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Rheumatoid Arthritis of the Cervical Spine – Key Aspects for the Orthopedic Surgeon

Artritis reumatoide de la columna cervical: Aspectos clave para el cirujano ortopédico

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Abstract

Rheumatoid arthritis is a chronic inflammatory autoimmune disease that frequently affects the cervical spine. The clinical diagnosis can be difficult; therefore, a systematic radiographic evaluation of all patients is recommended. The timely treatment of these lesions is important to preserve the self-reliance, the neurological function, and even the lives of the patients. The present article is an update of all the aspects pertaining to cervical spine rheumatoid arthritis that are relevant to the orthopedic surgeon.

Keywords
- atlantoaxial instability
- cervical spine
- morbidity
- rheumatoid arthritis
- surgery

Resumen

La artritis reumatoide es una enfermedad inflamatoria autoinmune crónica que afecta con frecuencia a la columna cervical. El diagnóstico clínico de la afección cervical puede ser difícil; por lo tanto, se recomienda la evaluación radiográfica sistemática de todos los pacientes. El tratamiento oportuno de estas lesiones es importante para preservar la independencia, la función neurológica, e, incluso, la vida de los pacientes. Este artículo es una revisión actualizada de todos los aspectos de la artritis reumatoide de la columna cervical relevantes para el cirujano ortopédico.

Palabras clave
- inestabilidad atlantoaxial
- columna cervical
- morbilidad
- artritis reumatoide
- cirugía

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease[1,2] that mainly affects small synovial joints.[3] Its clinical presentation varies, with general symptoms (including morning stiffness, fever, anorexia, and weight loss) and local symptoms (including pain for more than six weeks and periarticular soft tissue edema).

The prevalence of cervical involvement ranges from 25% to 90%. This prevalence is of 44% in patients on the waiting list for orthopedic surgery and of 61% in those undergoing total hip or knee arthroplasty.[4–7] The most frequent lesions

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in cervical spine RA are anterior C1-C2 subluxation, vertical subluxation, and subaxial subluxation.

The adequate diagnosis and management of cervical spine RA are paramount in improving the expectancy and quality of life of these patients. The introduction of new medical treatments has significantly decreased the incidence of anterior subluxation, but not of vertical subluxation or myelopathy associated with cervical RA.[8]

The present review addresses the clinical presentation, pathophysiology, natural history, relevant radiological measurements, criteria for decision-making during operative management, surgical techniques, and prognosis of cervical RA.

Clinical Presentation

The clinical diagnosis of cervical involvement is a challenge because 50% to 60% of the patients are asymptomatic,[5,6] and the clinical presentation is variable. In addition, extraspinal factors, such as joint involvement or peripheral nerve compression, make it difficult to detect radicular or myelopathic signs, which are typical of cervical RA.

We can divide symptomatic cases into three groups: axial neck pain, neurological compromise, and symptoms derived from C1-C2 mechanical instability.

Axial neck pain is the most common symptom. It can occur at the occipital level due to major (C2), minor (C1), retro-orbital, or temporal occipital nerve compromise. The clinical manifestations of spinal cord neurological involvement include myelopathic signs, pyramidal signs, loss of proprioception, pathological reflexes (such as positive Babinski sign, hyperreflexia, spasticity, clonus, and bladder or rectal incontinence), and gait disturbances eventually resulting in quadriparesis or quadriplegia. In contrast, compression at the level of the vertebral artery can cause symptoms of vertebrobasilar insufficiency, such as loss of consciousness, vertigo, dysphagia, tinnitus, nystagmus, balance disorders, and seizures.[9] Grading systems facilitate the neurological evaluation of RA patients by classifying the functional status and myelopathy severity. The most used system is the Ranawat classification, consisting of the following grades: I) neurologically intact patients; II) patients with subjective weakness, with hyperreflexia and dysesthesias; IIIa) Patients with objective weakness, with pyramidal signs but deambulatory; and IIIb) patients with objective weakness, with pyramidal signs, but not deambulatory. The functional status is important because it is related to postoperative prognosis.[10,11] Another global functional status classification, from the American Association of Rheumatology, has the following grades: I) patients with full ability for usual activities, without deficits; II) patients with normal ability for activities, with a deficit or limited mobility due to discomfort in one or more joints; III) patients with adequate ability for few or none of the usual or self-care activities; and IV) Patients with disability with total or virtually total confinement to bed or wheelchair and little or no self-care activities.[11]

Instability in C1-C2 can lead to the abnormal anterior vertebral displacement of C1 over C2, manifesting as cervical crepitus during flexion, as described by the Sharp-Purser test or head drop in flexion.

The main risk factors described in the literature for the development of cervical instability include the male gender;[12] significant peripheral joint involvement;[4,13–15] seropositivity; prolonged use of corticosteroids;[13] active RA;[4,13,15] history of musculoskeletal system surgery;[6,16] rheumatoid nodules;[4] and long-standing RA; however, the cervical damage is early in 23.5% of the cases.[14,17]

Pathophysiology

Synovial inflammation results from the interaction of genetic, environmental, and immunological factors. Genetic predisposition is due to several genes, including some histocompatibility antigens (such as the human leukocyte antigen, HLA), mainly HLA-DRB1, HLA-DPB1, HLA-DOA, and a growing number of non-HLA genes, such as *PADI4*, *PTPN22*, and *CTLA4*, among others, but HLA-DRB1 seems particularly significant.[18] Certain environmental factors, such as smoking, hormonal conditions, socioeconomic status, infectious factors, and exposure to silica or alcohol facilitate the activation of antigen-presenting cells (APCs). These APCs activate CD4 T lymphocytes, resulting in macrophage and B lymphocyte stimulation and plasma cell generation.[19]

Plasma cells produce autoantibodies, such as the rheumatoid factor (RF) and anti-cyclic citrullinated peptide (ACCP) antibodies, contributing to the inflammation.

