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Place de l'IRM dans le diagnostic des spondyloarthrites et évaluation de l'intérêt de l'injection de gadolinium : étude prospective monocentrique sur une période de 5 ans

Raphaëlle Meunier

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THESE POUR L'OBTENTION DU

DIPLOME D'ETAT de DOCTEUR EN MEDECINE

Présentée et soutenue publiquement

Par MEUNIER Raphaëlle

Née le 15 juillet 1992 à Bordeaux

Le 4 octobre 2019

**PLACE DE L'IRM DANS LE DIAGNOSTIC DES
SPONDYLOARTHRISES ET EVALUATION DE L'INTERET
DE L'INJECTION DE GADOLINIUM :
étude prospective monocentrique sur une période de 5 ans**

Sous la direction de Madame le Docteur Marie-Elise TRUCHETET

Membres du jury :

Monsieur le Professeur Christophe RICHEZ
Monsieur le Docteur Jean-Philippe VERNHES
Madame le Docteur Marie-Elise TRUCHETET
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LISTE DES ABREVIATIONS

Françaises

SpA = Spondyloarthrite

ASAS = Assessment of SpondyloArthritis international Society

Anglaises

SpA = Spondyloarthritis

ASAS = Assessment of SpondyloArthritis international Society

TNFi = Tumor necrosis factor inhibitors

SI = Sacroiliac

STIR = Short-tau Inversion Recovery

FS = Fat-saturation

NSAIDs = Non-steroidal anti-inflammatory drugs

IQR = Interquartile range

INTRODUCTION

La spondyloarthrite (SpA) est un rhumatisme inflammatoire complexe pouvant avoir différentes présentations phénotypiques rendant l'approche diagnostique difficile (1). En effet, elle combine de façon variable un syndrome axial, un syndrome articulaire périphérique, un syndrome enthésopathique et un syndrome extra-articulaire (uvéite, psoriasis, urétrite, entérocolopathie inflammatoire). Depuis quelques années, la classification a changé pour être plus proche des décisions thérapeutiques qui sont les conséquences directes du diagnostic (2–4). On distingue la SpA axiale radiographique ou non radiographique et la SPA périphérique articulaire ou enthésitique, associées ou non à des manifestations extra-articulaires.

Le diagnostic précoce de SpA est devenu un enjeu majeur pour le rhumatologue, depuis la mise à disposition des biothérapies dans les années 2000. En effet, les agents anti-tumor necrosis factor sont plus efficaces dans les formes récentes de la maladie et ont montré leur intérêt dans les formes pré-radiographiques de SpA (5,6). En revanche, leur prescription nécessite un diagnostic certain du fait de leur coût et de leurs potentiels effets indésirables.

L'imagerie occupe une place prépondérante dans l'algorithme diagnostique de la SpA. La radiographie standard représentait jusqu'alors la clé de voute du diagnostic de certitude dans les critères de New York modifiés publiés en 1984 (7). Ces critères permettaient de retenir le diagnostic en présence d'une sacro-iliite de grade 2 bilatérale ou de grade 3 unilatérale au minimum, associée à un critère clinique. C'est ainsi qu'en moyenne, il existait un délai de 5 à 8 ans entre les premiers symptômes et le diagnostic de certitude, correspondant au délai d'apparition des signes radiographiques de sacro-iliite.

Depuis 2009, les critères de l'Assessment of SpondyloArthritis international Society (ASAS) intègrent **l'IRM des sacro-iliaques** comme technique d'imagerie la plus pertinente pour le diagnostic et la classification de SpA axiale précoce pré-radiographique (8). L'œdème osseux suffit à définir la sacro-iliite à l'IRM s'il est présent sur au moins deux coupes consécutives en cas de localisation unique ou une seule coupe en cas de localisations multiples. Si elle est associée à au moins un critère clinique, le diagnostic de SpA peut alors être retenu avec une sensibilité de 97,2 % et une spécificité de 94,2 %.

Les critères ASAS ne prennent pas en compte **l'IRM du rachis**, alors que 15 à 30% des patients ayant une SpA ont une atteinte axiale sans atteinte des articulations sacro-iliaques (9–12). De même, l'injection de gadolinium n'est pas recommandée car elle ne sensibilise pas la détection des anomalies osseuses inflammatoires décrites dans ces critères.

Le protocole habituellement réalisé devant une suspicion clinique de SpA comprend des coupes T1 et T2 en saturation de graisse ou Short-tau Inversion Recovery (STIR), des articulations sacro-iliaques dans un plan coronal oblique mais aussi du rachis dorso-lombaire dans le plan sagittal.

Différentes lésions rachidiennes inflammatoires peuvent être retrouvées en IRM sur les corps vertébraux et l'arc postérieur rachidien (13). Au niveau des corps vertébraux, on décrit la spondylite antérieure et postérieure se manifestant sous forme d'un aspect inflammatoire des coins vertébraux et la spondylodiscite d'Andersson. Dans les éléments postérieurs, une atteinte articulaire (l'arthrite costo-vertébrale ou costo-transversaire, l'arthrite zygapophysaire postérieure) ou une atteinte enthésitique ligamentaire (des ligaments sus-épineux, inter-épineux ou ligaments jaunes) peuvent être retrouvées.

La mise en évidence de ces localisations enthésitiques du rachis et de la portion syndesmote des articulations sacro-iliaques, peut être sensibilisée par l'injection de gadolinium grâce à la diffusion du produit de contraste par l'hypervascularisation en lien avec l'inflammation.

Cependant, l'intérêt de l'étude des éléments postérieurs du rachis et de la réalisation systématique de séquences injectées restent controversés dans le diagnostic initial des SpA. En effet, il est décrit que les lésions rachidiennes manquent de spécificité car elles peuvent souvent être confondues avec des anomalies dégénératives. De plus, la séquence injectée a pour inconvénients d'être plus invasive, d'allonger le temps de l'examen et n'est pas totalement dénuée d'effets secondaires (14–16).

Nous avons mené une première étude en 2013 afin de déterminer la valeur de l'injection de gadolinium pour le diagnostic de SpA grâce à la détection de lésions actives du rachis et des sacro-iliaques. Pour cela, les IRM avec et sans injection de produit de contraste des patients consultant pour suspicion de SpA ont été relues de manière centralisée par 3 radiologues différents, en aveugle du diagnostic posé à la consultation. Cependant, le rhumatologue qui décidait du diagnostic à cette époque disposait des données cliniques et biologiques mais également des premières conclusions de l'IRM, interprétée avant la relecture réalisée pour

l'étude. Du fait de cet important facteur de confusion, il nous manquait un « gold standard » solide et indépendant, ce qui constituait donc la principale limite de ce travail. Nous avons décidé de prolonger cette étude pendant 5 ans pour réévaluer le diagnostic grâce à l'évolution des données cliniques et de la réponse thérapeutique. Le diagnostic après 5 ans de recul (critère composite prenant en compte de multiples paramètres) est donc le critère que nous avons choisi pour évaluer la performance de l'IRM avec ou sans produit de contraste réalisée en 2013.

L'objectif principal de notre étude est de préciser la performance diagnostique de l'IRM du rachis et des sacro-iliaques en 2013 et après 5 ans de recul dans le diagnostic de SpA, en prenant en compte l'évolution clinique et la réponse au traitement.

Nous avons également évalué l'intérêt de l'injection de gadolinium dans le diagnostic de SpA par la détection des anomalies des territoires enthésitiques du rachis et des articulations sacro-iliaques.

