessment of outcome, based on the ICF.

Methods

General methodology and Guideline Steering Committee

The revision of the guideline took place between September 2008 and January 2010, following national international methods for guideline development and implementation[9]. The guideline was developed by a Guideline Steering Committee comprising 10 expert physiotherapists. Based on the existing Dutch physiotherapy guideline on HKOA and relevant umbrella reviews, systematic reviews and guidelines published since 2001, two members (WP and TVV) proposed a preliminary list of topics to the Guideline Steering Committee. During a consensus meeting, 11 topics (3 for history taking and examination, 7 for treatment (interventions) and 1 for outcome measures) were selected.

Step 1: Literature search

A literature search was performed up tot June 2009 in the MEDLINE, EMBASE, CINAHL, PEDro, Web of Science and Cochrane Library databases to identify systematic reviews, meta-analysis, and randomized controlled trials (RCTs). The central search strategy 'Osteoarthritis' (MESH) was combined with 'Hip' and "Knee' and other MESH-headings and/or free text words such as 'physiotherapy', 'physical therapy' (MESH), 'physical therapy modalities' (MESH), 'exercise therapy', 'education', and 'self management' (MESH). Studies were selected if sufficient data were reported with regard to the physiotherapy treatment of HKOA patients. In case no systematic review or meta-analysis was found, RCTs were identified and selected for the therapeutic process. The quality of the RCTs was judged by two independent evaluators (WP and MJ) by using Delphi criteria[10]. Textbooks, review articles, umbrella review articles, and current guidelines on other, related conditions.

With respect to the literature on examination and assessment, in addition to the systematic literature search, textbooks, review articles, and current guidelines on other, related conditions were used.

Step 2: Categorizing evidence

The selected literature was critically appraised by assessing the type and quality of the study design. Evidence was graded according to the EBRO (Evidence Based Recommendation Development) (see Table I), which is in line with international classification schemes[11], such as the NICE (National Institute of Clinical Effectiveness) approach. EBRO is an initiative of the Dutch Cochrane Center and the Dutch Institute for Healthcare Improvement (CBO), a member of the Guidelines International Network (GIN)[12].

Step 3: Strength of recommendations

By means of five consensus meetings and eight feedback rounds of the Guideline Steering Committee, recommendations were formulated and their strength graded A–D, based on the category of efficacy evidence (Table I).

Step 4: Guideline review process

The first draft of the guideline was reviewed by a Guideline Review Committee, comprising 17 persons from various professional backgrounds was instituted, including rheumatologists, an orthopedic surgeon, rehabilitation specialists, general practitioners, and representatives of the Dutch Arthritis Foundation and the Arthritis Patient Organization. After adaptation, the second draft of

Table I. From scientific evidence and expert opinion to recommendations according to the EBRO (Evidence Based Recommendation Development), which is in line with international classification schemes, such as the NICE approach.

Level of evidence	1	One A1 study or at least two A2 studies
	2	One A2 study or at least two B studies
	3	One B or multiple C studies
	4	Expert opinion
Grades of recommendation	A1	Meta-analyses (systematic reviews), which include at least two Randomized Controlled Trials at quality level A2 that show consistent results between studies
	A2	Randomized Controlled Trials of a good methodological quality (randomized double blind controlled studies) with sufficient power and consistency
	B	Randomized Controlled Trials of a moderate methodological quality of with insufficient power, or non- randomized, cohort of patient-control group study involving intergroup comparisons
	C	Patient series
	D	Expert opinion

the guideline was reviewed and pilot tested by 45 physiotherapists. Among them 15 were specialized and members of an arthritis network. Almost all of the physiotherapists agree with the content. Some minor comments concerning the feasibility of the measurement instruments, including lack of time and space to perform are taken into account in the implementation process after publication of the guideline.

Results

I. Initial assessment

In the Netherlands, physiotherapy can be accessed with or without a referral from a doctor (also called "direct access").

The initial assessment comprises history taking, physical examination and analysis. History taking and physical examination are performed to get a comprehensive overview of the patient's health status. This assessment includes screening for red flags. The doctor must be consulted in case of a red flag after deliberation with the patient. With the analysis, the patient's main limitations and impairments are prioritized, and treatment goals and a treatment plan are formulated, and in close collaboration with the patient, treatment goals are set, with the focus on limitations of activity and restriction in participation.

The total initial assessment process is described in Figure 1.

Clinical question 1: In which way the patient's health status can be assessed?

RECOMMENDATION 1:

- The physiotherapist should assess the patient's health status primarily in terms of activity limitations and participation restrictions (level 4).
- In addition, the therapist may also assess impairments of body function and structure, as well as personal and environmental factors, insofar as these relate to the limitations and restrictions (level 4).

An overview of the most relevant health problems in HKOA patients was made, based on the short version of the International Classification of Functioning, Disability and Health (ICF) Core Set for Osteoarthritis[8], supplemented with clinical relevant items, best practiced based, and completed with a number of personal factors (Figure 2). This overview is recommended to be used for the setting of treatment goals, the formulation of the treatment plan and the evaluation.

Clinical question 2: Which contraindications for physiotherapy should be taken into account in patients with HKOA?

RECOMMENDATION 2: PHYSIOTHERAPISTS SHOULD EVALUATE THE PRESENCE OF "RED FLAGS" (LEVEL 4).

The following specific red flags in HKOA patients were defined:

- A warm, swollen (red) knee joint
- A swelling in the groin
- Severe blockade of the knee joint

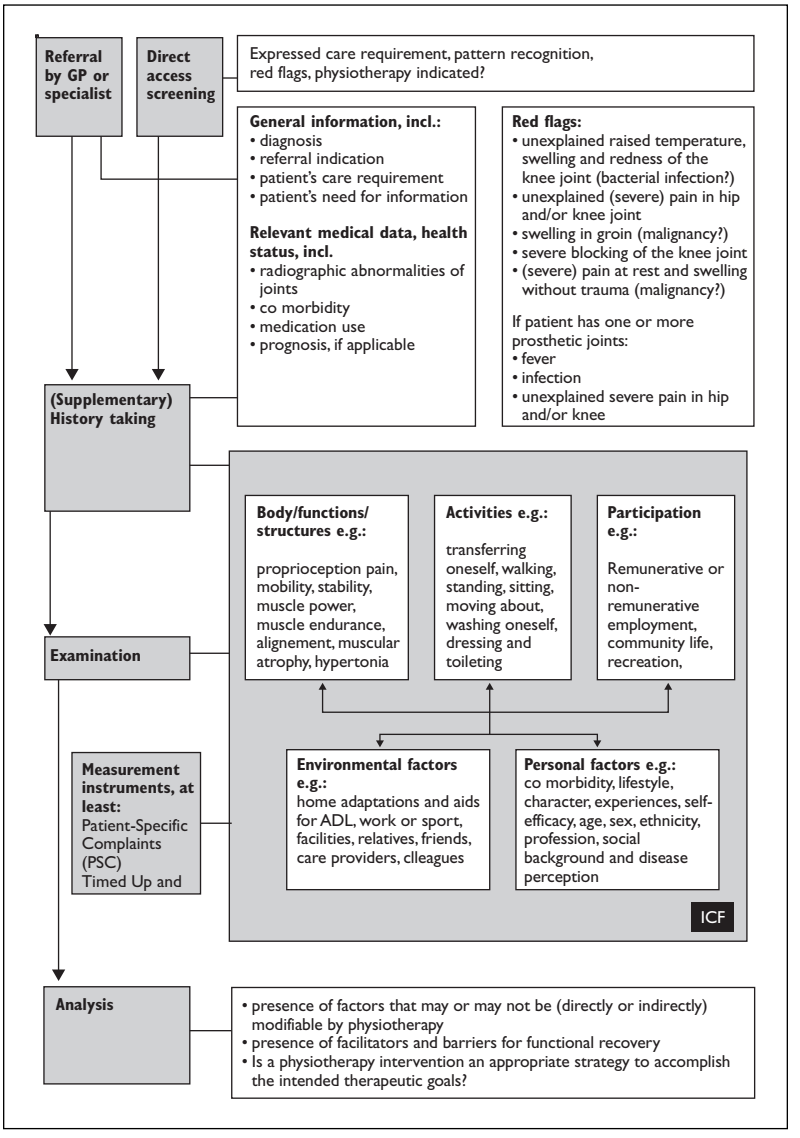

Figure 1. Overview of the initial assessment process.

- (Extreme) pain at rest
- And in the presence of one or more joint replacement prostheses:
- Fever
- Infection
- And inexplicable extreme pain in hip or knee joint.

Clinical Question 3: How does the physiotherapist set treatment goals?

RECOMMENDATION 3: BASED ON THE INFORMATION OBTAINED IN THE INITIAL ASSESSMENT, IN COOPERATION WITH THE PATIENT AND ACCORDING THE ICF, THE PHYSIOTHERAPIST SHOULD DEFINE THE THERAPEUTIC GOALS (LEVEL 4).

Based on of the description of the health status and the presence of barriers and facilitators, individual treatment goals should be defined. Goal setting is a shared process between the physiotherapist and the patient. Treatment goals are set in terms of the ICF, with the focus on limitations of activities and restriction in participation.

Goals should be formulated according to the SMART principles (specific, measurable, achievable, realistic, and timed)[13], for example: being able to walk 800 meters (from home to the supermarket and back) two times a week in six weeks.

II. Interventions

With respect to the literature search concerning the therapeutic process, 22 systematic reviews and 74 RCTs (published after these reviews) were selected.

Clinical question 4: Which physiotherapy intervention should or should not be given in HKOA?

RECOMMENDATION 4: (SUPERVISED) EXERCISE THERAPY AIMED AT REDUCING PAIN AND IMPROVING PHYSICAL FUNCTIONING SHOULD BE APPLIED DURING THE PHYSIOTHERAPY TREATMENT OF HKOA PATIENTS (LEVEL 1).

Based on the literature exercises are recommended[14-18], but no specific intensity of exercises could be defined[19]. However, although there is a lack of evidence concerning the optimal type of exercises and their intensity, most research pertained to programs including aerobic and/or muscle strengthening exercises, and possible combined with ROM and functional exercises.

In previously published international multidisciplinary guidelines and a Dutch multidisciplinary guideline in HKOA management exercise therapy is recommended[1]. There are no recommendations on intensity, specific exercise forms, number of treatment or follow up sessions, and supervision.

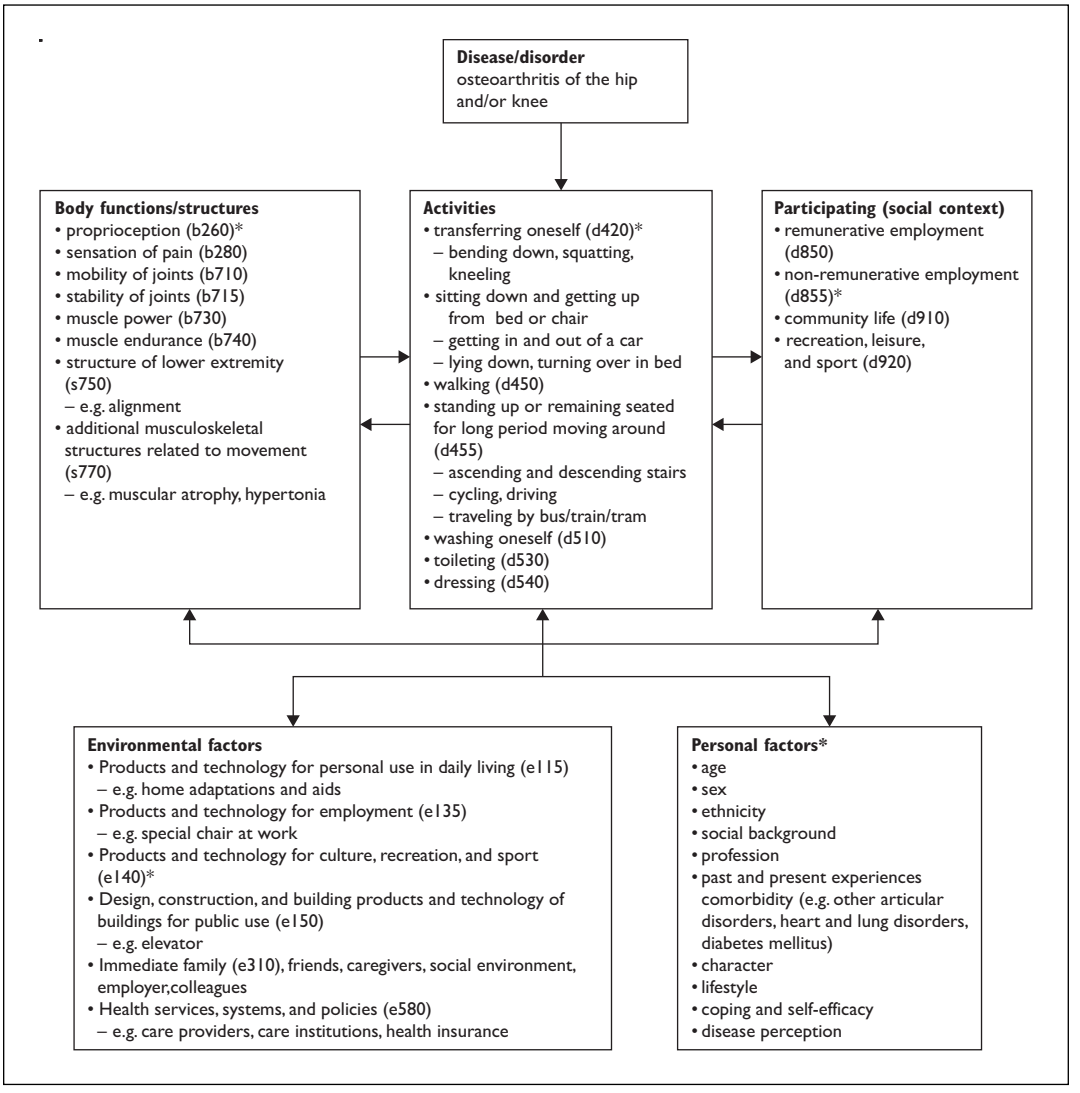

Figure 2. Overview of the most relevant health problems in Hip and Knee Osteoarthritis according to the International Classification of Functioning, Disability and Health (ICF) Core Set for Osteoarthritis (short version supplemented with clinically relevant items (*), based on expert opinion).

In addition to the abovementioned recommendation on exercise therapy, there was overall consensus within the Guideline Steering Committee that exercises should comprise at least muscle strengthening exercises, exercises to improve aerobic capacity, functional exercises, and gait training, either as a single treatment or combined with each other, depending on treatment goals. The exercise program must have a focus on limitations of activities and restrictions in participation. In some cases the exercise therapy could be adjusted to individual treatment goals. For example joint proprioception and balance training[20] or a behavioral graded activity strategy[21]. Decreasing the frequency of treatment sessions at the end of the treatment is needed to help the patient to achieve an independent adequate level of physical activity. To improve the transition to recreational or sport activities the HKOA patient must be guided by the physiotherapist.

RECOMMENDATION 5: PHYSIOTHERAPISTS SHOULD PROVIDE EDUCATION AND PROMOTE ADEQUATE SELF MANAGEMENT IN PATIENTS WITH HKOA (LEVEL 2).

Based on literature education and promotion of adequate self management are recommended, pro-

vided in combination with exercise therapy (level 2)[22-27]. Because of the variety of interventions in the literature, it is unclear which content of education or self management intervention is best in HKOA.

In international multidisciplinary guidelines and a Dutch multidisciplinary guideline in HKOA management education and self management is recommended as an effective intervention as an adjunction to exercise therapy [1,3-5].

The Guideline Steering Committee recommend that the content of the intervention comprise the following items: knowledge and understanding of HKOA; the consequences of HKOA on functions, activities and participation; the relation between the mental and physical load and carrying capacity; the way to deal with complaints caused by HKOA; an active and healthy lifestyle (moving, nurturing, overweight); change in moving behavior; joint protection and the use of (walking) aids (level 4).

The physiotherapist needs to support the patient in remaining a healthy physical activity level.

Recommendation 6: Exercise therapy should be combined with manual therapy in cases of pain and reversible limitation in joint mobility (level 2).
If there is pain in combination with a limitation in joint mobility it is recommended to add manual therapy to exercise therapy (level 2)[28-32]. In international multidisciplinary guidelines and a Dutch multidisciplinary guideline in HKOA management, manual therapy is not mentioned or classified by exercise therapy.

In the Netherlands it is common to use the combination of exercise therapy with manual therapy. Within the Guideline Steering Committee there was consensus that manual therapy could be considered as a preparation for exercise therapy in HKOA in case of pain and a reversible limitation in joint mobility. The manual therapy should comprise manipulation, manual traction, and muscle stretching exercises in Hip OA. In Knee OA anterior/posterior mobilizations of the tibia-femoral joint and the patella, and muscle stretching exercises could be considered.

Recommendation 7: Exercise therapy aimed at improving physical functioning should be applied after hip and knee joint replacement surgery (level 2).
Postoperative exercises are recommended in hip and knee joint replacement surgery and should comprise muscle strengthening exercises and exercises focusing on functional activities (level 2)[33-36].

No recommendations on postoperative exercises are given in international guidelines in HKOA management. In a Dutch multidisciplinary guideline on hip and knee OA, postoperative exercise therapy is recommended[1].

Recommendation 8: Taping the patella should be adjusted to muscle strengthening exercises and exercises focusing on functional activities to increase pain in patello-femoral OA (level 2).
There is evidence to recommend taping in patello-femoral OA[37,38]. In international and Dutch guidelines included no recommendations on taping and patello-femoral OA. In the Netherlands often taping is used as a support to make it more possible to do exercises in patello-femoral OA.

