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Increased Mortality Rate in Rheumatoid Arthritis Patients with Neurological Symptoms or Signs Secondary to Cervical Spine Subluxations – Reduced Mortality if Postoperative Ankylosis is Achieved

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1. Introduction

Patients in Norway with rheumatoid arthritis (RA) and involvement of the cervical column with subluxations during the years 1974-1999 were routinely referred to the Rheumasurgical Department of Oslo Sanitetsforening's Rheumatism Hospital in Oslo (OSR) for critical evaluation, treatment and follow-up. The patients were recruited from a large and widely dispersed area of the country.

The primary aim of the current study was to assess the mortality rate of operated patients with cervical neurological symptoms or signs in this cohort and compare the results with RA patients operated during the same period for cervical involvement without relevant neurology. Secondarily we wanted to disclose important factors affecting the mortality rate in operated RA patients with neurology. The results for the total RA population with cervical subluxations (n=532) treated during the same 25 year period (217 operated and 315 non-operated) have been published previously (Paus et al., 2008).

2. Material and methods

2.1 Patients

All patients referred with RA and neurological symptoms or signs related to involvement of the cervical column, were consecutively included from 1974 in the present prospective cohort study. Patients with other differential diagnoses, e.g. spondyl-arthritis, were excluded. After the end-point on December 31st 1999, all medical journals of included patients were revisited.

During this period 75 patients with RA and cervical spine subluxations with cervical radiculopathy, myelopathy or paresthesia were operated on in our department. There were 54 females (72%) and 21 males (28%) with a mean age at the first visit of 60 (SD, 11.9) years.

The RA diagnosis had been made at the mean age of 41 (SD, 13.7) years. By the end-point date, 51 (68%) patients had died at a mean age of 69 (SD, 9.3) years (Table 1).

	Operated with Neurology	**Operated without Neurology**	**Total**
Total number	75	142	217
Female/male	54/21	99/43	153/64
Age at RA diagnosis	41 (13.7)	39 (14.1)	40 (13.9)
Age at first visit	60 (11.9)	56 (12.3)	57 (12.3)
Age at operation	61 (11.5)	58 (12.0)	59 (11.9)
Follow-up period (years)	6.7 (5.5)	9.8 (5.8)	8.5 (5.9)
No of dead patients (%)	51 (68)	93 (65)	144 (66)
Age at death	69 (9.3)	69 (11.0)	69 (10.5)

Table 1. Various Data of Operated RA Patients with Cervical Subluxation with and without Neurological Symptoms or Signs. Mean Values with Standard Deviations (SD)

The total number of patients with RA and cervical problems operated in the neck during the same period was 217 patients, i.e. 142 patients without relevant, specific neurology.
The follow-up period after surgery till death or to Dec 31st 1999 for all the operated patients (n=217) was mean 8.5 (SD, 5.9) years, for those with relevant neurology (n=75) mean 6.7 (SD, 5.5) years and for those without (n=142) mean 9.8 (SD, 5.8) years. Fifty one (68%) of the patients with relevant neurology, and 93 (65%) of the patients without, died during the follow-up.
The defined selection criteriae for surgical intervention were existing or increasing atlantoaxial or subaxial subluxations above certain limits. The patients had cervical symptoms (e.g paresthesia) or neurological signs (e.g loss of sensibility, paresis or increased reflexes) from radiculopathy or myelopathy in addition to unspecific local pain not responding to conservative treatment. The neurological findings were paresthesia in 35 patients, paresis in 32, acute radiating pain in the arm(s) in 15, hyperreflexia in 14 and difficulties with urinary control in 8 patients. The localisation was in the upper extremity in 63 (84%), in the lower limb in 41 patients (55%) and in both extremity levels in 29 (39%) patients.
The aims of the operations were to remove or reduce neurological symptoms and signs with pain, stabilize the cervical spine to prevent further subluxations both horizontally and vertically, and to prevent future neurological involvement.
The medical treatment for the patients' RA was continued by the referring rheumatologist.
Operative methods changed over time, and different techniques were used with or without decompression of the spinal canal, depending on the type of cervical instability. Initially, atlantoaxial (AA) fusion would also include additional fusion to the occiput (Brattstrom & Granholm, 1976) but later AA fusion included spondylodesis of atlas and axis only. The applied methods consisted of fixation of occiput to atlas and axis in 12 patients (16%; two combined with laminectomy), fixation of atlas to axis only in 37 patients (49%; 5 of these in combination with laminectomy), 18 patients (24%) had a posterior fusion further down the cervical spine (16 of these combined with laminectomy), and 8 had laminectomy only (Table 2). The need for laminectomy was significantly (p<0.001) higher in the cohort with cervical neurology (31/75) than in the cohort of patients without (5/142).