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ARTICLE SCIENTIFIQUE

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ROLE OF MRI IN THE DIAGNOSIS OF SPONDYLOARTHRITIS AND EVALUATION OF THE BENEFIT OF GADOLINIUM INJECTION: A 5-YEAR PROSPECTIVE CLINICAL STUDY

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Abbreviations

SpA = Spondyloarthritis, ASAS = Assessment of SpondyloArthritis international Society, TNFi = tumor necrosis factor inhibitors, SI = Sacroiliac, STIR = Short inversion time inversion recovery, FS = Fat-saturation, NSAIDs = Non-steroidal anti-inflammatory drugs, IQR = Interquartile range

Summary

The sensitivity of MRI is increasingly used to make the diagnosis of spondyloarthritis during the 5-year follow-up and the gadolinium injection has the benefit to show a subgroup of patients with enthesitis, representing 20% of patients with spondyloarthritis.

Key points

- Between 2013 and 2018, the rheumatologist's diagnostic expertise have led to the decrease in the number of patients with spondyloarthritis from 60% to 40%, combined with an increase of sensitivity despite a decrease of specificity of the initial MRI.
- The injection of gadolinium alone had the same diagnostic performance with increased sensitivity and decreased specificity, verses non contrast enhanced MRI.
- The use of contrast enhanced MRI enabled identification of a subgroup with enthesitis lesions, representing 20% of the spondyloarthritis population in 2018.

ABSTRACT

Background : The performance of spinal MRI for the diagnosis of spondyloarthritis (SpA) is still contentious. However, MRI with injection of gadolinium could be more sensitive in demonstrating sites of enthesitis improving diagnostic strategy.

Purpose : To evaluate the performance of the MRI in 2013 with and without injection of contrast compared to the clinical evolution, 5 years after the initial diagnosis and to assess the benefit of the gadolinium injection in the SpA diagnosis strategy.

Materials and Methods : In this single-center prospective study, 165 patients with chronic low back pain who underwent both spinal and sacroiliac (SI) joints MRI in our radiology department were recruited between May 2013 and January 2014. Clinical, biological and radiologic parameters were collected. Three independent readers identified the presence of specific radiological features of SpA by using a five-point Likert scale to record the estimation of confidence. The centralized MRI interpretation from 2013 was compared to the established diagnosis in 2013 and at 5-year follow-up. The nonparametric Mann-Whitney, Fisher and McNemar X^2 tests were conducted to compare quantitative and qualitative variables and sensitivity and specificity respectively.

Results : A total of 145 patients were included in the final analysis. During the 5 years of follow-up, between 2013 and 2018, the evaluation by the rheumatologist led to a decrease of patients with SpA diagnosis from 93 to 58. Sensitivity of MRI realized in 2013 was increased and specificity was decreased. Compared to MRI without contrast, injection of gadolinium improved sensitivity but not specificity. By revealing enthesitis, the use of contrast injection increased correct diagnosis of SpA by 20% after 5 years of follow-up.

Conclusion : The injection of gadolinium improve the visualization of enthesitis, including spinal posterior elements and increase the sensitivity of the MRI in some doubtful cases of SpA.

Keywords : Spondyloarthritis, MRI, Gadolinium, Enthesitis

INTRODUCTION

Spondyloarthritis (SpA) is a complex inflammatory rheumatic disease with heterogeneous clinical presentation (1), making diagnosis challenging. The early diagnosis of SpA has become a major issue for rheumatologists, since the marketing of biotherapies in the 2000s. Indeed, patients fulfilling the Assessment of SpondyloArthritis international Society (ASAS) criteria for SpA can be treated with tumor necrosis factor inhibitors (TNFi) (2) in order to avoid the progression of structural damage (3) and long-term disability.

Imaging is a key component for classification of SpA, primarily due to the lack of specific clinical symptoms as well as varying disease activity over time. Initially, the modified New York criteria for the diagnosis of SpA published in 1984 (4) combined different clinical criteria with structural changes on conventional radiographs. However, this classification was unable to detect early form of the disease, because of the delay of appearance of radiographic damage (five to eight years). Since 2009, the ASAS criteria (5) included inflammation in the sacroiliac (SI) joints, represented by a bone marrow edema on MRI, as one of the major entry criteria. Indeed when early SpA is strongly suspected but standard radiographs of the SI joints are normal, MRI is increasingly recommended, demonstrating a significant evolution in the diagnosis strategy (6).

The preferred MRI protocol is Short-tau Inversion Recovery (STIR) or fat-suppressed (FS) sequences to assess for bone marrow edema and early signs of inflammation in the SI joints. Spinal MRI is not required to diagnose SpA, although acute inflammation can affect only the spine and spare the SI joints. The injection of gadolinium is not currently recommended because it does not increase the detection of bone marrow edema described in the ASAS criteria. Different inflammatory types of lesions are described on a spine MRI (7) notably enthesitis, frequently seen in the spinal ligaments. Posterior elements lesions on STIR images are less frequent than spondylitis in SpA but are highly specific (8) and their diagnosis can be improved by the injection of gadolinium.

We conducted our first study in 2013 in order to determine the added value of gadolinium injection to detect active spinal and SI joints lesions that may be suggestive of SpA. However, diagnosis of SpA made by the rheumatologist rested heavily on MRI data and it constituted main limit of this study. To overcome this diagnosis bias, we decided to extend the study and reconsider the diagnosis after 5 years of clinical evolution. We evaluated the

concordance between this new diagnosis in 2018 and the initial MRI in 2013 in order to estimate the performance of the first examination.

The objectives of this study are to evaluate the accuracy of the initial 2013 MRI in relation to the clinical evolution, 5 years after the first diagnosis and to assess the added value of gadolinium injection to MRI in the SpA diagnosis strategy.

MATERIALS AND METHODS

Participants and study design

A single-center prospective study was conducted on patients presenting chronic low back pain addressed to the rheumatology department of Bordeaux University Hospital or followed by a private rheumatologist in the region and who underwent a spinal and SI MRI in the radiology department of the Bordeaux University Hospital between May 2013 and January 2014.

To be included, patients had to be 16 years or older, with a back pain having started before they were 45 years old and which lasted for more than 3 months. Exclusion criteria were: contraindications for MRI examination or gadolinium injection and history of spinal surgery with metal implants. A total of 165 consecutive participants were included and underwent MRI examination. Informed consent was obtained from all patients included in the study for the use of clinical data.

Clinical data collection

The following demographic, clinical and biological data were collected: sex, date of birth, age at first symptom of back pain and at time of diagnosis consultation, duration and characteristics of back pain, personal history of arthritis, personal or family history of uveitis, inflammatory bowel disease and psoriasis, family history of SpA, non-steroidal anti-inflammatory drugs (NSAIDs) or biotherapy sensitivity and blood parameters such as Human Leucocyte Antigen B27 and C-reactive protein rate at diagnosis or relapse.

Data was collected using a standard data extraction form via the bioinformatics service of the hospital. When data was not available, the investigator (R.M.) contacted the specialist in charge of the patient and ultimately the patient himself.

The initial diagnosis was confronted to disease course outcome after 5 years.

With this information, patients were classified as having or not having SpA. If no consensus was reached on the diagnosis, the case was reviewed with an experienced rheumatologist (M.E.T.).

Imaging procedures and interpretation

MRI examinations were performed with a 3T magnet (General Electric Discovery MR-750W, Milwaukee, USA).