Macrophages synthesize inflammatory cytokines such as the tumor necrosis factor alpha (TNF-α), interleukin (IL)-1, and IL-6, and, among them, TNF-α plays a central role in attracting new lymphocytes and activating fibroblasts, which produce metalloproteinases. In addition, TNF-α activates the receptor activator of nuclear factor kappa-B ligand (RANKL), which stimulates osteoclast differentiation.

The inflammatory process, mediated by all the inflammatory cytokines, metalloproteinases, and new osteoclasts, damages the joint cartilage and ligaments. This damage results in articular and ligamentous laxity and bone resorption.

In the upper cervical spine, destruction of the transverse ligament, anterior and posterior atlantooccipital membrane, and tectorial membrane result in anterior or rotatory C1-C2 instability. Retro-odontoid pannus formation may lead to direct neural compression; erosions and bone resorption of the odontoid process can cause posterior C1-C2 subluxation, and resorption of the lateral masses of the atlas can cause vertical subluxation. In the lower cervical spine, destruction of the uncinate, facet, and ligaments may result in subaxial subluxation. Finally, all of the above combined can produce various degrees of mechanical compression and ischemia of the neural structures (►**Figure 1**).[11]

Natural History

Follow-up studies[4,17,20,21] usually confirm that untreated cervical RA tends to progress radiologically and neurologically. The overall prognosis is poor. Although there is a

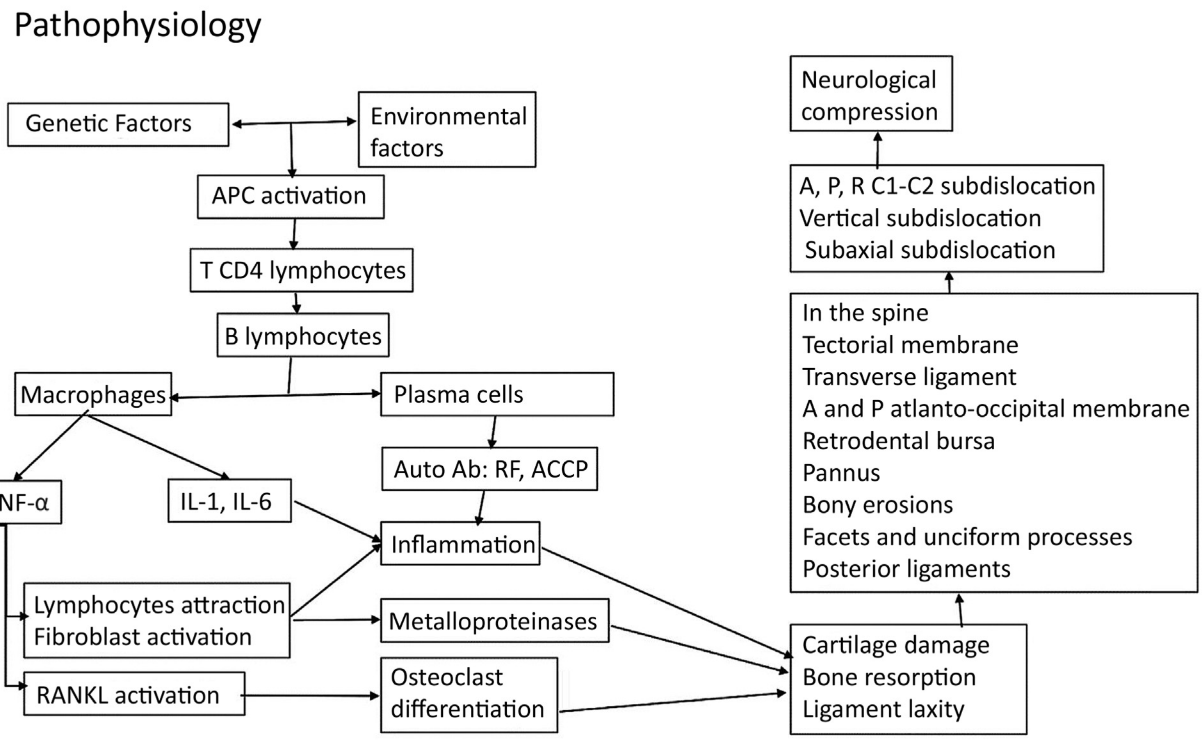

Fig. 1 Pathophysiology of cervical rheumatoid arthritis. Abbreviations: Ab, antibody; ACCP, anti-cyclic citrullinated peptide antibodies; APC, antigen-presenting cell; IL, interleukin; RANKL, receptor activator of nuclear factor kappa-B ligand; RF, rheumatoid factor; TNF, tumor necrosis factor.

relationship involving cervical involvement, the time of evolution, and the magnitude of RA damage in peripheral joints, cervical involvement may occur early, within 2 years.[12]

Radiologically, the condition progresses from reducible anterior C1-C2 instability to irreducible anterior instability to vertical subluxation.[4] Rana et al.[20] observed a progression rate of 27%. Pellicci et al.[17] showed an increase in incidence from 53% to 70% in a 5-year follow-up period. Furthermore, myelopathic involvement tends to get worse. Sunahara et al.[21] showed that 76% of patients with myelopathy tend to deteriorate, and that 100% lose the ability to walk in 3 years. In addition, there were no survivors in 7 years, including three cases of sudden death among 21 patients with vertical subluxation.[21] Mortality would be eight times higher compared with that of patients with no atlantoaxial subluxation, and the incidence rate of sudden death, due to compression of the medulla oblongata, would reach 10% in patients with C1-C2 instability.[22–24] According to Zoma et al.,[25] the mortality or disability rate due to severe neurological compromise is of 97%.

