Rheumatoid Diseases Involving the Cervical Spine I. History, Definition, and Diagnosis: New Trends and Technologies

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1 Cervical Spine Anatomy

Understanding the anatomy of the cervical spine is of outmost importance to understand its involvement in inflammatory rheumatic diseases. The craniovertebral junction (CCJ) separates the skull base from the subaxial cervical spine and provides cranial flexion, extension, and axial rotation functions. The components that make up the CCJ are responsible for support and protection of the cervicomedullary structures within. Ligaments and articulation of the occipitoatlantoaxial complex control the mobility and restriction of movement. The ring of atlas (C1) articulates with the skull base through to the occipital condyle and it is confined by the tectorial membrane. The atlas is also connected to the skull by the atlantooccipital membrane, which connects the C1 anterior arch to the anterior margin of the foramen magnum.

The anterior arch of C1 articulates with the odontoid process of C2 in a synovial joint that is constrained by the transverse ligament, which holds the dens to the anterior arch of C1 via a "strap-like" mechanism and avoids anterior translation of C1 relative to C2 [1].

Injuries to the cervical spine are namely atlanto-axial instability (AAI), atlanto-axial subluxation (AAS), vertical axis subluxation (VS) (also known as cranial settling), and subaxial subluxation (SAS).

The AAS is characterized by a weakening or rupture of ligaments and subchondral bone erosion in the atlanto-axial joints. It can be visualized on a plain radiograph by an anterior atlantodental interval (AADI) >3 mm and a posterior atlantodental interval (PADI) <14 mm.

Cranial settling is the vertical translocation of dens into the foramen magnum and is defined as a migration of the odontoid process >4.5 mm above the McGregor line. The SAS is defined by a subluxation in the joints C3–7 due to destruction of the joint surface and the ligaments between the processes spinosis. On a plain radiograph there is a horizontal displacement of vertebrae with an irreducible translation >3.5 mm [2].

Cervical spine disease may be seen in rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), and spondyloarthritis (SpA), especially psoriatic arthritis (PsA) [3], as shown in the following paragraphs.

2 Rheumatoid Arthritis

The prevalence of RA worldwide is approximately 0.5–1% of the population with a women to men ratio of a 3:1 [4]. Male incidence rises dramatically with age, whereas female incidence keeps on rising until the age of 45, has its plateau at the age of 75, and eventually falls in the elderly [5, 6]. Neck pain is the most frequent symptom of spinal involvement in RA; it occurs in 40–80% of patients and is mostly localized at the craniocervical junction [7]. Risk factors for cervical involvement are male sex, presence of rheumatoid factor and anti-citrullinated protein antibodies (ACPA), rheumatoid nodules, severe peripheral disease with early and extensive development of erosive damages, intense systemic inflammatory response at onset, long-term disease and prolonged use of corticosteroids. Moreover, a relationship between cervical arthritis and peripheral erosive disease has been established [8, 9]. In these patients, inflammation of the atlanto-axial joint produces odontoid erosion and ligamentous laxity [10]. Moreover, facet joint, uncovertebral joints, retrodental bursa, interspinous ligament, and ligament around the atlas involvement can be appreciated leading to cervical spine instability and subsequent myelopathy [11].

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Anterior AAS is the most common presentation, followed by lateral AAS (20%) and posterior AAS (7%). Posterior AAS takes place when the anterior arc of the atlas has shifted to the odontoid process. SAS can be found in 20% of cases.

Vertical subluxation (VS) occurs in 20% of patients with cervical spine involvement. VS is more common in patients with erosive or mutilating disease than those with minimal peripheral disease [12, 13].

Despite that most patients are asymptomatic [14], joint arthropathy, muscle wasting, decreased range of motion, compressive neuropathy, or a combination of these factors might be experienced and shall be promptly recognized to allow timely diagnosis. Neck pain may be present, and it occurs with the involvement of the craniovertebral-junction [15]. The latter takes place at atlanto-axial instability (AAI) or cranial settling which can compress occipital nerves between atlas and axis.

Compression of the C2 spinal nerve or greater auricular nerve can determine migraine or neck, mastoid, ear or facial pain [16].

Compression of brainstem and vertebral artery leads to tinnitus, vertigo, visual disturbance, diplopia, and dysphagia [14].