The imaging protocol included coronal-oblique T1-weighted and T2-FS sequences of the SI joints and sagittal T1-weighted and T2 FS sequences of the thoracolumbar spine (from T7 to S3). Gadolinium-enhanced T1-weighted FS sequences were performed on SI joints (coronal plane) and thoraco-lumbar spine (sagittal plane). Imaging protocol is summarized in Table 1.

Three radiologists (O.H., C.F., B.D., having 15, 10 and 1 year of experience in musculoskeletal imaging respectively and hereinafter referred to as reader 1, 2 and 3) performed the MRI interpretations in 2013, without knowledge of clinical and biological data. Readers 1 and 3 evaluated all the sequences starting first with the non-injected sequences and then following the complete protocol with injection. Reader 2 only dealt with the T1-Gadolinium sequence in order to evaluate the performance of the injection alone. Imaging was examined in a random order with a time interval of 3 to 5 weeks. A double-blind reading of the whole imaging was done for interobserver agreement. To assess the intraobserver agreement, reader 3 performed a second blinded reading after 3 months.

Basis for interpretation

MRI interpretation was based on standard recognized criteria (5) and on a semiotic atlas (developed from the literature and images of our radiology department) describing and illustrating spinal and SI involvement in SpA.

A five-point Likert scale was used to record the radiologists' estimates of confidence in specific radiological features and overall diagnosis. It considered 5 options: 1 = no abnormality (whether inflammatory, structural or sequelar), 2 = non inflammatory abnormalities, 3 = doubtful abnormalities, 4 = abnormalities evocative of SpA but not included in ASAS criteria, 5 = abnormalities included in ASAS criteria (i.e. sacroiliitis) (Table 2). Readings were classified

as positive for SpA if the Likert score was equal to or greater than 4, otherwise they were classified as negative.

The MRI interpretation from 2013 was compared to the clinical diagnosis made by the rheumatologists in 2013 and in 2018, after 5 years of follow-up.

Statistical analysis

Clinical analysis

Quantitative variables were presented as mean with standard deviation or as median with interquartile range (IQR), qualitative variables were presented as numbers and percentages. The nonparametric Mann-Whitney test was used to compare quantitative variables and the Fisher exact test was used for qualitative variables. Calculations were performed with STATA 13.1. P-values less than 0.05 were considered significant.

Radiologic analysis

Internal consistency was explored by calculating Cronbach's alpha. Receiver operating characteristic curves were obtained using the Likert scale as the test variable and the clinical result as the outcome variable. The McNemar χ^2 test was used to compare sensitivity between diseased patients and specificity between healthy individuals. Adjustment was performed for multiple pairwise comparisons of methods by Bonferroni adjustment. Linear weighted k coefficients were used to assess interobserver agreement. The k value was interpreted less than 0.40 as a fair agreement, between 0.41 and 0.60 as a moderate agreement, greater than 0.60 as a substantial agreement. Mean k coefficients across all possible combinations of the three readers was calculated. Calculations were performed with STATA 12. P-values less than 0.05 were considered significant.

RESULTS

Among the 165 participants included in the study (Figure 1), 11 were excluded because of an incomplete or suboptimal MRI (exam stopped prematurely n = 5, no spinal exam n = 5, too many artifacts n = 1), while 9 patients were lost to follow-up between 2013 and 2018;

therefore 145 patients were included in the final analysis. Characteristics of the participants in 2013 and in 2018 are shown in Table 3.

Of interest, the studied population counted more women ($n = 98/154$, 63% in 2013 and $93/145$, 64% in 2018). The most prevalent articular symptom was inflammatory low back pain ($n = 136/150$, 91% in 2013 and $n = 130/144$, 90% in 2018).

During the follow-up, 62 patients tried a TNFi, 39 had a second TNFi, 19 had a third TNFi, 10 had a fourth TNFi, 5 had a fifth TNFi and only one had a sixth TNFi. In 2018, 30 patients were still undergoing treatment. Reasons to change treatment were inefficacy, appearance of side effects or remission. In 2018, only one patient was treated by an IL12/23 antagonist (ustekinumab) and one by an IL17 inhibitor (secukinumab). Between 2013 and 2018, 2 other patients were treated by an IL17 inhibitor (secukinumab) which was later stopped as it turned out to be inefficient.

MRI performance compared to the clinical evolution of patients over 5 years.

In 2018, the diagnosis of SpA was maintained by the rheumatologist for 57 patients versus 93 in 2013 and conversely only one SpA was diagnosed during the follow-up, corresponding to 40% vs. 60% of the global population. Hence, the diagnosis of SpA had not withstood the test of time in 33 patients while 3 initial SpA were lost to follow-up. Among the patients diagnosed SpA in 2018, there were more women ($n = 36/58$, 62%). The most prevalent articular symptom was inflammatory low back pain ($n = 55/58$, 95%) followed by arthritis ($n = 22/58$, 40%). Their characteristics are described in Table 3. Table 4 compares final clinical diagnosis in 2013 and 2018. Main differential diagnosis were degenerative spinal lesions and fibromyalgia.

MRI classification according to the Likert scale and compared to clinical diagnosis after 5-year follow-up is found in Table 5. Sacroiliitis as defined in ASAS criteria (= Likert 5) was diagnosed for 11 patients by reader 1, 17 patients by reader 2 and 14 patients by reader 3. Among them, clinical diagnosis of SpA was established in 2018 for 8, 13 and 13 patients respectively. We observed that 15 patients with SpA (26%) had only spinal involvement without sacroiliitis.

Regarding to patients classified Likert 4 and 5, the sensitivity of MRI for the diagnosis of SpA increased from 37.63% (IQR [32.74-42.80]) in 2013 to 46.55% (IQR [37.74-55.59]) in 2018 and specificity decreased from 91.80% (IQR [82.85-96.29]) to 86.21% (IQR [79.35-

91.04]) for reader 1. In addition, sensitivity increased from 24.73% (IQR [21.26 -28.58]) to 36.21% (IQR [29.65-43.32]) and specificity decreased from 96.72% (IQR [88.51- 99.12]) to 95.52% (IQR [87.99-98.42]) for reader 3. MRI accuracy of SpA detection in 2013 and after 5-year follow-up are shown in Table 6. Internal consistency of the Likert rating scale was excellent and sufficiently high for certification purposes (Cronbach's alpha = 0.85). Inter-observer agreement for SpA diagnosis was fair between readers 1 and 3 ($k = 0.37$).

The benefit of gadolinium injection in the diagnosis of SpA : revelation of spinal enthesitis.

Contrast injection revealed that 27 patients had inflammation in spinal posterior elements, sorting them into Likert 4 i.e. abnormalities evocative of SpA but not included in ASAS criteria.

Before injection, 14 out of the 27 patients were classified as Likert 1 or 2 (group 1-2) i.e. no abnormalities or non-inflammatory abnormalities and 13 were classified Likert 3 (group 3) i.e. doubtful abnormalities. Figures 2 and 3 illustrate the change in MRI for the 2 subgroups. For the purpose of analysis, we compared these groups to the rest of the population considered as the control group (group 0). Their demographic and clinical characteristics are compared in Table 7.

In group 1-2, 8 out of 14 patients were diagnosed with SpA in 2013 while only 5 were still diagnosed with SpA in 2018 and while one was lost to follow-up. In addition, the SpA diagnosis was made for one patient formerly not identified with the disease. These 6 patients put together represented 10% (6/58) of SpA patients at the end of the follow-up. 5 of them were women and all patients presented inflammatory low back pain. One patient presented arthritis, another one had uveitis and two had psoriasis. However 3 patients did not respond to NSAIDs. 3 patients had received TNFi between 2013 and 2018: 2 were still undergoing treatment in 2018 and one discontinued permanently the biotherapy due to side effects. There were more women ($p = 0.03$) and uveitis ($p = 0.048$) in this group compared to the control group.