Fortunately, the incidence of cervical RA involvement has been declining. A systematic review[8] demonstrated a significant decrease in the incidence of anterior subluxation, from 36% in the 1960s to 24% today. The incidence rate for vertical subluxation, subaxial subluxation, and myelopathy remained the same.[8]

Disease-modifying antirheumatic drugs (DMARDs) significantly decreased the prevalence of anterior C1-C2 subluxation. In a study[26] with 195 patients with newly diagnosed RA, DMARDs reduced the prevalence of anterior subluxation to 3% when using a single drug, and to 0% as an associated treatment within 2 years. In another study,[27] 1 of 38 patients submitted to a combined regimen developed anterior subluxation in a period greater than 2 years. The recent Janus-kinase (JAK) inhibitors had good results in RA control, but there is no information about their effect on the spine.[28,29]

Frequent Lesions

The three most common rheumatic cervical spine injuries are anterior C1-C2 subluxation, vertical C1-C2 subluxation, and subaxial subluxation (►**Figure 2**).

Injuries to C1-C2 are the most frequent in RA, accounting for 60% of all cervical injuries. Most of these lesions are anterior instabilities; lateral, posterior, or rotational instability are less frequent. Instability in C1-C2 can be progressive in up to 20% of the cases and compromise the spinal cord.[9]

Vertical C1-C2 subluxation is progressive in 35% to 50% of the cases. It may compress the medulla oblongata, the high spinal cord, or the vertebral arteries.[23]

Subaxial subluxation results from the involvement of the facets and Lushka joints in the lower cervical spine.

Imaging

Radiography

The anteroposterior, lateral, dynamic, and transoral views of the cervical spine enable the measurement of the following indices: anterior atlanto-odontoid interval (AAOI), posterior atlanto-odontoid interval (PAOI), McGregor line, McRae line, Chamberlain line, Wackenheim line, Clark stages, Redlund-Johnell index, Ranawat index, and Sakaguchi-Kauppi index.

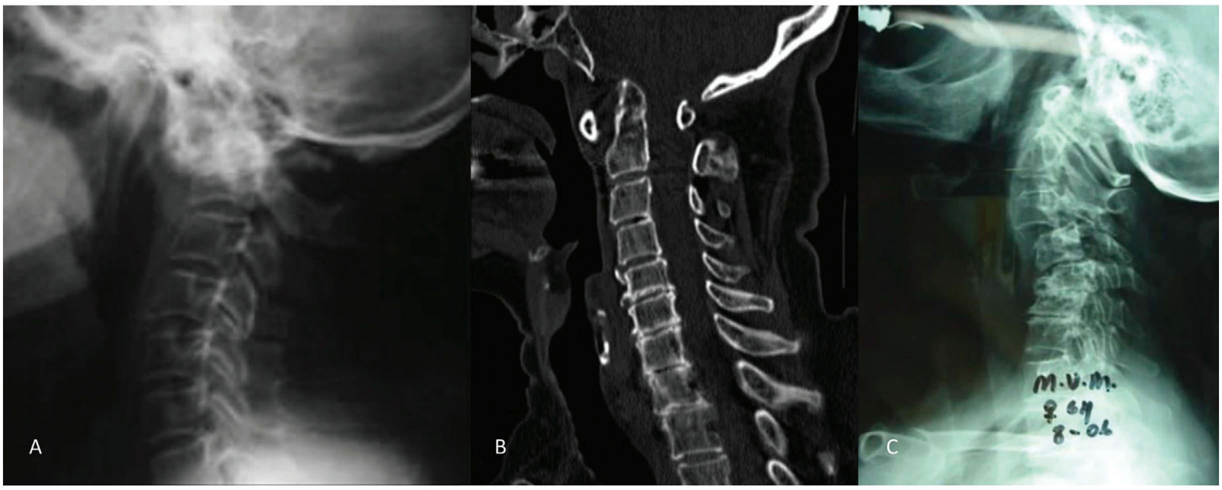

Fig. 2 (**A,B**) Vertical subluxation. (**C**) Subaxial subluxation.

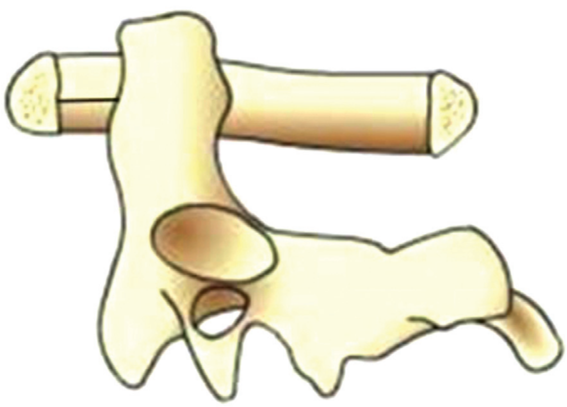

Fig. 3 Anterior atlanto-odontoid interval from the posterior border of anterior arch of the atlas to the anterior border of the odontoid.

