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Fatigue in early axial spondyloarthritis. Results from the French DESIR cohort.

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Abstract (word count: 247, limit 250)

Introduction: Fatigue is frequent in long-standing axial spondyloarthritis (axSpA); its frequency in early axSpA and its causes are unclear. The objective was to evaluate the magnitude of fatigue in early axSpA and to assess if fatigue appeared more strongly associated with patient- or with disease-related characteristics.

Patients and Methods: Patients were assessed in DESIR, a national observational cohort of patients with recent (<3 years duration) inflammatory back pain suggestive of axSpA. Magnitude of fatigue was assessed by a numeric rating scale (0-10) over one year. Factors associated with high fatigue ($\geq 5/10$) at 12 months were assessed by univariate and multivariate logistic regression, for patients fulfilling the ASAS axSpA criteria.

Results: Of the 708 patients, 486 fulfilled the ASAS criteria for axSpA: mean age 33 ± 9 years; 244 (50%) males. Magnitude of fatigue was high at baseline (mean fatigue, 5.7 ± 2.3) and decreased only slightly over the first year, and was overlapping in patients fulfilling the ASAS criteria or not. High fatigue at 12 months was well explained (variance explained, 0.84) by a higher ASDAS-CRP (odds ratio, OR, 3.05 [95% confidence interval, CI, 2.27-4.12], $p < 0.0001$), higher Bath Anylosing Spondylitis Patient Global BAS-G (OR, 3.51 [95% CI, 2.08-6.02], $p < 0.0001$) and with borderline significance, female gender (OR, 1.65 [95% CI, 1.00-2.71], $p = 0.049$).

Conclusion: Fatigue levels were high in this population, both for patients fulfilling or not, the ASAS criteria for axSpA. High fatigue was closely related to disease-related variables, indicating fatigue may be an integral part of the disease process in axSpA.

Key words: spondyloarthritis / ankylosing spondylitis, fatigue, quality of life, BASDAI.

Introduction

Fatigue is an important symptom in patients with chronic diseases, including rheumatic diseases and has been recently explored in rheumatoid arthritis (RA) and in psoriatic arthritis (PsA) [1-3]. It is a subjective experience that can be described as an overwhelming, sustained sense of dysfunctional exhaustion unrelated to effort and poorly dissipated with appropriate rest [4-5]. Fatigue impacts rheumatic patients' quality of life, and therefore, may involve significant economic consequences for society [6].

In long-standing axial spondyloarthritis (axSpA), fatigue seems to be frequent, with up to 50-65% of the patients reporting they feel fatigued [7-12]. Indeed, fatigue is recognised as a marker of axSpA since it is included in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), a widely used index for disease activity [13]. However, the magnitude of fatigue in early axSpA has not been established. It is possible that fatigue levels could be different in early disease since spinal ankylosis usually does not exist at this stage and quality of life may be less altered.

The causes of fatigue in inflammatory rheumatism such as axSpA or RA are unclear; fatigue in axSpA is diversely reported as being related either to patient characteristics, e.g., demographic, psychological and social factors, or to disease characteristics, e.g. disease activity. [10, 12, 14-15].

Thus, although fatigue is reported as frequent and important in SpA, its cause remains unclear and its presence in early SpA and in the different subgroups of SpA (predominant axial form or not, with or without radiographic sacro-iliitis) has been very little studied [12].

The objectives of the present study were to evaluate the magnitude of fatigue in early SpA (and in the different subtypes of SpA) and to assess if fatigue appeared more strongly associated with patient- or with disease-related characteristics.

Patients and Methods

Study design and patients: DESIR [16] is an observational prospective, multi-centre cohort of patients with inflammatory back pain suggestive of axSpA of less than 3 years duration. Treatments are not-protocolised and left to the judgment of the treating rheumatologist.

Assessment of fatigue

Fatigue was assessed by a numeric rating scale (NRS), range 0-10, during the first year of follow-up (i.e. at inclusion in the cohort, then at 6 and 12 months), by using the first question of the BASDAI: “How would you describe the overall level of fatigue / tiredness you have experienced in the past week?” [13]. High fatigue was defined (as has been done by other authors) as a fatigue $\geq 5/10$ [10,11].

Factors associated with fatigue

The association between high fatigue levels at 12 months, and other factors was analysed. The factors included (a) patient-related characteristics at baseline: demographic variables (age, gender, symptom duration, ethnicity), familial status (married or not, number of children) and years of education as a surrogate for socio-economic status; (b) disease activity-related characteristics at 12 months: disease activity variables (ASAS Disease Activity Score: ASDAS-CRP [17], Bath Ankylosing Spondylitis Patient Global Score: BAS-G, and Health Assessment Questionnaire adapted to AxSpA: HAQ-AS), and (c) other disease characteristics (HLA-B27 positivity, disease subtype according to the physician, extra-articular involvement yes/no, enthesal pain yes/no as assessed by the Maastricht Ankylosing Spondylitis Enthesitis Score, and sacroiliitis on radiographs or magnetic resonance imaging, according to local reading of the imaging).