In group 3, 10 out of 13 patients were diagnosed SpA in 2013 of which 6 were still diagnosed with SpA in 2018, corresponding to 10% (6/58) of SpA population. One patient initially diagnosed with fibromyalgia was lost to follow-up. There were 4 women all of whom presented inflammatory low back pain and had a good response to NSAIDs ($n = 5/6$, one missing data). Only 2 patients had arthritis, another one had uveitis and yet another one had psoriasis. 3 patients received TNFi and were still treated in 2018. There was no significant

statistical difference between this group and the control group, concerning their demographic and clinical characteristics.

Regarding these data, sensitivity was better with than without injection for reader 1 (46.55% IQR [37.74-55.59] vs 62.07% IQR [52.02-71.18] in 2018) and reader 3 (36.21% IQR[29.65-43.32] vs 44.83% IQR [36.22-53.76]). Considering the injected sequence only, the sensitivity increased even more after 5 years of follow-up (from 50.54% IQR [44.49-56.57] to 62.07% IQR [52.02-71.18] for reader 1, from 48.39% IQR [42.70-54.12] to 58.62% IQR [48.92-67.70] for reader 2 and from 32.26% IQR [27.37-37.57] to 44.83% IQR [36.22 -53.76] for reader 3). However, specificity decreased between 2013 and 2018 from 81.97% (IQR [72.08- 88.89]) to 77.01% (IQR [69.80- 82.92]) for reader 1 and from 90.16% (IQR [80.89- 95.21]) to 83.91% (IQR [76.78- 89.16]) for reader 2, but increased from 86.89% (IQR [77.63- 92.67]) to 87.36% (IQR [80.57- 92.01]) for reader 3. For the three readers, specificity was worse with than without injection.

After contrast injection, inter-observer agreement between readers 1 and 2 was substantial ($k = 0.72$) but moderate between readers 1 and 3 ($k = 0.47$) and readers 2 and 3 ($k = 0.42$). Intra-observer agreement was substantial between the 2 readings of contrast-enhanced MRI performed by reader 3 (0.75).

DISCUSSION

The present study showed that the sensitivity of MRI for the diagnosis of SpA increases during the 5-year follow-up while the specificity decreases. The use of contrast injection increases correct diagnosis of SpA by 20%.

To the best of our knowledge, this is the first study that evaluates the performance of the initial MRI after 5-year follow-up of patients with back pain. In 2018, rheumatologists expertise lead to the decrease of the number of patients with SpA diagnosis from 93 to 58, in favor of fibromyalgia or degenerative diseases. These results allow an increase of the sensitivity but a decrease of the specificity of MRI. This evolution can be explained both by the initial enthusiasm among rheumatologists in view of an increasingly earlier diagnosis thanks to MRI and to the higher sensitivity (82.9%) of the new ASAS classification criteria (9). This phenomenon has led to over-diagnosis, over-treatment and has had non negligible socio-economic impacts due to high biotherapy costs (10). Therefore reliable MRI interpretation by

an experienced radiologist with both high sensitivity (to avoid failing early diagnosis) and specificity is more important than ever.

In our SpA population, the prevalence of sacroiliitis is between 18 and 29%, depending on the radiologists, although the prevalence varies from 30-50% in the literature (11–14). This difference may be explained by the inclusion criteria which considers back pain but not buttock pain. In addition, we find 26% of patients with isolated spine lesions, without sacroiliitis; this result is in line with previous studies that report a prevalence between 14 and 30% (8,15–17). This is due to the fact that the ASAS MRI working group does not include findings on spine in their definition of SpA because of a lack of specificity (18). Indeed degenerative diseases in the spine are frequent and often indistinguishable from small inflammatory SpA lesions notably when they are in congestive phase (8,19). Also, abnormalities like bone marrow edema can also be detected in healthy subjects (8,20–23). However, our results presented here still justify inclusion of specific spinal criteria for SpA diagnosis in order to avoid the exclusion of this significant population of patients (26%).

The present study provides evidence that injection of gadolinium is useful to diagnose SpA by detecting axial enthesitis which was present in 20% of our SpA population although bone abnormalities are not typical or absent without contrast. Moreover, the evaluation of the injected sequence had a higher interobserver reproducibility and a better sensitivity. Injection seems to simplify the data interpretation and could help general radiologists who often perform MRI to explore back pain but are generally not used to discuss the diagnosis of SpA. The limit of the injection in our study is the lack of specificity. For several patients, the initial diagnosis of SpA was finally recused, because of a confusion with anatomic variations, degenerative lesions or polymyalgia rheumatica (Figure 4), which can also be found in MRI without contrast. Finally, the injection of gadolinium should be considered when clinical suspicion is strong in order to improve sensitivity and make an earlier diagnosis. We propose an algorithm for the use of contrast in accordance with our data (Figure 5). Of course, we do not suggest a systematic injection of gadolinium as there is no reason to extend the examination time when the diagnosis (positive or negative) is certain without contrast, avoiding pointless potential side effects of the product (gadolinium deposition in the brain, bones and skin sometimes associated with kidney nephrogenic systemic fibrosis and also systemic allergic reactions) (24–26).

Of interest, our SpA population is composed of 62% of women and this percentage is even higher in our group with isolated enthesitis, at 92%, which is its main characteristic. Although SpA predominately affects men, non-radiographic SpA has more balanced sex

distribution in the literature (11,27–29). In our group with isolated enthesitis, we have not been able to demonstrate if the presence of peripheral enthesitis was predictive of the presence of axial enthesitis. This can be explained by the fact that peripheral enthesitis were rarely found in the medical record and patients had difficulty remembering their precise symptoms, notably the inflammatory component. Even on clinical examination, it is often difficult to distinguish fibromyalgic painful points from enthesitis pain, as illustrated in our population without SpA in 2018 out of whom 30% were considered to have peripheral enthesitis. A prospective study focusing on the concordance between the presence of peripheral and axial enthesitis would be interesting to complete the characterization of this subgroup of SpA.

Our study has some limitations. All the results depend on the rheumatologists' diagnosis which is challenging and has to be reconsidered continuously according to the clinical evolution and the therapeutic response of the patient. This is why the MRI performance is subject to variations. We have tried to reduce this bias by following the evolution of the patients over 5 years. Moreover, the MRI readings were centralized in a specialized osteoarticular imaging department, which does not represent the real-world experience. We tried to reduce this bias with the participation of a less experimented reader, explaining the weak interobserver agreement and shows the great importance of the participation of experimented radiologists in difficult diagnosis. For the analysis of the enthesitis groups, the small size of each subgroup explains the insignificant results, which not allow us to identify specific clinical or biological characteristics or to evaluate the efficacy of TNFi. In addition, few anti-IL17 and anti-IL12/23 are used in our cohort because these treatments received their marketing authorization for SpA after 2013. However they have proven to resolve enthesitis in psoriatic arthritis (30,31) so it might be interesting to study their efficacy in the isolated enthesitis subgroup.

To conclude, based on the evolution of clinical data, spinal and SI MRI have an increase of sensitivity and a decrease of specificity over time. In precise cases such as doubtful MRI abnormalities or strong clinical suspicion of SpA, the injection of gadolinium is required to reveal the enthesitis, including spinal posterior elements. Finally, this study suggests to include spine assessment as a diagnosis criteria of SpA.

