FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2010/2011

Ana Filipa Terleira Camacho da Côrte

Cervical Spine Instability in Rheumatoid Arthritis

Abril, 2011

FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

Ana Filipa Terleira Camacho da Côrte

Cervical Spine Instability in Rheumatoid Arthritis

Mestrado Integrado em Medicina

Área: Ortopedia

Trabalho efectuado sob a Orientação de:

Dr. Nuno Neves

Revista Científica:

Acta Reumatológica Portuguesa

Abril, 2011

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR
PROJECTO DE OPÇÃO
DISSERTAÇÃO/MONOGRAFIA/RELATÓRIO DE ESTÁGIO

Projecto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

Unidade Curricular "Dissertação/Monografia/Relatório de Estágio Profissionalizante"

Eu, Ana Filipa Terleira Camacho da Côrte, abaixo assinado, nº mecanográfico 050801123, estudante do 6º ano do Mestrado Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter actuado com absoluta integridade na elaboração deste projecto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (acto pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 20/04/2011

Assinatura: Ana Filipa Terleira Camacho da Côrte

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

Faculdade de Medicina da Universidade do Porto

2010/2011

Unidade Curricular "Dissertação/Monografia/Relatório de Estágio Profissionalizante"

Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

Nome: Ana Filipa Terleira Camacho da Côrte

Endereço electrónico: med05123@med.up.pt

Telefone ou Telemóvel: 963163396

Número do Bilhete de Identidade: 13187114

Título da ~~Dissertação~~/Monografia/~~Relatório de Estágio Profissionalizante~~:

Cervical spine instability in rheumatoid arthritis

Orientador:

Dr. Nuno Silva de Morais Neves

Ano de conclusão: 2011

Designação da área do projecto:

Ortopedia

É autorizada a reprodução integral desta Dissertação/Monografia/Relatório de Estágio Profissionalizante (cortar o que não interessar) para efeitos de investigação e de divulgação pedagógica, em programas e projectos coordenados pela FMUP.

Faculdade de Medicina da Universidade do Porto, 20/04/2011

Assinatura: Ana Filipa Terleira Camacho da Côrte

Instabilidade Cervical na Artrite Reumatóide

Cervical Spine Instability in Rheumatoid Arthritis

Ana Filipa Côrte, T. C.[1]

Faculty of Medicine of the University of Porto

[1]6th year student of Masters Course in Medicine

Corresponding author

Ana Filipa Terleira Camacho da Côrte

Avenida do Paçô, nº 1267 Carreço

4900-280 Viana do Castelo

Telephone: 00351 963163396

E-mail: flipacorte@hotmail.com

Sources of support: No founding or conflict of interests to report.

INSTABILIDADE CERVICAL NA ARTRITE REUMATÓIDE

Resumo

A Artrite Reumatóide (AR) é o distúrbio inflamatório mais comum da coluna cervical (CC). Após mãos e pés, a CC é o local mais acometido, estando afectada em mais de metade dos casos de AR. Particularmente na CC, a AR pode causar degeneração dos ligamentos, resultando em laxidez, instabilidade e subluxação dos corpos vertebrais. Geralmente, os pacientes são assintomáticos, ou então, os seus sintomas são atribuídos erradamente às manifestações periféricas. No entanto, pode também ocorrer compressão da espinal medula (EM) e medula oblonga, levando a sintomas neurológicos severos ou mesmo à morte súbita.

Devido às sequelas potencialmente debilitantes e ameaçadores de vida, à progressão inevitável dos défices neurológicos uma vez instalados e à débil condição médica dos pacientes atingidos, o diagnóstico de envolvimento da CC pela AR continua a ser uma prioridade bem como o seu tratamento um desafio.

A abordagem cirúrgica tem como objectivo uma fixação sólida da CC, estabilizando-a, prevenindo a deterioração neurológica e a lesão da EM, permitindo a melhoria da função neurológica e a manutenção da integridade vascular e do equilíbrio. Devido aos recentes avanços nas técnicas cirúrgicas, à melhor compreensão da anatomia e à avaliação precisa pré-operatória houve um aumento da segurança e eficácia dos procedimentos que resultou numa diminuição das taxas de mortalidade.

Visto que, quando desenvolvida a mielopatia, a mortalidade a longo prazo aumenta e a possibilidade de recuperação neurológica é escassa, muitos autores afirmam que uma intervenção cirúrgica precoce, antes do surgimento de défices neurológicos, apresenta resultados mais favoráveis. No entanto, devido à falta de consenso sobre o tema, a altura precisa em que a cirurgia profilática deve ocorrer não está definida. Portanto, pacientes com instabilidade cervical comprovada radiograficamente mas sem evidência de défices neurológicos, continuam a ser os mais difíceis de orientar.

Palavras-chave: Artrite Reumatóide; Coluna cervical; Cirurgia

CERVICAL SPINE INSTABILITY IN RHEUMATOID ARTHRITIS

Abstract

Rheumatoid Arthritis (RA) is the most common inflammatory disease of cervical spine (CS). After hands and feet, CS is the most commonly involved, being present in more than half of patients with RA. Especially in the CS, RA may cause degeneration of ligaments, leading to laxity, instability and subluxation of the vertebral bodies. This is often asymptomatic or symptoms are erroneously attributed to peripheral manifestations. Otherwise this may cause compression of spinal cord (SC) and medulla oblongata leading to severe neurologic deficits and even sudden death.

Owing to its potentially debilitating and life-threatening sequelae, inevitable progression once neurological deficits occur and the poor medical condition of afflicted patients, CS involvement remains a priority in the diagnosis and its treatment will remain a challenge.

The surgical approach aims a solid fixation of the upper cervical spine (UCS), giving stability, preventing neurological deterioration and injury to the SC, leading to improved neurological function, vascular integrity and maintenance of sagittal balance. The recent advances in surgical techniques, complete understanding of the anatomy and precise pre-operative evaluation led to a safe and more effective procedures that have decreased complications rates.

Based on the fact that when patient becomes myelopathic the rate of long-term mortality increases and the chance of neurological recovery decreases, many authors agree that early surgical intervention, before the onset of neurologic deficits, gives a more satisfactory outcome. However, the timing that a prophylactic stabilization should occur is poorly defined and so, patients with radiographic instability but without evidence of neurological deficit, still are the most difficult to manage.

Keywords: Rheumatoid arthritis; Cervical spine; Surgery

Index

List of abbreviations

aAAS – *anterior atlantoaxial subluxation*

AADI – *anterior atlanto-dens interval*

AAS – *atlantoaxial subluxation*

CMA – *cervicomedullary angle*

CrS – *cranial settling*

CS – *cervical spine*

CT – *computer tomography*

CVJ – *craniovertebral junction*

Ig – *immunoglobulin*

MRI – *magnetic resonance imaging*

PADI – *posterior atlas-dens interval*

RA – *rheumatoid arthritis*

RF – *rheumatoid factor*

SAC – *space available for the spinal cord*

SAS – *subaxial subluxation*

SC – *spinal cord*

SSCD – *subaxial spinal canal diameter*

UCS – *upper cervical spine*

VA – *vertebral arteries*

Introduction

Rheumatoid Arthritis (RA) is a chronic, systemic and inflammatory disease with an unknown etiology [1]. There is an immunologic dysfunction that leads to hypertrophy of the synovial tissue with pannus formation which causes erosion of the articular cartilage and subchondral bone [1-2].