	All	Alive	Dead
Number	75	24 (32)	51 (68)
Operated with arthrodesis	67 (89)	18 (75)	49 (96)
Arthrodesis Occiput - C1 - C2	12 (16)	4 (17)	8 (16)
Arthrodesis C1 – C2	37 (49)	8 (33)	29 (57)
Arthrodesis below C1 – C2	18 (24)	6 (25)	12 (24)
Laminectomy	31 (41)	11 (46)	20 (39)
Postoperative ankylosis	51 (76)	18 (100)	33 (67)
Reoperation refixation	3 (4)	1 (6)	2 (4)
Reoperation cement removal	1 (1)	0	1 (2)
Release nervus occipitalis major	2 (3)	0	2 (4)

Table 2. Operated RA Patients with Cervical Subluxation and relevant Neurology. Levels of Fixation, Frequency of Laminectomy and Postoperative Results with Complications and Reoperations. Distribution among Alive and Dead during the Follow-up Period. Absolute Numbers (percentages)

2.2 Radiology

The diagnosis of instability was made from conventional lateral radiographs of the cervical spine in maximum extension and maximum flexion (Karhu et al., 2005; Kauppi & Neva, 1998; Kwek et al., 1998). Functional radiographs were often combined with plain tomography, and later during the study period with computer tomography (CT) or magnetic resonance imaging (MRI).

Radiographs were scored according to Teigland et al (1990) measuring both the anterior subluxation (AS) of atlas relative to axis and the vertical settling (VS) of atlas on axis measured as the so called 'AC distance'. In addition all posterior subluxations (PS) and subaxial subluxations (SS) were registered. The radiographs were not calibrated directly for distance measurements, but all examinations were taken in the same laboratory with the same equipment and with a standard distance and positioning of the head and neck relative to the film during exposures. The numbers and mean values of cervical spine subluxations for the various subgroups of patients are presented in Table 3. Bony ankylosis was evaluated by examination of ordinary 2-plane cervical radiographs.

2.3 Statistical analysis

Values are presented as absolute numbers N (proportions) or mean (SD). Student's t-test and chi square test were used for testing group differences for continuous and categorical variables, respectively. Cox Proportional Hazard regression analysis was used to identify possible predictors for survival. As reference point for the time-to-event analyses we used the time at operation. Martingale residuals were used to assess the validity of the models. As the assumption of proportionality of the hazard rates was violated, an interaction term between the indicator for cervical neurology and the time variable 'years survival following operation' was included in the final model.

All P-values equal to or below 0.05 were considered statistically significant. Statistical analyses were performed with SPSS software, version 12.0 (SPSS Inc., Chicago), R (R Foundation for Statistical Computing, http://www.R-project.org) and Statistical Analysis System (SAS version 9.1.3; Cary, North Carolina, USA).