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TABLES ET FIGURES

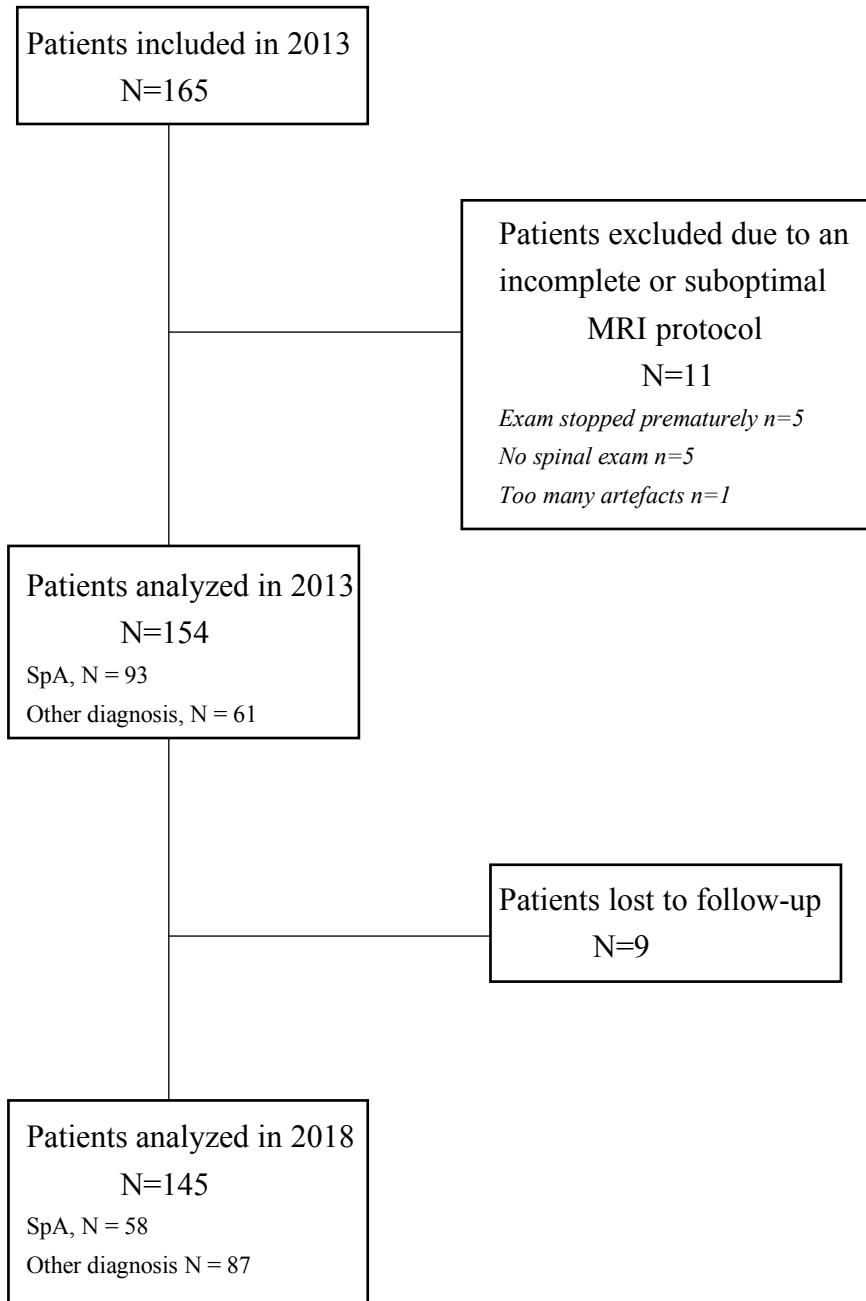


Figure 1 : Flow-Chart
SpA =spondyloarthritis

Table 1: MRI protocol with pulse frequency

	Repetition time (msec)	Echo time (msec)	Number of signals acquired	Slices thickness (mm)	Field of view (cm)
coronal-oblique T2 FS of SI joints	3935	85	4	3	28
coronal-oblique T1-weighted of SI joints	669	10.3	2	3	28
sagittal T2 FS of thoracolumbar spine	3016	75	3	4	36
sagittal T1-weighted of thoracolumbar spine	781	11.7	2	4	36
coronal-oblique gadolinium-enhanced T1-weighted FS of SI joints	839	8.9	2	3	28
sagittal gadolinium-enhanced T1-weighted FS of thoracolumbar spine	677	11.3	2	4	36

Note - SI = sacroiliac, FS = fat-saturation

Table 2: Likert scoring system for spondyloarthritis detection

	Likert 1	Likert 2	Likert 3	Likert 4	Likert 5
Description	No abnormality	Non inflammatory abnormalities	Doubtful abnormalities	Abnormalities evocative of SpA but not included in ASAS criteria	Abnormalities included in ASAS criteria

SpA = spondyloarthritis, ASAS = Assessment of SpondyloArthritis international Society.

Table 3: Characteristics of the participants

	In 2013	In 2018	SpA in 2018	Non SpA in 2018
	n = 154	n = 145	n = 58	n = 87
Women	98/154 (63%)	93/145 (64%)	36/58 (62%)	57/87 (66%)
Age at diagnosis (years)	38.5 ± 11.3	38.6 ± 11.3	36.0 ± 12.1	40.4 ± 10.5
		n = 144/145	n = 58/58	n = 86/87
Age at 1st symptom (years)	33.4 ± 11.7	33.3 ± 11.7	32.1 ± 12.1	34.1 ± 11.4
		n = 134/145	n = 55/58	n = 79/87
Symptoms duration (years)	5.4±7.4	5.5 ± 7.5	4.1 ± 6.5	6.5 ± 8.0
		n = 134/145	n = 55/58	n = 79/87
Inflammatory low back pain	136/150 (91%)		55/58 (95%)	75/86 (87%)
Arthritis	34/147 (23%)	130/144 (90%)		
Peripheral enthesitis	59/149 (40%)	33/141 (23%)	22/58 (40%)	11/83 (13%)
Uveitis	5/152 (3%)	55/143 (39%)	30/57 (53%)	25/84 (30%)
Inflammatory bowel disease	13/152 (9%)	5/145 (4%)	4/58 (6.9%)	1/87 (1%)
Psoriasis		10/145 (7%)	5/58 (8.6%)	5/87 (6%)
Family history	35/152 (23%)	35/145 (24%)	16/58 (28%)	19/87 (22%)
HLA B27 positivity	46/148 (31%)	44/143 (31%)	22/58 (38%)	22/85 (26%)
CRP (mg/L)	42/151 (28%)	41/145 (28%)	23/44 (52%)	18/61 (30%)
	11.4 ± 22.6	11.3 ± 23	12.5 ± 21.8	10.3 ± 24.2
		n = 113/145	n = 52/58	n = 61/87
Good response to NSAIDs	104/136 (77%)	100/130 (77%)	46/54 (85%)	54/76 (71%)
Current treatment				
NSAIDs	63/133 (47%)	43/129 (33%)	14/58 (24%)	29/71 (41%)
TNFi	32/133 (24%)	30/129 (23%)	28/58 (48%)	2/71 (3%)
None	21/133 (16%)	27/129 (21%)	10/58 (17%)	17/71 (24%)
DMARDS	8/133 (6%)	14/129 (11%)	5/58 (9%)	2/71 (3%)
Corticosteroids	3/133 (2%)	1/129 (1%)	0/58 (0%)	1/71 (72%)
Other*	17/133 (13%)	28/129 (22%)	0/58 (0%)	20/71 (28%)
Anti-IL17	0/133 (0%)	1/129 (0.8%)	0/58 (0%)	0/71 (0%)
Anti-IL12/23	0/133 (0%)	1/129 (0.8%)	1/58 (2%)	0/71 (0%)

Note - Data are numbers except means +/- standard deviation. Percentages were rounded.