Anterior atlanto-odontoid interval

This parameter establishes the diagnosis of C1-C2 instability. It is the distance between the posterior border of the anterior arch of the atlas and the anterior border of the odontoid bone. The diagnosis is established with an AAOI of 3 mm or more (►**Figure 3**).

Posterior atlanto-odontoid interval

It is the distance between the posterior border of the odontoid bone and the anterior border of the posterior arch of the atlas (►**Figure 4**).

McGregor line

The McGregor line goes from the posterior border of the hard palate to the lowest part of the occipital curve. An odontoid protrusion higher than 4.5 mm to 5 mm in cephalad direction diagnoses a vertical subluxation (►**Figure 5**).

McRae line

The McRae line is at the level of the foramen magnum, from the basion to the opisthion. The odontoid must be 1 mm below this line (►**Figure 5**).

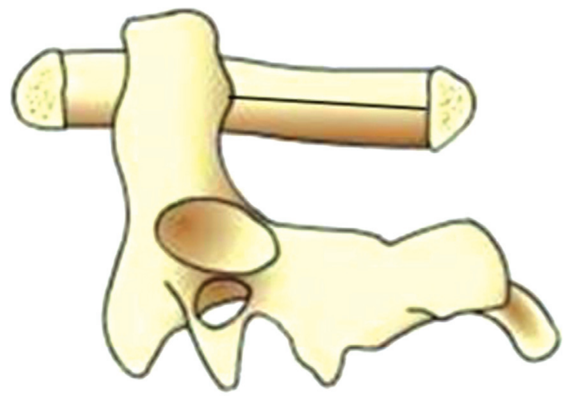

Fig. 4 Posterior atlanto-odontoid interval from the posterior border of the odontoid to the anterior border of the posterior arch of the atlas.

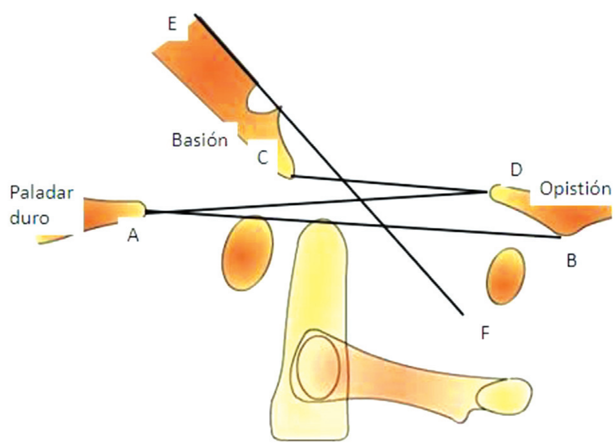

Fig. 5 McGregor line (**AB**), McRae line (**CD**), Chamberlain line (**AD**), and Wackenheim line (**EF**).

Chamberlain line

The Chamberlain line goes from the posterior border of the hard palate to the posterior border of the foramen magnum (opisthion). The odontoid must be 3 mm caudal to this line (►**Figure 5**).

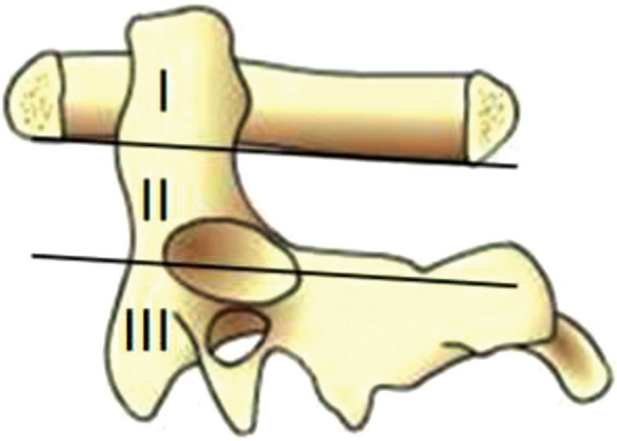

Fig. 6 Clark stages, dividing the odontoid in three parts.

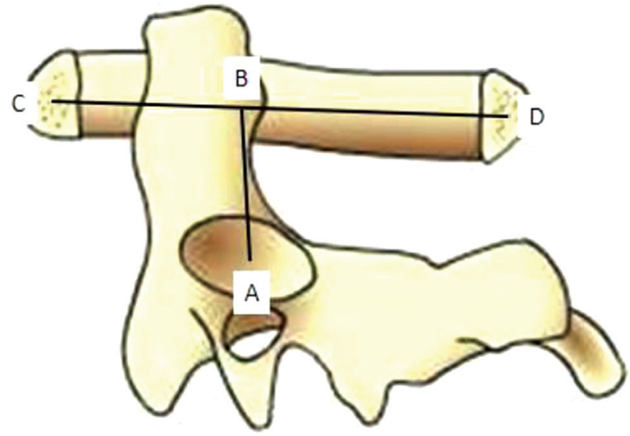

Fig. 8 Ranawat index (**AB**); distance from the center of the pedicle of the axis to the line joining the center of the anterior arch to the center of the posterior arch of the atlas (**CD**).

Wackenheim line

The Wackenheim line is parallel to the clivus. The odontoid must be behind this line (►**Figure 5**).