Statistical analyses

In the whole population: fatigue magnitude was assessed by descriptive statistics at baseline, 6 months and one year, in all patients in DESIR then on the subgroups fulfilling or not at baseline, the Assessment of SpondyloArthritis (ASAS) classification criteria for axSpA [18] and its different arms i.e., clinical versus imaging arms, and also according to disease subtype (purely axial versus axial+peripheral versus undifferentiated, as defined by the investigators).

At one year of follow-up: a univariate then multivariate logistic regression was performed to explain high fatigue, defined as fatigue NRS $\geq 5/10$ at 12 months, by the explanatory variables, through a stepwise selection. BASDAI was not entered in the analyses since the fatigue question was an integral part of the BASDAI and since correlation with ASDAS-CRP are high. The Bath Ankylosing Spondylitis Functional Index was also not analysed since highly correlated to the HAQ-AS. This analysis was performed in the group of patients fulfilling the ASAS criteria, and for exploratory purposes, after exclusion of BAS-G since patient global assessments and fatigue are often correlated, and also in the whole group of patients.

There was no imputation of missing data. The Statistical Analysis System (SAS) version 9.2 was used.

Results

Patient characteristics

Of the 708 DESIR patients (mean±standard deviation age 34±9 years; 327 (46%) males), 486 fulfilled the ASAS criteria for axSpA at baseline (mean age 33±9 years; 244 (50%) males). Symptom duration was short and BASDAI was high at inclusion in the cohort (Table 1); 206 (30.1%) had elevated C-reactive protein. Although all patients presented with axial symptoms, the investigators characterised the disease as axial (N=349), axial+peripheral (N=41), undifferentiated (N=225) or other/unclear (N=93). At one year of follow-up, 450 (72.9%) patients were treated with non-steroidal anti-inflammatory drugs, and 158 (22.3%) were treated with anti-tumor necrosis factor drugs.

Magnitude of fatigue was high at baseline (mean fatigue, 5.7±2.3). In patients fulfilling the ASAS criteria or not, numerical differences were noted (respectively, mean fatigue 5.5±2.4 and 6.0±2.2); however there was significant overlap between the 2 groups; median values of fatigue were identical in both groups (respectively, 6 [interquartile range 4-7] and 6 [5-8]) (Table 2). There were however differences according to the arms of the ASAS criteria: mean fatigue was 4.7±2.5 in the conventional radiography sacroiliitis arm ,i.e., ankylosing spondylitis arm (N=50), 5.6±2.3 in the MRI sacroiliitis (without radiography sacroiliitis) arm (N=98), versus 5.9±2.2 in the non-radiographic arm (N=197) (p=0.0009 versus the ankylosing spondylitis arm).

Fatigue levels according to the disease subtype were similar (in predominantly axial disease, mean fatigue 5.6±2.4, in peripheral forms 6.0±2.2 and in undifferentiated forms 5.7±2.3, respectively; p=0.6).

Fatigue decreased significantly but slightly over the first year of follow-up (mean fatigue at one

year, 4.9 ± 2.6 , $p=0.008$) (Table 2). This was similar to the decrease in pain (data not shown).

Factors associated with high fatigue levels at one year

Among the 428 patients fulfilling the ASAS criteria for axSpA and with full data available for this analysis, high fatigue level ($\geq 5/10$) concerned 210 (49%) patients at 12 months.

In univariate analysis, fatigue was associated with female gender ($p<0.0001$), higher ASDAS-CRP ($p<0.0001$), higher BAS-G ($p<0.0001$), higher HAQ-AS ($p<0.0001$), shorter length of schooling ($p=0.003$) and negativity of HLA B27 ($p=0.026$).

In multivariate analysis, high fatigue at 12 months was well explained (variance explained, 0.84) by the following independent elements (Table 3): higher ASDAS-CRP (odds ratio, OR, 3.05 [95% confidence interval, CI, 2.27-4.12], $p<0.0001$), higher BAS-G (OR, 3.51 [95% CI, 2.08-6.02], $p<0.0001$) and with borderline significance, female gender (OR, 1.65 [95% CI, 1.00-2.71], $p=0.049$). Patient-related characteristics apart from gender, were not significant to explain fatigue at 12 months in this multivariate analysis. When excluding BAS-G from the analysis, the explanatory factors remained disease-related (variance explained, 0.82; Table 3). In the whole population, high fatigue was explained by ASDAS-CRP (OR, 3.12 [95% CI, 2.31-4.20], $p<0.0001$), BAS-G (OR, 2.42 [95% CI, 1.53-3.84], $p=0.00021$) and HAQ-AS (OR for an increase of 0.2, 1.15 [95% CI, 1.03-1.30], $p=0.017$) (variance explained, 0.84).

