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SPONDYLOARTHRITIS (MA KHAN, SECTION EDITOR)

Pulmonary, renal and neurological comorbidities in patients with ankylosing spondylitis; implications for clinical practice

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Abstract Ankylosing spondylitis (AS) is associated with several comorbidities which contribute significantly to morbidity and mortality and add to the complexity of management. In addition to the well known extra-articular manifestations and increased cardiovascular risk, several pulmonary, renal, and neurological complications which have been associated with AS deserve equal attention. Whereas a clear link has been established for some manifestations, the evidence for other associations is less clear. Interstitial lung disease, apical fibrosis, secondary infection, and ventilatory restriction from reduced chest wall movement are well known pulmonary complications; more recently an association with sleep apnoea has been suggested. Renal amyloidosis and IgA nephropathy remain a treatment challenge which may respond to anti-TNF therapy. Atlanto axial subluxation and vertebral fractures can result in serious neurological complications and are notoriously difficult to diagnose unless a high level of suspicion is maintained. Despite several reports linking AS with demyelination a true link remains to be proved. This review discusses the prevalence, pathophysiology, and management of pulmonary, renal, and neurological complications, and implications for clinical practice.

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Introduction

AS is a chronic multi-organ inflammatory disorder primarily affecting the spine, sacro-iliac joints, and the entheses. Diagnosis requires radiological evidence of sacroiliitis and fulfilment of the New York classification criteria [1]. AS commonly presents in the third decade with low back pain and early morning stiffness as a result of chronic inflammation of the spine and sacroiliac joints. Prevalence varies across continents and is related to the prevalence of the HLA-B27 antigen. In a recent study the mean AS prevalence per 10,000 was 31.9 in North America, 23.8 in Europe, 16.7 in Asia, 10.2 in Latin America, and 7.4 in Africa [2].

AS belongs to a group of conditions termed spondyloarthritis (SpA) which can be classified as axial if affecting predominantly the spine [3] or peripheral if affecting the peripheral joints [4]. SpA includes AS, psoriatic arthritis, entheropathic arthritis, reactive arthritis, and undifferentiated SpA. The basis of treatment includes physical exercise, non-steroidal anti-inflammatory drugs (NSAIDs), sulfasalazine for peripheral arthritis, and anti-tumor necrosis factor alfa (anti-TNFα) therapy if NSAIDs have no effect. SpA is associated with several well known extra-articular manifestations, for example uveitis, psoriasis, inflammatory bowel disease and comorbidities such as cardiovascular disease and osteoporosis [5•]. Less commonly associated comorbidities include renal, neurological, and pulmonary manifestations.

The prognosis of AS varies and partly depends on the severity of spinal and peripheral arthritis and on the presence

and severity of comorbidities. Patients with comorbidities suffer from greater disability, worse quality of life, and mortality [6]. Comorbidities add to the complexity of diagnosis, prognosis, and management; treatment options may be limited and healthcare costs are increased. Understanding the natural history, causes, and effects of AS comorbidities is important to guide further research and treatment and the development of healthcare services which meet the needs of individuals with coexisting conditions.

Several respiratory, renal, and neurological conditions have been associated with AS. In some cases a clear link has been demonstrated whereas the evidence for other associations is less strong and debatable. Some of the literature is based on AS patients with severe and long-standing disease whereas nowadays milder and earlier cases are detected which might affect the prevalence of these comorbidities.

Chest wall abnormalities, apical fibrosis and interstitial lung disease (ILD) have long been associated with AS. The availability of high resolution CT (HRCT) scanning has enabled non-invasive detailed assessment of the lung parenchyma. Imaging studies show that 61 % of AS patients have parenchymal abnormalities which may be present early in the disease among asymptomatic individuals [7•]. The significance of these abnormalities and natural history, particularly among asymptomatic individuals is still unknown, and long-term studies are required. More recently a potential association of AS and obstructive sleep apnoe (OSA) has been suggested by a number of studies; this also warrants further investigation [8, 9].

Renal involvement is a rare but significant complication which may be overlooked, particularly in the younger age group. The most commonly associated aetiologies are AA amyloidosis and IgA nephropathy [10]. Tubulointerstitial nephritis caused by NSAIDs is another important cause of renal complications. A recent population study found kidney involvement, in 3.4 % of men and 2.1 % of women with AS, suggesting higher prevalence than previously thought [11•]. Chronic kidney disease and acute kidney injury accounted for most of the cases in this study. AS patients may suffer from such neurological manifestations as myelopathy, peripheral neuropathy, atlantoaxial subluxation (AAS) and vertebral fractures [12-15]. The association of AS and demyelination continues to be debated, particularly in the context of anti-TNF therapy.