Clark stages

The Clark stages divide the odontoid into three parts, and it is considered abnormal if the second or last third reaches the arch of the atlas (►**Figure 6**).

Redlund-Johnell index

It measures the distance between the McGregor line and the bottom edge of C2. It is equal to 34 mm in men and 29 mm in women (►**Figure 7**).

Ranawat index

It measures the distance between the center of the pedicle of C2 and a line joining the center of the anterior arch to the center of the posterior arch of the atlas. Values lower than 13 mm in women and 15 mm in men establish the diagnosis of C1-C2 vertical subluxation (►**Figure 8**).

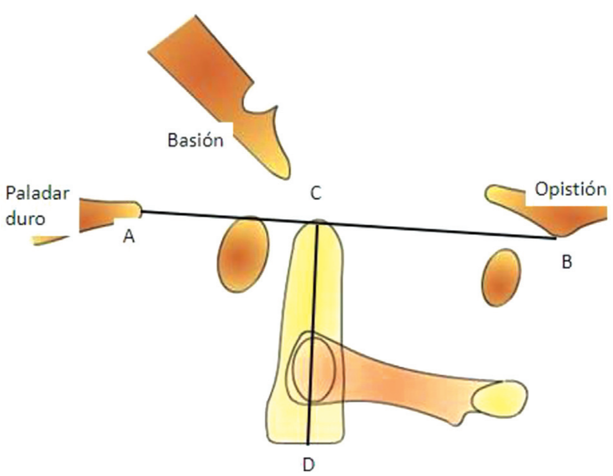

Fig. 7 Redlund-Johnell index (**CD**); distance from the McGregor line to the odontoid base (**AB**).

Sakaguchi-Kauppi index

Draw three parallel lines to the upper edge, middle area, and lower edge of C1. If the upper edge of the pedicle is under the lower line, there are no abnormalities. The vertical subluxation is grade 1 if the upper edge is between the lower and the middle lines, grade 2 if it is between the middle and the upper lines, and grade 3 if it is on the upper line (►**Figure 9**).

The association of the Clark stages, the Redlund-Johnell index, and the Ranawatt index result in a sensitivity rate of 94% and a negative predictive value of 91% for vertical subluxation.[30]

A PAOI longer than 9 mm or, even better, shorter than 14 mm increases the risk of neurological compression. A PAOI shorter than 10 mm is a poor prognostic index for postoperative neurological recovery.[31]

The reported prognosis for C1-C2 lateral subluxation is poor.

Computed Tomography

Cervical spine computed tomography (CT) is the best method to assess bone anatomy. It enables an excellent evaluation of the anatomical relationship between the odontoid and the

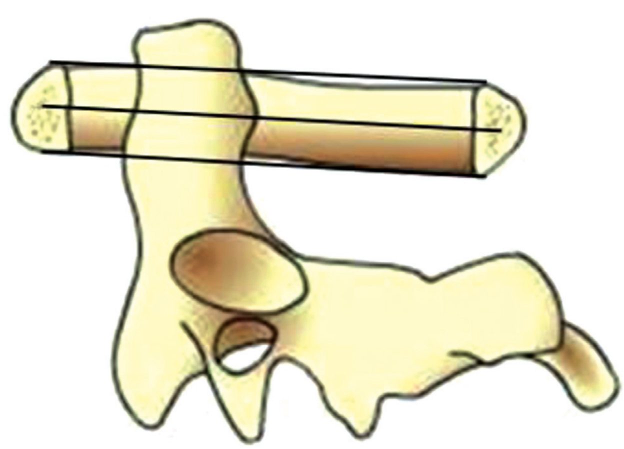

Fig. 9 Sakaguchi-Kauppi index.

foramen magnum. In addition, it enables an optimal assessment of erosions, and it is the best imaging technique for rotational subluxations. Combined with CT angiography, it enables the evaluation of the anatomy of the vertebral arteries, and it is an essential tool in preoperative planning.[32] Dynamic CT could be more sensitive in detecting C1-C2 instability than dynamic magnetic resonance imaging (MRI).[33,34]

Magnetic Resonance Imaging

Both the upper and lower cervical spines can be evaluated through MRI. The main parameters provided by MRI are the space available for the spinal cord, the spinal cord diameter, and the cervicomedullary angle.

The space available for the spinal cord is used for the evaluation of C1-C2 subluxation and subaxial subluxation. A value lower than 13 mm results in a risk of neurological compression.[33] A spinal cord diameter shorter than 6 mm in the upper cervical spine is a neurological risk factor.[35,36] The normal cervicomedullary angle ranges from 135° to 175°; if it is lower than 135°, it increases the neurological risk[37] (►**Figure 10**).