	Total N	AS (mm)	VS (mm)	SS N (%)
All	217	10.7 (3.6)	19.7 (7.0)	25 (12)
Alive	73	10.9 (3.4)	21.2 (5.9)	7 (10)
Dead	144	10.5 (4.0)	18.8 (7.5)	18 (13)
Operated with neurology	75	9.4 (4.5)	18.2 (8.3)	23 (31)
Alive	24	9.6 (4.6)	20.6 (7.6)	7 (29)
Dead	51	9.3 (5.2)	16.9 (8.6)	16 (31)
Operated without neurology	142	11.2 (2.9)	21.1 (5.3)	2 (1)
Alive	49	11.5 (2.4)	21.7 (4.3)	0
Dead	93	11.1 (3.1)	20.7 (5.9)	2 (2)

AS - Anterior subluxation
VS - Vertical settling
SS - Subaxial subluxation(s)

Table 3. Cervical Spine Subluxations in Operated RA Patients with and without Neurological Symptoms or signs. Distribution among Alive and Dead during the Follow-up Period. Total Numbers, Mean values with Standard Deviations (SD)

3. Results

In the group of patients with neurological signs or symptoms 66 patients (88%) had per definition (Teigland et al., 1990) a pathological AS of more than 2 mm, with an average of 10.7 (SD, 3.8) mm, and 40 patients (53%) had an AS of more than 10 mm, with an average of 13.2 (SD, 2.0) mm. In 24 patients (32%) the VS was 25 mm or less (normal values 30 mm or more), with 9 patients (12%) having an impaction between 5 and 9 mm, and 15 patients (20%) an impaction of 10 mm or more. In 23 patients (31%) SS was found in the cervical column, in 10 patients at 1 level, 6 patients at 2 levels, 2 patients at 3 levels, and in 5 patients at 4 levels. The levels were C2/C3 in 10 cases, C3/C4 in 15 cases, C4/C5 in 13 cases and C5/C6 in 10 cases. There was a significantly (p<0.001) higher incidence of SS in the group of patients

	Operated with Neurology N (%)	Operated without Neurology N (%)	*P*
Moderate AS 3 – 10 mm	26 (35)	32 (22)	0.055
Severe AS > 10 mm	40 (53)	107 (73)	0.001
Moderate VS 21 – 25 mm	9 (12)	13 (9)	0.13
Severe VS ≤20 mm	15 (20)	14 (10)	0.04
SS at one level	10 (13)	2 (1)	< 0.001
SS at two or more levels	13 (17)	0 (0)	< 0.001

AS - Anterior subluxation
VS - Vertical settling
SS - Subaxial subluxation(s)

Table 4. Operated RA Patients with Cervical Subluxation with (N=75) and without (N=142) Neurological Symptoms or signs. Severity of Dislocations Distributed between the two Groups with Statistical Differences. Absolute Numbers (percentages)

with cervical neurological symptoms or signs. In the group of patients operated without relevant neurology there were only 2 patients with SS. The incidence of severe VS was higher in the group of patients with relevant neurology (p=0.04). Interestingly, severe AS was significantly higher in the group of patients without relevant neurology (p=0.001) (Table 4).
The survival rate of the studied cohort with neurological symptoms or signs was significantly reduced (p<0.001) when compared to the cohort of RA patients without relevant neurology operated for involvement of the cervical column (Figure 1).