This review discusses the current literature on respiratory, renal, and neurological comorbidities in AS and implications for clinical practice.

Pulmonary co morbidities

Pulmonary involvement is a well-recognised comorbidity of AS, even among patients with early disease. The availability of HRCT has enabled better visualisation of the entire lung parenchyma and earlier identification of lung pathologies, ranging from mild to more severe involvement, which were previously missed on X-rays. Pulmonary involvement encompasses a wide range of well defined abnormalities including ILD, upper lobe fibrosis, mycetoma formation as a result of secondary infections, emphysema, bronchiectasis, ventilatory impairment as a result of chest wall restriction and sleep apnoea [16]. Non-specific pleuropulmonary changes including ground glass opacities, septal thickening, parenchymal micronodules, pleural thickening, parenchymal bands, bronchial wall thickening, and blebs have also been described [16] (Table 1). Later complications are upper lobe cavity lesions secondary to fungal and mycobacterial infections [17].

Reported prevalence of pleuropulmonary involvement varies widely, depending on the method of diagnosis and the duration of the disease among the AS population studied: 8 % in radiographic studies [18], between 40 to 80 % in chest HRCT studies [7•, 19, 20], and 18 to 42 % in lung spirometry studies [21, 22]. In a systematic review of 10 studies (303 patients), the prevalence of pulmonary abnormalities on chest HRCT of AS patients was 61 % [7•] and the mean (standard deviation, SD) disease duration of AS was 11.7 (5.2) years. Abnormalities were common in early disease and among asymptomatic individuals. Non-specific interstitial abnormalities, for example parenchymal bands and thickening of the interlobular septa, accounted for 33 %. Whereas HRCT has enabled non-invasive and more detailed assessment of lung involvement, histological studies which can help understanding of the pathophysiology of these abnormalities are scarce. Chronic inflammatory cell infiltrates and prominent interstitial fibrosis with elastic collagen and hyaline degeneration in needle biopsies and lobectomy specimens have been reported [23].

Apical fibrosis is one of the most well known pulmonary complications, particularly in severe cases with longer disease duration [24]. It can be unilateral or bilateral and is associated with cystic changes. In a systematic review, the overall prevalence of apical fibrosis was low at 7 % but increased to 21 % with disease duration of more than 10 years [7•]. The cause of the fibrosis is unclear but impaired ventilation as a result of reduced chest expansion, kyphosis, and rigidity of the thoracic spine may lead to recurrent aspiration and pneumonitis in patients with severe AS [17]. Superinfection of the upper lobe cysts and cavities with *Aspergillus* and *Mycobacterium ssp* may occur [25, 26]. In clinical practice, it is important to be able to differentiate between fibrosis and infection to avoid misdiagnosis, particularly as some patients might go on to anti-TNF therapy.

Both parenchymal involvement and restrictions of chest wall movement can contribute to a restrictive pulmonary function. Chest expansion may be reduced, because of pain

Table 1 Pulmonary, renal and neurological manifestations among AS patients

Respiratory complications
Parenchymal
Interstitial lung disease (ILD)
Apical fibrosis
Emphysema
Bronchiectasis
Ventilatory impairment
Chest wall restriction
Obstructive sleep apnoe (OSA)
Secondary infection
Mycetoma formation
Renal complications
AA amyloidosis
Glomerulonephritis (most commonly IgA nephropathy)
NSAID-related nephrotoxicity
Fluid and electrolyte disturbance
Acute renal dysfunction
Interstitial nephritis
Renal papillary necrosis
Neurological complications
Spinal cord compression
Atlanto axial subluxation (AAS)
Vertebral fractures
Demyelination
Multiple sclerosis

and stiffness of the thoracic vertebra, and the costochondral and sternomanubrial junctions [27, 28] and fusion and ankylosing of the spine and thoracic cage [28, 29]. Lung function of AS patients was reduced (18 % vs. 0 %, $P<0.001$) compared with controls, and restrictive lung function was associated with reduced chest wall and spinal mobility [21]. Associations of pulmonary function with disease activity, cardiorespiratory fitness, and physical function are conflicting [28-31].