Treatment

Surgical indication includes pain, neurological deficit, and risk-associated imaging findings. The goals of surgery are stabilization, decompression, pain treatment, and avoiding irreversible neurological damage, sudden death, and further unnecessary procedures.[38]

Dynamic cervical spine radiographs in flexion and extension are used to define instability. An unstable spine presents an AAOI longer than 3 mm on a lateral or dynamic flexion radiograph. Radiological criteria supporting surgery are an AAOI longer than 8 mm or 9 mm and, especially, a PAOI shorter than 14 mm or a cranial settlement of at least 5 mm. A POAI shorter than 10 mm is a poor prognostic criterion.[31]

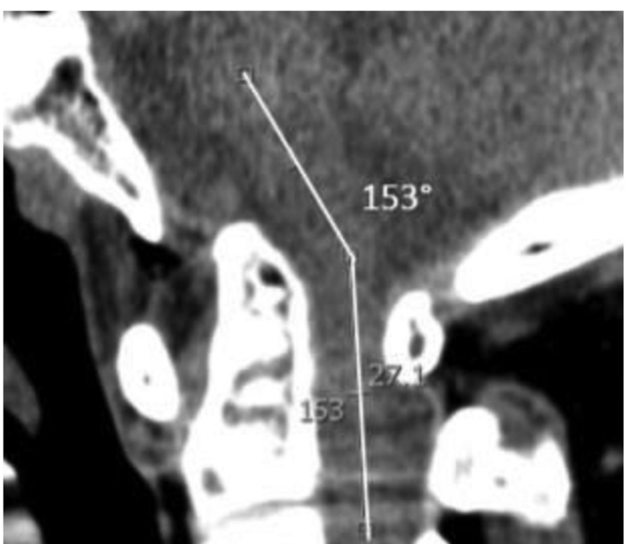

Fig. 10 Cervicomedullary angle.

Ranawat et al.[10] recommend a Gallie-type arthrodesis for anterior atlantoaxial subluxation, C0-C2 occipitocervical arthrodesis for vertical subluxation, and posterior arthrodesis for subaxial subluxation.

In a literature review, Beaulieu et al.[38] recommend a posterior C1-C2 arthrodesis in anterior C1-C2 instability when the PAOI is shorter than or equal to 14 mm with proven dynamic instability, or when the PAOI is shorter than or equal to 14 mm with findings of risk factors on MRI, such as a cervicomedullary angle lower than 135°, a spinal cord diameter in flexion shorter than 6 mm, or a bony canal diameter shorter than 13 mm (►**Figure 11**).

A pure C0-C2 arthrodesis is recommended for vertical subluxation in patients with risk factors on MRI and a reducible spine with traction maneuvers, and C0-C2 arthrodesis and decompression are recommended in patients with irreducible vertical instability[38] (►**Figure 12**). The contraindications for reduction maneuvers by traction are complex rotatory subluxations and posterior cranioatlanto-odontoid subluxation due to the risk of vertebral artery distraction.[39]

For subaxial subluxation, stabilization is recommended when the canal diameter is shorter than 14 mm or if there are more than 3.5 mm of subluxation. Finally, one must consider the progressive neurological deficit (►**Figure 13**).

Surgical Techniques

Occipitocervical arthrodesis typically extends to C2. However, if there is significant osteoporosis or subaxial subluxation, it may extend more distally. A resection of the posterior arch of C1 may or may not accompany this procedure.

Whenever possible, C1-C2 arthrodesis is the surgery of choice. In classic surgical techniques with wiring, such as Gallie and Brooks, the degree of pseudoarthrosis is of up to 20%, even with halo supplementation.[40,41]

The most modern techniques have significantly decreased the rates of pseudarthrosis. Goel and Laheri[42] described a C1-C2 fixation technique in 30 patients of varying ages and diagnoses, achieving 100% of fusion with no morbidity, mortality, or implant failure. The technique consists of fixation with plates and screws to the lateral masses of C1 and C2, with the possibility of placing a longer plate if occipitocervical fixation is required.[42] Later, Goel et al.[43] extended their study to 160 cases, achieving 100% of fusion; however, 3 patients died in their series.

After protecting the greater occipital nerve and the venous plexus, using a posterior approach, Magerl and Seemann's[44] transarticular screws are positioned in a cephalad direction from C2 to the lateral masses of C1 bilaterally.[44] The use of transarticular screws in C2 requires the study of vascular and bone anatomy. A "high-riding" vertebral artery, an inadequate bone stock in the lateral masses, and a narrow isthmus in C2 contraindicate this technique, since the isthmus must