SpA = Spondyloarthritis, HLA = human leucocyte antigen, CRP = C-reactive protein rate, NSAIDs = non-steroidal anti-inflammatory drugs, TNFi = tumor necrosis factor inhibitors

Other* included different analgesics, physiotherapy or surgery

Table 4 Summary of clinical diagnosis in 2013 et 2018

Diagnosis	2013	2018
Total	n = 154	n = 145
Spondyloarthritis	93	58
Degenerative arthritis	49	58
Fibromyalgia	4	14
Growth disorder	1	0
Whipple's disease	1	1
Polymyalgia rheumatica	1	1
Rheumatoïd arthritis	1	2
Still's disease	0	1
Undifferentiated arthritis	1	3
Sarcoïdosis	0	1
Unknown	3	6

Table 5: MRI classification according to the imaging score (Likert scale) compared to clinical conclusion established at 5-year follow-up

	Clinical diagnosis in 2018	Likert 1	Likert 2	Likert 3	Likert 4	Likert 5
Reader 1 no contrast	<i>No SpA (n=87)</i>	22 (25%)	39 (45%)	14 (16%)	9 [§] (10%)	3 [§] (4%)
	<i>SpA (n=58)</i>	6 (10%)	11 (19%)	14 (24%)	19* (33%)	8* (14%)
Reader 1 contrast	<i>No SpA (n=87)</i>	15 (17%)	31 (36%)	21 (24%)	17 [§] (20%)	3 [§] (4%)
	<i>SpA (n=58)</i>	4 (7%)	4 (7%)	14 (24%)	28* (48%)	8* (14%)
Reader 2 no contrast	<i>No SpA (n=87)</i>	19 (22%)	43 (49%)	11 (13%)	10 [§] (12%)	4 [§] (5%)
	<i>SpA (n=58)</i>	7 (12%)	10 (17%)	7 (12%)	21* (36%)	13* (22%)
Reader 3 no contrast	<i>No SpA (n=87)</i>	12 (14%)	64 (74%)	8 (9%)	2 [§] (2%)	1 [§] (1%)
	<i>SpA (n=58)</i>	2 (4%)	26 (45%)	9 (16%)	8* (14%)	13* (22%)
Reader 3 contrast	<i>No SpA (n=87)</i>	7 (8%)	51 (59%)	18 (21%)	8 [§] (9%)	3 [§] (4%)
	<i>SpA (n=58)</i>	2 (4%)	20 (35%)	10 (17%)	13* (22%)	13* (22%)

Note - Percentages were rounded.

**These patients are considered as true-positive.*

§These patients are considered as false-positive.

SpA = Spondyloarthritis

Table 6: Performance for spondyloarthritis detection at 1 and 5-year follow-up

	Reader 1 No Contrast		Reader 1 Contrast		Reader 2 Contrast		Reader 3 No contrast		Reader 3 Contrast	
	2013	2018	2013	2018	2013	2018	2013	2018	2013	2018
Follow-up										
Sensitivity (%)	37.63 [32.74-42.80]	46.55 [37.74-55.59]	50.54 [44.49-56.57]	62.07 [52.02-71.18]	48.39 [42.70-54.12]	58.62 [48.92-67.70]	24.73 [21.26-28.56]	36.21 [29.65-43.32]	32.26 [27.37-37.57]	44.83 [36.22-53.76]
Specificity (%)	91.80 [82.85-96.29]	86.21 [79.35-91.04]	81.97 [72.08-88.89]	77.01 [69.80-82.92]	90.16 [80.89-95.21]	83.91 [76.78-89.16]	96.72 [88.51-99.12]	95.52 [87.99-98.42]	86.89 [77.63-92.67]	87.36 [80.57-92.01]
PPV (%)	87.50 [73.20-95.81]	69.23 [52.43-82.98]	81.03 [68.59-90.13]	64.29 [50.36-76.64]	88.24 [76.13-95.56]	70.83 [55.94-83.05]	92.00 [73.97-99.02]	87.50 [67.64-97.34]	78.95 [62.68-90.45]	70.27 [53.02-84.13]
NPV (%)	49.12 [39.64-58.65]	70.75 [61.13-79.19]	52.08 [41.64-62.39]	75.28 [65.00-83.81]	53.40 [43.30-63.29]	75.26 [65.46-83.46]	45.74 [36.94-54.73]	63.37 [53.19-72.73]	45.69 [36.41-55.19]	70.37 [60.82-78.77]
Accuracy (%)	59.09 [50.89-66.94]	70.34 [62.20-77.64]	62.99 [54.84-70.62]	71.03 [62.93-78.26]	64.94 [56.84-72.44]	73.79 [65.85-80.74]	53.25 [45.05-61.32]	68.00 [59.07-76.06]	53.90 [45.69-61.95]	70.34 [62.20-77.64]
AUC	0.65 [0.59-0.71]	0.66 [0.59-0.74]	0.66 [0.59-0.73]	0.70 [0.62-0.77]	0.69 [0.63-0.76]	0.71 [0.64-0.79]	0.61 [0.56-0.66]	0.66 [0.60-0.73]	0.60 [0.53-0.66]	0.66 [0.59-0.73]

*Note - Percentages were rounded. Numbers in brackets are limits of confidence intervals 95%.
PPV = Positive predictive value NPV = Negative predictive value AUC = Area under the curve*

Table 7: Characteristics of the subgroup 1-2 and 3 compared to the control group (group 0)

	Group 0	Group 1-2	p*	Group 3	p**
Women	72/120 (60%)	12/13 (92%)	0.03	9/12 (75%)	0.37
Age at diagnosis (years)	38.5 ± 11.3 n = 119/120	42 ± 11.2 n = 13/13	0.24	36.8 ± 11.6 n = 12/12	0.44
Age at 1st symptom (years)	33.4 ± 11.7 n = 112/120	33.5 ± 12.7 n = 11/13	0.95	31.4 ± 12 n = 11/12	0.43
Symptoms duration (years)	5.3 ± 7.2 n = 112/120	8.2 ± 8.5 n = 11/13	0.11	5.1 ± 9.8 n = 11/12	0.66
Inflammatory low back pain	108/119 (91%)	11/13 (85%)	0.62	11/12 (92%)	>0.99
Arthritis	29/116 (25%)	2/13 (15%)	0.73	2/12 (17%)	0.73
Peripheral enthesitis	45/118 (38%)	6/13 (46%)	0.57	4/12 (33%)	0.01
Uveitis	2/120 (2%)	2/13 (15%)	0.048	1/12 (8%)	0.25
Inflammatory bowel disease	10/120 (8%)	0/13 (0%)	0.60	0/12 (0%)	0.37
Psoriasis	28/120 (23%)	5/13 (39%)	0.31	2/12 (17%)	0.73
Family history	38/118 (32%)	4/13 (31%)	>0.99	2/12 (17%)	0.34
HLA-B27 positivity	32/120 (27%)	5/13 (39%)	0.50	4/12 (33%)	0.86
CRP (mg/L)	11.4 ± 24.2 n = 94/120	6.5 ± 5.9 n = 10/13	0.42	15.8 ± 23.2 n = 9/12	0.65
Good response to NSAIDs	84/108 (78%)	7/12 (58%)	0.14	9/10 (90%)	0.08

Note - Data are numbers except means ± standard deviation.

