Risk Factors Associated With Cervical Spine Lesions in Patients With Rheumatoid Arthritis: The Role of Biological Agents

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Abstract

Purpose

To investigate the prevalence and risk factors of cervical lesions in patients with rheumatoid arthritis (RA) under current pharmacological treatments with biological agents.

Methods

One hundred and eighty-five consecutive patients with RA who underwent both cervical plain radiography and bone mineral density (BMD) scanning were enrolled. RA cervical lesions included atlantoaxial subluxation (AAS), vertical subluxation (VS), and subaxial subluxation (SAS). We assigned patients with AAS, VS, or SAS to the cervical-lesion group, and all other patients to the non-cervical-lesion group. Radiological findings, BMD, and clinical data on RA were collected. We used multivariate logistic regression analyses to assess the risk factors of cervical lesions in patients with RA.

Results

The cervical-lesion and non-cervical-lesion groups included 106 and 79 patients, respectively. There were 79 patients with AAS, 31 with VS, and 41 with SAS. The cervical-lesion group had younger age of onset, longer RA disease duration, and lower femoral neck BMD than those in the non-cervical-lesion group. Multivariate analyses showed that the risk factors of RA cervical lesions were RA disease duration, prednisolone usage, biological agents, and femoral neck BMD. Femoral neck BMD in patients with VS was lower than in those without VS.

Conclusions

Cervical lesions were confirmed in 57% of the patients. RA duration, prednisolone usage, biological agents, and femoral neck BMD were significant risk factors of cervical lesions in patients with RA. The general status of osteoporosis might contribute to the development of VS.

Introduction

Rheumatoid arthritis (RA) is a type of autoimmune arthritis that causes chronic inflammatory synovitis. RA lesions also invade the spine, and cervical lesions are particularly common in RA, which results in several characteristic deformities [1]. These deformities include atlantoaxial subluxation (AAS), vertical subluxation (VS), and subaxial subluxation (SAS). They possibly lead to cervical instabilities that may cause neurologic damage and induce a fatal status due to compression of the spinal cord or brain stem [2].

The treatment of RA has changed dramatically due to recent developments in biological agents. The available biological agents are the proinflammatory cytokine therapies, such as infliximab, which act by inhibition of tumor necrosis factor α (TNF α). These drugs are effective in blocking disease activities and joint degradation [3]. The incidence of cervical spine instability is 32–42%, which may be decreasing because of stable disease control due to the usage of biological agents [4, 5] Unfortunately, the incidence of cervical instability in patients with RA is still greater than 30%, which represents a major health issue.

There have been several reports on RA cervical lesions [4-9]. However, few reports have described the association between RA cervical lesions and osteoporosis, especially in patients with VS that could be induced by the collapse of lateral masses in the upper cervical spine [10, 1] Therefore, osteoporosis could affect the progression of VS, but the association between osteoporosis and VS development remains uncertain.

The purpose of our study was to investigate the prevalence and risk factors of cervical lesions in patients with RA under current pharmacologic treatment after the approval of biological agents. In addition, we investigated the relationship between osteoporosis and VS development.

Materials And Methods

Between 2008 and 2016, a total of 317 patients with RA who underwent cervical plain radiography were reviewed. Seventeen patients who had a history of cervical surgery were excluded. Finally, 185 patients who underwent both cervical plain radiography and bone mineral density (BMD) scans were included in this study. All patients fulfilled the American Rheumatism Association RA criteria [12]. All study participants provided informed consent, and the study design was reviewed and approved by the Ethical Committee for Clinical Research at Yokohama City University Medical Center.

Radiological findings and BMD data were collected from the electronic medical records. Clinical data on RA included age at RA onset and RA disease duration, and data on current medications including the use of prednisolone, methotrexate (MTX), and biological agents were also obtained. In addition, the Disease Activity Score based on C-reactive protein (DAS28-CRP) was reviewed. The patients were administered the following biological agents: abatacept (n=17), etanercept (n=12), infliximab (n=10), tocilizumab (n=8), certolizumab pegol (n=5), adalimumab (n=3), and golimumab (n=1).