Recent studies show a higher prevalence of pulmonary abnormalities than previously thought, particularly of mild non-specific changes. The significance among asymptomatic patients remains to be determined. Most of the literature is based on small cross-sectional single-centre studies limited by lack of controls matched for age, gender, and smoking. Furthermore few have studied lung abnormalities in relation to disease duration. Larger prospective longitudinal studies are required to determine the natural history of these abnormalities, and studies correlating histology from bronchoalveolar lavage and lung biopsies with abnormalities on imaging are required to help understand the pathophysiology. The effect of anti-TNF therapy on the structural and parenchymal abnormalities of the lung has yet to be evaluated. Although efficacy of anti-TNF therapy in terms of disease activity and quality of life (QoL) has been clearly demonstrated [32, 33], its effect on BASMI and prevention of radiographic progression, which could possibly affect chest abnormalities, is conflicting [34]. Whether earlier identification and treatment with anti-TNF therapy can alter the progression of parenchymal inflammation and fibrosis must be investigated. Because chest wall and spinal mobility are important determinants of pulmonary function, maintaining spinal muscle strength and flexibility are vital in AS management.

Recent studies suggest an association between OSA and AS [8, 9]. OSA is characterised by upper airway collapse and repeated episodes of apnoea and hypopnoea during sleep. OSA is also associated with increased mortality and morbidity, for example excessive daytime sleepiness, hypertension [35], cardiovascular disease [36], and fatigue. Similarly, sleep disturbance and fatigue are common features of AS [37].

Two small uncontrolled observational studies reported OSA in 22.6 % ($n=31$) [9] and 12 % ($n=17$) [8] of AS patients compared with 2–7 % of the general population [38]. Prevalence increased with age and disease duration but there was no association with reduced pulmonary function, disease activity, and spinal mobility [9]. In a recent cross sectional study ($n=63$) OSA was less common among SpA patients receiving anti-TNF therapy (57 %) than among patients not taking anti-TNF therapy (91 %) ($P=0.01$) [39]. The overall prevalence of OSA in this study was 76 %, which is much higher than that reported previously. Old age and higher BMI may have contributed to the greater prevalence. None of the biological trials addressed OSA specifically, but improved sleep was demonstrated after treatment with golimumab and adalimumab [32, 33].

Several causative mechanisms linking AS with OSA have been postulated, for example compression of the oropharyngeal airway by cervical bridging syndesmophytes, central respiratory depression from compression of the respiratory centres in the medulla from subluxation of the cervical spine, and restrictive pulmonary function [8]. However, none of these studies found an association between OSA and structural spinal changes or restrictive pulmonary disease. It has been suggested that OSA and SpA may share common inflammatory pathways. In OSA, intermittent hypoxia activates nuclear factor-κB which, in turn, stimulates cytokine production, for example TNF-α [40], which results in upper airway inflammation. The inflamed upper airways are more likely to collapse and lead to OSA [41]. OSA patients have high TNF levels which drop after treatment with continuous positive airway pressure (CPAP) [42, 43]. Patients with OSA have also been shown to be at higher risk of developing autoimmune conditions. A longitudinal population study demonstrated a hazard risk of developing an autoimmune disease of 1.91 (95 % CI=1.32–2.77, $P<0.001$) compared with controls [44].

OSA is associated with increased morbidity, for example fatigue and cardiovascular mortality. Awareness of this association and treatment improves patient's QoL and survival [45]. There are no clear guidelines about how to screen for pulmonary manifestations, and the effect of anti-TNF therapy must be studied.

Large prospective studies are needed to determine the true prevalence of OSA in AS, and whether early diagnosis and treatment could alter outcome. Better data are required to support routine pulmonary screening of patients with AS. In the circumstances, a pragmatic approach would be to be aware of, and have a low threshold for, investigation of symptoms suggestive of OSA, for example poor quality sleep, daytime sleepiness, and fatigue, and, if diagnosed, to treat with CPAP (continuous positive airway pressure), smoking cessation, and weight loss.