*p** for comparing characteristics of Group 1-2 to Group 0.

*p*** for comparing characteristic of Group 3 to Group 0.

HLA = human leucocyte antigen, *CRP* = C-reactive protein rate, *NSAIDs* = non-steroidal anti-inflammatory drugs



Figure 2 : Injection of Gadolinium reveal isolated enthesitis, helping the diagnosis of spondyloarthritis although there is no bone abnormality

A. T1 sequence B. T2 STIR sequence C. T1 FS gadolinium sequence D. T1 FS gadolinium sequence

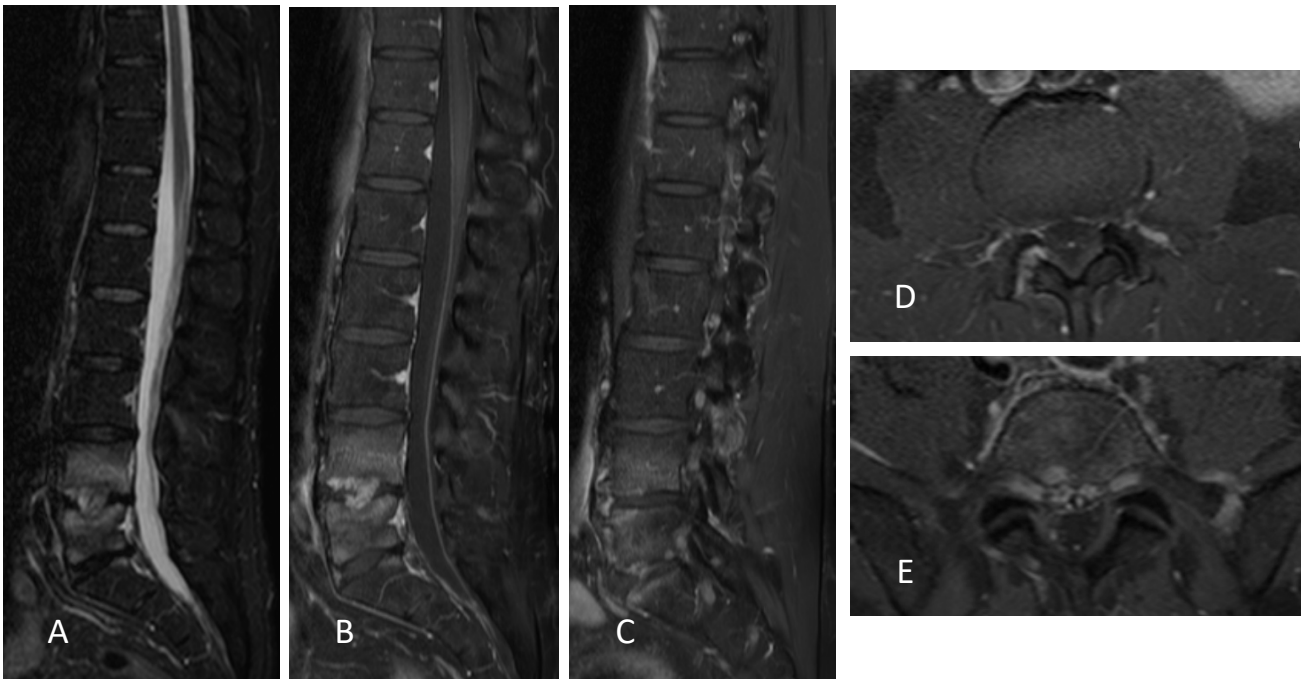


Figure 3 Injection of Gadolinium reveal enthesitis helping the diagnosis of spondyloarthritis although there is just atypical bone lesions

A. T2 STIR sequence B. T1 FS gadolinium sequence C. T1 FS gadolinium sequence D. T1 FS gadolinium sequence E. T1 FS gadolinium sequence

FS = Fat-saturation

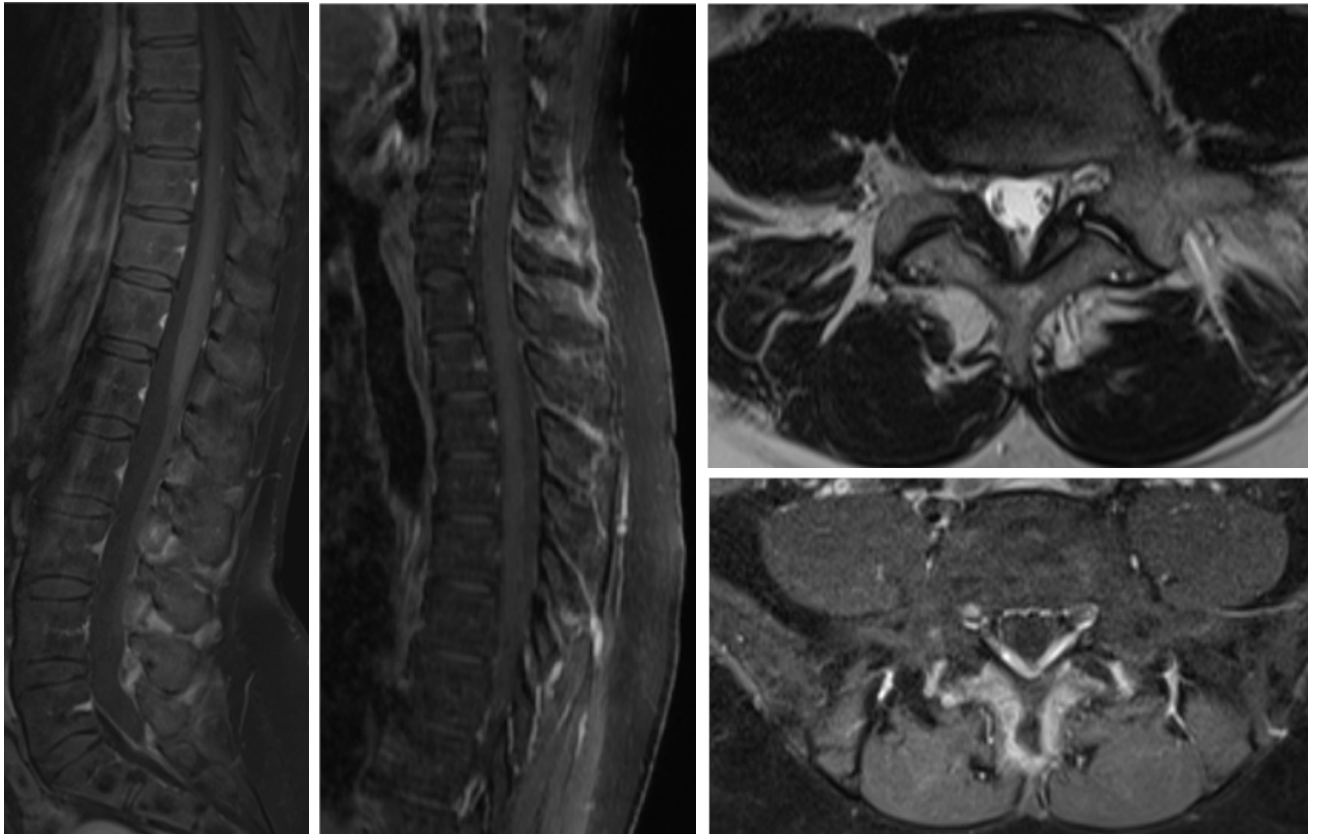


Figure 4 Polymyalgia rheumatica: a differential diagnosis of spondyloarthritis on spinal MRI.
A. T1 FS gadolinium sequence. B. T1 FS gadolinium sequence. C. T2 sequence D. T1 FS gadolinium sequence.
FS = Fat-saturation