Compression of the vagus and glossopharyngeal nerve provokes dysphagia, compression of the hypoglossal nerve dysarthria, compression of the spinal trigeminal tract facial dysestesia [16], and compression of the superior spinal cords and cervicomedullary junction the Lhermitte's sign (an electric shock sensation with forward flection of the head) [14, 16].

Spinal cord compression brings about myelopathy and its symptomatology: muscle weakness and atrophy, gait impairment, limb paresthesia, hyperreflexia, spasticity, lack of proprioception, bladder and bowel disorders.

In extreme cases paralysis can be present for syringomyelia or locked-in syndrome [8].

3   Spondyloarthritis

This group includes seronegative diseases (negative rheumatoid factor), such as ankylosing spondylitis (AS), PsA, reactive arthritis, arthritis associated with inflammatory bowel disease, and undifferentiated SpA. SpA do not frequently involve the cervical spine, while PsA tends to involve the cervical spine early in the disease, AS involves the cervical spine in advanced disease [17]. In SpA, instabilities are rare, probably due to new bone formation, as the characteristic lesions of the disease are syndesmophytes, parasyndesmophytes, and ankylosis [17].

AS occurs in 0.02% of the population [18] and affects the spine and the sacroiliac joints, while extra-axial manifestations include acute uveitis, peripheral arthritis, enthesitis, psoriasis, aortic root, and gut inflammation. Although once believed to affect men predominantly, recent evidence suggests women are affected equally but experience milder symptoms.

In the most severe forms, the condition is associated with macroscopic changes such as the progressive ossification of the spinal ligaments and ankylosis of the facet joints eventually leading to a totally stiff spine (the so-called "bamboo spine" appearance on the radiographs) [19].

The primary symptom in AS is inflammatory back pain, usually dull and insidious in onset and felt deep in the lower back or buttocks. It is frequently associated with morning rigidity (lasting for 30 min or more), fatigue, enthesitis, and peripheral arthritis. The fused spinal column is associated with stiffness, restricted spinal movements, and osteoporosis which increases the risk of fractures of the spine in these patients with devastating neurological complications [20]. Although atlantoaxial instability can occur in patients with AS, it is not as common as in patients with RA [17].

Among the different types of cervical injuries, anterior atlanto-axial subluxation (AAS) is present in up to 21% of cases, while vertical AAS is only found in 2%, and it has been found to correlate with high levels of C reactive protein (CRP), peripheral arthritis, the degree of sacroiliitis, uveitis, and the use of biological treatment [21]. Clinically significant spontaneous AAS can lead to spinal cord compression if it is not recognized and stabilized. In 16% of the AS population ossification of the posterior longitudinal ligament is seen and it may lead to myelopathy [22].

The study by Maas et al. [23] showed that cervical facet joints were frequently involved in AS: 52% of AS patients had syndesmophytes and 25% had ankylosis of the facet joints. Interestingly, in this study, 26% and 13% of patients who underwent biological treatment developed new syndesmophytes and facet joint ankylosis, respectively, within 4 years. Among the predisposing conditions linked to the destruction of the facet joints a longer disease duration, presence of uveitis, psoriasis, or inflammatory bowel diseases, as well as high disease activity, a high modified stroke ankylosing spondylitis spinal score (mSASSS), the presence of syndesmophytes, and an increased occiput to wall distance measured at clinical assessment were included.

PsA is an inflammatory musculoskeletal disease associated with cutaneous psoriasis. Psoriasis has a prevalence of 2–4% in Western adults [24] and 20–30% of psoriatic patients will develop PsA [24].

Men and women are almost equally affected between the ages of 40 and 50 years. Cervical spine involvement in psoriatic arthritis is observed in 35–75% of cases and it occurs most frequently in severe psoriatic arthritis with a long-standing disease [17], especially in patients with the polyarticular subtype of PsA [25].

In a previous study, the duration of psoriatic arthritis and the presence of radiocarpal erosions were prognostic factors for cervical spine disease, but no correlation was found regarding the severity of skin or nail disease [26].

Blau et al. categorized C-spine involvement in PsA into two heterogeneous groups: ankylosing and rheumatoid-like. While the first group is more commonly encountered and is characterized by the presence of ankylosis, syndesmophytes, and ligamental calcification, rheumatoid-like PsA tends to be erosive and is associated with AAS [27].

In a study conducted by Laiho et al., inflammatory cervical spine changes were not commonly seen in patients with PsA. The most common change was apophysial joint ankylosis, accounting for 11% of patients, followed by anterior AAS, seen in 8% of patients [28].