Renal comorbidities

Renal involvement in AS is a rare but important complication with significant morbidity and mortality (Table 1). Clinical presentation varies from asymptomatic deterioration of renal function, microscopic haematuria, and proteinuria to nephrotic syndrome and end-stage renal failure. Early hospital-based studies and case reports suggest that the most common aetiologies are renal AA amyloidosis (62 %), followed by IgA nephropathy (30 %). Cases of mesangioproliferative glomerulonephritis, membranous nephropathy, focal segmental glomerulosclerosis, and focal proliferative glomerulonephritis have rarely been reported [10, 46-48]. Amyloid nephropathy presents most commonly as significant proteinuria [10], which can progress to nephrotic syndrome and renal insufficiency. Haematuria is unusual in renal amyloidosis but is more common in IgA nephropathy. Nephrotoxicity as a result of long-term NSAIDs is rare if kidney function is normal [50]. However, for patients with impaired renal function, prostaglandin production mediated by cyclooxygenase-1 (COX-1) and COX-2 has a major compensatory effect in maintaining renal haemodynamic function [51]. In these circumstances, inhibition of prostaglandin by NSAIDs may result in serious renal dysfunction [50]. Acute complications, for example fluid and electrolyte imbalance and interstitial nephritis typically occur after 2–18 months of treatment and are more likely to be reversible whereas chronic renal papillary necrosis is irreversible [51].

The literature on renal involvement in AS is sparse and largely consists of case reports and hospital cohorts, which tend to include more severely affected and complex patients and are, therefore, not necessarily generalisable. Renal complications are often difficult to diagnose and may remain asymptomatic until late. Prevalence of renal complications varied between 2 and 13 % [10, 11•, 49, 52], partly because of selection and reporting bias and partly because of how renal complications were defined, for example, what constitutes significant proteinuria, haematuria, and renal impairment, and whether amyloidosis was diagnosed on renal, rectal, or abdominal fat biopsy.

In a recent population-based study (8,616 AS patients and 50,699 controls) of administrative data acquired between 1996 and 2006, the occurrence of renal complications (acute kidney injury, chronic kidney disease, amyloidosis and hypertensive renal disease) was 3.4 % of men and 2.1 % of women with AS compared with 2.0 % of men and 1.6 % of women of the normal population [11•]. Chronic kidney disease and acute kidney injury were the most common complications whereas amyloidosis and hypertensive kidney disease were rare. The overall standardized prevalence ratio for any kidney condition was 1.5 (CI 1.5–2.0). The prevalence of renal complications increased with age, and was higher among men, but the excess risk was greatest among the young. The prevalence ratio was highest among the young (20–39 years), 2.4 (CI 1.4–4.3) for males and 2.8 (CI 1.6–5.0) for females, and lowest in the over-60 years age group, 1.5 (CI 1.2–1.8) for males and 1.0 (0.7–1.4) for females [11•]. In addition, occurrence of hypertension increased the risk of all renal complications in all age groups [11•]. A Brazilian multicentre study of SpA patients identified 1.2 % with IgA nephropathy and chronic haematuria whereas no cases of amyloidosis were reported. A low prevalence of amyloidosis in Latin America has previously been noted [53].

In a retrospective single-centre study, 8 % of 683 AS patients had an abnormal urinalysis: proteinuria (5.9 %), haematuria (2.8 %), or both (0.7 %). Six patients who had >1 g day^{-1} proteinuria underwent a renal biopsy: two were diagnosed with IgA nephropathy, one with amyloidosis, and three with non-specific glomerulonephropathy [49]. In another single-centre study [54], biopsy-proved (renal or rectal) amyloidosis was found in 1.1 % of 730 AS patients. Subclinical amyloidosis in abdominal fat biopsies was identified in approximately 7 % of asymptomatic patients, and after five years 3.65 % showed clinical signs of amyloidosis [55]. Compared with controls, patients with amyloidosis were older [49, 54-56], and had longer disease duration [49, 54, 56], higher disease activity [54, 55], reduced spinal mobility [56], and peripheral arthritis [54]. Further studies are needed to clarify the disease progression of subclinical amyloidosis and whether early detection will affect the outcome.

The outcome for patients with renal amyloidosis is poor and associated with reduced survival [59]. Untreated patients are at risk from end-stage renal disease, infections, heart failure, bowel perforation, or gastrointestinal bleeding. Secondary amyloidosis was the cause of death for 13 % of AS patients who were admitted to hospital [52] although this may be an overestimate because these were probably patients suffering from severe disease. An early study from the Finnish

registry revealed a stable incidence of the number of patients with amyloidosis associated with inflammatory rheumatic diseases requiring renal replacement therapy (RRT) between 1987 and 2002 [58]. Median survival after starting RRT was 2.37 years (95 % CI 1.11–4.31) and five-year survival was 30 % [58]. A more recent study revealed a decline in the incidence of end-stage renal disease as a result of amyloidosis in rheumatic diseases; this probably reflects better treatment [57].