The BMD of the lumbar spine and femoral neck was measured using Hologic Horizon A dual X-ray bone densitometry (Hologic, Marlborough, MA, USA). The BMD is described as a young adult mean score. We divided the patients into two groups based on the results of their radiographic evaluation of the cervical spine: the cervical-lesion group included patients with AAS, VS, or SAS, and the non-cervical-lesion group included patients with no cervical lesions. In the cervical-lesion group, we subdivided the patients into two subgroups: the VS group that included patients with VS, and the non-VS group that included patients with no VS.

Radiographic evaluation

Lateral cervical radiographs were obtained in neutral, extension, and flexion positions. We measured the atlantodental interval, Ranawat value, and subluxation. AAS was defined as atlantodental interval more than 3 mm [13], VS was defined as a Ranawat value less than 13 mm [14], and SAS was defined as vertebral translation more than 2 mm without osteophyte formation [15].

Statistical analysis

The results are expressed as mean $\pm$ standard deviation. Statistical comparisons between the groups were performed using the student's t-test, Mann-Whitney U test, chi-square test, or Fisher's exact test as appropriate. Multivariate logistic regression analysis was performed to assess the risk factors of cervical lesions. *P*-values of less than 0.05 were considered statistically significant. All statistical analyses were performed using JMP 12 (SAS Institute Inc., Cary, NC, USA).

Results

The enrolled patients included 12 males and 173 females with a mean age of 67.1 years. The mean age at RA onset was 52.9 years, and the mean RA disease duration was 14.3 years (Table 1).

There were 106 (57%) patients in the cervical-lesion group and 79 (43%) patients in the non-cervical-lesion group. There were 78 patients with AAS, 42 with SAS, and 31 with VS.

In the univariate analysis comparing the cervical-lesion and non-cervical-lesion groups, the age at onset and BMD of the femoral neck in the cervical-lesion group was significantly lower than that in the non-cervical-lesion group. RA disease duration in the cervical-lesion group was significantly higher than that in the non-cervical-lesion group. The usage ratios of prednisolone and biological agents in the cervical-lesion group were significantly higher than those in the non-cervical-lesion group (Table 2).

Multiple logistic regression analysis revealed that RA duration, use of prednisolone, use of biological agents, and BMD of the femoral neck were significant risk factors of cervical lesions in patients with RA (Table 3). In the univariate analysis comparing the VS and non-VS groups, the BMD of the femoral neck in the VS group was significantly lower than that in the non-VS group (Table 4). However, multiple logistic regression analysis for VS development did not show any significant differences.

Discussion

In this study, the prevalence of patients with cervical lesions was 57%. RA disease duration, use of prednisolone, biological agents, and BMD of the femoral neck were identified as risk factors of cervical lesions.

The cervical spine is frequently involved in patients with RA, and neural impairment is a consequent complication. Irreversible spinal cord damage, difficulty with ambulation, respiratory dysfunction, and even sudden death can occur [2]. Once neurological deficits occur, neural impairment becomes

progressive [16], and even surgical treatment cannot prevent neurological deterioration [17]. Therefore, RA cervical lesions are still a major health concern. Several studies have reported the risk factors of cervical lesions in RA patients [6-8]. However, it has not been well investigated after the use of biological agents became more popular.

The registration of biological agents has changed the standard of care for patients with rheumatoid arthritis. The available biological agents are anti-proinflammatory cytokine therapies, such as TNF α blockers and a T cell activation inhibitor [3].

Terashima et al. reported that mutilating changes at baseline, corticosteroid administration, and previous joint surgery were predictors of severe aggravation of cervical spine instabilities in RA [8]. Kaito et al. also reported that disease duration and Steinbrocker stage were identified as independent risk factors for the incidence of cervical lesions [5]. In this study, the multivariate analysis showed that RA disease duration, use of prednisolone, use of biological agents, and BMD of the femoral neck were risk factors of cervical lesions. Although biological agents can prevent the onset of cervical lesions, pre-existing cervical lesions cannot be reversed [9].