A recently reported case of a PsA patient presenting with four limb paresthesia and gain difficulty caused by C1–C2 instability was successfully treated with instrumented posterior arthrodesis C1, C2, C3, C4, and C5 associated with laminectomy C3, C4, and C5 [29], suggesting that C1–C2 instability should be systematically checked on the dynamic cervical spine X-ray, in the case of neurological symptoms.

In the Van Tilt et al. study [30] three PsA patients with increasing cervical pain and loss of mobility were described. Each of them showed specific radiographic characteristics, suggesting that in psoriatic arthritis different mechanisms underlie the cervical involvement. Specifically, two patients reported bone edema at MRI, while one patient showed new bone formation around the odontoid process with ossification of the ligamentum transversum. These findings suggest a possible entheseal involvement as seen in spondyloarthropathies in general, underscoring a different nature from the one occurring in RA.

4   Juvenile Idiopathic Arthritis

JIA is the most common idiopathic inflammatory arthritis affecting children younger than 16 years of age and lasting 6 weeks or longer [31]. JIA is a heterogeneous group of arthritis characterized primarily by peripheral joint arthritis. Although chronic arthritis is mandatory for all subtypes, the extraarticular and the systemic manifestations characterized every specific subtype [31]. Disease complications of JIA can vary from growth retardation and osteoporosis secondary to treatment and disease activity, to life-threatening macrophage activation syndrome with multi-organ insufficiency. In the JIA, the cervical spine can be affected in up to 80% of patients, most commonly in those with the polyarticular subtype, followed by enthesitis-related arthritis group. Rate of occurrence in seronegative and seropositive patients is similar [32]. In JIA, early apophyseal bone ankylosis is characteristic, in addition to impaired spinal growth [16].

According to a recent review [17], the most striking features of JIA are early cervical spine apophyseal joint ankyloses, observed in up to 41% of patients, accompanied by bone growth developmental disturbances, such as vertebral or disc hypoplasia caused by chronic inflammation and long-term steroid use. Fusion typically begins at the C2/C3 level, and patients with early-onset JIA are at increased risk. Erosions and subluxations, similar to those observed in RA, also occur. Other less specific features include ligamental calcifications.

Regarding subluxations, anterior AAS has been observed in up to 33% of seropositive patients which were predisposed to severe anterior AAS. Dens erosions were seen in up to 19% of cases, while SAS was seen in up to 7% [33].

5   Imaging Modalities

The first line imaging modality for assessing cervical involvement in the above mentioned inflammatory arthropathies is radiography, both static and dynamic. Classic radiography is relatively effective in the detection of bone lesions and C-spine alignment. The most used views include lateral and anteroposterior (AP) projections, with the latter used for alignment and Luschka joint assessment. On the other hand, in rheumatology settings, functional lateral projections are often requested to assess subluxations, especially at the C1, C2 level. The significant limitation of plain radiography of the craniovertebral junction is the superimposition of anatomical structures, which is especially common when rotational instability is present. The lack of functional views and reliance only on lateral neutral projection leads to failed radiological diagnosis in almost 50% of cases [34].

Plain radiographs are indeed limited to appreciate visualization of bony erosions, craniocervical junction, cervicothoracic junction, and pannus and spinal cord compression.

The indication to repeat such imaging comes every 2 years or upon arrival of new symptomatology [33]. CT and MRI are suggested to patients when cervical spine disease is confirmed or when neurological symptomatology is detected [12].

Computed tomography (CT) is mainly used preoperatively; although it is superior in the assessment of soft tissue involvement when compared to radiography, it is still inferior to MRI, especially in the context of spinal cord and nerve root imaging. CT scans on one hand provide valuable information concerning erosions, assessment of ankylosis or pseudoarthrosis, but on the other hand, it must be taken into account that CT scans provide little soft tissue information at a price of high radiation dosage [33].