Treatment depends on the aetiology of the renal complication. There is no specific treatment for AA amyloidosis and the treatment should be directed at the underlying source of inflammation. According to the literature, a variety of immunosuppressive drugs have been used to treat AA amyloidosis, including cyclophosphamide, azathioprine, methotrexate, and chlorambucil [59-61]. However, outcome was often unsatisfactory and the potential toxicity of some of these medications was high. Anti-TNF therapy used to control disease activity may reduce the risk of developing amyloidosis in the longer term and may improve survival with established disease [49, 54, 62].

TNF seems to be important in the pathogenesis of amyloidosis, which makes it a potential therapeutic target. TNF enhances IL-1, IL-6, and SAA production by the liver and proteolysis of SAA to AA in macrophages [63, 64]. TNF promotes expression of receptors for advanced glycation endproducts (RAGE), which interact with amyloid fibrils and lead to cytotoxicity and tissue damage by sustained activation of NF-κB [64]. Anti-TNF may reduce amyloid synthesis [65], deposition, and consequent tissue damage [66]. SAA levels dropped after etanercept therapy [61]. Increased levels of serum SAA were found in AS patients with active disease and decreased during anti-TNF therapy [67]. In addition, TNF enhances glomerular inflammation and permeability [68]. Therefore anti-TNF therapy may reduce proteinuria, irrespective of the primary aetiology [69].

The few retrospective case reports and series in the literature looking at efficacy of anti-TNF in amyloidosis and IgA nephropathy associated with rheumatology conditions report variable outcomes. Overall, anti-TNF therapy seems to resolve or reduce proteinuria but the effect on renal function is at best modest. Outcomes from anti-TNF treatment are shown in Table 2. Response was better for patients with normal creatinine levels than for those with renal insufficiency, so pre-treatment renal function may be indicative of the likely efficacy of treatment for renal amyloidosis and glomerulonephritis [49].

The selective increase in serum IgA in both IgA nephropathy and AS, particularly during disease exacerbation, support a common pathogenesis involving IgA-containing immune complexes [71]. IgA and immune complex deposition activate mesangial cells and induce such pro-inflammatory cytokines as IL-6, IL-1, MIP, and TNF-alpha, and further proliferation of mesangial cells and extra-cellular matrix [72]. Evidence of the efficacy of anti-TNF therapy against IgA nephropathy is sparse, and further studies are required. In one report, IgA nephropathy did not respond to biological therapy despite a good response of the rheumatological symptoms [69].

Renal complications may be easily overlooked, particularly among the young. It is, currently, difficult to identify specifically patients at risk of developing renal complications. The patients' interests are probably best served by regular monitoring of renal function and other risk factors predisposing to renal impairment, for example hypertension. Patients with significant proteinuria and haematuria should be properly investigated and, if necessary, undergo a renal biopsy, because this has prognostic and treatment implications. Anti-TNF therapy may be an option in renal amyloidosis and glomerulonephritis. Innovative treatments which reduce SAA levels and amyloid deposition, improve renal function, and reduce proteinuria are needed. Whether anti-TNF therapy is justified solely on the basis of renal complications among patients without active musculoskeletal disease remains to be established. Multicentre prospective trails assessing long-term safety, efficacy, and effect on survival are required to guide the best treatment approach.

Neurology co morbidities

A wide range of neurological complications have been described in AS, including spinal cord or nerve compression as a result of atlantoaxial subluxation or vertebral fractures, cauda equina [73], transverse myelitis [74], and monophasic myelopathy [75]. The potential association of AS and MS has also been debated.

AS patients are at greater higher risk of vertebral fractures and spinal cord injury, particularly of the lower cervical spine, which may be easily missed unless a high index of suspicion is maintained [13-15]. Fractures may occur with minimum trauma, and diagnosis may be delayed as pain may be attributed to disease activity. Vertebral fractures may result in several neurological complications ranging from subclinical neuropathy and myelopathy to paraparesis and tetraparesis [76].