Recommendation 9: The provision of hydrotherapy, balneotherapy, thermotherapy, preoperative physiotherapy in HKOA, and Transcutane Electrical Neuro Stimulation (TENS) in knee OA , and Continuous Passive Motion (CPM) in postoperative knee OA, can neither be recommended nor discouraged (level 1, 4).
There is conflicting evidence that hydrotherapy is effective in HKOA (level 1)[39-44]. An international guideline (OARSI) recommends hydrotherapy in patient with hip OA[5].

In daily practice in the Netherlands hydrotherapy is used and experienced as a pleasant intervention by the patient. There was overall consensus within the Guideline Steering Committee that hydrotherapy could be applied in case of severe pain and no effect of alternative interventions as exercise therapy on land, medication or surgery. Hydrotherapy could also be used as preparation for exercise therapy on land in cases with severe pain.

There is also conflicting evidence that balneotherapy is effective in HKOA (level 1)[45-47]. No recommendations are made in international and Dutch guidelines. In the Netherland it is no common intervention, but in some countries Spa therapy has a benefit in HKOA patient's physical en mental wellbeing.

There is some evidence that ice massage is effective as a cold application in knee OA[48]. An international guideline (OARSI) is mentioning that in some circumstances warmth or could applications could be beneficial in relieving pain[5]. There was overall consensus within the Guideline Steering Committee that an application of cold could be considered if there is severe pain in knee OA. The

application of warmth could be considered as preparation for exercise therapy in patients with severe joint stiffness or difficulty in relaxing the muscles. The Guideline Steering Committee advises against the use of local heat application in case of active joint inflammation which sometimes occurs in knee OA (level 4).

There is conflicting evidence that TENS is effective to relieve pain in knee OA (level 1)[49;50]. An international guideline recommends TENS for the short term (OARSI) and a Dutch multidisciplinary guideline[1,5] recommend TENS to decrease pain and stiffness as a second choice if medication and exercises turned out to be not effective.

The Guideline Steering Committee suggests that TENS could be considered as a support for exercise therapy in individual cases with severe pain but not as a first choice (level 4).

Concerning physiotherapy around joint replacement surgery there is conflicting evidence that CPM is effective after total knee surgery[51-54]. CPM is a common intervention after knee surgery to increase knee joint mobility. There is lack of evidence after knee surgery to recommend CPM according a Dutch multidisciplinary guideline[1].

The Guideline Steering Committee could not recommend or advise against CPM (level 1).

Preoperative exercises could not be recommended based on current evidence (level 3)[55-58]. There are no recommendations mentioned in international guidelines on HKOA management. A Dutch multidisciplinary guideline could not recommend preoperative exercises[1]. But literature indicates that a good functional status before surgery is a important predictor on postoperative recovery. Within the Guideline Steering Committee there was an overall consensus that preoperative exercises could be considered in cases of poor preoperative status in patients with multiple co morbidity and other affected joints (level 4).

Finally preoperative education could be considered according the Guideline Steering Committee if there is much anxiety for the operation (level 4). The education should then be focused on information about the operation and the period the patient stays in the hospital.

RECOMMENDATION 10: THE PROVISION OF MASSAGE, ULTRASOUND, ELECTROTHERAPY, ELECTROMAGNETIC FIELD AND LOW LEVEL LASER THERAPY (LLLT) CAN NOT BE RECOMMENDED IN HKOA (LEVEL 1, 2, 4).

There is little evidence that massage is effective in knee OA (level 2)[59]. In the Netherlands massage was a common physiotherapy intervention. Nowadays there is no place for massage in the active treatment strategy for HKOA.

There is conflicting evidence for the use of ultrasound in knee OA (level 2)[60,61]. The Health Council of the Netherlands (Gezondheidsraad) has advised against the use of ultrasound, except for the application in patients with a tennis elbow. Therefore the Guideline Steering Committee decided not to recommend ultrasound.

For electrotherapy there is conflicting evidence for the effectiveness in knee OA (level 3)[49,50]. Electrotherapy is not common in the Netherlands as treatment for knee OA. Based on the current evidenced and best practice electrotherapy can not be recommended.

No evidence can be found to support the use of electromagnetic field in de treatment of HKOA (level1)[50,62,63].

There is evidence that LLLT is effective in decreasing pain (level 1)[50], but it is a very uncommon intervention in the Netherlands. Further there are other interventions that can be recommended to decrease pain why the Guideline Steering Committee did not recommend LLLT in knee OA (level 4).

In international and Dutch guidelines there are no recommendations for the use of massage, ultrasound, electrotherapy, electromagnetic field en LLLT in the treatment of HKOA[1,3-7].

III. Assessment of outcome

For the evaluation of treatment goals in HKOA patients several measurement instruments are available. Recommended measurement instruments pertained to ICF chapters activities and participation and body functions and structures and were chosen based on their psychometric properties: validity, reproducibility, responsiveness as well as there practical applicability. The latter included the availability of a Dutch version must be available, no special training should be necessary and the measurement should have a good applicability in daily clinical practice. The measurement instruments classified according the ICF are shown in Figure 3.

Clinical question 5: Which measurement instrument should be used to evaluate treatment?

RECOMMENDATION 11: A COMBINATION OF QUESTIONNAIRES (PREFERABLY THE PATIENT SPECIFIC COMPLAINT LIST (PSK)) AND PERFORMANCE TESTING (PREFERABLY THE TIMED UP AND GO TEST (TUG)) IS RECOMMENDED TO USE

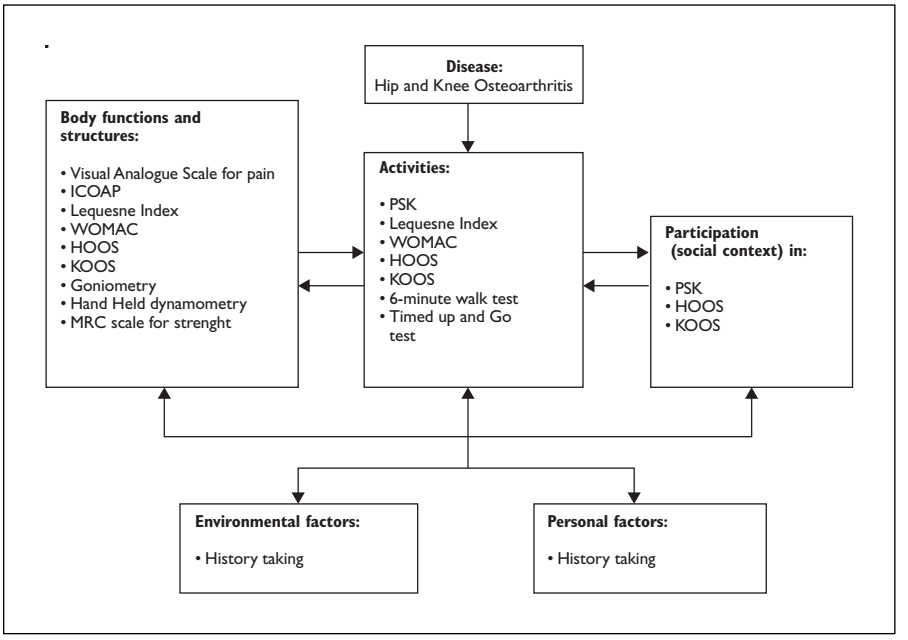

Figure 3. Measurement instruments in Hip and Knee Osteoarthritis according a ICF classification (some measurement instruments are suitable in more than one ICF component).

PSK = Patient Specific Complaint list, ICOAP = Intermittent and Constant OsteoArthrtis Pain, WOMAC = Western Ontario and McMaster Universities Osteoarthritis index, HOOS = Hip disability and Osteoarthritis Outcome Score, KOOS = Knee injury and Osteoarthritis Outcome Score, MRC = Medical Research Council

IN THE INITIAL ASSESSMENT AND EVALUATING TREATMENT GOALS AND SHOULD HAVE THE FOCUS ON THE ICF COMPONENT IN WHICH THE PATIENT PRESENTS HIS COMPLAINTS. The physiotherapists in the field prefer a recommendation for one or two best measurement instruments. Despite more measurement instruments are useful in daily practice depending on treatment goals, the Guideline Steering Committee prefer to recommend one questionnaire and one performance test. They were chosen primarily for their good applicability in daily practice:

Patient Specific Complaint list In the Netherlands the PSK (Patiënt Specifieke Klachten) is developed[64] as an instrument to record patient specific complaints. The patient has to choose the three most limited activities from a list of activities in which patients can be limited because of HKOA. On a 100 mm visual analogue scale the degree of limitation can be outlined by the patient for each activity. With on the left end "no limitation in the activity" and on the right end "the activity is not feasible" the patient express how the degree of limitation of the activity is by means of a vertical line. The score is determined by measuring the distance in millimeters from the left end of the line to the point that the patient marks.

Timed Up and Go (TUG) test The TUG test[65,66] measures the time in seconds in which the patient stand up from a chair, walk three meters, turn around, walk back and sit down on the chair. The test must take place in comfortable speed.

Other measurement instruments that are recommended in HKOA patients are shown in Figure 2. In this figure the connections between the measurement instruments to the different components of the ICF are clarified.

For measuring pain there is a choice to use two different scales: *A Visual Analogue Scale (VAS) for pain*[67] is usually a horizontal line of 100 millimeters. The VAS is filled in by the patient as described at the PSK. If the pain is intermittent, which occur in HKOA patient the *Intermittent and Constant OsteoArthritis Pain (ICOAP)*[68] could be used. This questionnaire is taken into account intermittent pain experience by the patient, for example in using pain medication by the patient.

For measuring strength the use of a *handheld dynamometer*[67] is recommended or if that is not available, the *Medical Research Council (MRC) for strength*[69] is recommended as an alternative.

The Range Of Motion (ROM) should be measured by using *goniometry*[70]. A Measurement instrument to measure walking and aerobic capacity is *the 6 minute walk test*[65,66]. During the 6-minutes walk test the patients have to walk 6 minutes at a self chosen walking speed and they have to try to overcome as much distance as possible, without running. The accomplished distance is the total distance at the end of the 6 minutes.

Finally to measure limitation in activities and restrictions in participation four different questionnaires are recommended. The choice between those four depends on the joint and the treatment goals. *The Western Ontario and McMaster Universities osteoarthritis index (WOMAC)*[71,72] measures limitations in activities as well as pain and stiffness in HKOA patients. *The Lequesne index* [73] has its focus on limitations in walking distance and pain during walking in HKOA. The *HOOS* [74] and the *KOOS* [75] ask besides limitation in activities also for restrictions in participation in sports and recreational activities and quality of life, respectively in Hip OA and Knee OA.

Table II shows an overview of all recommendations.

Discussion

This study describes the development of a physiotherapy (PT) specific guideline for the management of HKOA. This guideline is based on recent research evidence and expert opinion. It was developed according to standardised procedures for formulating recommendations. The guideline describes the process of initial assessment, including

Table II. Summary of recommendations and level of evidence

Initial assessment

1. The physiotherapist should assess the patient's health status primarily in terms of activity limitations and participation restrictions. In addition, the therapist may also assess impairments of body function and structure, as well as personal and environmental factors, insofar as these relate to the limitations and restrictions (level 4).
2. Physiotherapists should evaluate the presence of "red flags" (level 4).
3. Based on the information obtained in the initial assessment, in cooperation with the patient and according the ICF, the physiotherapist should define the therapeutic goals (level 4).

Interventions

4. (Supervised) exercise therapy aimed at reducing pain and improving physical functioning should be applied during the physiotherapy treatment of hip and knee osteoarthritis patients (level 1).
5. Physiotherapists should provide hip and knee osteoarthritis patients education and must promote adequate self management (level 2).
6. Exercise therapy should be combined with manual therapy in cases of pain and reversible limitation in joint mobility (level 2).
7. Exercise therapy aimed at improving physical functioning should be applied after hip and knee joint replacement surgery (level 2).
8. Taping the patella should be adjusted to muscle strengthening exercises and exercises focusing on functional activities to increase pain in patellofemoral OA (level 2).
9. The provision of hydrotherapy, balneotherapy, thermotherapy, preoperative physiotherapy in hip and knee osteoarthritis, and Transcutane Electrical Neuro Stimulation (TENS) in knee OA , and Continuous Passive Motion (CPM) in postoperative knee OA, can neither be recommended nor discouraged (level 1, 4).
10. The provision of massage, ultrasound, electrotherapy, electromagnetic field and low level laser therapy (LLLT) can not be recommended in hip and knee osteoarthritis (level 1, 2, 4).

Assessment of outcome

11. A combination of questionnaires (preferably the Patient Specific Complaint list (PSK)) and performance testing (preferably the Timed Up and Go test (TUG)) is recommended to use in the initial assessment and evaluating treatment goals and should have the focus on the ICF component in which the patient presents his complaints (level 4).

history taking, physical examination, analysis, PT interventions and various measurement instruments that can be used to evaluate treatment.

In contrast with other guidelines, this guideline gives recommendations on initial assessment en evaluation of treatment. The ICF framework[8] has a central place in this guideline. An overview is added concerning the ICF linked health related problems and measurement instruments. This linking on the ICF is also been used in two recently developed PT guidelines on hip osteoarthritis[76] and meniscal and articular cartilage lesions of the knee[77].

Another difference between this guideline and other (multidisciplanairy) guidelines on HKOA is that the recommendations are formulated not only based on literature but also considerations from daily practice are playing an important role in formulating recommendations. For example: although there is evidence that laser therapy could be effective in knee OA, it is not a common intervention in the Netherlands and furthermore the National Health Counsel (Gezondheidsraad) is not recommending the use of laser in knee OA patients. Concerning other interventions (hydrotherapy and thermotherapy ao.) in which the evidence is sometimes weak, the guideline steering committee decided that the intervention only could be considered in specific individual cases after good clinical reasoning.

Among multidisciplinary guidelines ICSI Health Care[78] is giving annotations in the initial assessment. But in treatment they have a more passive approach since recommendations on electrical therapy and massage were given for pain relief, while this guideline has a clearly active approach without recommendations on passive modalities like massage, electrotherapy, laser, ultrasound and electromagnetic field.

Exercise, education and self management interventions are overall recommended in national and international multidisciplinary guidelines on HKOA. For exercises and manual therapy the recommendations are comparable with those from the Ottawa panel[79]. Also TENS in knee OA is overall recommended. But this guideline is more cautious based on recent evidence [49].

In contrast with other national[2] and international multidisciplinary guidelines on HKOA[3-7] this guideline gives recommendations concerning physical therapy treatment before and after total hip or knee replacement in osteoarthritis. Only the Dutch multidisciplinary CBO guideline[1] comprise some individual exceptions for pre-operative exercises based on expert opinion for example in case of worse physical status of the patient before surgery.

The MOVE consensus[7] mentions contra-indicators and barriers for exercise. The Dutch PT guideline pre-empt this by formulating general en specific red flags for HKOA. But these red flags are not only concerning exercises but also PT treatment in general. Besides barriers also facilitators which can influence outcome of treatment, are described.

Guidelines, recommendations and protocols on hip and knee will be available in many different countries, published or not. Discrepancies exist based on date (of publication) or the different national usual method of treatment. International cooperation between PT societies may be a following step in consensus on a guideline for the treatment of HKOA patients.

To facilitate the use of guidelines in daily practice it is important to apply an implementation strategy. Implementation studies with regard to other PT guidelines have shown that didactic education and passive dissemination strategies were ineffective[80]. Multifaceted interventions, interactive education and clinical reminder systems have been shown to be more effective to implement PT guidelines[81]. In a following study a more effective implementation strategy will be researched.

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ENDOCARDITE COM HEMOCULTURAS NEGATIVAS E ALTERAÇÕES IMUNOLÓGICAS: UM GRANDE DESAFIO

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Resumo

A endocardite infecciosa subaguda pode cursar com fenómenos imunológicos e manifestações extracardiacas como anemia e dores musculoesqueléticas que podem simular doenças reumatológicas. É relatado o caso de um paciente com endocardite infecciosa que apresentou sintomatologia semelhante à polimialgia reumática, além de um quadro agudo de nefrite após início da antibioticoterapia. São considerados aspectos do diagnostico diferencial entre endocardite de Libman-Sacks e endocardite infecciosa.

Palavras-chave: Endocardite Bacteriana Subaguda; Polimialgia Reumática; Fatores Imunológicos; Glomerulonefrites; Endocardite de Libman-Sacks.

Abstract

Subacute Infectious endocarditis can present immunological phenomena and extracardiac manifestations such as anemia and musculoskeletal pain which can mimic rheumatological disease. It is related a case on infectious endocarditis presenting symptomatology similar to Polymyalgia Rheumatica despite acute nephritis after antibiotic. The differential diagnostic features of Libman-Sacks endocarditis versus infective endocarditis are discussed.

Keywords: Endocarditis Subacute Bacterial; Polymyalgia Rheumatica; Immunologic Factor; Glomerulonephritis; Libman-Sacks Disease.

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Introdução

A endocardite infecciosa (EI) é uma doença grave que ocasiona grande morbidade e uma alta taxa de mortalidade. Na maioria dos estudos, sua incidência varia de 2 a 10 episódios por 100.000 pessoas-ano, alcançando cerca de 20 episódios por 100.000 pessoas-ano na população idosa. Aproximadamente 15.000 novos casos são diagnosticados nos Estados Unidos a cada ano. A mortalidade situa-se entre 15 a 20% e as principais complicações da doença são: insuficiência cardíaca, formação de abscessos intra cardíacos e eventos embólicos[1].