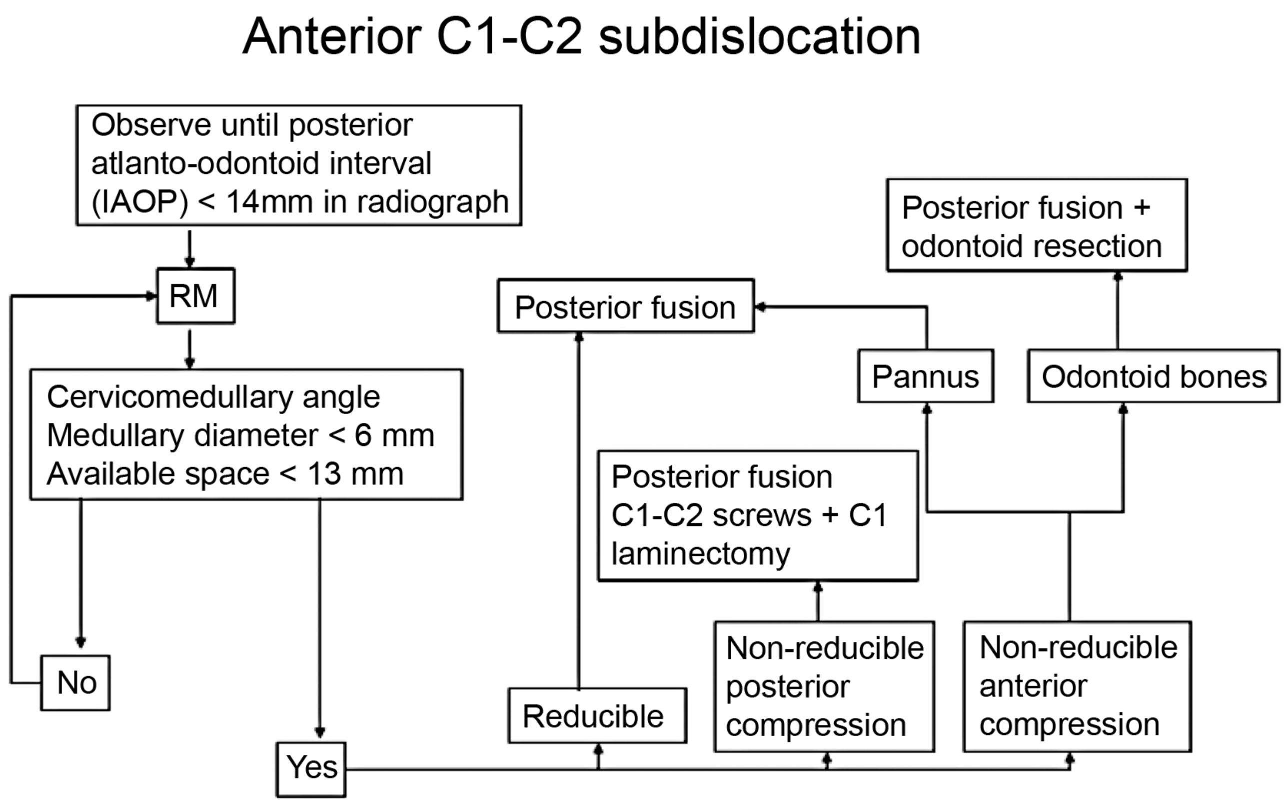

Fig. 11 Decision-making in anterior C1-C2 subluxation. Modified from Beaulieu et al.[38]

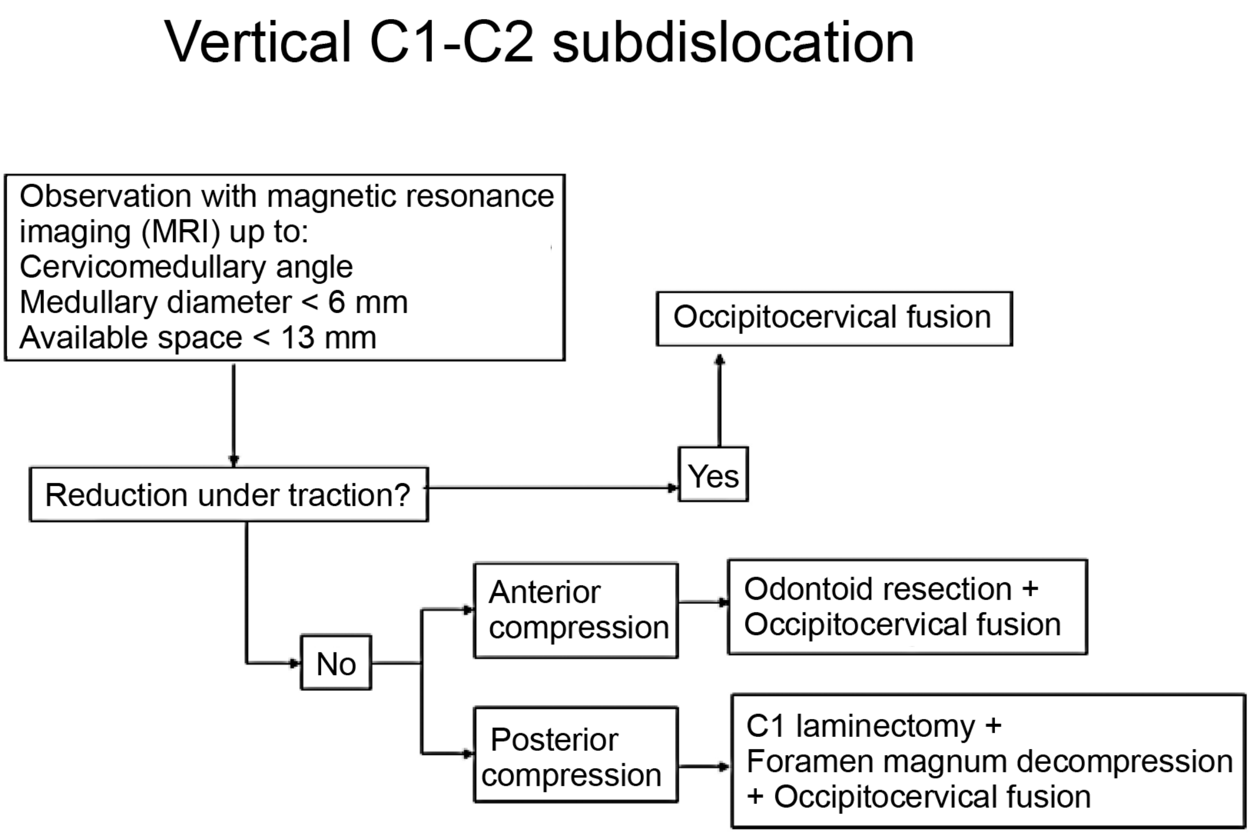

Fig. 12 Decision-making in vertical C1-C2 subluxation. Modified from Beaulieu et al.[38]