MRI allows for a more precise diagnosis of C-spine lesions, especially in terms of early diagnosis. MRI is the most sensitive imaging technique to establish cervical spine

involvement [35, 36]. It is considered the gold standard for brainstem, spinal cord, or nerve root involvement. MRI shows cysts, erosions of the dens or spinous processes, or vertebral endplates and spinal cord involvement in the cervical spine. Typical MRI protocols include sagittal T1 and T2-weighted sequences, T2 STIR (short tau inversion recovery), and axial T2-weighted images. Optionally, the coronal T2-weighted sequence can be used, primarily to evaluate lateral subluxation. Furthermore, sagittal post contrast T1-weighted images can be used to assess active inflammatory lesions, mainly synovitis. Fluid sensitive sequences with fat saturation are preferred for visualizing bone marrow edema [37]. Drawbacks of MRI include that it is expensive, time-consuming, and not eligible for carriers of ferromagnetic implants and pacemakers [38].

6   Rheumatoid Arthritis

Myelopathy can be classified according to the Ranawat classification. It is useful in evaluating patients, deciding treatment and assessing results. Class I patients have no neural deficit, Class II patients have subjective weakness with hyperreflexia and dysesthesia, and Class III has been subdivided into IIIA for ambulatory patients and IIIB for the remnants [8].

According to Zoli et al., conventional radiography allowed detection of 41.3% of patients with craniocervical involvement, but only in advanced stages of the disease. However, MR imaging had the unique potential of direct and detailed synovial visualization, especially in the gadolinium enhanced axial images, resulting in the early diagnosis of craniocervical RA [35]. The same concept is underlined by Di Gregorio et al. who carried out a study where 38 patients affected by RA were screened for craniocervical involvement by conventional radiography, unenhanced Computed Tomography (CT) and Gadolinium-enhanced Magnetic Resonance Imaging (MRI) of the cervical spine. Eventually, the cervical spine involvement was assessed in 25/38 (66%) patients (20 women and 5 men). In particular, in 13 of them (mean disease duration 12.7 years), the diagnosis was made by radiography which showed atlantoaxial and subaxial subluxations and/or erosions. Of the 12 patients with negative conventional radiography (mean disease duration 2.5 years), 4 were identified with both CT and MRI (synovial pannus and erosions), 3 with MRI only (joint effusion/hypervascularized synovial pannus), and five exhibited questionable CT findings which were clarified only by MR demonstration. This study strengthen the idea that MRI is the most sensitive imaging tool [39].

A great-deal of information can be derived by imaging but precious data is also gained by bioptical specimen. Interestingly O'Brien et al. have undergone a histologic review of surgical specimens of dens in 33 myelopathic chronic RA patients. The histologic specimens suggested that ligamentous destruction was followed by replacement of the rheumatoid synovium with fibrous tissue, whereas the osseous structures revealed severe destruction secondary to mechanical instability, rather than to an acute inflammatory process. Therefore, this study was in line with the idea that early, preemptive surgical intervention can prevent the development of spinal cord injuries caused by instability [10]. Moreover, two different histologic patterns were determined. Type I synovium had a recognizable synovial structure without no hyperplastic synovial layer, no significant inflammatory cell population, and no lymphocytic infiltration typical of early active rheumatoid synovium. Type II synovium was a bland, fibrous, hypercellular and hypovascular tissue with little synovium and few inflammatory cells. Patients with Type II synovium were older and presented with more advanced neurologic involvement caused by spinal cord compression [10].

The former study agrees with the concept later expressed by Shen FH et al. according to which if such patients are left untreated a large percentage of them will progress toward complex instability patterns resulting in significant morbidity and mortality. Moreover, it was underlined that once myelopathy occurs, prognosis for neurologic recovery and long-term survival is poor [40].

7   Juvenile Inflammatory Arthritis

A very recently published study [41] aimed to assess the frequency of cervical spine lesions on radiographs and MRI in JIA patients with clinical signs of cervical spine involvement and to verify if with the addition of MRI, the use of radiographs could be abandoned. This retrospective study evaluated 34 children with JIA and with clinical involvement of cervical spine. In each patient, both radiographs and MRI of the cervical spine were performed. Authors concluded that the cervical spine lesions are still a frequent complication affecting up to 35% of JIA patients. Most of them develop serious complications, such as AAS and ankylosis. Despite advantages of MRI in terms of the imaging of the atlantoaxial region, radiography shows superiority in diagnosis of AAS and SAS.

8   Conclusions

Cervical involvement in inflammatory rheumatic diseases is still frequent and quite disabling, yet few data are present in the recent literature. However, such involvement may lead to severe acute complications that might be masked by the chronic pain frequently experienced by these patients.

Therefore, cervical spine involvement should always be investigated by the physician to avoid the dramatic neurological consequences that it could bring about.

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