A participação do sistema imunológico na EI é importante e associada a muitas manifestações clínicas, como: mialgia, perda de peso, febre e glomerulopatia, sintomas esses, que podem ser confundidos com polimialgia reumática, uma enfermidade inflamatória caracterizada por dores predominantemente em cintura escapular e pélvica, anemia e aumento da velocidade de sedimentação (VS)[2,3].

Várias condições clínicas, além da polimialgia reumática, devem ser consideradas no diagnóstico diferencial da EI, entre elas a endocardite de Libman-Sacks (ELS) e a endocardite marantica (EM). A ELS pode ser manifestação do lúpus eritematoso sistémico e mais recentemente da síndrome antifosfolípidio, embora, tipicamente seja assintomática, pode ocasionar insuficiência valvular severa, eventos embólicos, EI e em alguns casos cursar com febre e artrite[4]. A EM é definida como uma ou mais vegetações intracardíacas não infectadas, estando mais comumente associada com malignidade[5].

Caso clínico

Paciente de 80 anos, sexo masculino, portador de diabetes mellitus e hipertensão arterial, com início da doença em abril de 2009, apresentando quadro

álgico difuso predominando em cintura escapular e pélvica, além de dor abdominal em crises, principalmente noturna. Teve um emagrecimento de 5 Kg em 4 meses e gradativa obstipação intestinal. Durante este período apresentava exame físico sem grandes alterações, a não ser dor nos sítios citados e em região periumbilical e coluna lombar. No início da doença não havia febre, porém já apresentava alterações laboratoriais: anemia com hemoglobina: 11g/dL (normal 13,5 a 16,5g/dL), VS: 110 mm na primeira hora (normal até 20 mm), hipoproteinemia com albumina: 2,3 g/dL (normal 3,5 a 5,5 g/dL) e fosfatase alcalina: 425 U/L (normal até 100 U/L). A contagem de leucócitos era normal.

Com a finalidade de esclarecer o quadro de dor musculoesquelética e abdominal, foram solicitados: endoscopia digestiva alta, colonoscopia, Raio X de tórax, angiotomografia de artérias mesentéricas, tomografia computadorizada (TC) de abdómen, cintilografia óssea e trânsito intestinal com resultados normais. Após a investigação foi diagnosticado como polimialgia reumática e iniciada prednisona na dose de 10 mg por dia. A melhoria foi significativa nas 2 primeiras semanas, com redução da VS para metade do valor inicial; entretanto, após a 3ª semana, houve decréscimo da resposta terapêutica e nova elevação da VS, quando foi decidido a suspensão da corticoterapia e prosseguimento da investigação diagnóstica.

Após 6 meses do início da doença e com uma melhoria parcial da sintomatologia, embora persistissem dor na cintura escapular e pélvica e VS acelerada, evoluiu com edema nos membros inferiores e inicialmente com pequena elevação da temperatura axilar no período vespertino, variando de 37,5ºC a 38ºC de caráter diário e persistente. Após 1 semana houve elevação progressiva da temperatura atingindo 39°C. Foi solicitada uma TC de tórax que evidenciava um aumento discreto da área cardíaca e a presença de um pequeno derrame pleural bilateral. Devido à presença de febre e ao surgimento de sopro diastólico no foco aórtico (+/4), foi realizado ecocardiograma transtorácico que detectou a presença de uma vegetação de 6 mm na válvula aórtica com regurgitação e ecocardiograma transesofágico que confirmou o diagnóstico (Figura 1 e Figura 2).

Foram realizadas colheitas de urina e sangue para culturas, e iniciado esquema antimicrobiano com a associação de ampicilina/sulbactam e ciprofloxacina, visando a cobertura de *Streptococcus viridans*, *Enterococcus*, gram negativos e bactérias do grupo HACEK (***H****aemomophilus sp,* ***A****ctinobacillus actinomycetemcomitans,* ***C****ardiobacterium hominis,* ***E****ikenella corrodens e* ***K****ingella sp.*). A cultura de urina e 5 amostras de hemocultura apresentaram resultados negativos, apesar do paciente não ter utilizado antibióticos previamente.

Após uma semana de antibioticoterapia, não havia febre, mas permanecia o quadro álgico difuso com elevação da ureia e creatinina, que até ao momento apresentavam valores normais, e a presença de proteinúria em níveis nefróticos, além de hematúria microscópica, caracterizando acometimento glomerular.

Uma nova investigação laboratorial detectou os seguintes resultados: Anticorpo antinuclear (ANA)

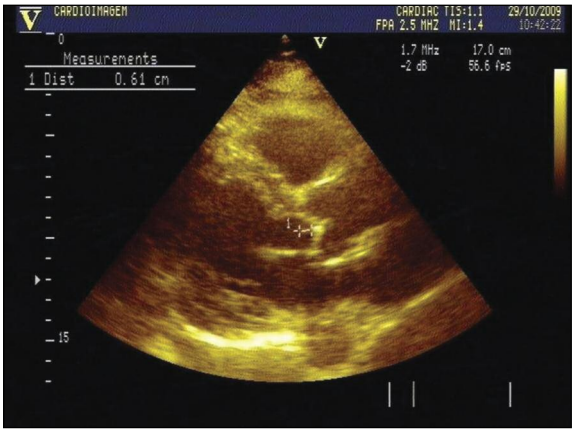

Figura 1. Ecocardiograma evidenciando vegetação na válvula aórtica

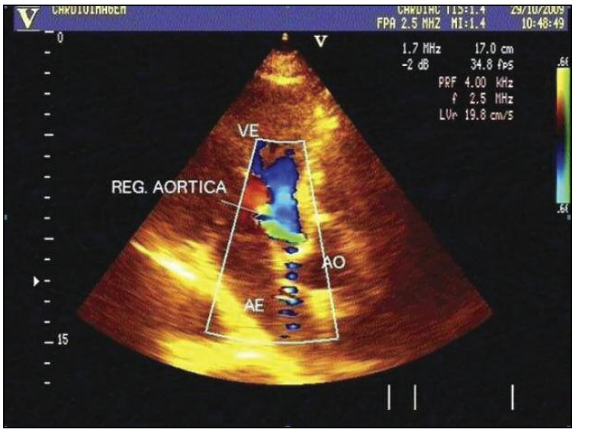

Figura 2. Ecocardiograma evidenciando regurgitação na válvula aórtica

positivo em títulos 1:320, com padrão misto nuclear pontilhado fino, citoplasmático e pontilhado reticular. Imunocomplexos circulantes: 82 mcg/mL (normal até 34 mcg/mL), fator reumatóide negativo, consumo das frações do complemento C3: 75 mg/dL (normal de 77-152 mg/dL) e C4: 3,8 mg/dL (normal de 16-38 mg/dL). VDRL positivo 1:32 , anticardiolipina IgG: 89,7 GPL e IgM: 97 MPL (valores considerados de forte reatividade), Anticorpos anticitoplasma de neutrófilos (ANCA), P - ANCA negativo e C – ANCA positivo 1:20 (valores considerados normais= negativo), Anti Ro, Anti Sm e Anti DNA negativos. A proteinúria de 24 horas evidenciava valores de 8 g (normal até 150mg/24h). A creatinina atingiu valores de 2,8 mg/dL e a ureia de 98 mg/dl.

Após 10 dias do início das manifestações renais, houve melhoria gradual dos níveis de ureia e creatinina, com normalização em cerca de 30 dias, não havendo a necessidade da realização de biopsia renal ou tratamento com imunossupressores.

A sintomatologia de polimialgia reumática teve regressão total após 4 semanas do início da antibioticoterapia, com queda significativa nos valores das provas inflamatórias, confirmando que as manifestações reumatológicas eram secundárias a EI, pois não houve a introdução de qualquer outra medicação.

Exames realizados após 6 meses da resolução do processo indicaram negativação dos marcadores imunológicos previamente positivos e normalização das provas inflamatórias e das frações do complemento, permanecendo positivo apenas o C--ANCA em título de 1:20. Um novo ecocardiograma realizado evidenciava regressão da lesão na válvula aórtica.

Discussão

O diagnóstico de polimialgia reumática constitui um desafio, pois baseia-se exclusivamente na presença de dor proximal escapular e pélvica, anemia e VS acelerada na ausência de outra possível doença . Não há teste específico que comprove o diagnóstico. Em determinadas situações, pacientes presumivelmente com suspeita de polimialgia reumática, podem após semanas ou meses receberem o diagnóstico correto de sua doença, como relatado por Mourão *et al* que ressaltam a importância da história clínica para se estabelecer o diagnóstico de polimialgia reumática, sendo fundamental excluir com segurança outras patologias, que possam apresentar sintomatologia semelhante[6].

A EI é uma infecção endovascular causada principalmente por bactéria, que acomete não só as válvulas cardíacas como todo o organismo. As manifestações reumatológicas ocorrem em 27% dos indivíduos, principalmente homens, em idade avançada, de origem rural e com degeneração das válvulas cardíacas, sendo a válvula aórtica a mais acometida. Esses sintomas podem retardar o correto diagnóstico da doença[3,7,8,9].

Pacientes portadores de EI propensos a desenvolver sintomas similares a polimialgia reumática possuem mais de 50 anos, sua mialgia está associada à rigidez matinal por mais de um mês e ocorre em pelo menos duas das seguintes regiões: cervical, cintura escapular ou pélvica. A VS geralmente está acelerada[9].

O paciente não apresentou nenhum sinal clássico da EI, entretanto as suas válvulas cardíacas estavam calcificadas devido à idade avançada. O seu quadro álgico na cintura escapular e pélvica, a perda de peso, a VS acelerada e a ausência inicial de febre, simularam um quadro de polimialgia reumática, dificultando o diagnóstico[7,10].

O diagnóstico de EI foi firmado utilizando os critérios modificados de Duke adaptados de Li *et al,* com a presença de 1 critério maior (ecocardiograma positivo) e 3 menores (lesão prévia de calcificação em válvula aórtica, detectada em ecocardiograma prévio, febre acima de 38º C e fenómenos imunológicos, evidenciado pela glomerulonefrite)[11].

Quanto à etiologia da infecção, é provável que o agente infeccioso tivesse acesso ao organismo através do uso de agulhas, por vezes reutilizadas pelo paciente para aplicação diária de insulina. Houve o relato da ocorrência de reação inflamatória em algumas das administrações. A negatividade das 5 hemoculturas colhidas pode ser explicada pela presença de patogéneos de difícil cultura. Num estudo realizado por Fournier *et al,* observou-se que os pacientes com EI apresentaram 31% das hemoculturas negativas. Isso se deve a microorganismos de colonização restrita como *Coxiella burnetti e Bartonella species*[12]. Não foi possível no caso relatado chegar ao diagnóstico etiológico.

A participação do sistema imune é marcante no caso relatado, evidenciado pelas várias alterações laboratoriais encontradas e que serão comentadas a seguir. As frações C3 e C4 do complemento en-

contram-se diminuídas na EI, devido à ativação das vias clássicas e alternativas do sistema complemento como meio de combater a infecção, o que é observado mais comumente quando há uma vasculite associada[9].

Embora não houvesse positividade do fator reumatóide, esse pode ser encontrado em 35% á 50% na EI subaguda e correlaciona-se com a formação constante de anticorpos e consequentemente com a presença prolongada de antigénios microbianos[2,9].

A positivação do anticorpo anticitoplasma de neutrófilo (C-ANCA) está associada às vasculites como a granulomatose de Wegener, mas também pode estar presente na EI subaguda, significando envolvimento cutâneo ou renal da doença. Em geral é acompanhada da presença de outros anticorpos, da elevação de imunocomplexos e da queda de complemento, devido à ativação policlonal do linfócito B. Os exames que mais comumente se alteram com o C-ANCA são: fator reumatóide, FAN, crioglobulinas e anticardiolipina. Os títulos, em geral, se normalizam com a resolução da doença[13].

Os níveis de imunocomplexos circulantes possuem relação direta com fenómenos extravalvulares e com o tempo de duração da doença, atingindo sua normalidade, assim como os demais marcadores sorológicos, com a instituição da antibioticoterapia e cura da doença. A permanência de títulos elevados significa ineficácia do tratamento[2].

A EI também está associada aos resultados falso positivos de VRDL. Essa elevação ocorre na maioria dos casos, em conjunto com os anticorpos antifosfolipídios, com fator reumatóide e com as queixas de origem reumatológicas[14].

A elevação de anticorpos anticardiolipina IgM e IgG que geralmente está associado a fenómenos trombóticos no lúpus eritematoso sistémico pode ocorrer em 18% dos pacientes com EI, entretanto, não ocasiona patogenicidade[14].

As glomerulopatias são complicações possíveis na EI e podem ser desencadeadas por fenómenos embólicos ou como no caso relatado por imunocomplexos. A glomerulonefrite de origem imune é principalmente de caráter subagudo e ocorre entre 28% a 68% dos casos, com a presença de hematúria macro ou microscópica, edema, redução da função renal, uremia e proteinúria em níveis nefróticos. Além disso, outros achados que indicam tal situação é a redução das frações de complemento, presença do fator reumatóide, crioglobulina, e elevação de imunocomplexos nos exames laboratoriais. O C-ANCA está intimamente relacionado ao diagnóstico da glomerulonefrite[2,10].

Embora alguns estudos, como o trabalho de Koya *et al,* defenda o uso de corticosteróides, optou-se apenas por manter os antibióticos[15]. Com a instituição da antibioticoterapia os sintomas tendem a regredir na grande maioria dos casos[8,10].

Juanatey *et al* elaboraram um estudo avaliando pacientes com manifestações reumatológicas e concluiram que em alguns casos não se pode diferenciá-los de outros portadores da forma clássica da EI[9].

Alguns aspectos são relevantes no caso clínico apresentado, entre eles: complexidade de apresentação clínica e laboratorial, semelhança dos sintomas com polimialgia reumática e necessidade do diagnóstico diferencial com ELS. Embora julgamos tratar-se de EI, baseado na evolução clínica com remissão do quadro após início da antibioticoterapia (desaparecimento da febre, remissão do quadro álgico e normalização das provas inflamatórias) não podemos deixar de considerar a possibilidade de ELS devido aos seguintes aspectos: contagem normal de leucócitos durante a evolução da doença, altos níveis de anticorpos anticardiolipina e hemoculturas negativas. No trabalho de Lee *et al* é considerada a grande dificuldade do diagnóstico diferencial entre EI e ELS devido a semelhança de apresentação clínica em alguns casos[4].

Conclui-se que o diagnostico de EI pode ser difícil e manifestações reumatológicas devem ser incluídas como forma de apresentação clínica, retardando o correto diagnóstico. Na avaliação inicial deve-se incluir uma propedêutica cardíaca e na presença de altos títulos de anticorpos anticardiolipina pensar na possibilidade de ELS.

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PAGET'S DISEASE OF BONE AND ITS COMPLICATIONS DUE TO DELAY IN DIAGNOSIS

Lorena Penha de Almeida*, Juliana Alves Scrignoli*, Kelly Simone Castro dos Santos**, Luiz Fernando de Souza Passos***, Sandra Lúcia Euzébio Ribeiro***

Abstract

Paget's disease of bone is an osteometabolic focal disease characterized by defects in bone remodeling. It may be asymptomatic, but often is associated with bone pain, deformity, pathological fracture, secondary osteoarthrosis and deafness. The diagnosis is usually made by radiological and laboratory findings. This report describes a male patient, 74 years old, native of Amazon, without European ancestry, with polyostotic Paget's disease, with clinical, radiological and laboratory diagnosis after 30 years of disease. The authors emphasize several complications of Paget's disease due to delayed diagnosis and the rarity of the disease in this population group.

Keywords: Osteitis Deformans; Paget; Fractures; Bone; Bone Diseases.

Introduction

Paget's bone disease is a chronic focal non-inflammatory osteometabolic disease with a strong genetic background, with defects in bone remodeling affecting one (monostotic) or more points (polyostotic) of the skeleton. Recognized and described by Sir James Paget in 1877, it is typically found in people after the fourth decade of life, being slightly more common in caucasoid men. Its etiology remains unknown, although an autoimmune disorder associated with viral infections have been suggested. Long bones, pelvis, vertebral spine and skull are most often affected[1].

Paget's bone disease may run an asymptomatic curse, but often manifests as skeletal pain which may be related to disease activity or complications such as degenerative joint disease, fractures, osteosarcoma and neural impingement[2]. Four to nine years is the average lag time between the first symptoms and diagnosis[3,4], which is eventually made by the clinical history along with image and laboratorial finding[5], Herein, the authors report a case of a patient with Paget's bone disease with many complications related to delay in establishing the diagnosis.

Case Report

Male patient, 74 years old, brown skin, native of Amazon, retired driver, presented with a 30 years history of mild skeletal pain that has begun at the sacroiliac region, not continuous, which worsened with physical effort, and, sometimes, relapsed at night. Later, the skeletal pain has affected the lower limbs, diffusely, burning, associated with paresthesias. Deformities developed progressively in the left leg (arching) and in the vertebral spine. The patient walks with difficulty due to functional impairment caused by deformity and pain, with limitation for daily activities and work capacity.

The patient complained of bilateral hearing loss and intestinal constipation but had no weight loss. Previous diagnosis of congestive heart failure, systemic arterial hypertension and ischemic heart disease had been made. He had never been subjected to transfusions or surgeries. There was no history of familiar osteoporosis with fractures or other metabolic bone disease. He denied the use of corticosteroids or other drugs related to osteopenia. There was no personal history of renal failure, disease of the thyroid, hyperparathyroidism, hipogonadism or collagen-vascular disease. He

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smoked cigarettes, 50 packets/year, and consumed alcoholic beverages socially.