Discussion

Fatigue levels were high in this large cohort of patients with symptoms suggestive of early axSpA, independently of the fulfillment of the ASAS criteria. High fatigue at one year was closely related to disease activity rather than to patient-related variables, supporting the concept that fatigue is an integral part of disease activity also in early axSpA.

This is to our knowledge, the first study exploring fatigue and its associated factors in early axSpA. Due to reference shifts, symptoms such as fatigue may be very different in early disease; however fatigue levels here were similar to those observed in established axSpA.

This study has strengths and weaknesses. The study sample was large, and represents the spectrum of patients with inflammatory back pain suggestive of axSpA in France [16]. Nonetheless, fatigue may be influenced by cultural background [19]; thus studies in other countries are warranted. The BASDAI fatigue question was used to assess fatigue, rather than a specific fatigue scale such as the Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-F) for example. However, good correlations have been shown between the fatigue NRS and more complex scales [10, 20]. Finally, some important elements such as sleep disturbances, and psychological status including anxiety/depression were not analysed in the present study.

Fatigue is a frequent symptom in rheumatic diseases, with around half the patients describing high fatigue levels, in RA as well as in PsA or axSpA [2-4, 10]. In established axSpA specifically, fatigue levels appeared very similar to the ones observed in the present early disease population [10, 12]. Fatigue levels in axSpA should however be put in context using the healthy population as comparator since fatigue is frequently experienced by healthy adults with a prevalence comprised between 14 and 25% and female predominance [11].

In the present study, although fatigue levels decreased slightly after inclusion in the cohort, 55% of patients still had a fatigue $\geq 5/10$ at one year. The decrease of fatigue over the first year of follow-up in DESIR, is possibly due to the treatments given, or to an effect of regression towards the mean. Similar observations have been made in early RA cohorts [21]. In the present cohort, use of anti-TNF therapies was low over the first year of follow-up, and was not specifically analysed here. The high levels of fatigue seen in axSpA and potential consequence of fatigue, are offset by few publications on this subject: a systematic literature review evidenced only 3 papers on fatigue in SpA over a 10-year period in Europe, versus 16 papers in RA over the same period [22].

The present results indicate fatigue levels were similar in this population of patients with symptoms suggestive of axSpA, whether the patients fulfilled or not, the ASAS criteria for axSpA. This indicates fatigue should not be used as a diagnostic element when faced with inflammatory back pain suggestive of axSpA. Although non-radiographic axSpA patients had higher levels of fatigue than the radiographic ones, there was important overlap between these populations as well as with the patients not fulfilling the axSpA classification criteria [12]. The question of concomitant fibromyalgia in patients with non-radiographic axSpA could be raised here.

Fatigue is difficult to deal with for rheumatologists. Firstly, because as we have shown here, fatigue does not seem to be helpful for diagnosis/ classification. Secondly because fatigue is not always a marker of disease activity thus does not always lead to disease-modifying drug changes; and thirdly because its treatment, as isolated symptom, is difficult.

Fatigue was closely related to disease activity rather than to patient-related variables in the present study. Female gender appears to be associated with higher fatigue, both in the general population [11], and in established axSpA [12]. Fatigue in established axSpA has

been reported as being related to demographic, psychological and social factors, but also to disease activity. [10, 12, 14-15, 23]. We found, like other authors, that fatigue was highly associated to other patient-reported outcomes such as patient global assessment and quality of life [10, 12]: this is one of the difficulties of dealing with fatigue in terms of psychometric properties, but also indicates the potential importance of fatigue from the patient's perspective [24]. To try to distinguish between disease-related causes and patient-reported symptoms in the origin of fatigue we performed analyses first including then excluding patient global assessment (BAS-G), and we used the ASDAS-CRP as a marker of disease activity. The results still evidenced as associated factors, mainly outcomes related to the disease rather than the patient. Thus we could hypothesize fatigue appears more closely related to the disease process in SpA than in RA. It is however noteworthy that fatigue was not selected in the ASDAS score [17] suggesting low predictive validity, at least in established disease.

To date there are no specific treatments targeting fatigue in axSpA. Indeed, the mechanisms underlying fatigue in axSpA remain poorly understood, and may involve the inflammatory process / pro-inflammatory cytokines, and/or psychological distress for example. A recent study based on 3T-magnetic resonance imaging of the brain indicated fatigue in axSpA may involve sensory salience and attention brain networks. [19] In any case, the efficacy of the usual treatments prescribed by rheumatologists, including biologics, on fatigue, is only moderate in RA [25]. In RA also, non-pharmacological interventions such as cognitive behavioural therapy have been shown efficacious; such interventions remain to be assessed in axSpA [26].