RA prevalence has been estimated to be 1-2% of the world´s adult population [3] and the incidence is 27 per 100.000 of the general population [4].

The major distinctive feature of RA is chronic, symmetric and erosive synovitis of peripheral joints. However, it has a predilection for the cervical spine (CS) too, being the most common inflammatory disorder affecting the spine [5]. Despite being three times more frequent in women, men have greater risk of advanced cervical involvement [6-7]. RA can cause degeneration of the ligaments of the upper CS, leading to laxity, instability, and subluxation of the vertebral bodies in 17-85% of cases [8-10]. Atlantoaxial dislocation occurs in 25% of RA patients, either alone or in combination with atlantooccipital involvement responsible for cranial settling (CrS). Less common, is the involvement of the lower CS that occurs later in the course of the disease, and manifests as multilevel anterior dislocation [11-13].

The severity of craniovertebral junction (CVJ) involvement is a factor of disease duration and severity. Cervical involvement typically begins early in the disease process, and its progression has been closely correlated with the extent of peripheral disease activity. Oda et al. found that none of the patients with minimal peripheral disease had CrS of the odontoid, whereas 52% of patients with more erosive disease had advanced CrS [14].

In the majority of cases, radiologic abnormalities remain asymptomatic for years, but patients with progressive UCS involvement nonetheless do run the risk of myelopathy or even sudden death during conservative treatment with disease modifying antirheumatic drugs [15].

High neck or occipital pain and radiographic evidence of instability are present in 10-85% of RA patients. However only 10-60% of RA patients have neurologic deficits [6, 9]. These results make defining operative criteria difficult. Although most will agree on surgical stabilization of patients with neurologic deficits, there is no consensus about the treatment of patients who have no neurologic deficits but show radiographic instability and have minimal or no pain [9].

Pathophysiology

The same process that affects the peripheral joints in patients with RA also affects the neck [6]. Although the etiology is unknown, the disease process is thought to be initiated by an autoimmune response to an antigen expressed on synovial cells [16].

The chronic release of this antigenic stimulus triggers the body to produce rheumatoid factor (RF), an immunoglobulin (Ig) M molecule against autologous IgG. However, the presence of RF alone will not result in the clinical expression of RA. A stimulus, which is theorized to be a virus, is required [5]. The ensuing T-lymphocyte-mediated process results in an inflammatory response that causes the formation of rheumatoid pannus [16]. Rheumatoid pannus, composed of proliferating fibroblasts and inflammatory cells, is formed by granulation tissue during the inflammatory process. This pannus contributes to chronic synovitis since it produces collagenases and other proteolytic enzymes capable of destroying ligaments, tendons, cartilage and bone in the CS. These damages potentially result in ligamentous laxity and bone erosions, which may lead to subluxation and instability [5].

Neurologic deficit may develop mainly from a direct compressive effect on the SC or ischemic etiology. Compression of the SC or brainstem can result from static or dynamic subluxation of the spine or from direct pressure by a synovial retrodental pannus. Otherwise, rheumatoid involvement of the cervical facet joints can lead to stenosis of the nearby vertebral arteries (VA), which in turn leads to ischemia of the SC attributable to the VA contribution to the anterior spinal artery [6].

The normal CS has many joints and is therefore highly susceptible to the devastating action of the RA. Since the occipitut C1 and the C1-C2 articulations are purely synovial joints lacking intervertebral discs, they are primary targets for rheumatoid involvement. This, in adition to the increased range of motion required in the upper cervical spine, makes it the most affected part [5].

The most common patterns of instability seen are atlantoaxial subluxation (AAS, 65% of RA cervical involvement), followed by cranial settling (CrS, 20% of RA cervical involvement) and subaxial subluxation (SAS, 15-25% of RA cervical involvement) [6, 17]. Although these processes present a spectrum of instabilities, there is often combined involvement [17].

1. Atlantoaxial subluxation

This is the most common pattern of instability due to involvement of the synovial lined bursa between the odontoid and the transverse ligament. Although this ligament is the primary stabilizer of the C1-C2 joint, significant instability (>3-4mm) occurs only with incompetence of the alar-apical ligament complex or erosion of the dens itself [16].

Anterior AAS

Anterior AAS (aAAS) accounts for 75% of all cases of AAS. C1 cannot slip anteriorly over C2 unless the transverse ligament is disrupted. Thus, aAAS results from the weakening and rupture of the transverse, then alar and apical ligaments combined with erosions of the atlantoaxial joint. Further, the C1-C2 facets are oriented in the axial plane, and there is no bony interlocking to prevent subluxation [9].

AAS is characterized by an increase in the atlas-dens interval to more than 3 mm on a plain radiograph taken in the neutral position or with the neck flexed [16]. Radiographs taken with the neck extended are useful for determining whether the dislocation is reducible, partially reducible or fixed; this is an important determination since they have different treatments [11].

Lateral AAS

Lateral AAS accounts for 20% of cases of AAS and occurs secondary to a combination of rotational deformities, indicating unilateral or asymmetric involvement of the lateral atlantoaxial joint. Loss of all the cartilage and no more than 1 mm of subchondral bone on the lateral mass of C1 or articular process of C2 allow a 2.5 mm lateral shift of C1. If more than 1 mm of bone is lost, the displacement can reach 5 mm and is limited by contact between the lateral mass of C1 and the dens. Besides being shifted laterally C1 is also tilted. Because lateral radiographs do not show evidence of AAS, diagnosis is provided with an anteroposterior open-mouth radiograph which shows one or both C1-C2 joints involved with a greater than 2 mm shift and tilting of C1 on C2 [8].

Posterior AAS

Posterior AAS accounts for only 7% of all cases of AAS. The mechanism responsible for this displacement is the destruction of the dens by the pannus allowing posterior slippage of C1. While the anterior arch of C1 moves upward the posterior arch tilts downward until it lodges in front of the spinous process of C2 [18].

Although posterior and lateral AAS occur less frequently than anterior subluxation, they may actually carry a higher risk of cord compression [6, 17].

2. <u>Vertical translocation of the dens or atlantoaxial impaction or cranial settling</u>

Cranial settling (CrS) is the second most common deformity in the rheumatoid spine, being found in 4-35% of RA patients [19-20]. This displacement is due to an erosion of the occipital condyles, superior articular processes of C2, and lateral masses of C1. It is the collapse of the damaged joints that causes the skull to settle onto the CS and the subsequent relative superior migration of the dens into the foramen magnum. This causes entrapment of

the dens in the foramen and reduces the translational dislocation between the atlas and the axis. This can be erroneously interpreted as improvement of the atlantoaxial instability but in reality, there is a worsening of the situation [12, 21]. Superior migration of the odontoid can lead to direct compression of the brainstem, vascular compromise of the SC or cause neurologic injury or death by placing the cervicomedullary junction into excessive kyphosis [5]. CrS is almost always preceded by AAS and usually presents with a more advanced neurological status and a poorer prognosis [22].