At physical examination, there was a paravertebral protuberance at the thoracolumbar region, warm bone deformities (bowing) at the lower limbs and an increased cranial circumference. He had small stature and walked with short steps and waddling gait. The range of motion was limited at the hips and knees, which impaired the performance of certain maneuvers, such as the evaluation of Lasegue sign. Patellar reflex was absent and there was reduced strength in extension and flexion of the hallux. The muscles of the lower limbs were hypotrophic, but proximal muscle strength and sensitivity were preserved.

Lab tests showed serum calcium: 9,0mg/dL (VR= 8,8 –11); Phosphorus: 4,0mg/dL (VR= 2,5-4,5); glucose: 92mg/dL; urine calcium: 32,9mg/24hs (VR=60-180); urine protein: 75mg/24hs; serum alkaline phosphatase: 1657U/L (VR= 644), C-Reactive protein: 12mg/dL; erythrocyte sedimentation rate: 34mm; lactic dehidrogenase: 181UI; prostatic specific antigen: 0,5ng/mL; uric acid: 4,0mg/dL.

A magnetic resonance study of the lumbar spine showed a partial collapse of the fourth vertebra, and low intensity lesions with T1 and heterogenic signal with T2, which captures contrast medium, spreaded along lumbar vertebras and the sacrum. There was bone destruction with collapse and soft tissues invasion at the twelfth vertebra, with backward projection of the posterior borders of the vertebral bodies of D11, D12, L1 and L4, narrowing the vertebral channel and compression the dural sac. A tomografic study of the pelvis showed a coarse thickening of bone trabeculae with an insufflated aspect, and sclerotic areas superposed on lytic lesions in pelvic bones (Figures 1 and 2). A tomographic study of the legs showed an expansive and insufflated lesion all along the left tibia, with diffuse and irregular thickening of cortical bone and disordered bone trabeculae (Figure 3). A tomographic study of toraco-lumbar spine showed destruction of vertebral bodies at D12, L1 and L2, with invasion of soft tissues, the medular channel and neural foramen at this level, and shrinking of intervertebral spaces at L3-L4 and L4-L5, with traces of air within the disks. Vertebral bone trabeculae were diffusely disarranged and showed a reactive zone (Figure 4). There was widespread inter-apophysary osteoarthritis. A radioisotope scanning showed excessive label capture at the abnormal bone, suggesting a metabolic disorder.

During the 30 years of disease, because of insidious mild pain, despite the major deformities, the patient was consulted only during periods of pain exacerbation, in the emergency room, not pursuing a diagnosis. Difficulty of access to a public health specialist also contributed to delay in diagnosis. In 2005, he consulted an orthopedist, when the first radiographs were taken and Paget's

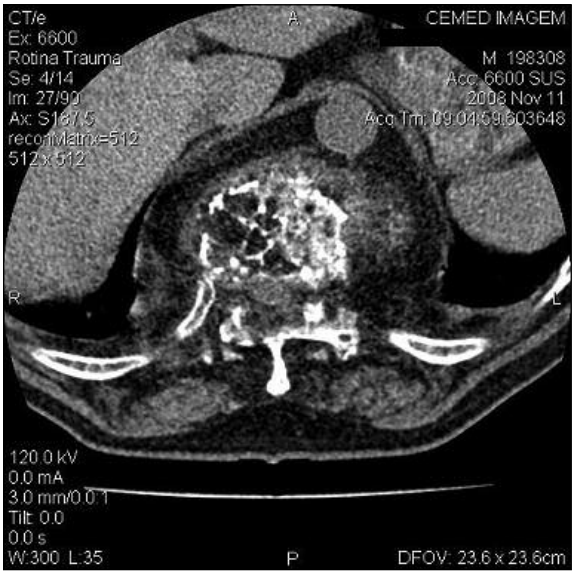

Figure 1. Tomographic study of pelvic bones showing lytic images

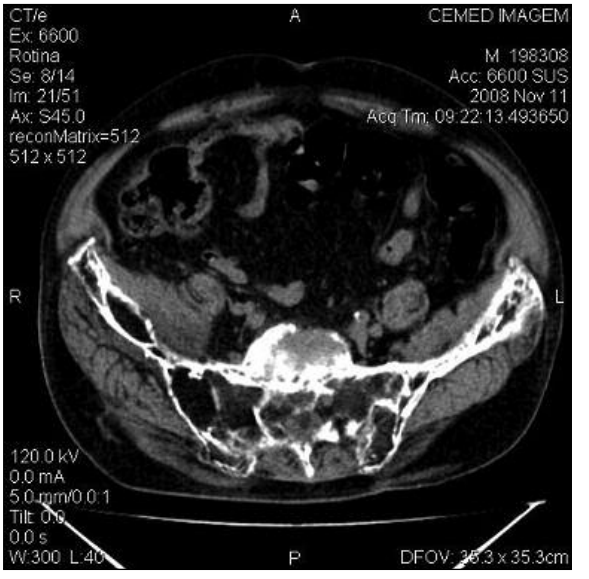

Figure 2. Tomographic study of pelvic bones showing lytic images

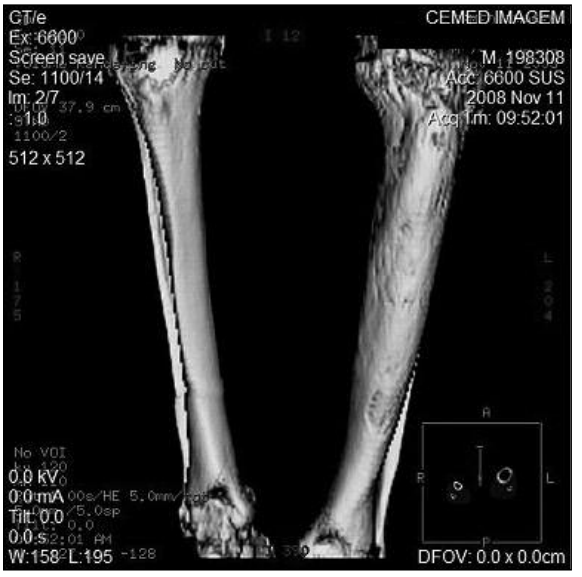

Figure 3. Tomographic study showing lytic images and thickening of cortical bone

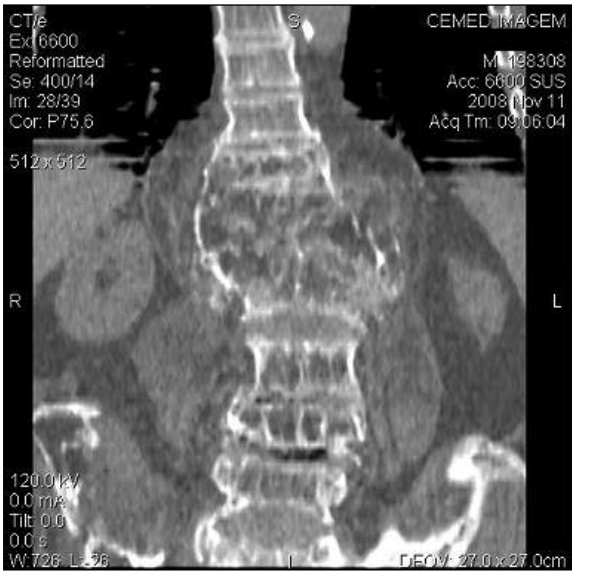

Figure 4. Destruction of multiple vertebrae with lytic lesions and areas of repair (reactive zone).

disease was suspected. Subsequently, he was referred to a rheumatologist, but he came to our Department of Rheumatology only in 2010. After a thorough clinical and laboratory evaluation, the diagnosis of Paget disease of bone was established, and specific treatment with zolendronic acid was tried, but the patient still could not get the medication because of financial reasons. Thus, alternatively, alendronate 40mg/day was used with gradually reduction of alcaline phosphatase: 1283 UI/ /L after three months and 1083 UI/L after six months of starting treatment.

Discussion

Paget's disease is the second most common metabolic bone disease, second only to osteoporosis. It is difficult to estimate its impact because, in most cases it is asymptomatic[6], but is more frequent in Countries of European and Anglo-Saxon extraction and is rare in the Americas[5,7]. In Latin America, 1149 cases were reported in the last 30 years, and the fact common to these patients is that the vast majority have European ancestry[8]. In Brazil, most cases are found in the city of Recife, owing to its peculiar mixed European colonization over approximately four centuries[9] and for being a reference center for Paget's disease in the country. The patient reported is native of Amazon, without European ancestry, which makes the case interesting due to the rarity in this population. The axial skeleton is more often involved[1], but proximal long bones may also be committed in 25 to 35% of cases[10]. Appendicular involvement is usually unilateral[10]. Polyostotic disease is found in 65 to 90% of patients, representing the most common form at diagnosis[10,11].

Disease's etiology remains uncertain[8], but genetic, environmental [9,12] and viral factors[13] are considered. Typical manifestations of Paget's disease are related to its complications[2], which may be classified according to the body system affected: skeletal (bone pain, bone deformities, osteoarthrosis, fractures and spinal channel stenosis), neural (deafness, cranial nerves dysfunction, high intracranial pressure), cardiovascular (ischemic heart disease, aortic valve stenosis, intracavitary calcifications, widespread atherosclerosis, high output congestive heart failure), metabolic (hypercalciuria, hypercalcemia, hyperuricemia, nephrolitiasis), and neoplasia (osteosarcoma, condrosarcoma, fibrosarcoma, giant cell tumor)[14]. At the time of diagnosis, the patient already had several complications of the disease, such as fractures, bone deformities, deafness, and congestive cardiac failure, which reflects the delay in diagnostic.

Diagnosis is ultimately made through image and laboratory findings. Radioisotope bone scanning is the most sensible method to detect early lesions.

Most patients with Paget's disease are identified by an elevation on the levels of alkaline phosphatase which cannot be explained by hepatobiliary pathology or another osteometabolic disorder. Altogether, image findings rely on disease progression to be classified in three distinct stages: lytic phase, with initial reabsorption characterized by osteolysis,established by osteoclast activity; mixed phase, with vascular and osteoblastic repair, leading to thickening and distortion of cortical and trabecular bone; and a blastic phase, which curses with appositional new bone, with an sclerosing scaring aspect[5]. The patient's diagnostic was suspected by the elevated levels of alkaline phosphatase and by radiological imaging characteristics.

Drug treatment is made with bisphosphonates, which are shown to diminish bone pain and biochemical markers of bone remodeling in randomized clinical trials, achieving restoration of histological and radiographic patterns[15]. The first bisphosphonate to be used was etidronate. However, more potent biphosphonates have proved to be more effective, leading to more prolonged periods of remission[16]. Oral alendronate, in a dose of 40 mg/day, for 6 months, leads to a 77% decrease in alkaline phosphatase, compared with the 44% decrease produced by etidronate[17]. Zoledronic acid is 10.000 times more potent than etidronate in reducing the biochemical markers of bone remodeling[18] and patients with resistance to other bisphosphonates usually respond to this drug[19]. As the only bisphosphonate available in public services, the patient has been treated with alendronate sodium 40 mg/d, improving complaints of pain and reducing gradually alkaline phosphatase levels. The apparent slow response to treatment may have been by the major bone involvement at diagnosis, and the fact that the drug considered more potent for the treatment of Paget's disease (zolendronic acid) was not performed, due to financial reasons.

Paget's disease diagnosis is rather difficult to be made, as long as the disease runs a large and variable clinical spectrum, involves many topographies in the body with different degrees of metabolic intensity, a difficulty most marked in asymptomatic patients. Nevertheless, in cases such as the one reported herein, with bone pain and deformities, the possibility of Paget's disease should always be concerned, considering the high impact of the complications brought forward by a delay in disease diagnosis and treatment.

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POLICONDRITE RECIDIVANTE, DERMATITE INTERSTICIAL GRANULOMATOSA E SÍNDROME ANTIFOSFOLÍPIDO: UMA ASSOCIAÇÃO CLÍNICA INVULGAR

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Resumo

Os autores apresentam o caso clínico de um doente do sexo masculino, de 49 anos de idade, com antecedentes de Síndrome antifosfolípido desde há 3 anos, internado através do Serviço de Urgência para esclarecimento de lesões cutâneas eritemato-nodulares na face e pescoço, com uma semana de evolução. As biopsias das referidas lesões revelaram aspectos sugestivos de Dermatite Intersticial granulomatosa. O doente referiu quadro compatível com condrite auricular bilateral duas semanas antes do aparecimento das lesões cutâneas, com resolução espontânea ao fim de 3 dias. Tinha antecedentes de condrite nasal 2 anos antes, tendo surgido outro episódio ao 7º dia de internamento. Estes achados, associados a antecedentes pessoais de poliartrite seronegativa não erosiva há 5 anos, permitiram estabelecer o diagnóstico de Policondrite Recidivante.

Palavras-chave: Dermatite Intersticial Granulomatosa; Biopsia Cutânea; Policondrite Recidivante; Síndrome Antifosfolípido.

Abstract

The authors describe the case of a 49 year-old male patient with a 3-year history of antiphospholipid syndrome, admitted after presenting in the emergency room with erythematous nodular skin lesions, affecting the face and neck, with a week's duration. Local biopsies were suggestive of interstitial granulomatous dermatitis. The patient described lesions compatible with bilateral auricular chondritis, two weeks prior to the appearance of the nodules, which resolved spontaneously after 3 days. There was a previous episode of nasal chondritis, two years previously, and another episode starting at the 7th day of hospitalization. These findings, taken together with a diagnosis of seronegative polyarthritis established 5 years before the current events, lead to a diagnosis of relapsing polychondritis.

Keywords: Interstitial Granulomatous Dermatitis; Skin Biopsy; Relapsing Polychondritis; Antiphospholipid Syndrome.

Introdução

A Policondrite Recidivante é uma doença auto-imune rara e de etiologia desconhecida, caracterizada por episódios inflamatórios recorrentes, envolvendo estruturas cartilagíneas, com risco de destruição, atrofia e deformação das mesmas. Pode ocorrer isoladamente ou em associação a outras doenças.

A Dermatite Intersticial Granulomatosa (DIG) é uma afecção cutânea rara que ocorre em associação com várias doenças sistémicas auto-imunes, fármacos ou neoplasias. A histologia das lesões cutâneas é típica, com infiltrado inflamatório difuso, e disposição celular em paliçada entre os feixes de colagénio na derme reticular profunda.

O Síndrome Antifosfolípido (SAF) é uma doença auto-imune caracterizada por trombose vascular recorrente e/ou morbilidade gestacional, associada à presença de títulos elevados de anticorpos

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antifosfolípidos.

A associação SAF e DIG[1] já foi reportada na literatura, mas não a associação entre estas três entidades.

Os autores revêem os aspectos importantes deste caso clínico, com particular destaque para as entidades mais raras, a Policondrite Recidivante e a Dermatite Intersticial Granulomatosa.

Caso Clínico

Doente do sexo masculino, 49 anos, raça branca, internado em Setembro de 2008 através do Serviço de Urgência para esclarecimento de lesões cutâneas eritemato-nodulares da face e pescoço e vasculite das mãos, com uma semana de evolução. Associadamente, referia astenia e anorexia com o mesmo tempo de evolução. Negava febre, ou outras queixas sistémicas ou articulares.

Duas semanas antes do aparecimento das lesões cutâneas referiu dor, edema e rubor de ambos os pavilhões auriculares, poupando os lobos, quadro esse que cessou espontaneamente ao fim de 3 dias. Teve episódio semelhante, mas dessa vez com atingimento da cartilagem nasal, 2 anos antes.

O doente tinha antecedentes de Fenómeno de Raynaud desde há 20 anos, Síndrome Antifosfolípido desde há 4 anos (com 4 episódios de trombose venosa profunda e um de tromboembolia pulmonar) e hipertensão arterial desde há 5 anos. Foi seguido no hospital da sua área de residência, por quadro de poliartrite bilateral e simétrica envolvendo punhos e pequenas articulações das mãos, seronegativa e não erosiva, diagnosticada 5 anos antes. Nessa altura foi medicado com corticosteróides orais e metotrexato 10 mg/semana, com remissão da doença ao fim de 5 meses. Manteve por mais dois anos a referida medicação, tendo depois suspendido por completo.

Estava medicado em ambulatório com Varfarina 5 mg (1 id), Diosmina 500 mg (2 id), e Amlodipina 5 mg (1 id).

Relativamente aos antecedentes profissionais, estava actualmente reformado devido ao elevado risco trombótico, tendo exercido profissões de mineiro e trabalhador da construção civil.

Ao exame objectivo apresentava-se com bom estado geral, apirético, normotenso, sem adenomegálias palpáveis ou alterações ao exame toraco-abdominal e membros inferiores. Na face e pescoço, eram visíveis nódulos eritematosos, inflamatórios, de cerca de 0,5 cm de diâmetro, um deles localizado na região cervical direita, com componente purpúrico central (Figura 1). As mãos evidenciavam pequenas máculas eritematosas em algumas polpas digitais, que não desapareciam à digitopressão, e diversos focos de hemorragia subungueal, lesões estas sugestivas de vasculite (Figura 2). Sem outras alterações de relevo no exame físico.