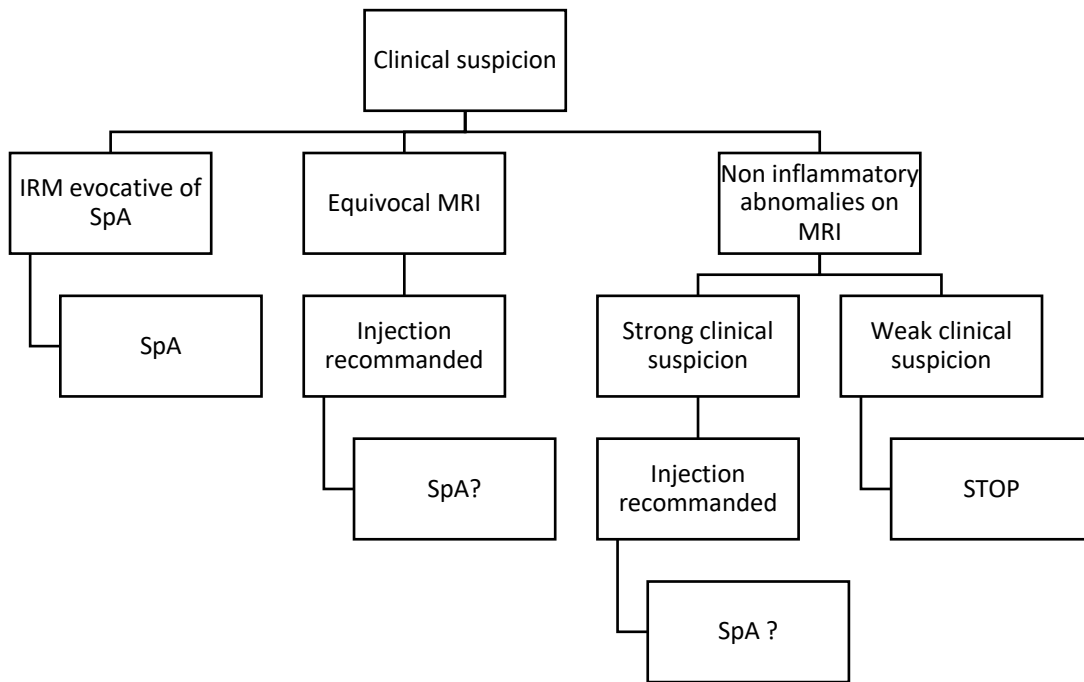


Figure 5 Algorithm for the use of contrast in spondyloarthritis diagnosis
 Note - SpA = Spondyloarthritis

SERMENT D'HIPPOCRATE

Au moment d'être admise à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admise dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçue à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés. J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonorée et méprisée si j'y manque.

Place de l'IRM dans le diagnostic des spondyloarthrites et évaluation de l'intérêt de l'injection de gadolinium : étude prospective monocentrique sur une période de 5 ans.

Introduction : La réalisation de l'IRM du rachis pour le diagnostic de spondyloarthrite (SpA) est toujours controversée. Cependant, l'injection de gadolinium permettrait de mettre en évidence les anomalies des territoires enthésitiques et pourrait être utile dans l'enquête diagnostique.

Objectif : Évaluer la performance de l'IRM en 2013 avec et sans injection de produit de contraste par rapport à l'évolution clinique, à 5 ans du diagnostic initial et déterminer l'intérêt de l'injection dans la stratégie diagnostique des SpA.

Matériels et Méthodes : Dans cette étude prospective monocentrique, 165 patients lombalgiques chroniques ayant eu une IRM du rachis et des sacro-iliaques (SI) dans notre service de radiologie ont été recrutés entre mai 2013 et janvier 2014. Les paramètres cliniques, biologiques et radiologiques de chaque patient ont été recueillis. Trois radiologues ont identifié la présence de lésions radiologiques spécifiques de SpA en utilisant une échelle de Likert. L'interprétation centralisée de l'IRM en 2013 a été comparée au diagnostic établi en 2013 et après 5 ans de suivi. Les tests non paramétriques de Mann-Whitney, Fisher et McNemar X² ont été utilisés pour comparer respectivement les variables quantitatives et qualitatives, la sensibilité et la spécificité.

Résultats : 145 patients ont été inclus dans l'analyse finale. Entre 2013 et 2019, le nombre de patients ayant un diagnostic de SpA a diminué, passant de 93 à 58, après 5 ans de suivi. La sensibilité de l'IRM réalisée en 2013 a augmentée, au détriment de la spécificité. Comparée à l'IRM non-injectée, l'injection de gadolinium a permis d'améliorer la sensibilité mais pas la spécificité, en révélant des enthésites pour 20% des SpA confirmées après 5 ans d'évolution.

Conclusion : L'injection de gadolinium montre la présence d'enthésites, notamment celles des éléments postérieurs rachidiens et permet d'augmenter la sensibilité de l'IRM dans certains cas de SpA douteuses.

Mots clés : Spondyloarthrite, IRM, Gadolinium, Enthésites

Role of MRI in the diagnosis of spondyloarthritis and evaluation of the benefit of gadolinium injection: a 5-year prospective clinical study.

Background : The performance of spinal MRI for the diagnosis of spondyloarthritis (SpA) is still contentious. However, MRI with injection of gadolinium could be more sensitive in demonstrating sites of enthesitis improving diagnostic strategy.

Purpose : To evaluate the performance of the MRI in 2013 with and without injection of contrast compared to the clinical evolution, 5 years after the initial diagnosis and to assess the benefit of the gadolinium injection in the SpA diagnosis strategy.

Materials and Methods : In this single-center prospective study, 165 patients with chronic low back pain who underwent both spinal and sacroiliac (SI) joints MRI in a radiology department were recruited between May 2013 and January 2014. Clinical, biological and radiologic parameters were collected. Three independent readers identified the presence of specific radiological features of SpA by using a five-point Likert scale to record the estimation of confidence. The centralized MRI interpretation from 2013 was compared to the established diagnosis in 2013 and at 5-year follow-up. The nonparametric Mann-Whitney, Fisher and McNemar X² tests were conducted to compare quantitative and qualitative variables and sensitivity and specificity respectively.

Results : A total of 145 patients were included in the final analysis. During the 5 years of follow-up, between 2013 and 2018, the evaluation by the rheumatologist led to a decrease of patients with SpA diagnosis from 93 to 58. Sensitivity of MRI realized in 2013 was increased and specificity was decreased. Compared to MRI without contrast, injection of gadolinium improved sensitivity but not specificity. By revealing enthesitis, the use of contrast injection increased correct diagnosis of SpA by 20% after 5 years of follow-up.

Conclusion : The injection of gadolinium improve the visualization of enthesitis, including spinal posterior elements and increase the sensitivity of the MRI in some doubtful cases of SpA.

Keywords : Spondyloarthritis, MRI, Gadolinium, Enthesitis

Discipline : Rhumatologie
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