3. Subaxial subluxation

Single or multiple level involvement of the lower cervical spine occurs in 7-29% of patients. It is the least common and usually occurs later in the disease process than do other forms of cervical involvement. It occurs secondary to destruction of the facet joints, interspinous ligament and discovertebral junction. On lateral radiographs, it is characterized by a "stepladder deformity" with anterior translation of one vertebra on another at multiple steps. Often, cervical kyphosis is present as well [16-17]. Subaxial subluxation has also been reported to occur after previous upper cervical fusions because of resultant increased biomechanical stresses in the lower cervical spine [16].

Clinical manifestations

As a result of frequently diffuse involvement, the physical examination of patients with RA can be difficult [16]. Clinical signs and symptoms as a result of AAS vary from asymptomatic to total incapacitation [10]. An usual error is the attribution of minor functional changes to severe peripheral disease. Muscle atrophy, joint subluxation, tendon ruptures and peripheral nerve entrapment can make findings difficult to interpret. Therefore, a tight vigilance of RA patients is necessary to avoid missing the subtle findings that suggest cervical involvement and neurologic impairment [16].

Symptoms caused by instability like neck pain, headache and occipital neuralgia are the most common and earliest findings, but they remain nonspecific[23]. Pain that is worse when upright and relieved with recumbency is usually due to compression of the greater occipital branch of C2, whereas involvement of the auricular branch of C2 causes ear pain. Pain associated with subluxation and joint destruction generally aggravates with neck motion. Patients may actually feel that their head is falling forward with flexion and they can describe a clunking sensation with extension, indicating reduction of the atlantoaxial joint [17].

Spinal cord and brainstem compression are most important clinically. However, diagnose of myelopathy can be difficult due to the peripheral RA. Clumsiness of the hand, gait disturbances, and sensation of heaviness or fatigability in the legs can be some of the first signs of early myelopathy. Therefore, CS involvement should be suspected in patients who were previously ambulatory, even if with crutches or a walker, who become wheelchair dependent. Physical examination may demonstrate weakness, spasticity, clumsiness and the presence of pathologic reflexes, such as hyperreflexia and Babinsky and Hoffman signs [17]. These reflexes can become false negative in the presence of severe peripheral RA [22]. Lhermitte´s sign can be provoked by flexing the head [6, 9]. Sphincter disturbances are unusual and occur late in the disease progress [17].

Less commonly, patients with RA may present with findings consistent with vertebrobasilar insufficiency [17, 24] which is commonly associated with CrS [6]. Once vertebrobasilar vascular system perfuses several regions of the brain, the clinician should be highly suspicious when the patient complains of vertigo, syncope, tinnitus, nausea, vomiting, dysarthria, dysphagia, visual disturbance, diplopia or cerebellar signs [9, 17]. If the vascular compression is intermittent and positional, these symptoms may be transient, making a more difficult diagnose [24].

Natural history

Understanding the natural history of RA is an important issue to determine operative interventions that may improve long-term function and prognosis. Previously, the rheumatoid involvement of the CS was believed to have a benign clinical course [16]. However, nowadays we know that CS involvement is seen in up to 85% of patients, and is frequently progressive and potentially devastating [6, 17].

Early studies suggested that up to 50% of patients develop some degree of AAS within five years of the serologic diagnosis of RA [25]. On the other hand, Collins et al. [26] reported that 50% of RA patients who had AAS had no symptoms. Therefore, it is critical to predict who are in risk of progressive disease. No single factor is entirely predictive and risk factors like disease duration, male gender, RF seropositive, severe peripheral disease, prolonged steroid use and increased C-reactive protein level, they all portend a worse prognosis [16].

Apart the cause, it seems that once involved, cervical instability is often progressive. Pellici and colleagues [23] prospectively studied 106 patients with RA and CS involvement over 5 years and found progression of radiologic findings in 80% of patients and neurologic deterioration in 36%. During 12 years, Rana [27] studied 41 patients with AAS, only 12% demonstrated radiographic evidence of a decrease in subluxation, whereas the remaining 88% had either progression or no change. If left untreated, the AAS progresses toward more complex instability patterns, in particular CrS [23]. Moreover, of the patients who demonstrate a decreased in the AAS, 80% occurred secondary to an increase in CrS [27].

A scale developed by Pellicci and Ranawat [28] is available for evaluating rheumatoid myelopathy (Table I) and is useful in evaluating patients, planning treatment and evaluating prognosis. Prognosis is negatively affected once the presence of myelopathy manifests and patients are left untreated. Matsunaga et al. [29] reported that myelopathic patients treated

conservatively have poor functional recovery and low survival rates. In their series, without surgical intervention, 76% of patients had neurological deterioration, being bedridden in three years after the onset of the myelopathy. Crockard and Grob [30] demonstrated that if left untreated, 50% of myelopathic patients die within one year.

After reviewing their patients, Santavirta et al. [31-32] concluded that nonoperative treatment did not prevent progression of existing cervical disease. Further, there is evidence that suggest that early atlantoaxial fusion may prevent CrS [33].

Imaging Studies

Imaging studies help to define cervical deformity and instability but, more importantly, identify patients potentially at risk for neurologic injury [34].

Plain x-rays remain the initial imaging modality of choice in RA patients. Although there is no consensus about indications, it is reasonable to order x-rays for patients with long-standing neck pain, neurologic symptoms, rapid decline in general function or progressive and destructive peripheral disease. The initial screening examination should consist of anteroposterior, lateral, and open-mouth views in neutral alignment as well as lateral views in flexion and extension [16].

Historically, the distance between the posterior aspect of the anterior ring of C1 and the anterior surface of the odontoid process (anterior atlanto-dens interval, AADI), was considered the most important indicator of C1-C2 subluxation. In adults, AADI should be no more than 3mm [16]. However, Boden et al. [11] found that the distance between posterior margin of the dens and the anterior rim of the posterior arch of C1 (posterior atlas-dens interval, PADI) had a stronger correlation with both paralysis and neurologic recovery after surgery, whereas AADI had no predictive value. According to his study all patients whose PADI was smaller than 14 mm had neurological abnormalities.

The CrS can be evaluated on a lateral radiograph, using McGregor´s line or Chamberlain´s line (Figure I) and on an anteroposterior radiograph, using the line connecting the tips of the mastoid processes or the line connecting the digastrics muscle fossae [8, 17]. However, these measures are not always reliable. When erosion of the tip of the dens is present, the Ranawat index and Redlund-Johnel (Figure I) for analyzing lateral views are more reliable [17]. Riew et al. [35], found that no single measurement alone is sufficient to identify atlantoaxial settling. To achieve sensitivity greater than 90% the Clark station (Figure II), the Ranawat index and Redlund-Johnel measurements all have to be evaluated together.