Analiticamente apresentava hemograma normal, com velocidade de eritrossedimentação de 56 mm/h, INR de 1,2, protrombinémia de 78%, proteína C reactiva de 1,9 mg/dL, com restante bioquímica normal. Sumária de urina, proteinograma electroforético, fracções do complemento, C3 e C4, normais. Factor reumatóide, Ac anti-peptídeo citrulinado 2 (Anti-CCP 2) e serologias para

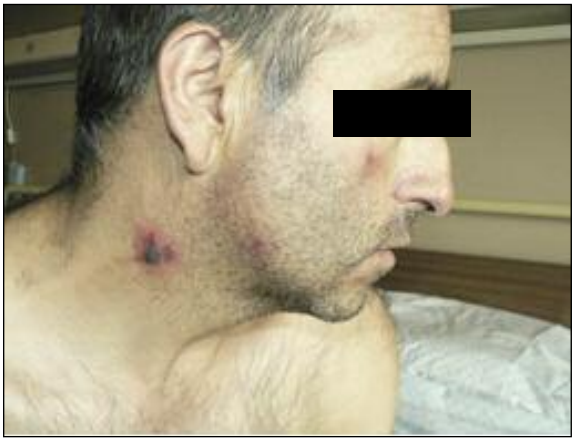

Figura 1. Nódulos eritematosos na face e região cervical direita, um deles com componente purpúrico central

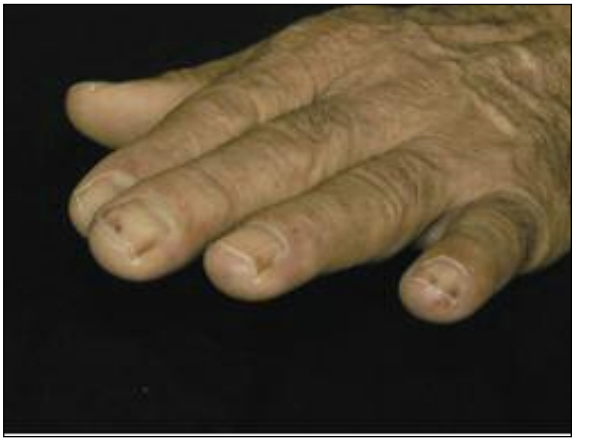

Figura 2. Máculas eritematosas nas polpas digitais e focos de hemorragia sub-ungueal

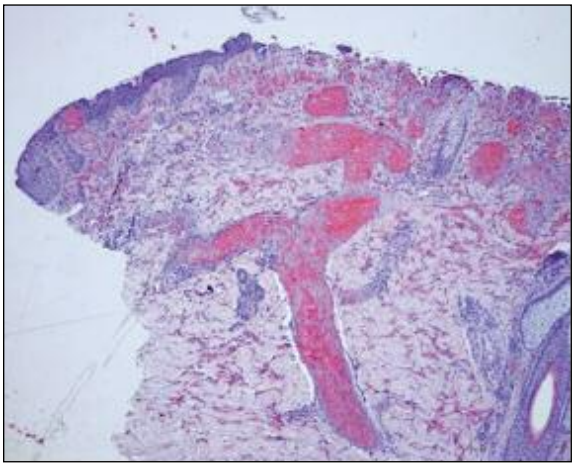

Figura 3. Biopsia de lesão cutânea – Vasculite Leucocitoclásica

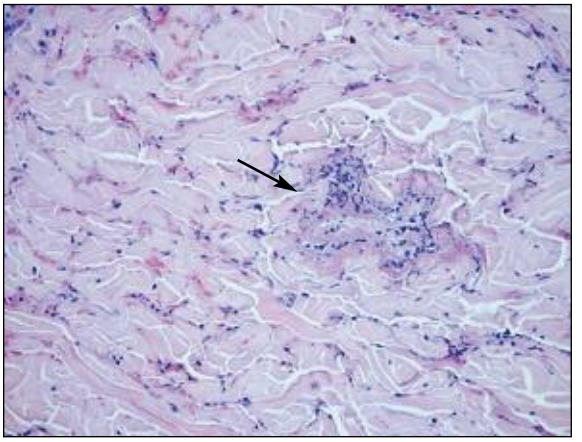

Figura 4. Biopsia de lesão cutânea – disposição dos neutrófilos em paliçada, com formação focal de imagens do tipo de granuloma de Churg-Strauss (seta)

hepatite B, C e HIV, negativas.

Autoimunidade positiva para ANA s (+++), padrão granular fino denso, com ENA s negativos; Anti-cardiolipinas IgM (> 150 U/mL) positivo, Anticoagulante lúpico positivo, ANCAs e doseamento de crioglobulinas negativos. Estudo das trombofilias (proteínas C e S, factor V de Leiden, anti-trombina III, entre outros) sem alterações. Capilaroscopia com várias tortuosidades capilares, alterações sugestivas de doença do tecido conjuntivo. A radiografia do tórax, mãos e pés, electrocardiograma, ecocardiograma e ecografia abdominal, não apresentavam alterações.

Durante o internamento ocorreram 2 episódios de rectorragias, sem dor abdominal, existindo contexto de antecedentes de hemorróidas de longa data. No entanto, foi pedida Angio-TAC abdominal para exclusão de vasculite sistémica, que não detectou alterações.

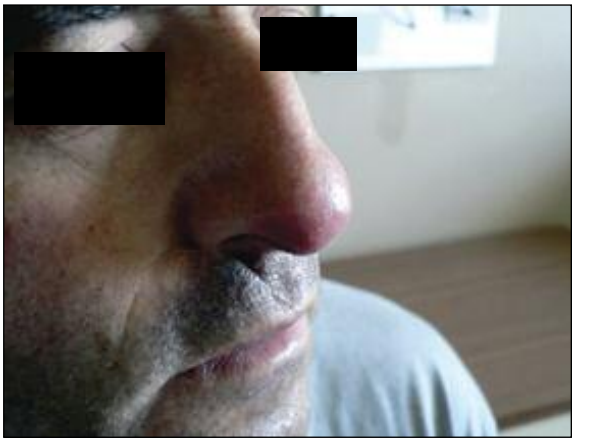

Figura 5. Condrite nasal

Realizou biopsia das lesões da face, que identificou: «na derme média dilatação dos vasos sanguíneos com trombose luminal e marcado infiltrado inflamatório neutrofílico, com carioclasia, acompanhado por necrose fibrinóide. Associadamente e de particular interesse, é a disposição dos neutrófilos no interstício, entre os feixes de colagénio, com formação focal de imagens do tipo de granuloma de Churg-Strauss. Trata-se, portanto, de uma vasculite leucocitoclásica, chamando-se a atenção para o aspecto intersticial, granulomatoso, focal do infiltrado neutrofílico, sugestivo de **Dermatite Intersticial Granulomatosa»** (Figuras 3 e 4).

As lesões cutâneas referidas resolveram espontaneamente ao fim de 3 dias, sem sequelas.

Ao sétimo dia de internamento surgiu condrite nasal, que resolveu com AINES (Naproxeno 500mg, 2id) ao fim de 4 dias (Figura 5).

A existência de condrites recorrentes associadas ao antecedente de poliartrite, permitiu estabelecer o diagnóstico de Policondrite Recidivante. O doente esteve internado por um total de 15 dias, sem outras intercorrências. Teve alta com indicação de manter o INR entre 2,5 e 3, ficando orientado para a Consulta de Reumatologia. Até à data, não se registaram novos episódios de condrite ou eventos trombóticos.

Discussão

A Policondrite Recidivante (PR) é uma doença sis-

témica rara, que se caracteriza por inflamação recorrente das estruturas cartilagíneas, com risco de destruição das mesmas. Afecta primariamente a cartilagem auricular e nasal, as articulações periféricas e o tracto respiratório superior. As estruturas ricas em proteoglicanos, como o olho, o ouvido interno, a pele, o coração, os vasos sanguíneos e o rim, também podem ser afectadas[2]. A PR foi inicialmente descrita em 1923, por Jaksch-Wartenhorst, como «policondropatia» e posteriormente designada de «condromalácia» ou «policondrite crónica atrófica». Foi finalmente reclassificada como Policondrite Recidivante, por Pearson *et al.*, em 1960. Estima-se uma incidência de 3,5/milhão[2]. Pode surgir em todas as raças, mas tem sido reportada com mais frequência em caucasianos[3]. A idade de diagnóstico oscila entre os 20 e os 60 anos, com pico de incidência aos 40 anos, e tem um *ratio* sexo feminino:masculino de 1:1 em algumas séries de casos, mas Trentham *et al.*, reportaram um *ratio* de 3:1[3]. Não existe predisposição hereditária, apesar de ter sido descrito uma maior associação ao HLA-DR4[3]. A etiopatogenia é desconhecida, mas foram identificados anticorpos contra o colagénio tipo II, em 33% dos casos de PR , o que favorece a suposição do mecanismo fisiopatológico ser auto-imune[2].

Os critérios de diagnóstico da PR foram inicialmente estabelecidos por McAdam *et al.*, em 1976, e incluíam pelo menos 3 de 6 características: condrite auricular bilateral, condrite nasal, poliartrite não erosiva seronegativa, inflamação ocular, condrite do tracto respiratório, ou alterações audio-vestibulares[6]. Mais tarde, Diamiani e Levine, reviram os critérios de McAdam e propuseram, para o diagnóstico, 3 dos critérios de McAdam ou, um critério de McAdam e a histologia positiva ou 2 critérios de McAdam e resposta a corticóides ou dapsona[7]. Mais recentemente, em 1986, Michet definiu como critérios a existência de condrite em duas de três localizações (auricular, nasal, laringo-traqueal) ou condrite num desses locais e duas outras características, incluindo inflamação ocular, alterações audio-vestibulares ou artrite seronegativa, não sendo necessário que estas alterações ocorram em simultâneo.

A biopsia é geralmente desnecessária[6]. Não existem marcadores bioquímicos de diagnóstico, sendo a elevação da velocidade de eritrossedimentação o achado laboratorial mais consistente, que geralmente se correlaciona com a actividade da doença[3].

A condrite auricular e a artrite são os sintomas de apresentação da doença mais frequentes. A condrite auricular desenvolve-se em até 89% dos doentes com PR e caracteriza-se pela existência de sinais inflamatórios da cartilagem, com dor e rubor intensos, tipicamente poupando o lobo do pavilhão auricular. É bilateral em 95% dos casos, podendo persistir durante alguns dias a semanas, sendo geralmente recorrente. A inflamação repetida desta estrutura pode conduzir à destruição da mesma, com deformações importantes e típicas, como o pavilhão em «couve-flor»[3]. Além do pavilhão auricular, o ouvido externo, médio e interno podem ser atingidos. O ouvido externo é envolvido pela extensão da inflamação ao canal auditivo externo; o médio, pela obstrução tubárica; e o interno, por fenómenos de vasculite dos vasos cocleo-vestibulares[10]. A condrite nasal ocorre em 54% dos casos, podendo conduzir ao colapso da cartilagem, com deformação «em sela» do nariz[8]. A artrite, que surge em 50-80% dos casos, pode ser oligo ou poliarticular, e envolve com frequência as articulações condro-costais, esterno-claviculares, membros superiores, coxofemorais ou joelhos. Geralmente é migratória, não erosiva, não deformante e seronegativa, com duração de semanas a meses, podendo preceder em anos o aparecimento de condrite nasal ou auricular[8]. O envolvimento ocular surge em 60-70% dos casos, podendo incluir queratite, esclerite, episclerite, conjuntivite, uveíte ou irite. As alterações laringo-traqueais surgem em 50% dos casos, podendo este atingimento ser fatal por destruição e colapso da árvore traqueo-brônquica[8].

As manifestações dermatológicas podem ocorrer em 35 a 50% dos casos. Podem preceder a doença em 10 a 20 anos, sendo a primeira manifestação da doença em 12% dos casos[7]. As alterações mais frequentemente encontradas são a aftose oral, nódulos cutâneos *«eritema nodoso-like»* e púrpura, sendo a vasculite o achado histológico mais frequentemente identificado[8]. Outras alterações incluem urticária, angioedema, eritema multiforme, livedo reticularis, paniculite, dermatoses neutrofílicas, pústulas estéreis e tromboflebite superficial migratória. A inespecificidade das diversas manifestações dermatológicas, explica porque não foram incluidas nos critérios de diagnóstico propostos por Michet *et al.*, em 1986[9].

Embora mais raramente, os sistemas cardíaco, neurológico e renal podem também ser atingidos[3].

A PR pode ocorrer isolada ou associada a outras

doenças autoimunes, em 25 a 35% dos casos. A associação mais frequentemente reportada foi a vasculite, incluindo vasculite cutânea leucocitoclásica e outras vasculites sistémicas (Granulomatose de Wegener, Poliarterite Nodosa, Síndrome de Churg-Strauss, Doença de Behçet e Síndrome MAGIC)[8]. Doenças reumáticas como a Artrite Reumatóide, o Lúpus Eritematoso Sistémico, Síndrome de Sjögren e a Doença mista do tecido conjuntivo, podem coexistir em 20% dos casos. Associação com outras doenças auto-imunes como o hipotiroidismo, anemia perniciosa, diabetes mellitus, miastenia gravis e colite ulcerosa foram também reportadas[7].

As neoplasias mais frequentemente coexistentes com a PR são as Síndromes mielodisplásicos e outras doenças hematológicas malignas[7]. Curiosamente, as manifestações cutâneas têm sido notadas com mais frequência em casos de PR associada a mielodisplasias[8]. Outros tumores sólidos podem também estar associados à PR, entre os quais, cancro da mama, pulmão, colo do útero, cólon, recto, pâncreas, próstata, tiróide e testículo[7].

O diagnóstico diferencial da PR varia consoante as manifestações clínicas, podendo incluir a condrite infecciosa, sarcoidose, tuberculose, lepra, granulomatose de Wegener, entre outras[3].

O prognóstico é variável, desde remissões espontâneas a um curso crónico persistente[3]. A principal causa de morte é infecção pulmonar devida quer à corticoterapia quer à obstrução das vias aéreas; outras causas incluem falência respiratória aguda por colapso aéreo, vasculite sistémica e falência renal[7]. São considerados factores de mau prognóstico, a anemia, o nariz «em sela», vasculite, artrite, atingimento laringo-traqueal e hematúria à data do diagnóstico[7].

Não existem protocolos *standard* para o tratamento da PR. Nos casos mais ligeiros os anti-inflamatórios não esteróides, a dapsona ou a colchicina podem ser usados, com alguma eficácia demonstrada[7]. Nos casos mais graves a corticoterapia é o *gold standard*, devendo ser usada na dose de 0,5 a 1 mg/Kg/dia. Tem bons resultados no controlo do episódio agudo e na redução da frequência das crises. Em algumas séries de casos têm sido reportados o uso de outros agentes imunossupressores como o metotrexato, azatioprina, hidroxicloroquina, ciclosporina, ciclosfofamida, rituximab, entre outros, com eficácia variável[3].

No presente caso clínico o diagnóstico de PR foi efectuado com base na existência de condrite auricular e nasal, e poliartrite. A resolução rápida e espontânea dos episódios de condrite, associada à ausência de deformações cartilagíneas e de atingimento traqueobrônquico, permitiram presumir um melhor prognóstico a este caso, pelo que se optou por não introduzir corticoterapia até à data actual. A coexistência com o SAF evidencia um «terreno» auto-imune mais marcado, neste caso com manifestações trombóticas várias, a sugerir maior gravidade. Quanto às manifestações dermatológicas, surgiram nódulos inflamatórios purpúricos cuja histologia revelou, além de um componente vasculítico, alterações que permitiram o diagnóstico de Dermatite Intersticial Granulomatosa. A sua evolução foi benigna, com resolução espontânea ao fim de alguns dias.

A dermatite Intersticial Granulomatosa é uma entidade histopatológica rara, inicialmente descrita por Ackerman *et al.*, em 1993[12]. Já conhecida desde 1983, quando Finan e Winkelmann descreveram uma condição semelhante, que designaram de Granuloma de Churg-Strauss ou granuloma cutâneo extravascular necrotizante[14]. Outros termos lhe têm sido posteriormente atribuídos, tais como pápulas reumatóides, necrobiose reumatóide superficial ulcerada ou Dermatite granulomatosa neutrofílica em paliçada[14]. Tem sido descrita a sua associação mais frequente a diversas doenças autoimunes, entre as quais, a artrite reumatóide, o lúpus eritematoso sistémico, o síndrome antifosfolípido primário, a tiroidite autoimune, vasculites sistémicas, hepatites auto-imunes e um caso associado a Doença de Behçet[13,14]. Outras patologias associadas incluem silicose pulmonar, leucemia promielocítica, uveíte crónica e carcinoma brônquico como manifestação paraneoplásica[13]. A etiologia farmacológica também já foi reportada, sendo os fármacos mais frequentemente envolvidos, os anti-hipertensores (inibidores da enzima de conversão da angiotensina, bloqueadores dos canais de cálcio, beta-bloqueantes), hipolipemiantes, inibidores do TNFα, anti-histamínicos, antidepressivos e anticonvulsivantes[11].

A apresentação clínica é variável, podendo incluir nódulos, pápulas ou placas, ou ainda, mais raramente, petéquias, livedo reticularis ou urticária. Os nódulos são o tipo mais comum, raramente excedendo os 2 cm de diâmetro, com consistência firme e coloração variando de vermelha a violácea[13,14]. A epiderme das lesões pode ser normal, mas estão descritas úlceras. Na maioria dos casos são assintomáticas mas podem ser dolorosas ou prurigino-

sas. A localização mais frequente é nas extremidades e no tronco, sendo a face raras vezes atingida[14].

O diagnóstico é histológico, caracterizando-se por infiltrado intersticial denso, difuso, na derme reticular, composto primariamente por histiócitos com disposição em paliçada. Por vezes porções de colagénio necrobiótico são envolvidos por neutrófilos e/ou eosinófilos, formando estruturas que lembram granulomas de Churg-Strauss. Pode existir vasculite leucocitoclástica associada, sendo que certos autores defendem que pode ser a alteração histológica inicial deste processo[11,15].