Several studies have shown that the prevalence of cervical lesions in RA patients ranged from 32% to 57% [4-8]. Fujiwara et al. prospectively examined 173 patients to clarify the development and progression of cervical spinal involvement in RA. The incidence of cervical lesions was 43% at 12.3 years of RA and 57% at 16.5 years of RA. As follow-up proceeded, more cases of cervical lesions have become apparent, indicating that cervical lesions are progressive [6]. In Japan, biological agents were approved in 2003. This might have had an influence on stabilizing RA cervical lesions. In fact, Takahashi et al. reported that 42% of 220 patients from 2010 to 2011 had cervical spine instability. The prevalence has decreased since the approval of biological agents. However, there were no effects of MTX and biological agents on cervical instability [4]. Kaito et al. reported that the incidence of patients with RA onset after 2000 with any cervical lesions was 31.8%. Biological agents effectively prevented the emergence of new cervical lesions but could not prevent the progression of pre-existing cervical lesions [5, 9].

Our study indicated that the prevalence of patients with cervical lesions was 57%. There were 78 patients with AAS, 42 with SAS, and 31 with VS. This prevalence is higher than that in recent studies in this era of biological agents [4, 5]. This might be due to the mean RA disease duration in our study, which was 14.3 years compared to the 8.5 and 11.1 years

reported in previous studies. In addition, a large proportion of patients with more advanced diseases might be treated by the use of biological agents.

There have been few reports that described the association between RA cervical lesions and osteoporosis. Neva et al. reported that the severity of atlantoaxial disorders positively correlated with the grade of destruction in evaluated joints. Furthermore, patients with atlantoaxial disorders presented with decreased BMD of the femoral neck [10]. VS usually occurs after AAS. VS is considered to be a serious condition in patients with RA because it can be associated with a poor survival rate and sudden death [2].

Dokai et al. hypothesized that osteoporosis could affect the progression of VS. Their results indicated that VS could be induced by the collapse of the lateral masses in the upper cervical spine. The risk factors for VS development were age, RA symptom duration, and BMD (lumbar). However, they could not show a statistically significant relationship between osteoporosis and VS development [11]. In our current study, the prevalence of BMD of the femoral neck was 58.4% in the VS group, which was significantly lower than the 65.9% observed in the non-VS group. However, the difference in BMD of the lumbar spine did not show any statistical significance. This discrepancy might be due to osteophytes and endplate erosions that have been described to affect the measurement of BMD at the lumbar spine [10, 18]. Nevertheless, our results indicated that the general status of osteoporosis could contribute to the development of VS. The appropriate treatment of BMD deficiency may prevent the development of VS. Tanaka et al. reported that denosumab could prevent the progression of bone erosion in the early stage of RA and play a useful role in anti-osteoporotic therapy. However, denosumab has no effect on joint inflammation or cartilage destruction in RA [19]. The complex osteoimmunological network in patients with RA suggests that the powerful anti-inflammatory activity of biological agents beyond the control of the disease was likely to reduce osteoporosis and fracture risk [20]. Therefore, a combination of biological agents and denosumab may be effective for the prevention of VS. Further studies are required to establish these treatments.

There are several limitations to this study. First, in this cross-sectional study, we reviewed patients with varying degrees of spinal instability, and we did not consider the duration of RA treatment and the dosage of medications. This may have led to a selection bias, which may have resulted in the use of biological agents being identified as a risk factor of RA cervical lesions. Second, we did not access the data on clinical and neurological symptoms. Only patients with RA who complained of symptoms of cervical lesions were included in this study. It is possible that only more frail patients had a bone scan as opposed to all patients with RA to limit selection bias towards patients with lower BMD. Third, this was a cross-sectional study; consequently, disease activity was only reflected over a certain period of time. A longitudinal evaluation was not performed.

Conclusions

In conclusion, the prevalence of patients with cervical lesions was 57%. The incidence of RA is still a major health issue. Age at RA onset and BMD of the femoral neck in the cervical-lesion group were significantly lower in the cervical-lesion group than in the non-cervical-lesion group. RA disease duration in the cervical-lesion group was significantly higher than that in the non-cervical-lesion group. RA disease duration, usage of prednisolone, biological agents, and BMD of the femoral neck were significant risk factors of cervical lesions in patients with RA. The BMD of the femoral neck was lower in the VS group than in the non-VS group. Finally, the general status of osteoporosis could contribute to the development of VS.