On plain x-rays, SAS is measured by the amount of displacement of one vertebra on another, and translation of more than 3.5 mm signifies clinically relevant subluxation [16]. However, more recently, has been shown that the subaxial spinal canal diameter (SSCD, distance from the posterior aspect of the vertebral body to the spinolaminar line) is a more important predictor of neurologic function than is the amount of subluxation [34].

Despite the temptation to proceed directly to more advanced imaging techniques, there are specific indications for doing so. Computed tomography (CT) scans should be reserved for preoperative evaluation by spine surgeons [16] or, when combined with myelography, can be used to evaluate SC compression in patients who cannot tolerate magnetic resonance imaging (MRI) [36]. The preferred modality for RA patients with significant cervical involvement is MRI, since it provides information about the size of rheumatoid pannus, the extent of bony and soft-tissue destruction, the status of the SC, and the relationship between structures in the UCS. MRI assesses migration of the odontoid, by measuring the cervicomedullary angle (CMA). The angle is measured by drawning lines along the anterior aspects of the SC and along the medulla. A normal angle is between 135º and 175º. Values less than 135º are significant for vertical settling and correlate with myelopathy [37]. However, it should be ordered only in patients with neurologic deficits or with plain x-rays showing PADI or SSCD of less than 14 mm or basilar invagination. MRI allows a more correct determination of the SAC than the x-rays, since it measures the pannus size in the canal [16].

Conservative treatment versus Surgery

Surgery contributes to prolonging the life span of rheumatoid patients with myelopathy [38]. Conservatively treated patients have a much higher mortality rate [39-43] and a lower probability of neurologic improvement. If surgery is not taken in consideration, progression of neurologic deficits is expected.

Several studies support what has been said before. In a study presented by Casey et al. [39], three of the Class IIIb patients chose not to proceed with surgery and all of them died within 6 months from the time of their original referral. Sunahara et al, [42] found no survivors in patients with RA who developed myelopathy as a result of UCS lesions and were treated conservatively for up to 7 years. Omura et al, [43] reported that six nonsurgical rheumatoid patients with mutilating type joint involvement had worsened activities of daily living scores and were completely bedridden or dead by the time of the final follow-up examination. Otherwise, Matsunaga et al. [44] reported a survival rate of 38% 10 years after surgery with 60% of their subjects categorized as Ranawat Class IIIb exhibiting postoperative improvement in symptoms. In nonsurgical management, patients were bedridden within 3 years after the onset of myelopathy and after 8 years all patients had died. In the largest reported series that exclusively dealt with Class IIIb patients, at a follow-up of 24 to 48 months, 40% improved by at least one grade in their Ranawat disability score and 29% were able to walk again after surgery [39]. Nannapanemi et al [45] reported that at a mean follow-up of 39 months, 56% of class IIIb patients were able to ambulate after surgery.

In a recent study, Wolfs and colleagues [15], achieved similar results to previous studies. Taking in consideration his results and these, it is timely to assert that, currently, surgical treatment of the CS for RA involvement is a relatively safe procedure with low morbidity and mortality rates, especially among patients with Ranawat I and II. However, patients classified as Ranawat I and II who are treated conservatively seem to have a good

neurologic outcome and survival as well. Once cervical myelopathy is estabilished, mortality appears to be common for both surgical and conservative patients [4, 39, 45]. But if Ranawat IIIA or IIIB patients are treated surgically, there is a chance of neurologic improvement and that cannot be expected with conservative treatment.

According to the previously reviewed, surgical neurologic outcomes were superior to conservative treatment in all of the patients, and in patients who were asymptomatic (Ranawat I), surgically and conservatively treated patients had similar outcomes [15].

Surgical Indications

The primary surgical goals are to relieve neural compression by reduction of subluxation or direct decompression, achieve stabilization of affected segments, reduce pannus formation and improve pain. Generally accepted indications for surgical intervention include AAS with intractable pain and/or neurologic deficits, severe CrS with compromise of the VA, or evidence of myelopathy by increased signal intensity within the spinal cord on T1-weighted MRI sequences [2]. The controversial condition that might make a surgeon hesitate is significant cervical instability or subluxation without neurologic deficit and with minimal pain [9, 17, 46]. Shen et al. [17], advocated that in patients with normal neurology, observation is acceptable if the PADI in flexion is greater than 14 mm and there is minimal evidence of CrS. For patients with PADI less than 14 mm in the flexed position, an MRI should be obtained to look for the true SAC. If the SAC is less than 13 mm, cord diameter in flexion less than 6 mm or the CMA less than 135º, prophylactic arthrodesis is recommended. However, the role of CS surgery in the treatment of asymptomatic patients with RA remains controversial [2].

Surgery as a prophylactic procedure

There is no consensus on the optimal timing for surgical intervention: whether surgery should be performed prophylactically or once neurologic deficits have become apparent [15].

The divergence of opinion as to when surgery is appropriate arises from the unpredictability of radiological progression and, perhaps more important, the poor correlation between an increasing atlanto-dens interval and the development of neurological signs [12, 23, 27, 34]. This is why many rheumatologists favour conservative management, with close clinical surveillance and referral for surgery if neurological symptoms or signs develop. However, neurological abnormalities are notoriously difficult to establish in the presence of a painful deforming arthritis and, often, associated muscular atrophy or peripheral neuropathy [47]; consequently there are many such patients who do not see a surgeon until they are quadriparetic, wheelchair bound, or even bed-bound [4].

Patients with significant neurological deficits are frail and debilitated from a combination of long-standing multisystem disease, poor bone quality, poor nutritional status, prolonged corticosteroid and cytotoxic therapy, and coexisting systemic and orthopedic involvement. Any surgical procedure carries the risk of perioperative morbidity and mortality, a high rate of nonunion, and the occurrence of instability at levels adjacent to the fusion [48-49]. Morbidity and mortality after surgery in rheumatoid patients are so, influenced by the preoperative grade [39].Walking is a sensitive measure of long tract dysfunction and may be used as a stand alone marker for overall myelopathic severity [45]. There is almost a doubling of complication in bedridden and nonambulatory patients (class IIIb) compared with those having objective signs of myelopathy but still able to walk (class IIIa). Casey et al. [39] suggested that surgery in class IIIb patients carries significant risk with little realistic prospect of any long term functional neurologic recovery. Van Asselt et al. [50] observed that postoperative mortality was largely increased (50%) in Ranawat IIIB group, another argument

indicating that mortality is particularly related to the severity of the underlying disease. The strong likelihood of surgical complications, the poor survival, and the limited prospects for functional recovery in non-ambulant patients make a strong case for earlier surgical intervention. At a late stage of disease most patients will have irreversible cord damage [4].