A fisiopatologia é desconhecida, sendo a deposição de imunocomplexos nos vasos dérmicos a causa mais consensual. Em muitos casos foram identificados depósitos de IgM e C3 nos vasos dérmicos e na junção dermoepidérmica no estudo da imunofluorescência directa. O modelo patogénico mais aceite propõe que a deposição destes imunocomplexos nos vasos dérmicos cause uma vasculite leucocitoclástica, degeneração das fibras colagénicas e dermatite granulomatosa em paliçada, com eventual fibrose dérmica em estágios terminais[15].

A terapêutica de eleição não está bem definida, dada a inexistência de estudos.

Diferentes opções terapêuticas têm sido reportadas na literatura, com graus variados de sucesso, entre as quais, anti-inflamatórios não esteróides, corticosteróides tópicos ou orais (dose >30mg/dia), colchicina, ciclosporina, ciclofosfamida, hidroxicloroquina e dapsona[14]. Resolução espontânea e formas resistentes também foram descritas[13]. Com ou sem tratamento, as lesões geralmente evoluem por semanas a meses. Na maioria dos casos não há recorrências, mas pode haver *flares* e remissões[13].

Neste caso clínico, a localização das lesões e a sua rápida e espontânea resolução, torna este caso menos habitual relativamente aos outros descritos.

Este é um caso que combina a existência de três condições auto-imunes, sendo duas delas raras, a PR e a DIG. Existem referências prévias a associação do SAF e a DIG[1], mas a associação desta última com a PR ainda não tinha sido reportada na literatura.

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CRIOGLOBULINÉMIA MISTA

Roque R*, Ramiro S*, Vinagre F*, Cordeiro A*, Godinho F*, Santos MJ*, Gonçalves P*, Canas da Silva J*

Resumo

Os autores descrevem dois casos clínicos de crioglobulinémia. O primeiro, uma doente do sexo feminino de 70 anos, com úlceras cutâneas e parestesias dos membros inferiores, artralgias e sintomas constitucionais com agravamento progressivo ao longo de 10 meses. Dos exames complementares destacava-se discreta anemia, elevação dos parâmetros inflamatórios e transaminases, crioglobulinas e factor reumatóide presentes no soro, e diminuição acentuada de C4. A serologia para o vírus da hepatite C (VHC) foi negativa. Diagnosticou-se crioglobulinémia mista idiopática e iniciou terapêutica com prednisolona a que se associou posteriormente ciclofosfamida e plasmaférese por ausência de resposta. Veio a falecer em choque séptico. O segundo caso, refere-se a uma doente do sexo feminino de 41 anos, com antecedentes de hepatite C não tratada, que apresentava desde há 6 meses lesões petequiais e livedóides nos membros inferiores, polineuropatia periférica e sintomas constitucionais com agravamento progressivo a que se associou um quadro de necrose intestinal. Os exames complementares foram compatíveis com crioglobulinémia mista associada a VHC. Iniciou terapêutica com ribavarina e alfa-interferão pegilado, com melhoria clínica e laboratorial.

Palavras-chave: Crioglobulinémia mista; Vasculite Crioglobulinemica; Manifestações Clínicas; VHC; Tratamento.

Abstract

The authors describe two clinical cases of cryoglobulinemia. A 70 years old woman, having skin ulcers on lower limbs, arthralgias, paresthesias and constitutional symptoms, for about 10 months. Exams revealed mild anemia, elevation of the biological parameters of inflammation and aminotransferases, positive cryoglobulin and rheumatoid factor in serum, and a severe reduction in C4 complement fraction. Hepatitis C virus (HCV) serology was negative. Idiopathic mixed cryoglobulinemia was diagnosed and corticosteroid therapy started. Given the lack of response, cyclophosphamide and plasmapheresis were added. Two weeks later the patient died in septic shock. The second case refers to a 41 years old female, with untreated hepatitis C who developed over a 6 month period petechiae and livedoid lesions on the lower limbs, peripheral neuropathy, and constitutional symptoms and was admitted with intestinal necrosis. Exams were consistent with the diagnosis of mixed cryoglobulinemia associated, with HCV. She started therapy with ribavirin and pegylated interferon-alpha, with improvement.

Keywords: Mixed Cryoglobulinemia; Cryoglobulinemic Vasculitis; Clinical Features; HCV; Treatment.

Introdução

A crioglobulinémia mista (CM) é uma vasculite sistémica que envolve vasos de pequeno e médio calibre por deposição de complexos imunes (crioglobulinas/factor reumatóide-FR) e fracções de complemento[1,2]. Define-se pela presença de crioglobulinas (imunoglobulinas-Ig) no soro que precipitam a temperaturas menores que 37º C e que se dissolvem novamente com o aquecimento[3]. A CM apresenta um largo espectro de manifestações clínicas que varia desde uma síndrome crioglobulinémica típica com púrpura, artralgias, astenia, até casos de lesões mais graves com envolvimento renal, neurológico e intestinal. Está associada a infecção pelo vírus da hepatite C (VHC) em cerca de 80 a 90 % dos casos, sendo nos restantes idiopática. Aproximadamente 15 a 20 % dos doentes apresentam uma vasculite sistémica grave que coloca em risco a vida[1,2].

Os autores descrevem dois casos clínicos de crio-

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globulinémia com envolvimento sistémico grave, um deles com desfecho fatal

Caso Clínico

Caso 1: Doente do sexo feminino de 70 anos, raça branca, com antecedentes pessoais de hipertensão arterial controlada com lercanidipina, infecção pelo vírus de hepatite B (VHB) curada, insuficiência venosa periférica e dislipidémia. Observada em consulta de reumatologia 10 meses após inicio de quadro clínico caracterizado por lesões cutâneas púrpuricas, não pruriginosas inicialmente intermitentes, posteriormente associadas a múltiplas úlceras necróticas muito dolorosas e de difícil cicatrização a nível das pernas, edemas maleolares bilaterais, astenia, perda ponderal de 20%, artralgias difusas, mialgias e parestesias a nível da face inferior do 5 º dedo dos pés bilateralmente. Tinha efectuado tratamento sintomático com analgésicos orais e anti-inflamatórios não esteróides (AINE's) tópicos, mas com agravamento progressivo das queixas. Do exame objectivo, nesta fase, salientava-se a existência de múltiplas lesões cutâneas purpúricas necróticas e ulceradas de diversos tamanhos (de diâmetros compreendidos entre 1 e 3 cm) a nível ambas as pernas, (Figuras 1, 2 e 3) associadas a lesões petequiais do tipo vasculítico (Figura 4) dispersas pela região anterior do tórax, abdómen, coxas e antebraço esquerdo. Apresentava discreta hipostesia a nível da face inferior dos pés bilateralmente. Não apresentava sinais de artrite ou tenosinovite e a força muscular estava mantida. As alterações analíticas estão sumarizadas na Tabela I. O resultado histológico da biopsia de pele revelou necrose da epiderme, vasculite leucocitoclástica envolvendo os vasos dérmicos e hipodérmicos com trombos intraluminais PAS + sugestivo de crioglobulinémia mista. Realizou electromiograma dos membros inferiores e ecocardiograma que não apresentavam alterações. Fez tomografia computorizada (TC) toraco-abdomino-pélvica que revelou hipotransparência parenquimatosa bibasal pulmonar, aumento do lobo hepático esquerdo de contornos irregulares, parênquima heterogéneo e ligeira esplenomegalia homogénea. Tendo em conta o quadro clínico e exames complementares chegou-se ao diagnóstico definitivo de crioglobulinémia mista idiopática do tipo II. A doente iniciou prednisolona na dose de (1mg/Kg/dia) oral associada a cálcio e vitamina D, ibandronato 150 mg mensal, omeprazol 20 mg/dia e irbesartan + hidroclorotiazida. Após 4 meses de terapêutica a doente mantinha lesões ulceradas a nível das pernas, muito dolorosas e de difícil cicatrização, associadas a lesões vasculíticas de novo, a nível do tronco e abdómen. Pelo agravamento do quadro, apesar da terapêutica anterior foi administrado pulso de ciclofosfamida (500mg/$/m^2$) associado a plasmaférese e prednisolona 1 mg/Kg/dia oral. No entanto, cerca de 2 semanas

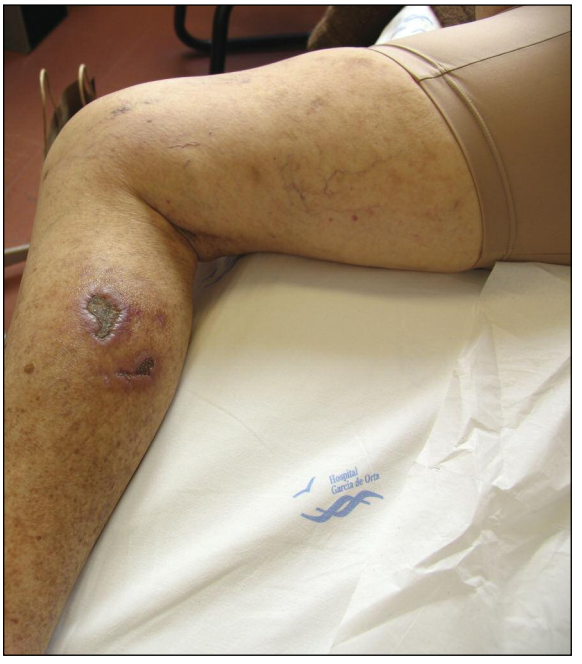

Figura 1. Lesão cutânea necrótica úlcerada

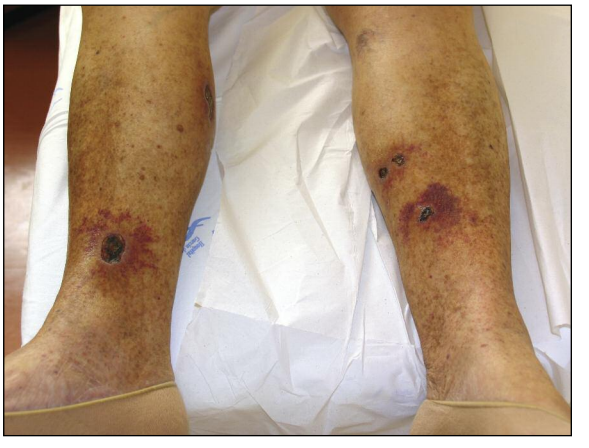

Figura 2. Múltiplas lesões cutâneas necróticas e ulceradas

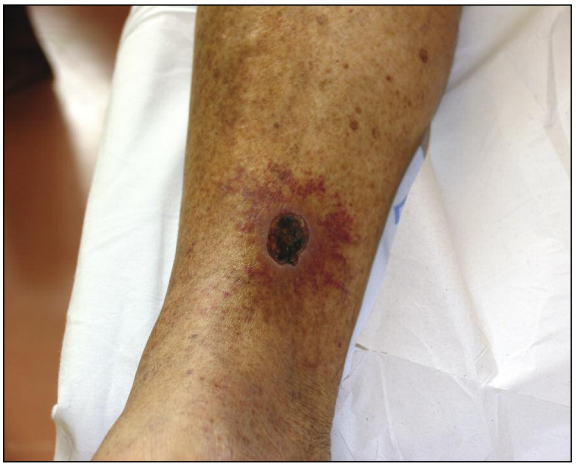

Figura 3. Lesão cutânea necrótica e ulcerada

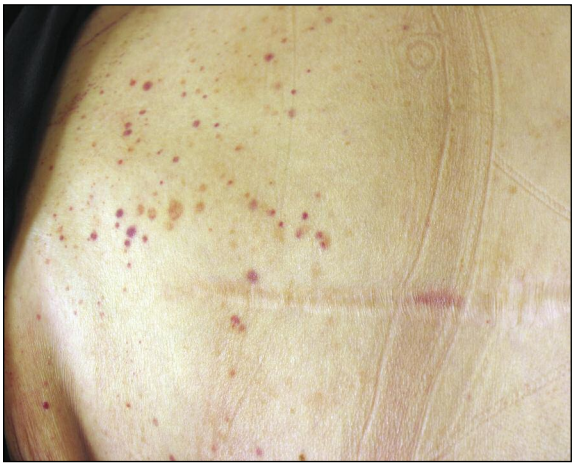

Figura 4. Lesões petequiais vasculíticas

Tabela I. Avaliação laboratorial das doentes

	Doente 1	Doente 2
Hemoglobina	11,8 g/dL	10,1 g/dL
Leucócitos	4700	6700
VS	42	96
PCR	1 mg/dL	2,2 mg/dL
Urina II	Normal	Normal
Creatinémia	0,9 mg/dL	0,2 mg/dL
AST	52 UI/l	19 UI/l
ALT	31 UI/l	29 UI/l
G-GT	139 UI/l	94 UI/l
ANA	Negativo	Negativo
Especificidades ANA	Negativo	Negativo
VHC	Negativo	Positivo (Genotipo Ia)
Ac HBs e HBc 1.773.700cópias	Positivos	
Ac HBe	Negativo	RNA/ml
Ag HBe e HBs	Negativos	Negativos
VIH1 e 2	Negativos	Negativos
FR	Positivo	Negativo
Ac anti-citrulina	Negativo	Negativo
C3	89 mg/dl (90-180)	135 (90-150)
C4	2 mg/dl (10-40)	1.4 (10-40)
Criogloubulina	Positiva (IgMk)	Positiva (IgMk)

VS – Velocidade de sedimentação; PCR – Proteína C Reactiva; ANA – Anticorpo antinuclear; AST – Aspartato Aminotransferase; ALT – Alanina Aminotransferase; VHB – Vírus da Hepatite B; VHC – Vírus da Hepatite C; VIH –Vírus da Imunodeficiência Humana; FR – Factor Reumatóide; C3 e C4 – fracção de complemento 3 e 4

depois, a doente entrou em aplasia medular, complicada de choque séptico, sendo necessária a transferência para Unidade de Cuidados Intensivos. Da avaliação analítica nesta fase, destacava-se hemoglobina 7,7 g/dL, leucopenia (300 leucócitos) com neutropenia (200 neutrófilos), plaquetas 71.000; velocidade de sedimentação (VS) de 89 mm 1ªh e proteína C reactiva (PCR) de 9 mg/dL. Foram isolados múltiplos microrganismos em culturas de sangue (*Staphylococus aureus*, *Enterobacter cloacae*, *Citrobacter feudi*) e ponta de cateter central (*Candida tropicalis*). Necessitou de antibioterapia de largo espectro, entubação orotraqueal e ventilação mecânica, suporte vasoactivo com noradrenalina, factores de crescimento (G-CSF), corticoterapia em dose de choque séptico e gamaglobulina humana endovenosa 400mg/Kg/dia (5 dias). Apesar das medidas terapêuticas acima referidas, verificou-se o óbito após 3 semanas nos cuidados intensivos.

Caso 2: Doente do sexo feminino, 41 anos, raça branca, professora. Com antecedentes pessoais de hepatite C diagnosticada em 2003, sem terapêutica, fumadora de 10 UMA. Apresentava quadro com 6 meses de evolução de diarreia crónica com muco e sangue, dor abdominal, anorexia, perda ponderal de 4 % e astenia. Foi observada em consulta de Gastroenterologia por suspeita de doença inflamatória do intestino e foi medicada com azatioprina 50 mg/dia (1mg/Kg/dia), prednisolona 5 mg/dia, isoniazida 300mg/dia, suplementos de ferro e ácido fólico. No entanto, verificou-se agravamento da dor abdominal, com empastamento doloroso na fossa ilíaca esquerda (FIE) e hipogastro, e sinais de defesa abdominal com dor à des-

compressão. O quadro de abdómen agudo estava associado a leucocitose com neutrofilia e PCR de 7 mg/dL. A TC abdominal e a colonoscopia revelaram estenose do cólon sigmóideu e necrose intestinal. Foi submetida a hemicolectomia esquerda alargada e, posteriormente, a colectomia total e ileostomia terminal, devido a necrose isquémica subsequente do restante cólon. Foi referenciada a reumatologia, dois meses após a cirurgia intestinal, devido ao aparecimento de dor na região gemelar e pés, parestesias e sensação de diminuição da força muscular distal dos membros inferiores bilateralmente. Referia ainda algumas lesões petequiais nas pernas e progressivo agravamento de lesões livedóides nos membros inferiores (MI). Ao exame objectivo salientava-se hipostesia dos pés, disestesia do terço inferior das pernas, força muscular grau IV dos MI (distal) com reflexos osteotendinosos mantidos. Dos exames complementares destacavam-se, anemia normocitica normocrómica, aumento de VS, FR e crioglobulinas presentes no soro e infecção a VHC (Tabela I). A radiografia de tórax e a angiografia do tronco celíaco, artérias renais e mesentérica superior não apresentavam alterações. A ressonância magnética (RM) hepática revelou nódulo hepático de 3 cm sobreponível a exame anterior e sem relevância clínica. O electromiograma dos membros inferiores revelou polineuropatia crural sensitiva e motora (assimétrica e de predomínio sensitivo). O resultado histológico de biopsia intestinal (peça operatória) mostrou microtrombos venosos e arteriais, infiltrado inflamatório e microaneurismas, achados sugestivos de vasculite. Após o diagnóstico de crioglobulinémia mista associada a VHC, a doente iniciou tratamento com alfa-interferão pegilado B na dose de 80 mcg/semana/sc, ribavarina 800 mg/dia, gabapentina 900 mg/dia, amitriptilina 25 mg/dia e paracetamol (até 3g/dia). Houve melhoria laboratorial com descida da carga viral e parâmetros biológicos de inflamação em cerca de 6 meses de seguimento em consulta, mas a doente mantém queixas neuropáticas exuberantes, sem tradução objectiva, ou outras manifestações de novo.