AAS is a complication which rarely occurs as the first presentation [77]. AAS, defined by an anterior atlantodental interval >3 mm, was found in 14 % (n=819) of patients and progression occurred in 32 % [12]. Similar progression was noted in another study after a two-year follow up [78]. The presence of peripheral arthritis, raised CRP, and failure of anti-inflammatory medication resulted in an increased risk of developing AAS [12]. Approximately a third presented with neck pain , another third with cranial neuropathy, and up to two thirds with sensory disturbance [79]. The most common clinical signs were myelopathy (75 %), weakness (50 %), and limited cervical movement (37 %). Early

Table 2 Studies of the efficacy of anti-TNF therapy for amyloidosis and glomerulonephritis. The first three studies consisted only of AS patients whereas the last two included patients with other types of inflammatory arthritis

	Number of AS patients	Renal pathology	Anti-TNF	Outcome						Length of treatment (months)
				Proteinuria			Renal function			
				Improved	Stable	Worse	Improved	Stable	Worse	
AS only studies										
Lee 2013 [49]	6	1 amyloidosis	ETA	1			Not available			12
		2 IgA nephropathy	INF, ADA	1	1					
		2 GN	INF, ETA	2						
		1 GBM disease	ADA		1					
Kobak 2007 [62]	3	Amyloidosis	ETA	3				3		12
Donmez 2013 [54]	6[a]	Amyloidosis	INF, ETA, ADA	4			1	4	1	Range 6–36
Inflammatory arthritis studies										
Fernandez Nebro 2005 [70]	5	Amyloidosis	ETA, INF	2	1	1	1	4		Range 6–24
Gottenberg 2003 [66]	6	Amyloidosis	INF, ETA	3	1	2	2	3	1	Range 3–18

[a] Two patients did not have proteinuria

Glomerular basement membrane disease (GBM), glomerulonephritis (GN), end stage renal failure (ESRF), etanercept (ETA), infliximab (INF), adalimumab (ADA)

recognition and surgical stabilisation is the basis of treatment to prevent spinal cord compression.

Coexistence of AS and multiple sclerosis (MS) has rarely been reported. A potential association has significant implications for disability and QoL and poses a significant treatment challenge. Although this association was reported more than three decades ago [80], whether this is a true association is still unclear [81, 82•]. Several reports and case series continue to be reported, possibly reflecting heightened awareness. To date, no definitive population case–control studies have emerged. More recently the link has received greater attention with regard to an increasing number of cases of demyelination and MS among AS patients receiving anti-TNF therapy [83-85].

The aetiologies of AS and MS are largely unknown but probably result from interaction of genetic, epigenetic, and environmental factors. Autoimmune diseases comprise a wide range of disorders which often overlap and are usually of unknown aetiology. MS is characterised by inflammation, demyelination, and axon degeneration whereas AS is characterised by inflammation and new bone formation affecting predominantly the spine and entheses. Several reports have suggested that patients and their families are prone to more than one autoimmune condition which supports the case for a common aetiological pathway which is currently unknown [86, 87]. Although MS is primarily an organ-specific autoimmune disease, it might arise from a general increased susceptibility to autoimmunity. In a hospital case study of 155 MS patients and 200 controls greater prevalence of RA and psoriasis was observed (OR=2.96, 95 % CI 1.23–7.66) [88]. Clustering of multiple autoimmune diseases has been demonstrated for some conditions, for example diabetes mellitus and RA, but seems to be less strong for AS [87].

The HLA region encodes several molecules crucially involved in a variety of autoimmune diseases. The association of HLA-B27 and AS has been well described. Other non-MHC genetic associations have emerged in AS, for example IL23R and ERAP1, which is now known to be restricted to HLA-B27-positive patients [89]. MS, however, is primarily linked to HLA-DRB1 [90]. Genome-wide association studies suggest that many other non-MHC genes may be involved in MS. IL-23(IL-12B) and IL-23R gene single nucleotide polymorphisms (SNP) were found to increase susceptibility to MS in some studies but not others [91, 92].

MS is largely T cell-driven by Th 1, Th 17 (mediated in part by IL23), and regulatory T cells [93]. Involvement of the IL12B/IL23R pathway in MS is supported by immunological studies [94]. The TNF and IL23/IL17 inflammatory pathways are important in AS [95]. In fact, TNF inhibition has been a major achievement in the treatment of AS. The involvement of TNF in MS is complex and poorly understood. TNF seems to have pro-inflammatory and immunosuppressive function, suggesting a pleitropic role of TNF in CNS damage and repair [96]. Whereas TNF inhibition improved demyelination in murine studies [97] in two older studies it failed or even exacerbated MS in humans [98, 99].