An interesting point of view was analyzed by Casey and colleagues [51]. They found two different histologic subtypes of synovial tissue in chronic RA patients with Ranawat classification from grade II-IIIb. Type I (chronic active rheumatoid synovium) represents an earlier stage of the chronic disease with some continued inflammatory activity – metabolic mechanism; and type II (end stage rheumatoid synovium) that represents the joint´s response to instability, with the synovium being reduced to a fibrous cicatrix – mechanical mechanism. The type II synovium is associated with elderly patients, myelopathy, and radiographic findings of advanced osseous destruction, with smaller SC area resulting from subluxation, erosion of the dens, and vertical translocation, which results from destruction of the lateral atlantoaxial joints. The clinical implications are that "early" intervention to stabilize a hypermobile CVJ may prevent the formation of synovium type II and the sequelae of end-stage disease: severe myelopathy, pain, instability, deformity and death.

Advances in the perioperative management and in anesthetic, diagnostic, and operative techniques have considerably improved the surgical results. Hamilton et al. have noted that surgical outcome after CS stabilization has apparently improved during the past 10 years because of earlier neurosurgical referral and a lower complication rate [52-55]. Surgery in patients without neurological deficits is easier and less complex compared to patients with neurologic impairments [45, 53, 56-58]. An important issue analyzed by Agarwal [59] was that no CrS appeared after "early" atlantoaxial fixation in patients with aAAS, being a proof that earlier surgery prevents further progression of the instability.

In conclusion, patients with RA and cervical instability should be treated surgically before the appearance of neurological symptoms for the following two reasons: 1) in most cases the cervical instability is progressive and can lead to myelomalacia and associated neurological deficits; 2) the outcome of the surgical stabilization is better when performed as a preventive measure – before the onset of any neurological deficits [46].

Surgery on Ranawat IIIb patients

The damning results of surgery on Ranawat IIIb patients observed in previous studies [23, 60] strengthens the theory that a more timely treatment can bring better results. But what should be done for those rheumatoid patients who have already reached the bedridden and nonambulatory stage? Is the scenario for this class IIIb so dismal that surgery offers little hope? [45]

Contrary to earlier studies, more recent studies have achieved good results in terms of neurological improvement. Van Asselt et al. [50] reported neurologic improvement in 73% and 67% of the myelopathic patients, 3 months and 2 years after surgery respectively. Likewise, Nannapaneni et al. [45] reported a 56% ambulatory rate after surgery in non-ambulatory patients. Furthermore, a meta-analysis of five retrospective series found significant functional neurologic recovery in 34% of Ranawat IIIb patients [32, 34, 39, 58, 61]. Based on such findings, an operation for patients with Ranawat classes IIIA and IIIB is recommended because neural improvement is possible and may result in improved mobility.

Approximately one-third of patients with CVJ rheumatic myelopathy may reach Ranawat IIIB. Improvement of even one grade in their Ranawat score from class IIIb to class IIIa brought about by surgery confers on them a huge benefit in terms of their quality of life and survival. If nothing is done, the progression of the disease and death are certain. Then surgery (despite high morbidity) often remains the best therapeutic option available to these patients and their last chance of getting some recovery. They certainly cannot be dismissed as "unsalvageable" cases [45].

Surgical Management

The hallmark of surgical management of the rheumatoid neck is spinal fusion. C1-C2 fusion is the procedure of choice for patients with reducible AAS. The commonly used traditional wiring techniques, such as the Brooks or Gallie procedures, are now being gradually substituted for newer procedures, such as the Magerl technique and the Harms fusion, since they are stronger and avoid the need for a cervical collar after surgery [16].

An occipital-cervical fusion is required in CrS and irreducible AAS to stabilize the UCS. A variety of methods are available, including Bohlman triple-wire technique, as well as by the use of newer plates, rods, and screws [16]. Cervical traction should be initiated first, if evidence of cord compression exists. If despite traction, compression persists, then a decompression can be performed, either by removal of the posteror arch of C1 or through a transoral odontoid resection [17].

In SAS, posterior fusion techniques include interspinous wiring, lateral mass screw and pedicle screw fixation. In the presence of an isolated single-level SAS, interspinous technique is an acceptable fixation method. Patients with multiple level instability and stepladder deformity the lateral mass fixation is preferred [17]. An anterior approach may be necessary if a nonreducible kyphotic alignment is present [16]. It is critical to identify patients with combined deformities and instabilities. In particular, fixation of UCS instabilities without addressing SAS, will result in rapid deterioration of the caudal levels [17].

Conclusions

Rheumatoid arthritis involvement of the CS is a common, progressive and potentially devastating health condition. If left untreated, a significant morbidity and mortality can arise from the progression towards complex instability patterns. Once the patient becomes myelopathic, the rate of long term mortality increases and the chance of neurological recovery decreases. Early and aggressive surgical intervention is so recommended to prevent neurologic injuries and preserve remaining function. Even non-ambulant patients should be offered the benefit of the only chance they have and not be deterred from seeking surgical intervention.

Acknowledgements

The author wishes to thank Dr. Nuno Neves, leader of this monograph, the availability and cooperation given.

References

1. Moskovich R, C.H., Shott S, Ransford AO, *Occipitocervical stabilization for myelopathy in patients with rheumatoid arthritis. Implications of not bone-grafting.* J Bone Joint Surg Am, 2000. **82**: p. 349-365.
2. D., B., *Inflammatory arthritides of the spine: surgical versus nonsurgical treatment* Clin Orthop Relat Res, 2006. **443**: p. 208-21.
3. Linos AA, W.J., O´Fallon WK, Kurland LT., *The epidemiology of rheumatoid arthritis in Rochester, Minnesota: a study of incidence, prevalence and mortality.* Am J Epidemiol 1980. **111**: p. 87-98.
4. Casey AT, C.H., Bland JM, Stevens J, Moskovich R, Ransford AO, *Surgery on the rheumatoid cervical spine for the non-ambulant myelopathic patient - too much, too late?* Lancet, 1996. **347**: p. 1004-1007.
5. Reiter MF, B.S., *Inflammatory disorders of the cervical spine.* Spine 1998. **23**: p. 2755-66.
6. Dreyer SJ, B.S., *Natural history of rheumatoid arthritis of the cervical spine.* Clin Orthop 1999. **366**: p. 98-106.
7. Weissman BN, A.P., Weinfield MS, et al. , *Prognostic features of atlantoaxial subluxation in rheumatoid arthritis patients.* Radiology, 1982. **144**: p. 745-51.
8. Bouchaud-Chabot A, L.F., *Cervical spine involvement in rheumatoid arthritis: a review.* Joint Bone Spine, 2002. **69**: p. 141-54.
9. Nguyen HV, L.S., Silber J, Gelb DE, Anderson PA, Frank L, et al., *Rheumatoid arthritis of the cervical spine.* Spine J, 2004. **4**: p. 329-34.
10. Wolfs JF, P.W., Boers M, van Tulder MW, Brand R, van Houwelingen HJ, et al., *Rationale and design of The Delfi Trial-I (RCT)2: international randomized clinical trial of rheumatoid craniocervical treatment, an intervention-prognostic trial comparing "early" surgery with conservative treatment* BMC Musculoskelet Disord, 2006. **7**: p. 14.
11. Boden S, D.L., Bohlmann H, Rechtine G, *Rheumatoid arthritis of the cervical spine.* J Bone Joint Surg 1993. **75A**: p. 1282-97.
12. J, M., *Atlanto-axial subluxation in rheumatoid arthritis. A five years follow-up study. .* Ann Rheum Dis, 1974. **33**: p. 526-31.
13. J, B., *Rheumatoid subluxation of the cervical spine* J Rheumatol, 1990. **17**: p. 134-7.
14. Oda T, F.K., Yonenobu K, et al., *Natural course of cervical spine lesions in rheumatoid arthritis.* Spine, 1995. **20**: p. 1128-35.
15. Wolfs JF, K.M., Fehlings MG, van Tulder MW, Boers M, Peul WC, *Neurologic outcome of surgical and conservative treatment of rheumatoid cervical spine subluxation: a systematic review.* Arthritis & Rheumatism, 2009. **61**: p. 1743-52.
16. Wollowick Al, e.a., *Rheumatoid arthritis in the cervical spine: what you need to know.* The American Journal of Orthopedics, 2007: p. 401-406.
17. Shen FH, S.D., Jenis LG, An HS, *Rheumatoid arthritis: evaluation and surgical management of the cervical spine.* Spine J, 2004. **4**: p. 689-700.
18. S, L., *Cervical myelopathy and posterior atlanto-axial subluxations in patients with rheumatoid arthritis.* J Bone Joint Surg, 1985. **67 A**: p. 593-7.
19. Cabot A, B.A., *The cervical spine in Rheumatoid arthritis.* Clin Orthop, 1978. **131**: p. 130-40.
20. S, L., *Rheumatoid arthritis of the cervical spine.* Clin Orthop, 1984. **182**: p. 143-9.
21. Menezes AH, v.G.J., Clark CR, elKhoury G, *Odontoid upward migration in rheumatoid arthritis: an analysis of 45 patients with cranial settling.* J Neurosurgery, 1985. **63**: p. 500-566.