Discussão

A característica patológica da CM é a existência de uma vasculite leucocitoclástica secundária à deposição de complexos imunes circulantes (IgG e IgM) e fracções de complemento a nível dos vasos, que é responsável pelo envolvimento cutâneo e de órgãos[1,3,4].

Brouet *et al.*, classificaram três tipos de crioglobulinémia: tipo I- com uma imunoglobulina (Ig) monoclonal; tipo II ou mista- com uma IgG policlonal combinada com uma IgM que mostra actividade de factor reumatóide (FR); tipo III- com imunoglobulinas policlonais[5].

A crioglobulinemia mista apresenta uma patogenia complexa, estando associada em 90% dos casos à infecção pelo VHC e, nos restantes casos, é idiopática[6,7]. Vários estudos demonstraram a presença de Antigénio (Ag) Hbs e/ou Anticorpo (Ac) Hbs em doentes com CM, mas mais tarde verificou-se que a prevalência destes marcadores é semelhante nos indivíduos com CM e na população geral[3]. Os casos clínicos descritos reflectem estas características.

A CM é uma síndrome clínica muito heterogénea na sua forma de apresentação clínica, extensão e gravidade de envolvimento de órgãos, alterações imunológicas e evolução clínica. Na apresentação clínica mais frequente existe uma tríade clássica de púrpura, astenia e artralgias, podendo haver envolvimento multiorgânico sistémico, nomeadamente intestinal, com microaneurismas e risco de enfarte e necrose do intestino[4,8]. No primeiro caso descrito a forma de apresentação foi clássica, enquanto a segunda doente revelou envolvimento de órgão alvo com necrose intestinal por vasculite numa fase mais inicial do quadro.

A manifestação clínica mais típica da CM é a existência de púrpura palpável, predominando nos membros inferiores quando estão afectados os vasos de pequeno calibre. Com o envolvimento dos vasos de médio calibre formam-se úlceras cutâneas. Cerca de 50 a 80 % dos doentes têm artralgias difusas. Verifica-se envolvimento renal em 25% dos doentes, que habitualmente, consiste na existência de proteinúria que poderá ter agravamento progressivo e culminar em insuficiência renal nos casos não tratados. Histologicamente, a lesão renal mais frequente é a de glomerulonefrite membranosa proliferativa. A neuropatia periférica varia entre 7 a 60 % dos casos, envolve, de forma preferencial, os nervos sensitivos e traduz-se em parestesias, dor ou perda de sensibilidade[8,9]. Ambas as doentes apresentaram queixas neuropáticas, preferencialmente sensitivas, tal como descrito na literatura. A CM está associada a algumas alterações laboratoriais, sendo mais caracte-

rística a presença sérica de crioglobulinas, associadas a factor reumatóide e a diminuição da fracção de complemento C4. Nos dois casos descritos verificou-se a presença destas alterações laboratoriais descritas. Podem existir também alterações inespecíficas, tais como discreta anemia normocítica normocrómica, elevação dos parâmetros biológicos de inflamação, alterações da função renal, se existir glomerulonefrite, aumento discreto das transaminases, presença no soro de anticorpos antinucleares e serologia para VHC positiva em 90 % dos casos[8,10]. Tendo em conta a maior frequência de crioglobulinémia associada ao VHC, o caso da primeira doente assume uma maior relevância dado a sua raridade.

Devido ao seu pleiomorfismo, a crioglobulinémia mista pode confundir-se com várias doenças autoimunes, neoplasias, outras vasculites sistémicas, síndrome de Sjögren, hepatite autoimune e doenças linfoproliferativas de células B[4].

O tratamento da CM deve ser individualizado de acordo com o doente e a gravidade das manifestações. Nos casos em que há infecção a VHC, utiliza-se alfa-interferão pegilado associado a ribavarina[11]. Os corticosteróides isolados ou em combinação com plasmaférese ou ciclofosfamida podem ser utilizados como terapêutica de 1ª linha. A ciclofosfamida oral (1mg/m^2) diária durante 3 meses associada a corticosteróides em doses de 1-2 mg/Kg/dia e/ou plasmaférese é a forma de tratamento mais frequentemente preconizada nas formas graves de CM, nomeadamente quando há associação a glomerulonefrite, neuropatia sensitivo-motora recente ou vasculite generalizada[4].

Mais recentemente, tem sido utilizado o Rituximab (anticorpo monoclonal anti-CD20) com sucesso em doentes com CM sem efeitos secundários significativos. No entanto, são necessários ensaios clínicos controlados para verificar a sua eficácia e segurança a longo prazo[12]. A CM é uma doença rara e dado o seu pleomorfismo clínico é frequente haver atraso no diagnóstico e no início da terapêutica eficaz o que compromete o prognóstico do doente[13]. Os doentes com CM têm maior taxa de mortalidade que a população geral. Esta taxa parece ser semelhante nos casos de CM essencial e associada a VHC. Os factores de mau prognóstico são a idade superior a 60 anos na ocasião do diagnóstico, o sexo masculino e o envolvimento renal[1,8]. As causas de morte mais frequentes são a insuficiência renal, a hepatite crónica com cirrose, a vasculite sistémica disseminada, a infecção e o linfoma não Hodgkin de células B[1,3].

A primeira doente apresentou uma complicação menos frequentemente descrita, mas muito típica, que foram as úlceras cutâneas nas pernas, refratárias ao tratamento com corticoesteróides, necessitando de tratamento com ciclofosfamida e plasmaférese. Estas duas modalidades terapêuticas estão indicadas e são eficazes nestes casos, tal como descrito na literatura, mas a imunosupressão tem riscos associados, e a infecção é um dos principais motivos de morte nesta patologia, tal como se veio a verificar neste caso. A segunda doente apresentava CM associada a hepatite C, situação mais frequente, contudo a forma de apresentação foi menos típica. Tal como referido na literatura, a CM é uma vasculite de difícil diagnóstico dada a variedade de apresentações clínicas. Nesta doente, a principal manifestação foi a necrose intestinal por vasculite sistémica grave, associada a neuropatia periférica e lesões cutâneas, não se verificando envolvimento renal nem artrite.

Em conclusão, a CM é uma vasculite sistémica que apesar de rara é potencialmente fatal. A variedade de manifestações clínicas pode atrasar o diagnóstico e o tratamento atempado, que são essenciais para a melhoria do prognóstico e da qualidade de vida do doente.

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KAWASAKI DISEASE IN A YOUNG INFANT: DIAGNOSTIC CHALLENGES

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Abstract

Kawasaki disease (KD) is a multisystem vasculitis condition with a relatively unknown etiology. It has a high prevalence in children ages 6 months to 5 years, and patients often present with high fever, rash, cervical lymphadenopathy and mucocutaneous abnormalities. Visceral manifestations can be present, being coronary complications the most frequent. There is no diagnostic test for KD, its presentation can be complete or incomplete and, in some cases, it can be atypical. We report a case of a 3-month-old infant with 3-weeks of fever and aseptic meningitis. Infectious diseases were excluded and there was no response to antibiotics. Echocardiography was normal in the second week. Genetic test for CINCA syndrome was negative. In the third week, dilatation of coronary arteries determined Kawasaki disease's diagnosis. Prolonged fever, accompanied by nonspecific clinical symptoms were the only manifestations, becoming a challenging diagnosis. KD must be considered when prolonged fever is present, mainly in young children in whom the incomplete forms of the disease are more frequent.

Keywords: Kawasaki Disease; Vasculitis; Incomplete; Coronary Artery Aneurysms; CINCA Syndrome.

Introduction

Kawasaki disease (KD) is an acute, multisystem and self-limited vasculitis of unknown etiology that has a striking predilection for the coronary arteries of infants and young children[1]. Since its first description by Tomisaku Kawasaki in 1967, this enigmatic illness has surpassed acute rheumatic fever as the leading cause of acquired heart disease among children in developed countries[1,2].

Incomplete KD is more common in young infants than in older children, making accurate diagnosis especially important because of their higher risk for developing coronary abnormalities[6,7]. Coronary artery aneurysms occur in 20 to 25% of untreated children, predominantly in young children, with 80% of patients being younger than 5 years old[1].

Therapy with IVIG must be started within the first 10 days of illness because timely diagnosis and early treatment are two crucial points for KD's prognosis[6,8,10]. However, even when treated appropriately, 5% of children develop coronary artery dilatation and 1% develop giant aneurysms.

Case report

A previously healthy 3-month-old caucasian female infant, born to non-consanguineous parents, with an unremarkable past medical history, presented with a two-weeks high-grade (39ºC) continuous fever with diarrhea during the first three days. Before hospital admission, she was prescribed amoxicillin clavulanate for suspected urinary tract infection. Physical examination revealed a febrile (38,7ºC), but "non-ill appearance" child. Bilateral cervical and inguinal lymph nodes were enlarged (<1cm in diameter), accompanied by a subtle hepatomegaly. Cardiopulmonary examination was normal. There was no rash, conjunctival injection, changes in the lips or oral cavity or edema/erythema of the hands.

Laboratory findings showed normocytic anemia (haemoglobin – 8.7 g/dL), leukocytosis of 13,100/mm³ (44% neutrophils; 42.5% lymphocytes), thrombocytosis of 891,000 platelets/mm³, C-reactive protein of 11.39 mg/dL, erythrocyte sedimentation rate of 110mm/1st hr. Chest radiogra-

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phy was normal.

Examination of the cerebrospinal fluid (CSF) was compatible with meningitis - white blood cell count – 25/mm³ with polymorphonuclear predominance, protein – 70.1 mg/dL, glucose – 52 mg/dL, and intravenous ceftriaxone was started. Transfontanelar ultrassonography was normal. CSF Gram stain and culture were sterile and protein-chain reaction for herpes simplex 1 and 2 was negative. Additional analytic findings: hypoalbuminemia (2.6g/dL), hyperferritinemia (360ng/mL) and mild elevation of hepatic aminotransferases. Abdominal ultrassonography showed an heterogenous hepatomegaly.

Echocardiography excluded cardiac involvement and ophthalmologic evaluation was normal.

The patient remained febrile until day 20 of illness, with no response to antibiotics and persistently elevated acute phase reactants (Figure 1). Exhaustive laboratory searching for infectious and autoimmune diseases was negative (Table I). Considering the association of persistent high fever with aseptic meningitis, genetic test for *chronic neurologic cutaneous and articular* (CINCA) Syndrome was performed and it was negative.

On day 22 of illness she developed a maculopapular erythematous rash of the trunk, palms and soles followed by periungual desquamation of the fingers and toes. At that time echocardiography showed right and left coronary arteries dilatation (3,4 and 4,2 mm in diameter respectively – Figures 2 and 3). IVIG 2 g/kg and acetylsalicylic acid 100 mg/kg/day were started, with significant clinical and analytic improvement (Figure 1). On hospital day 39 of illness, the patient was discharged home on high-dose aspirin, which was reduced to 5mg/kg/day two weeks later. Follow-up echocardiography at week 4 of therapy showed persistent coronary arteries dilatation (4mm) which was subsequently improved at week 8. Aspirin was discontinued after complete resolution of coronary involvement, demonstrated by coronary angiocomputed tomography, at 4 months of treatment.

Discussion

Although KD primarily affects young children

					IVIG ↓	Discharge ↓				
Day of illness	**D11**	**D14**	**D17**	**D20**	**D22**	**D28**	**D34**	**D49**	**D83**	**Units**
Hemoglobin	8.7	8.7	8.0	7.9	8.9	9.4	10	11.2	10.8	**g/dL**
White blood cell	9,300	11,900	12,400	6,700	10,900	12,700	8,200	8,900	7,400	**X10³/µl**
Platelets	891	987	891	891	891	891	588	413	421	**X10³/µl**
C-reactive protein	11.39	11.24	10.84	6	6.7	2.55	2.37	1.51	0.53	**mg/dL**
Erythrocyte sedimentation rate	110	100	80	80	122	110	79	–	23	**mm/1st h**

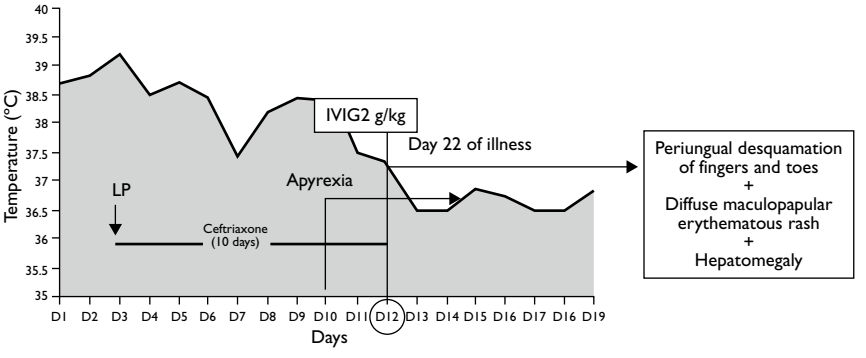

Figure 1. Clinical and laboratory evolution during hospitalization and after discharge
Legend: LP – lumbar punction; IVIG – Intravenous Immunoglobulin

Table I. First laboratory searching for infectious and autoimmune diseases

Infectious Etiology	
Antistreptolysin O test (ASO); anti-Dnase B	Normal; <200 U/ml
Venereal Disease Research Laboratory (VDRL)	Negative
PCR for *Enterovirus* and *Adenovirus* (stool) and *Human Herpesvirus type 6* (blood)	Negative
Serologic evaluation for *Cytomegalovirus, Epstein-Barr* virus, *Parvovirus, Adenovirus, Respiratory syncytial virus* (RSV), *Influenza and Parainfluenza* virus, *Rickettsias, Mycoplasma pn, Chlamydia pn, Human immunodeficiency virus* (HIV) 1 and 2, *Hepatitis B virus* (HBV), *Hepatitis C virus* (HCV), *Toxoplasma gondii, Brucella* and *Leishmania*	Negative
Tuberculin test	Anergic
Cultures from blood (2), stool (3), sputum and urine	Sterile
Immunologic Evaluation	
Antinuclear, anti-DNAds, anti-sm, anti-RNP and anti-smoth muscle antibodies	Negative

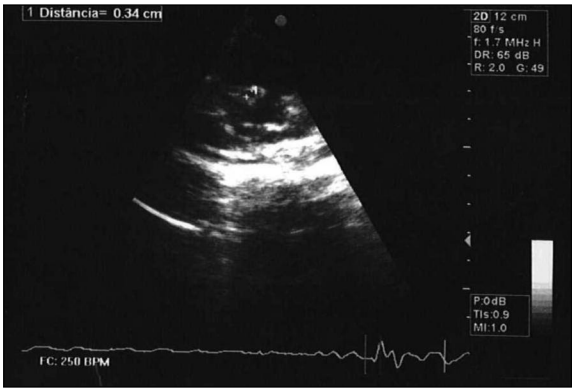

Figure 2. Echocardiography image showing right coronary artery dilatation (3.4mm in diameter)

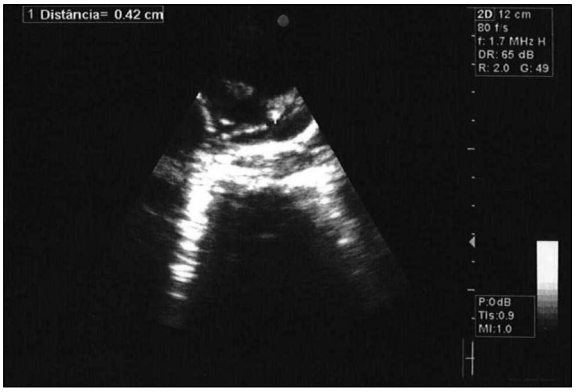

Figure 3. Echocardiography image showing main left coronary artery dilatation (4.2mm in diameter)

(peak incidence - 2 years), it is uncommon in children younger than 6 months-old and quite more under 3 months-old, accounting for only 1.6% of all patients with KD[11-13].

Patients who do not fulfil classic criteria for KD's diagnosis, besides the presence of five or more days of fever, should be referred as "incomplete" KD rather than the past designation of "atypical" KD, which should be reserved for patients who have unusual manifestations[3]. KD under 6 months-old is more likely to be incomplete and associated with coronary artery aneurysms[1,5,12]. Remains unclear whether young infants have a greater propensity to develop coronary artery aneurysms or if this complication results from delayed diagnosis in incomplete KD. Sometimes the presence of coronary artery aneurysms may be the only definite means to diagnose incomplete KD[7]. On the other hand, diagnosis may be delayed because signs and symptoms are not present simultaneously, but appear sequentially, as it was seen in our patient[5,14].

In fact, our patient had incomplete KD. Besides the 3-weeks long fever, she only had two diagnostic criteria: the diffuse maculopapular erythematous rash and the periungual desquamation of fingers and toes, and those only appeared on the third week of the disease. She had cervical lymphadenopathies, but they were bilateral and had less than 1.5cm in diameter. Other signs and symptoms occasionally associated with KD include diarrhea and hepatitis[1], which were present in this infant but also common in other clinical situations.

No specific laboratory test exists for KD but universal findings include leukocytosis, thrombocytosis and elevated acute phase reactants (erythrocyte sedimentation rate and C-reactive protein), which were present in our patient (Figure 1). Mild-to-moderate normochromic anemia and hypoalbuminemia were also present and it is often related to a more severe and prolonged inflammatory disease. During the subacute stage, platelet count elevation is the outstanding marker, and in the convalescent stage platelets levels and other mar-

kers begin to return to values within the reference range, requiring 6-8 weeks to normalize, as it was seen in our patient (Figure 1)[9].

In the reported child, the presence of a "non-toxic look" helped in the suspicion of KD. However, in a 3 month-old child disease's clinical patterns are not specific and it was mandatory to exclude infectious diseases.