Abbreviations

AAS, atlantoaxial subluxation

BMD, bone mineral density

RA, Rheumatoid arthritis

SAS, subaxial subluxation

TNF α tumor necrosis factor α

VS, vertical subluxation

Declarations

Ethics Approval and consent to participate: This study was conducted according to the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethical Committee for Clinical Research at Yokohama City University Medical Center (D1401017). All study participants provided written informed consent.

Consent for publication: Not applicable for that section

Availability of data and materials:

The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions:

YU, TI, TH were involved in study design and data interpretations. All authors critically revised the report, commented on draft of the manuscript, and approved the final report.

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Tables

Table 1. Patient demographics and clinical parameters

Number of patients	185
Age	67.1±9.7
Sex (male:female)	120:173
Age of RA onset	52.9±14.8
RA disease duration (years)	14.3±12.1
DAS28-CRP	2.6±1.1
Prednisolone	49% (90/185)
MTX	63% (116/185)
Biological agents	30% (56/185)
BMD of the lumbar spine (YAM)	83.5±17.9%
BMD of the femoral neck (YAM)	67.4±14.8%

BMD, bone mineral density; DAS28-CRP, Disease Activity Score based on C-reactive protein; MTX, methotrexate; YAM; young adult mean

Table 2. Comparison between the cervical and non-cervical lesion groups (univariate analysis)

	cervical lesion group (n=106)	Non-cervical lesion group (n=79)	P-value [‡]
Sex (male:female)	60:100	60:73	0.60
Age (years)	66.9±9.3	67.5±10.2	0.66
Age of onset (years)	49.1±14.5	57.8±13.9	<0.01
RA disease duration (years)	17.9±12.3	9.6±10.2	<0.01
DAS28-CRP	2.5±1.1	2.6±1.3	0.76
Prednisolone	58% (61/106)	37% (29/79)	<0.01
MTX	60% (64/106)	66% (52/79)	0.45
Biological agents	53% (56/106)	19% (15/79)	<0.01
BMD of the lumbar spine (YAM)	81.3±17.8%	85.9±17.8%	0.09
BMD of the femoral neck (YAM)	64.6±12.4%	70.6±16.6%	<0.01

BMD, bone mineral density; DAS28-CRP, Disease Activity Score based on C-reactive protein; MTX, methotrexate; RA, rheumatoid arthritis; YAM, young adult mean.

[‡]P-value was calculated using the chi-square test, student's t-test, or Mann-Whitney U test.

Table 3. Multivariate analysis for risk factors of the cervical lesions

	P-value	Odds ratio	95% CI
RA disease duration	<0.01	22.32	4.80-122.29
Biological agents	0.013	2.63	1.22-5.90
Prednisolone	<0.01	3.13	1.55-6.54
BMD of the femoral neck	<0.01	0.05	0.005-0.353

BMD, bone mineral density; CI, confidence interval; RA, rheumatoid arthritis.

Table 4. A comparison between with or without VS group (univariate analysis)

	VS group (n=31)	Non-VS group (n=75)	P-value [‡]
Sex (male:female)	4:27	2:73	0.06
Age (years)	65.5±10.4	67.4±8.8	0.35
Age of onset (years)	45.4±12.0	50.6±15.2	0.09
RA duration (years)	19.9±9.8	17.1±13.1	0.11
DAS28-CRP	3.1±1.2	2.4±1.1	0.07
Prednisolone	68% (21/31)	53% (40/75)	0.17
MTX	52% (16/31)	64% (48/75)	0.24
Biological agents	42% (13/31)	37% (28/75)	0.66
BMD of the lumbar spine (%)	81.9±20.0	80.4±17.6	0.71
BMD of the femoral neck (%)	58.4±14.8	65.9±11.6	<0.05

BMD, bone mineral density; DAS28-CRP, Disease Activity Score based on C-reactive protein; MTX, methotrexate; RA, rheumatoid arthritis; VS, vertical subluxation.

[‡]P-value was calculated using the Fisher's exact test, Mann-Whitney U test, student's t-test, or chi-square test