22. M, N., *Treatment of the upper cervical spine involvement in rheumatoid arthritis patients* Mod Rheumatol, 2008. **18**: p. 327-335.
23. Pellici PM, R.C., Tsairis P, Bryan WH, *A prospective study of the progression of the rheumatoid arthritis of the cervical spine.* J Bone Joint Surg Am, 1981. **63**: p. 342-350.
24. Maekawa T, S.K., Iida H, Yamashita K, Sakaida M, *Atlantoaxial arthrodesis for vertebrobasilar insufficiency due to rheumatoid arthritis: a case report.* J Bone Joint Surg Am, 2003. **85**: p. 711-14.
25. Falope ZF, G.I., Platt PN, Todd NV, *Cervical myelopathy and rheumatoid arthritis: a retrospective analysis of management.* Clin Rehabil, 2002. **16**: p. 625-629.
26. Collins DN, B.C., Fitzrandolph RL, *Cervical spine instability in rheumatoid patients having total hip or knee arthroplasty.* Clin Orthop., 1991. **272**: p. 127-35.
27. NA, R., *Natural history of atlanto axial subluxation in rheumatoid arthritis.* Spine, 1989. **14**: p. 1054-6.
28. Ranawat CS, O.L.P., Pellicci PM, Tsairis P, Marchisello P, Dorr L, *Cervical spine fusion in rheumatoid arthritis.* J Bone Joint Surg [Am], 1979. **61A**: p. 1003-1010.
29. Matsunaga S, S.T., Onishi T, Hayashi K, Taketomi E, Sunahara N, et al., *Prognosis of patients with upper cervical lesions caused by rheumatoid arthritis: comparison of occipito-cervical fusion between C1 laminectomy and nonsurgical management.* Spine, 2003. **28**(1581-7).
30. Crockard A, G.D., *Rheumatoid arthritis: upper cervical involvement.* . In: Clark CR (ed). The cervical spine. Philadelphia: Lippincott-Raven, 1998: p. 705-14.
31. Santavirta S, S.P., Kankaanpaa U, Sandelin J, Laasonen E, *Treatment of the cervical spine in rheumatoid arthritis.* J Bone Joint Surg [Am], 1988. **70**: p. 658-67.
32. Santavirta S, K.Y., Laasonen E, Honkanen V, Antti-Poika I, Kauppi M., *Ten year-results of operations for rheumatoid cervical spine disorders.* J Bone Joint Surg [Br], 1991. **73**: p. 116-20.
33. Kraus DR, P.W., Agarwal KC, DeLeeuw HW, Donaldson WFr *Incidence of subaxial subluxation in patients with generalized rheumatoid arthritis who have had previous occipital cervical fusions.* Spine, 1991. **16**: p. S486-9.
34. Boden SD, D.L., Bohlman HH, Rechtine GR, *Rheumatoid arthritis of the cervical spine. A long term analysis with predictors of paralysis and recovery.* J Bone Joint Surg Am, 1993. **75**: p. 1282-97.
35. Riew KD, H.A., Palumbo MA, Sethi N, Bohlman HH, *Diagnosing basilar invagination in the rheumatoid patient. The reliability of radiographic criteria.* J Bone Joint Surg Am, 2001. **83**: p. 194-200.
36. Braunstein EM, W.B., Seltzer SE, Sosman JL, Wang AM, Zamani A, *Computed tomography and conventional radiographs of the craniocervical region in rheumatoid arthritis. A comparison.* Arthritis Rheum, 1984. **27**: p. 26-31.
37. Bundschuh C, M.M., Kearney F, et al., *Rheumatoid arthritis of the cervical spine.* Am J Roentgenol, 1988. **151**: p. 181-7.
38. Mori T, M.S., Sunahara N, Takashi S, *3- to 11-year follow up of occipitocervical fusion for rheumatoid arthritis.* Clin Orthop 1998. **1**: p. 169-179.
39. Casey AT, C.H., Bland JM, Stevens J, Moskovich R, Ransford AO, *Predictors of outcome in the quadriparetic nonambulatory myelopathic patient with rheumatoid arthritis: A prospective study of 55 surgically treated Ranawat class IIIb patients.* J Neurosurgery, 1996. **85**: p. 574-581.
40. Marks JS, S.J., *Rheumatoid cervical myelopathy.* Q J Med, 1981. **199**: p. 307-319.
41. Meijers KA, V.B.G., Luyendijk W, Duijfjes F, *Dislocation of the cervical spine with cord compression in rheumatoid arthritis.* Clin Exp Rheumatol, 1984. **2**: p. 239-245.