Fever, rash, lymphadenopathy and hepatomegaly are common features in many childhood illnesses[1]. If those who have KD undergo lumbar puncture, approximately 50% have evidence of aseptic meningitis[1,2]. Differential diagnosis with CINCA syndrome should be kept in mind when an infant, in the first months of life, presents with fever, rash, lymphadenopathy, hepatomegaly, aseptic meningitis and high acute phase reactants[1] . CINCA syndrome, also known as neonatal onset multisystem inflammatory disease, is one of the CIAS1 syndromes characterized by fever and a persisting urticarial rash, often present at birth or in the first few months of life, accompanied by arthropathy with overgrowth (in about half), chronic meningitis with neutrophilic pleocytosis and, later on, cerebral atrophy, sensorineural deafness with developmental delay and growth delay[15]. Another differential diagnosis to be considered is systemic-onset juvenile idiopatic arthritis if arthritis was present[1]. However, her age (this autoimmune disease is rare before six months-old, with a median age of onset of 5 years old) make this hypothesis less probable.

The association of some infectious diseases with KD is well recognised, but rarely documented. Treatment with antibiotics doesn't change the disease's course, and fever persists unless IVIG is given, in responsive patients, as it was seen in our patient[14]. Considering delayed diagnosis and treatment in this child, it was expected a worse outcome then the observed, because 20% to 25% of untreated children develop coronary artery aneurysms[2,8].

Conclusion

KD should be considered in any infant or child, mainly if younger than 6 months-old, with persistent and unexplained fever and laboratory evidence of systemic inflammation, even without more clinical criteria suggestive of the disease, because early recognition and treatment may prevent development of coronary artery dilatation and aneurysm formation. On the other hand, this case report showed that it's important to perform serial cardiac evaluations because complications can develop only some weeks later. The clinical challenge lies in distinguishing cases of KD that do not fully meet the diagnostic criteria from those that strongly resemble a variety of common childhood disorders.

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SCHWANNOMA OF THE POSTERIOR TIBIAL NERVE IN LEPROSY PATIENT: IMAGING FEATURES

Erilane Leite Guedes*, Sandra Lúcia Euzébio Ribeiro**, Paula Frassinetti Bessa Rebello***, Denis Esteves Raid****, Ernani Júnior Guedes de Freitas*****

Schwannoma is a slow growing tumor, usually encapsulated, which rarely undergo malignant transformation. Represents 5% of soft tissue tumors, most commonly found between the fourth to sixth decades of life[1-2]. The tumor has a predilection for the head, neck and flexor surfaces of the upper and lower extremities but posterior tibial nerve schwannoma has also been described[3]. Man and women are equally affected[1,4].

Case Report

The author's describe a 51 year old male, with arthralgia on the right elbow, and multiple painful purpuric macules and plaques with asymmetric distribution in the trunk and in the extremities. He had pain and thickening in left ulnar and cubital nerves course suggestive of neuritis. He was diagnosed of lepromatous leprosy and started a multidrug therapy for leprosy and prednisone 60 mg/day to neuritis, with a clinical improvement after 5 months of treatment. Subsequently developed severe pain in right leg, first episode of neuritis in the posterior tibial nerve and was submitted to neurolysis, but the pain in foot persisted. After 6 months he had a palpable and painfull mass in popliteal fossa and image studies were requested. Ultrasonography (US) showed a well-defined, hypoechoic, heterogeneous and oval mass measuring 2.4 x 1.9 cm and 1.5 x 1.2 cm, along the tibial nerve (Figure 1). Magnetic resonance imaging (MRI) of the knee was performed. On spin-echo T1-weighted MR images, the lesion was homogeneous and isointense relative to skeletal muscle (Figure 2A) and T2-weighted MR images demonstrated the lesion to be mildly heterogeneous, with a signal intensity greater than that of fat (Figure 2B), measuring 2.5 x 2.2 cm and 1.5 x 1.2 cm.

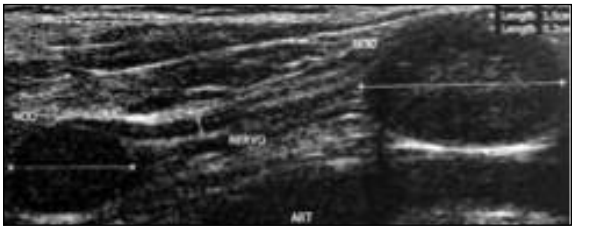

Figure 1. Longitudinal US - over the right popliteal fossa showed a well-defined, hypoechoic, heterogeneous and oval mass (2.4 x 1.9 cm and 1.5 x 1.2 cm), along the tibial nerve.

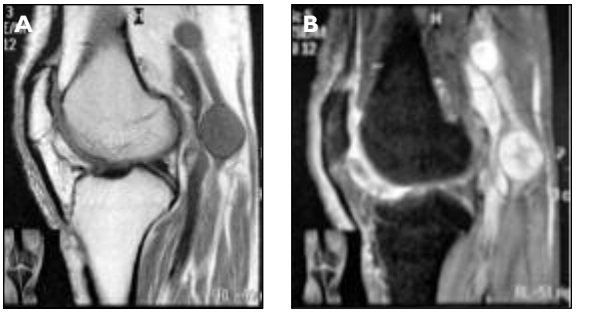

Figure 2. Sagital spin-echo T1-weighted MR image of the knee shows the mass to be homogeneous and isointense relative to skeletal muscle (Figure 2A) and T2-weighted MR image shows a well-defined mass within the popliteal fossa. The mass is mildly heterogeneous with a signal intensity greater than that of fat (Figure 2B), measuring 2.5 x 2.2 cm and 1.5 x 1.2 cm.

The diagnosis of schwannoma was made, based on clinical and radiological findings. Clinical symp-

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toms resulted from tumor location and size, with neurologic dysfunction from local mass effect[4]. US is a non-invasive convenient tool that can be used to evaluate a soft-tissue mass as schwannoma, and important features include the presence of a capsule, the eccentric position of the nerve relative to the mass, and a cystic lesion within it[2]. The MR imaging appearance of the schwannoma in this case is similar to that of others reported in the literature[5]. Surgical resection of schwannoma is the treatment of choice[6]. The recurrence on long term follow up, after complete surgical excision, is rare[6].

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OLANZAPINE TREATMENT IMPROVED QUALITY OF LIFE IN A PATIENT WITH FIBROMYALGIA SYNDROME: A PSYCHOLOGICAL EVALUATION

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Dear Editor,

Fibromyalgia Syndrome (FMS) is a disabling condition characterized by widespread chronic muscular pain, fatigue and a range of functional disorders, affecting 0.1% to 3.0% of the general population. The etiology of FMS remain uncertain, involving somatic, psychological and social factors[1]. Currently, no treatment has been demonstrated to be fully effective on all FMS symptoms, nor any consensus on how to manage the condition has been reached. Treatment recommendations propose palliating symptoms, along with a multimodal approach[1,3]. Anecdotic evidences and few studies support the efficacy of olanzapine (OLZ) in treating FMS[4-6]. Nevertheless, benefits of OLZ on the quality of life have not been investigated exhaustively.

We herein report a 56-years-old married white female presenting with diffuse musculoskeletal pain, morning stiffness, headache and chronic fatigue for 2 years. Comorbidity for anxiety, depression and dysphoric mood was also reported.

The diagnosis of FMS was based, according the American College of Rheumatology criteria[1,2], on the presence of chronic (>3 months) pain in all four quadrants of the body and tenderness in at least 11 of 18 tender-points at pre-defined locations.

At the time of the initial evaluation, she was taking amitriptiline 50 mg/day at bedtime and prazepam 30 mg/day. Abuse of various non-steroidal anti-inflammatory drugs was also reported. Due to unsatisfactory response, treatment with amitriptiline was substituted by duloxetine 60 mg/day, obtaining only partial efficacy in mood disorders but no significant improvement in pain. Add-on pregabalin 150 mg/day did not significantly improved her disturbances. Therefore, OLZ was introduced at 2,5 mg/day at bedtime. Further dosage increments were not needed. Indeed within a few weeks patient referred an improvement of her daily aching pain symptoms and an increased sense of well-being.

After three months OLZ-treatment, patient only presented slight muscular pain, so she strongly reduced the use of non-steroidal anti-inflammatory drugs, and she was able to discontinue pregabalin and to reduce prazepam to 20 mg/day. Patient is now on duloxetine 60 mg/day, OLZ 2,5 mg/day and prazepam 20 mg/day, without any significant side-effect. The Fibromyalgia Impact Questionnaire, the Short-Form Health Survey and the Coping Orientation to the Problems Experienced, were administered to assess the disease impact on daily activities and quality of life before OLZ introduction and at the three months follow-up[7-9]. Results are summarized in the figure (Figure 1)

The only study evaluating OLZ influence on pain and quality of life used uniquely the Brief Pain Inventory to explore patient's pain and functioning[4]. Another study on a series of 25 FMS patients focused on OLZ effectiveness without exploring patients' quality of life[5]. To our knowledge the current article is the first including a FMS symptom-specific tool and a psychological evaluation to assess how OLZ treatment influences the quality of life in a FMS patient.

Antagonism for 5HT-2 and 5HT-3 receptors was proposed as a possible mechanism of action for OLZ-induced pain relief[4,6]. As OLZ plasma levels are not modified by add-on duloxetine, we can reasonably exclude that pharmacokinetic interactions between duloxetine and OLZ could account for the clinical and psychological improvement in this subject[10].

Our case provides further evidence that OLZ can be a valuable therapeutic option in patients with FMS. Notably, just a very low OLZ dosage (2,5 mg/day) was able to provide substantial benefits to the patient, fact that is relevant because tolerabili-

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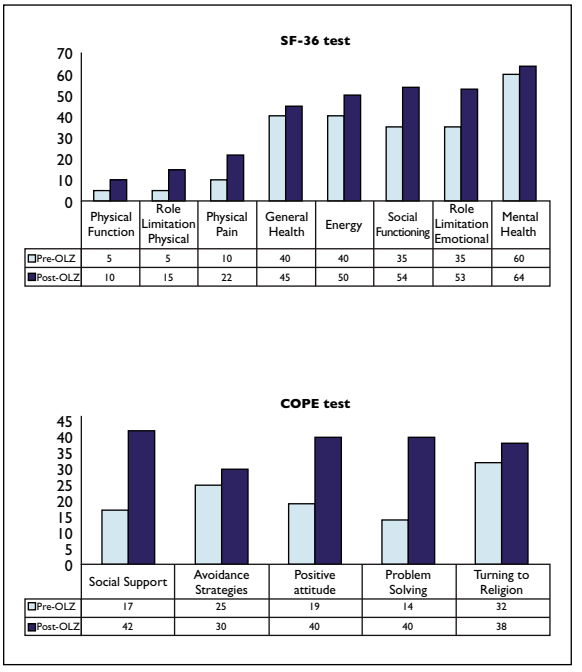

Figure 1. Tests scores before and after OLZ treatment. SF-36, Short Form Health Survey; COPE, Coping Orientation to the Problems Experienced; OLZ, Olanzapine; FIQ, Fibromyalgia Impact Questionnaire.

ty appeared as the main limit to OLZ use in this pathology[5]. Therefore, association therapy of OLZ and other pain-effective medication could be considered as a feasible therapeutic choice for the management of pain and emotional symptoms in FMS patients. Obviously, these findings need to be explored in controlled studies on a larger number of patients.

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NEUROPATIA PERIFÉRICA E LEFLUNOMIDA

Santiago T*, Rovisco J*, Silva J**, Malcata A***

Ao Exmo. Editor

A leflunomida (LEF) é um fármaco com propriedades anti-inflamatórias que resultam da conversão do seu metabolito activo, o A77 1726, inibindo a síntese dos nucleótidos de pirimidina. Esta acção é mediada fundamentalmente pela enzima dihidroorotato desidrogenase. Trata-se de um fármaco modificador da doença aprovado para o tratamento da artrite reumatóide, quer em monoterapia quer em terapêutica de combinação (com o metotrexato), estruturalmente diferente de outros imunomoduladores e com um mecanismo de acção único no tratamento da artrite reumatóide[1].

Os efeitos colaterais mais comummente observados em doentes sob LEF são diarreia, elevação de enzimas hepáticas, alopécia, *rash* e hipertensão arterial[2,3].

Os autores descrevem um caso de neuropatia periférica associada à LEF. Descreve-se o caso clínico de um doente do sexo masculino, 62 anos, com artrite reumatóide erosiva seronegativa, com 20 anos de evolução, previamente tratado com metotrexato, sulfassalazina e hidroxicloroquina, que iniciou LEF numa dose de manutenção de 20mg/dia. Dos antecedentes pessoais salienta-se enfarte agudo do miocárdio e hipertensão arterial. Após 3 anos de terapêutica com LEF iniciou quadro de disestesias na perna esquerda com distribuição em meia, associada a hiporeflexia e diminuição da força muscular. A LEF foi suspensa. A restante medicação consistia em metilprednisolona, omeprazol, sinvastatina, ramipril, que o doente já tomava há alguns anos e sem efeitos adversos. A glicémia, vitamina B12, ácido fólico, função tiróideia, proteínas séricas, proteinograma electroforético, crioglobulinas, ANA s e ANCA s, VDRL, hepatite B e C, pesquisa de substância amilóide na gordura abdominal, estavam normais ou negativas.

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O estudo electromiográfico confirmou uma polineuropatia axonal sensitiva. Após 10 meses da suspensão de LEF, o doente apresenta melhoria sintomática, comprovada clinicamente.

No caso clínico descrito decorreu uma larga relação temporal entre o início dos sintomas e o uso de LEF. No entanto, verificou-se melhoria significativa da neuropatia após suspensão da LEF, enquanto todos os outros medicamentos, incluindo a dose de corticóides foi mantida. Apesar da polineuropatia sensitiva ser reconhecida como manifestação extra-articular da artrite reumatóide, na verdade, o doente não tinha nódulos reumatóides, e para além disso, o início da neuropatia ocorreu durante uma fase de doença pouco activa, parecendo pouco provável a associação com a doença de base.

A neuropatia periférica reversível é um efeito adverso para o qual o clínico deve estar alerta, ocorrendo nalguns doentes tratados com LEF[4].

A acumulação dos metabolitos tóxicos da LEF provocam morte axonal podendo ocasionar irreversibilidade da neuropatia[5]. A suspensão do fármaco e a administração de colestiramina para aumentar a depuração, têm bons resultados[6]. Uma revisão de 80 casos reportados à *Food and Drug Administration*, mostrou que sintomas de disfunção do sistema nervoso periférico, tipicamente com polineuropatia axonal, iniciavam-se 6 meses após o início do fármaco, embora possa variar entre 3 a 1126 dias[5]. A maioria dos casos apresentam-se com quadro de parestesias periféricas, disestesias, dor, sensação de frio nas extremidades distais, ou fraqueza extrema.

Num outro estudo, 5 de 50 doentes com artrite reumatóide sob LEF, desenvolveram sintomas de neuropatia periférica, melhorando após a suspensão do fármaco[7].

Dadas as limitações inerentes a relatos de casos isolados, seriam úteis estudos adicionais para melhor estabelecer a natureza da associação entre o uso de LEF e neuropatia periférica.

Ao considerar o diagnóstico de neuropatia periférica devem ser excluídas outras causas, nomea-

damente metabólicas e medicamentosas, e posteriormente confirmar com estudos electromiográficos. Deste modo, os reumatologistas deverão ter em consideração esta causa possível de neuropatia periférica em doentes com artrite reumatóide.

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A case report should not exceed 2,000 words and 25 references. It should present illustrative figures. The number of Tables/Figures should not exceed 6.

From the second page on, all pages should have a short title on footnote.

References: References should be cited by the numerical system, superscript and listed, in the order cited in the text. Journal titles are abbreviated in accordance with the style of Index Medicus.

List all authors when 6 or less; when 7 or more list only first 3 and add "et al".

Do not abbreviate the page number (i.e. correct: 565--569 and not: 565-9).

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References of unpublished work, presentations or personal observations should be inserted in the text (in parenthesis) and not as a "classical" or true reference.

Authors are responsible for the accuracy of the references.

Examples:

– Journal article

Name(s) and initials of author(s). Article title. Journal name Year; Volume or number: Page(s).

Ex: Hill J, Bird HA, Hopkins R, Lawton C, Wright V. Survey of satisfaction with care in a rheumatology outpatient clinic: Ann Rheum Dis 1992; 51: 195-197.

– Article published Online (insert DOI)

Ex.: Peter A Merkel, David Curthbertson, Bernhard Hellmich et al. Comparison of disease activity measures for ANCA-associated vasculitis. Ann Rheum Dis Published Online First: 29 July 2008. doi:10.1136/ard.2008.097758

– Chapter in Book

Name(s) and initials of author(s) of chapter. Chapter title. In: Name(s) and initials of editor(s). Book title. City: Name of publisher, year of publication: pages.

Ex: Stewart AF. Hypercalcemia resulting from medications. In: Favus MD, ed Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. New York: Raven Press, 1991: 177-178.

– Book

Name(s) and initials of author(s). Book title. City: Name of publisher, year of publication: page(s).

Ex: Lorig K. Patient Education. A practical approach. St Louis: Mosby-Year Book, 1992: 51.

– Online document

Ex:Programa Nacional de Luta Contra a Tuberculose. Sistema de Vigilância (SVIG-TB). Direcção-Geral da Saúde - Divisão de Doenças Transmissíveis, Março de 2005 http://www.dgsaude.pt/upload/membro.id/ ficheiros/i006875.pdf. Accessed em 25 Janeiro de 2008

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