In conclusion, fatigue is a frequent symptom also in early axSpA which appears strongly associated to the disease process; consequences of and treatments for this fatigue should be further evaluated.

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Pediatric Quality Of Life (PedsQL) Multi-Dimensional Fatigue Scale, Profile of Fatigue (ProF), Short Form 36 Vitality Subscale (SF-36 VT), and Visual Analog Scales (VAS). *Arthritis Care Res (Hoboken)*. 2011;63 Suppl 11:S263-86.

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Table 1. Characteristics of patients in the DESIR cohort at inclusion

Characteristic at inclusion	Whole population (N=708)	ASAS criteria fulfilled (N=486)	ASAS criteria not fulfilled (N=206)
Age, years, mean (SD)	33.7 (8.6)	33.0 (8.6)	35.4 (8.4)
Males, N (%)	327 (46.2)	244 (50.2)	76 (36.9)
Symptom duration at inclusion (months), mean (SD)	18.1 (10.4)	18.5 (10.6)	17.2 (10.0)
HLA B27 positivity, N (%)*	410 (58.0)	406 (83.7)	3 (1.5)
Radiographic sacro-iliitis, N (%)*	187 (27.0)	187 (38.9)	0
Peripheral synovitis, N (%)	51 (7.2)	35 (7.2)	13 (6.3)
Enthesal pain, N (%)	347 (49.0)	227 (46.7)	114 (55.3)
Any extra-articular manifestation at inclusion, N (%)	188 (26.6)	132 (27.2)	53 (25.7)
BASDAI (0-100), mean (SD)	44.7 (20.0)	42.9 (20.4)	48.4 (18.4)
ASDAS-CRP, mean (SD)	2.5 (1.0)	2.5 (1.1)	2.5 (0.9)
Axial pain NRS (0-10), mean (SD)	5.0 (2.7)	4.7 (2.8)	5.6 (2.4)
BASFI (0-100), mean (SD)	30.4 (\pm 22.8)	29.7 (\pm 22.5)	32.3 (\pm 23.5)
BAS-G (0-10), mean (SD)	5.1 (2.6)	4.9 (2.6)	5.6 (2.3)

HAQ-AS (0-3), mean (SD)	0.6 (\pm 0.5)	0.6 (\pm 0.5)	0.6 (\pm 0.5)
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For 16 patients (2.2%) the ASAS classification criteria could not be calculated due to missing data.

SD: standard deviation, NRS: numeric rating scale, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index [13], ASDAS-CRP: ASAS Disease Activity Score-CRP [17], BASFI: Bath Ankylosing Spondylitis Functional Index, BAS-G: Bath Ankylosing Spondylitis Global, HAQ-AS: Health Assessment Questionnaire adapted to axSpA.

* percentages are percentages of available data

Table 2. Magnitude of fatigue over the first year in the DESIR cohort.

Fatigue NRS (0-10), mean (SD)	Whole population (N=708)	ASAS criteria fulfilled (N=486)	ASAS criteria not fulfilled (N=206)	P value*
Baseline	5.7 (2.3)	5.5 (2.4)	6.0 (2.2)	0.009
After 6 months	4.9 (2.6)	4.7 (2.6)	5.5 (2.5)	0.001
After 12 months	4.9 (2.6)	4.7 (2.6)	5.5 (2.4)	0.001

* p-value comparing patients fulfilling or not, the ASAS classification criteria for axSpA at baseline [18]

Table 3. Factors associated with high fatigue at 12 months of follow-up in the DESIR cohort.

Characteristic at 12 months	Level in 'high fatigue' patients (N=217)	Level in 'low fatigue' patients (N=211)	Full model Odds ratio [95% confidence interval] (p value)	Model excluding BAS-G Odds ratio [95% confidence interval] (p value)
Female gender	137 (63.1)	80 (37.9)	1.65 [1.00-2.71] (0.049)	1.85 [1.15-2.99] (0.01)
ASDAS-CRP	2.5 (\pm 1.0)	1.5 (\pm 0.8)	3.05 [2.27-4.12] (<0.0001)	3.01 [2.20-4.11] (<0.0001)
BAS-G	4.8 (\pm 2.5)	2.5 (\pm 2.2)	3.51 [2.08-6.02] (<0.0001)	Not included
HAQ-AS	0.66 (0.53)	0.25 (0.35)	Not significant	2.17 [1.14-4.16] (0.02)

Multivariate logistic regression in 428 patients fulfilling the ASAS classification criteria for axSpA and with full data available. Levels of each variable in the high fatigue and low fatigue groups are given for indicative purposes, as N (%) or mean (standard deviation). Odds ratios were calculated for an increase of 1.0 of the ASDAS-CRP, for an increase of 5 units for BAS-G and for an increase of 0.2 points of HAQ-AS.