42. Sunahara N, M.S., Mori T, Ijiri K, Sakou T, *Clinical course of conservatively managed rheumatoid arthritis patients with myelopathy.* Spine, 1997. **22**: p. 2603-2607.
43. Omura K, S.H., Katsuura A, Saruhashi A, Imanaka T, Imai S, *Evaluation of posterior long fusion versus conservative treatment for the progressive rheumatoid cervical spine.* Spine, 2002. **27**: p. 1336-1345.
44. Matsunaga S, I.K., Koga H, *Results of a longer than 10 year-follow-up of patients with rheumatoid arthritis treated by occipitocervical fusion.* Spine, 2000. **25**: p. 1749-1753.
45. Nannapaneni R, B.S., Todd NV, *Surgical outcome in rheumatoid ranawat class IIIB myelopathy.* Neurosurgery, 2005. **56**: p. 706-715.
46. Schmitt-Sody M, K.C., Buhmann S, Metz P, Birkenmaier C, Troullier H, et al., *Timing of cervical spine stabilization and outcome in patients with rheumatoid arthritis.* Int Orthop, 2008. **32**: p. 511-516.
47. Agarwal AK, P.W., Kraus DR, Eisenbeis CH Jr, *The cervical spine in rheumatoid arthritis.* BMJ, 1993. **306**: p. 79-80.
48. Pham XV, B.P., Menkes CJ, Kahan A, *Upper cervical spine surgery in rheumatoid arthritis: Retrospective study of 30 followed for two years or more after Cotrel-Dubousset instrumentation.* Joint Bone Spine, 2000. **67**: p. 434-440.
49. Sandhu FA, P.G., Benzel E, Henderson FC, *Occipital cervical fusion for rheumatoid arthritis using inside-outside stabilization technique* Spine, 2003. **28**: p. 414-19.
50. Van Asselt KM, L.W., Bongartz EB, Hamburger HL, Drossaers-Bakker KW, Dijkmans BAC, van Soesbergen RM, *Outcome of cervical spine surgery in patients with rheumatoid arthritis.* Ann Rheum Dis 2001. **60**: p. 448-452.
51. O´Brien MF, C.A., Crockard HA, Stevens J, *Histology of the craniocervical junction in chronic rheumatoid arthritis: a clinicopathologic analysis of 33 operative cases.* Spine, 2002. **20**: p. 2245-2254.
52. Hamilton JD, G.M.J.R., Madhok R, Capell HA, *Improved medical and surgical management of cervical spine disease in patients with rheumatoid arthritis over10 years.* Ann Rheum Dis, 2000. **59**: p. 434-438.
53. Mizutani J, T.S., Fukouka M, Otsuka T, Matsui N, *Surgical treatment of the rheumatoid cervical spine in patients aged 70 years old or older.* Rheumatology, 2002. **41**: p. 910-916.
54. Zoma A, S.R., Fisher WD, Freeman PA, Hamblen D, *Surgical stabilization of the rheumatoid cervical spine. A review of indications and results.* J Bone Joint Surg Br, 1987. **69**: p. 8-12.
55. McRorie ER, M.P., Russell T, Beggs I, Nuki G, Hurst NP, *Cervical spine surgery in patients with RA: an appraisal.* Ann Rheum Dis, 1996. **55**: p. 99-104.
56. D, G., *Atlantoaxial immobilization in rheumatoid arthritis: a prophylactic procedure?* Eur Spine J, 2000. **9**: p. 404-409.
57. Grob D, W.R., Grauer W, Sturzenegger J, Dvorak J, *Atlantoaxial fusion and retrodental pannus in rheumatoid arthritis.* Spine, 1997. **22**: p. 1580-1583.
58. Peppelmen WC, K.D., Donaldson WF III, Agarwal A, *Cervical spine surgery in rheumatoid arthritis: improvement of neurologic deficit after cervical spine fusion.* Spine, 1993. **18**: p. 2375-2379.
59. Agarwal AK, P.W., Kraus DR, Pollock BH, Stolzer BL, Eisenbeis CH Jr, Donaldson WF III, *Recurrence of cervical instability in rheumatoid arthritis following previous fusion: Can disease progression be prevented by early surgery?* J Rheumatol, 1992. **19**: p. 1364-1370.

60. Casey AT, C.H., Bland JM, Stevens J, Moskovich R, Ransford AO, *Surgery on the rheumatoid cervical spine for the non-ambulant myelopathic patient - too much, too late?* Lancet, 1996. **347**: p. 1004-07.
61. Milbrink J, W.A.S.t.o.a.s.i.r.a., *Surgical treatment of atlantoaxial subluxation in rheumatoid arthritis.* . J Orthop Rheumatol, 1989. **2**: p. 191-199.

Tables

Table I – Ranawat classification of rheumatoid myelopathy

Class I	Class II	Class IIIa	Class IIIb
Neurologically intact	Subjective weakness Hyperreflexia and dysesthesia	Objective weakness Long tract signs Ambulatory	Quadriparesis Nonambulatory

From [28].

Figures

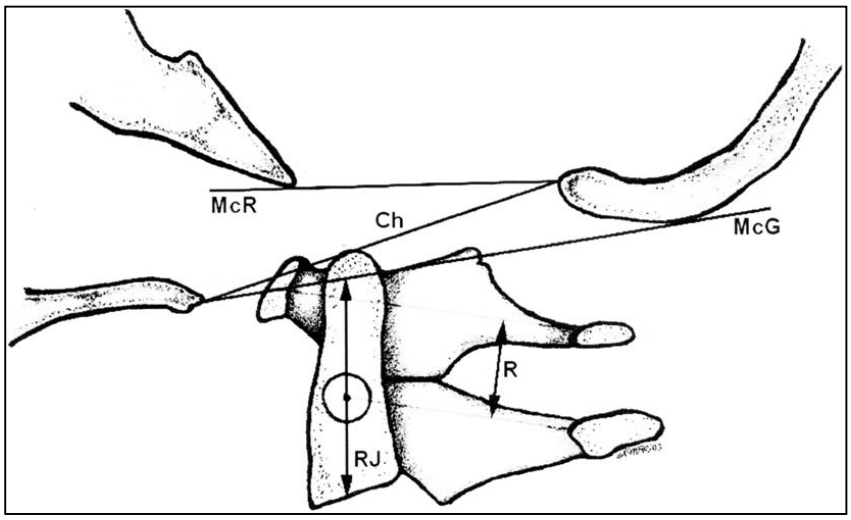

Figure I [17]

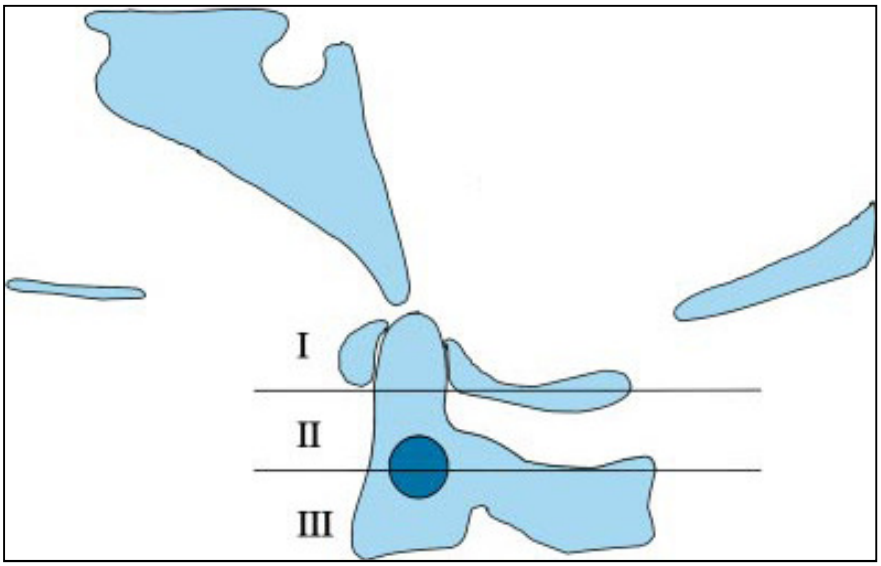

Figure II [35]