Over the years, several case reports have been published describing both AS and possible or definite MS in the same patient [80, 100-105]. Increased occurrence of abnormal evoked potentials in AS patients has been suggested [106], but this was not confirmed by other studies [107]. In the vast majority of the cases AS preceded diagnosis of MS and did

not seem to alter the clinical course of MS. The largest case series included 21 cases of co-existing SpA (17 cases fulfilled the New York criteria for AS) and MS [82•]. In two thirds of cases diagnosis of SpA (mean age 37 years, range 18–58) preceded diagnosis of MS (mean age 36 years, range 21–50). The estimated prevalence of SpA in MS in this study was 0.7 %.

To enable interpretation of increased prevalence and incidence of AS and MS coexistence it is important to study the prevalence of MS and AS in the general population. MS prevalence varied geographically from 0/100,000 to 350/100,000 and the mean prevalence was 67.83/100,000 [108]. The mean AS prevalence ranged from 74/100,000 in Africa to 319/100,000 in North America [2]. Taking into account prevalence in the general population, the likelihood of reporting bias, and the possible generally increased susceptibility of these patients to autoimmune conditions, the overall number of case reports published thus far argues against a true association, and the likelihood of developing both AS and MS may still occur purely by chance [81].

A causal relationship with MS after anti-TNF therapy remains unclear. Several mechanisms have been proposed; anti-TNF may cause demyelination or unmask latent disease, or patients maybe predisposed to develop MS irrespective of exposure [96]. Several case reports have been published implying causality on the basis of chronology, improvement of signs and symptoms after withdrawal, and recurrence on rechallenge. For a quarter of patients demyelination persisted after drug withdrawal, suggesting that anti-TNF therapy could initiate the demyelination process, which then progresses irrespective of anti-TNF therapy [85]. It is, however, possible that these patients would have developed demyelination anyway. Data from the Food and Drug Administration Adverse Event Reporting System (FAERS), clinical trials, and observational studies failed to prove a definitive association and the number of cases does not seems to exceed that which might be expected in the general population [109].

AS patients with neurological signs and symptoms should be thoroughly investigated for such structural complications as AAS, vertebral fractures, peripheral neuropathies, myelopathy, and cauda equina, irrespective of any history of trauma. Because vertebral fractures are notoriously missed on plain films, further imaging with CT scan and MRI maybe needed. Although the association of demyelination and AS remains unproved, it is still important to bear the possibility of MS in mind, particularly in the context of anti-TNF treatment. Given that anti-TNF can potentially cause or exacerbate demyelination, its use for patients with MS or atypical demyelination should be discouraged. Patients who develop neurological symptoms whilst on anti-TNF therapy require proper evaluation; in addition to stopping anti-TNF therapy, specific neurological expertise should be sought.

Conclusion

AS is a chronic multisystem disease often associated with multiple comorbidities which add to the burden of the disease. This poses a substantial challenge from the perspectives of diagnosis, management, and healthcare costs. In addition to the well-known extra-articular features, uveitis, psoriasis, and inflammatory bowel disease, increased cardiovascular risk, and osteoporosis, emerging evidence supports the association of important respiratory, renal, and neurological complications which deserve equal attention. Regular monitoring of renal function and hypertension seems a reasonable approach, particularly for patients on long term NSAIDs, given that renal involvement is often asymptomatic in the early stages. Renal amyloidosis and glomerulonephritis are rare but may respond to anti-TNF therapy. Although the significance of lung parenchymal abnormalities among asymptomatic individuals is yet to be determined, patients with respiratory symptoms require further investigations and studies are required to determine the best treatment approach. The association of AS and demyelination remains to be proved and may be explained by chance. AAS and vertebral fractures are important complications with high morbidity and mortality which may be difficult to diagnose unless high suspicion is maintained. Physicians should be aware of these comorbidities when treating AS patients, take them into account when designing management plans, and refer to other specialists, when required, in a timely manner.

Compliance with Ethics Guidelines

Conflict of Interest Cecilia Mercieca, Irene E. van der Horst-Bruinsma, and Andrew A. Borg declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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