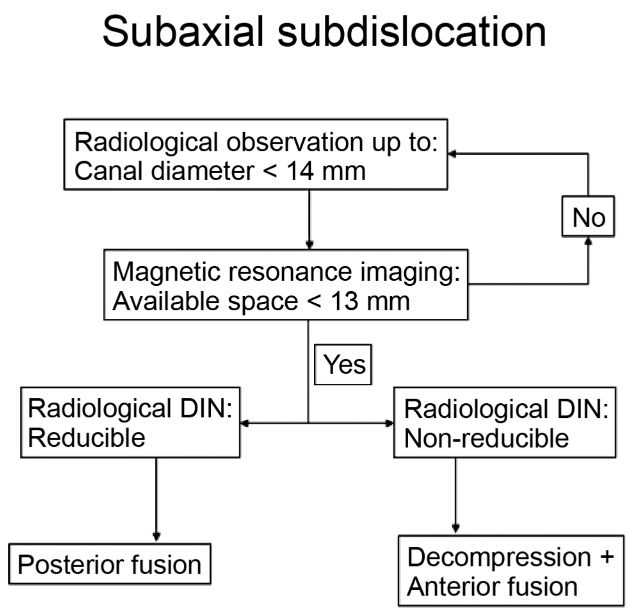

Fig. 13 Decision-making in subaxial C1-C2 subluxation. Modified from Beaulieu et al.[38]

enable the placement of 3.5-mm screws. Inadequate bone stock in C1 masses and irreducible subluxations are also contraindications.[45]

Harms and Melcher[46] subsequently developed a polyaxial screw fixation technique for the lateral masses of C1 and pedicles of C2 through the pars. This technique overcomes the limitations of transarticular screws. The reference points to place the screws in C1 and C2 are the C1-C2 joint and the pars of C2 respectively.[46] The Magerl and Seemann[44] and Harms and Melcher[46] techniques have fusion rates higher than 90%, with no significant differences between them.[47–50]

A narrow pedicle or pars contraindicates the use of screws in C2. Similarly, the presence of a ponticulus posticus contraindicates screw placement in C1.[51] In C2 pedicles smaller than 6 mm, the rate of cortical gaps is of 37%, compared with 21% in pedicles greater than 6 mm.[52]

The literature[47,53] suggests that the Harms and Melcher[46] technique could have a lower incidence of vascular injury than transarticular screws, and that placing screws in the pars of C2 would result in a lower incidence of vascular injury compared to the pedicles of C2.

If the bone or vascular anatomy contraindicates transarticular or pedicle screws in C2, a good alternative is to place the screws in the C2 laminae, as described by Wright,[54] eliminating the risk of damage to the vertebral arteries. Anatomical studies show that the average thickness of the C2 laminae is of 5.77 mm in adults[55] and higher than 3.5 mm in children from 3 to 10 years old. As such, this is a useful technique in both populations.[56]

Prognosis

Patients with RA have a higher prevalence of comorbidities and incidence rate of complications than patients without RA in primary "non-cervical" spine surgery.[57] A risk factor analysis detected 20% of complications in 139 RA patients submitted to cervical spine surgery. The risk factors for major complications included the use of high doses of prednisolone, diagnosis of subaxial subluxation, occipito-cervical arthrodesis, and long arthrodesis. A total of 40% of the complications were infections, and half of them were in surgical wounds.[58] However, another study[57] found no relationship between infections and treatment with prednisolone, methotrexate, biological agents, or JAK inhibitors.

The postoperative prognosis of patients with cervical rheumatoid disease depends on their neurological status, particularly their ability to walk. Ranawat et al.[10] showed the relationship between the preoperative neurological status and the postoperative outcome. In a series of 33 patients, only one patient went from Ranawat stage III to stage II, while only two subjects went from stages IIIB to IIIA.[10] Schmitt-Sody et al.[59] showed that out of 10 Ranawatt-II patients, 7 improved to Ranawatt I; however, only 1 in 11 Ranawatt-IIIA patients improved to II, while 2 worsened to IIIB. Stage-IIIB patients have a poor prognosis.

In a systematic review[60] including 25 articles, 53% of Ranawat-II patients and 56% of Ranawat-IIIA patients improved by at least 1 stage. Around 4% of stage-I, 7% of stage-II, and 9% of stage-IIA patients present postoperative neurological deterioration. Among the Ranawat-IIIB patients, 36% improved by 1 stage, and 21% improved by 2 or more stages. In addition, their mortality rate was o 43%, which was significantly higher compared with the other stages (Ranawat I: 13%; II: 20%; and IIIA: 26%). Mortality was significantly higher in stage-IIIA than in stage-I patients, and there were no significant differences between stages I and II.[60]

The imaging criteria for poor prognosis are PAOI shorter than 10 mm, a bone canal shorter than 13 mm, a medullary diameter shorter than 6 mm with a flexed spine, a cervicomedullary angle lower than 135°, and a medullary area smaller than 44 mm^2.[10,31,35–37] Among the patients operated on for C1-C2 instability, 39% developed subaxial subluxation, and 54% required further surgery.[61]

Recommendations

Due to the potentially fatal complications, consider cervical involvement by RA regardless of the presence of symptoms. Timely diagnosis, imaging tests, and treatment improve the quality of life and life expectancy of patients and avoid serious complications. Similarly, adequate planning of the surgical treatment is essential to prevent potential complications. The development of new surgical techniques has improved fusion rates. Detailed knowledge of bone and vascular anatomy can prevent intraoperative complications.

Conflict of Interests
The authors have no conflict of interests to declare.

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