Legends

Figure I – Lateral illustration of the UCS and lower occiput depicting radiographic measurement criteria to determine CrS. Chamberlain´s line (Ch) is depicted as the line from the posterior region of the hard palate to the posterior lip of the foramen magnum. Projection of the odontoid more than 3 mm past this line is considered abnormal. McGregor´s line represents the margin between the posterior margin of the hard palate to the most caudal aspect of the occiput. Ranawat´s line (R), measured along the long axis of the odontoid, is measured from the sclerotic ring of C2 to the transverse axis of the atlas. As CrS increases, this distance becomes shorter. A distance less than 13 mm is considered abnormal. Redlund-Johnell´s (RJ) occipitoatlantoaxial index of CrS is measured by the distance from the McG to the sagittal midpoint at the base of the axis. Abnormality is noted if the distance is less than 33mm for men and less than 27 for women [17].

Figure II – Clark stations. The station of the first cervical vertebra is determined by dividing the odontoid process into three equal parts in the saggital plane. If the anterior ring of the atlas is level with the middle third (station II) or caudal third (station III) of the odontoid process, CrS is diagnosed [35].

Instructions for authors

Acta Reumatologica Portuguesa publishes original articles, reviews, case reports, images and letters to the editor on all subjects related to Rheumatology.

Acta Reumatologica Portuguesa subscribes the requirements for the acceptance of manuscripts in biomedical journals proposed by the International Committee of Medical Journal Editors, published initially in N Engl J Med 1991; 324: 424-28, updated in October 2008 and available in www.ICMJE.org. The editorial policy of Acta Reumatológica Portuguesa follows the Editorial Policy Statements published by the Council of Science Editors, available in www.councilscienceeditors.org/services/draft_approved.cfm.

The Journal is indexed on PubMed/Medline. The articles are available online with open and free access.

The articles should be written in English. Portuguese written manuscripts can also be submitted.

The accuracy of the manuscript contents as well as written opinions are of the exclusive responsibility of the author(s).

Published articles will remain property of the journal and cannot be reproduced, as a whole or as a part, without the authorization of the editor.

For accepted articles a statement signed by all authors transferring the copyright to Acta Reumatologica is mandatory and should be send by e-mail.

Authors have to disclose potential conflicts of interest.

The acceptance of articles is subjected to the evaluation of the editorial board. Articles may be:

a) accepted without changes;

b) accepted after modifications suggested by the board;

c) refused.

All the comments made by the reviewers will be sent to the author.

When changes are proposed, the author should send reply letters to the editor and to each of the reviewers answering to all the raised questions. The author should also send a reviewed version of the manuscript with the changes highlighted in a different colour within 1 month.

Instructions to authors

Manuscripts not in accordance with the instructions may be sent for modification before review by the editorial board.

All manuscripts must be sent by e-mail to:
edtecnicarp@gmail.com

Manuscripts must be accompanied by a cover letter, signed by all authors, stating the name of the article, that it is an original work, that the authors held the copyright of the manuscript, that it does not represent any conflict of interest, and that they transfer the copyright to the journal (se form below).

Text should be sent in digital support by e-mail, typed double-spaced, type 12, with 1-inch margins, in Word for Windows. All pages must be sequentially numbered.

Images should be sent independently from the text in JPEG or TIFF file.

Manuscripts should be organized as explained below:

Page 1

a) Title in Portuguese and in English;

b) Authors' names and affiliations;

c) Institution(s) to which the work should be attributed;

d) Source(s) of grants support;

e) Name, address and e-mail of the corresponding author

f) Short running title.

Page 2

a) Title (without authors)

b) Abstract

Abstract in English structured as follows for the original articles: Objectives; Patients and Methods; Results; Conclusions. The abstract should not exceed 350 words for original articles and 180 words for case reports.

c) Keywords

A maximum of 5 keywords – must be MeSH terms – should be presented after the abstract.

Page 3 and following pages

Original papers: The text of original papers should be presented with the following subtitles: Introduction, Objectives, Patients and Methods, Results, Discussion, Conclusions, Acknowledgements, References.

Original papers should not exceed 4,000 words, 6 Tables/Figures and 60 references.

Case report: Subtitles for case reports should be: Introduction, Case report, Discussion, References.

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).

The Journal number and the month of publication should not be presented.

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 AE 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

Tables: Tables should be cited in the text with Roman numerals. Each table should be double typed on a separate sheet, have a title and contain no vertical rulers. Horizontal lines should be used only as separators between titles and subtitles. Explain all abbreviations at the bottom.

The number of tables should be limited as described above.

Figures: Cite each figure in the text in consecutive order using Arabic numerals. Legends should be listed at the end of the manuscript, after the references, double typed. Send the figures in separate files to each figure in the format JPEG or TIFF.

The number of figures should be limited as described above.

Editorials: Editorials will be requested by the editor and will be comments on important issues or on articles published in the journal. Editorials should not exceed 1200 words, with a maximum of 15 references and no tables or figures.

Review articles: Review articles will be commissioned by the editor. However, authors interested in presenting a review article are welcomed to contact the editor.

Review articles should not exceed 4000 words, 6 tables/figures and 100 references.

Letters: Letters to the editor must be a comment on a journal article or a short clinical study or case report. They cannot exceed 600 words, a maximum of 10 references and one table or one figure.

Images in Rheumatology: Images of particularly interest can be submitted. They should contain a maximum of 4 figures, in JPEG or TIFF format. The accompanying text must have a maximum of 500 words.

Modifications and proofreading: Articles accepted subject to modifications, will be sent to the authors that will have 1 month to modify them according to suggestions. A letter should be written for each reviewer and the changes should be highlighted in the main manuscript with a different font color. Contributors will receive page proofs of the accepted papers for approval.

Cover Letter draft:

Send with manuscript to The Editor: **edtecnicarp@gmail.com**

The authors certify that the manuscript entitled _____ (ref ARP_____) is original, all data are based on their own research and that the manuscript does not violate copyright or privacy regulations. They further state that the manuscript hasn't been partly or totally published or submitted to publication elsewhere.
The authors declare that they hold total copyright for this paper and that they assume collective responsibility for its contents and also that any conflict of interest is acknowledged.
And submitting this paper, the authors transfer copyrights interests to Acta Reumatológica Portuguesa.

All authors must sign.

Name (capitals): _____

Date:_____

Signature: _____