

Non-radiographic axial spondyloarthritis: a classification or a diagnosis?

Sirs,

The ASAS classification criteria (1, 2) were developed because the modified New York (mNY) criteria (3) and the ESSG criteria (4) were not sensitive enough to identify patients with early axial spondyloarthritis (axSpA). Another major reason to initiate the development of new classification criteria was the efficacy of biologics targeting TNF- α (5-9). Furthermore, the capacity of magnetic resonance imaging (MRI) to detect sacroiliitis and spondylitis was demonstrated (10, 11), and definitions for the evaluation of MRI findings have been proposed (12, 13). Based on the ASAS criteria, axSpA patients have been differentiated in being 'radiographic' (AS) or 'non-radiographic' (nr-axSpA) depending on the presence or absence of structural changes in the sacroiliac joints (SIJ). In this letter we discuss the major problems and propose not to use this terminology for diagnosis.

Since structural changes in the SIJ are present in almost all patients with AS (3), many rheumatologists have used this also for diagnosis – despite evidence that AS may manifest with only spinal changes (14). The validity of the mNY criteria has been recently challenged because the quantification of structural SIJ changes is hardly reproducible when no clear-cut erosions and/or ankylosis are present, and this can not even be improved by education (15). However, there was no better proposal, and syndesmophytes, although of help for diagnosis in individual cases (14), have never been considered suitable for classification because the differentiation towards spondylophytes is reportedly difficult (16). The best method to detect structural changes in the SIJ is computed tomography (CT, 17), but this has never been promoted because of the radiation exposure. This may change with low dose CT techniques (18).

The main reason, why this whole topic has recently attracted attention is that anti-TNF agents approved for AS are now aimed for approval for nr-axSpA. This has focused the interest on the 'cut-off' between nr-axSpA and AS – e.g. 'definite' structural changes in the SIJ. Using this cut-off has different implications – for example that axSpA patients have to be excluded even from studies in early disease if their structural SIJ changes are scored

as 'definite'. This has induced much discussion on whether local or central reading of radiographs is the method of choice to perform this task. The methodological challenges have been recently well described (19, 20). While central reading may be more reliable, local reading, closer to daily practice, may better allow for individual corrections especially for age – a potentially important factor (13). As a matter of fact, disagreement between local and central readers but also between central readers has been reported to occur in 20–30 % of cases (19, 20). The experience in the first nr-axSpA trial (9) was even that the central revised the local judgement in 50% of cases. Since this questioned the 'diagnosis' of nr-axSpA, adalimumab did not get approval for nr-axSpA in the USA. Somewhat earlier the EMA had decided differently (9). Importantly, one study clearly showed that the response rates in AS and nr-axSpA are almost identical (7), and major differences between these subgroups except for gender and inflammation were also not found in other studies (22). However, in contrast to AS, anti-TNF approvals for nr-axSpA are restricted to patients with elevated CRP or positive MRI (21).

Unfortunately, the actual definitions do allow SpA patients to be classified as 'non-radiographic' in the presence of syndesmophytes if their SIJ show no definite changes. On the other hand, patients without definite changes in the SIJ may have spinal inflammation as depicted by MRI (23) – these are currently not classified as axSpA, since there is increasing evidence for substantial 'background noise' of positive MRI findings, often due to Modic lesions (24, 25). Their impact on a 'positive MRI' in axSpA (12, 13) is incompletely understood, and inclusion of spinal inflammation into classification criteria is currently not supported by ASAS.

However, the specificity of the ASAS classification criteria could be improved by adding 'exclusion of other diagnoses' as it is also the case for RA (26). Hereby, the significance of important differential diagnoses such as degenerative disc disease, infectious sacroiliitis and spondylitis, rarely lymphoma and fractures which may all cause bone marrow oedema in the axial skeleton would be stressed (27, 28). Thus, even though the rheumatologist can refer to the ASAS classification criteria to make a diagnosis of axSpA, this should not be used to prove that somebody 'really' has the disease. On the other hand, one can provide reasons why the diagnosis

was made even though the criteria were not fulfilled (29) – this is the difference between classification (for groups) and diagnosis (for individuals).

What does all this matter in daily clinical practice? In our opinion a great deal, since an artificial cut-off to differentiate between axSpA subgroups is clearly not needed if there is enough reason to diagnose axSpA. However, what seems much more important than the discussed cut-off for conventional radiographs of the SIJ is the time until the first structural changes appear. After 2 years of inflammatory back pain (30), 20–30% of axSpA patients already have radiographic changes in the SIJ (31). Thus, if nr-axSpA trials attempting for early interventions use the NY criteria to exclude AS, 20–30% of the potentially severe patients risk, by definition, not being included in the trial! Therefore, if the aim is early treatment, it should be rather the duration of symptoms than the presence of structural changes in the SIJ that needs to be considered as the most important parameter for patients with axSpA.

Taken together, in clinical practice there is no need to differentiate between a diagnosis of nr-axSpA and AS, since the only reason and purpose is classification. Fortunately, established recommendations for management of axSpA have already widened the disease spectrum considerably (32, 33). Finally, there are exceptions – a formal differentiation between nr-axSpA and AS may become necessary related to (i) an indication for anti-TNF therapy, when off-label use of for nr-axSpA not approved biologics may need to be avoided, and (ii) in insurance cases where the question of structural changes being present or not may become very relevant for patients.

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