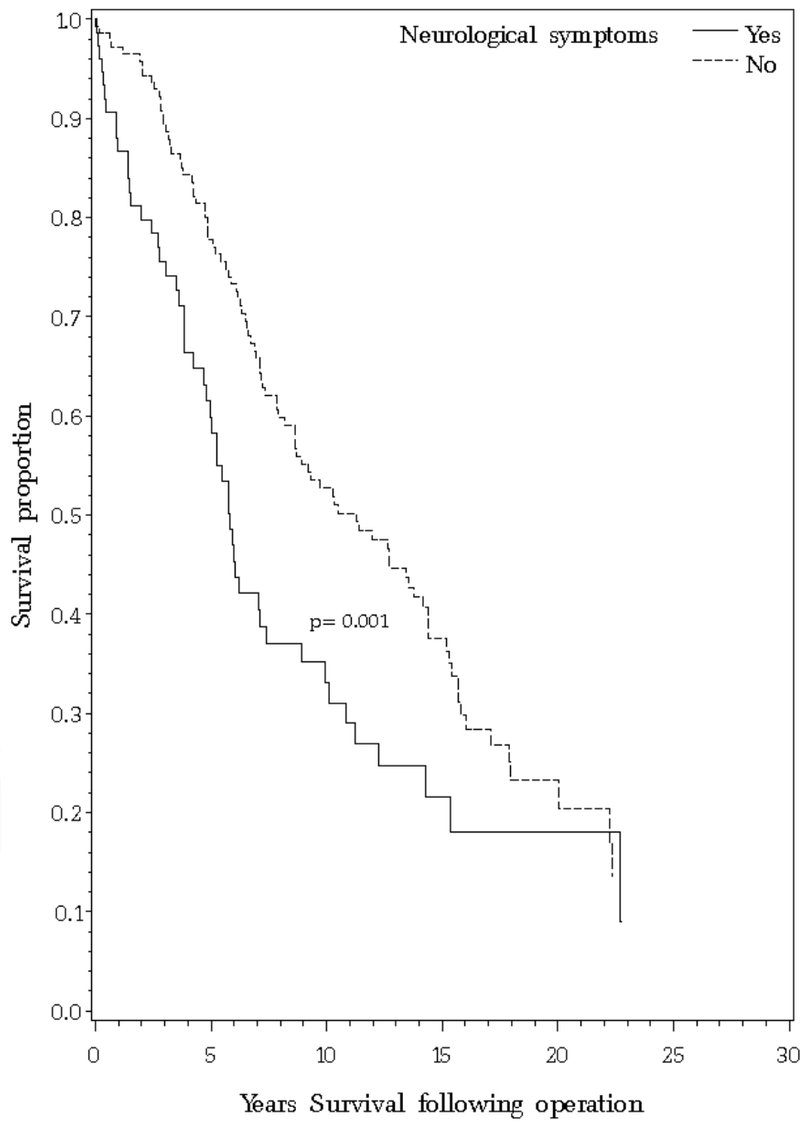

Fig. 1. Survival for operated RA patients with and without preoperative cervical neurological symptoms and signs.

The presence of a significant interaction term (p=0.015) indicates that the hazard for death changes over time postoperatively for the group with cervical neurological findings. The hazard ratio for this group compared with the group without relevant neurology starts at 2.69 for the first time period following operation decreasing to 2.47 at about 6 years postoperatively, indicating that the postoperative hazard ratio is different for the group with relevant neurology than for the group without. The older the patient is at operation, the hazard for death increases with 6% for each year of age (p<0.001), and the patients with relevant neurology have a 169% increased hazard each year (p=0.001). We also calculated that males have a 40% higher annual risk, but this difference was not statistically significant (p=0.07) (Table 5).

	HR	**95% CI**	***P***
Age at operation	1.06	1.04 - 1.08	< 0.001
Neurology as indication for operation	2.69	1.48 - 4.88	0.001
Time of follow-up	0.92	0.85 - 0.99	0.03
Gender	1.40	0.97 - 2.00	0.07

HR indicates Cox proportional hazard ratio; CI=95% Confidence interval

Table 5. Cox Proportional Hazard Ratio Regression for Survival in Operated Patients with and without Neurological Symptoms or signs.

Postoperatively 7 (9%) of the patients experienced residual neurological symptoms or signs. None of these were alive at the end of the study, indicating a poor prognosis for patients with residual cervical neurology after surgery (p=0.015).

In 4 patients (5%) reoperation was performed: rearthrodesis in 3 patients, fistula with removal of cement in 1. Additional operation with local superficial release of the greater occipital nerve was necessary in 2 patients (Table 2)

Among those still alive at the end of the follow-up 18 patients had had an arthrodesis performed, and all of these developed bony ankylosis. In the group of patients that died during the follow-up period 49 had had an arthrodesis performed, but only 33 achieved bony ankylosis which is a significantly poorer result (p=0.004).

Only 3 of the patients without neurological symptoms or signs before the operation developed relevant neurology during the follow-up period.

4. Discussion

RA is an independent risk factor for increased mortality (Hakoda et al., 2005; Sihvonen et al., 2004). When the cervical spine is involved this risk is increased (Paus et al., 2008; Riise et al., 2001; Shen et al., 2004). In the RA population the estimates of the number of patients with cervical involvement varies from 12% (Naranjo et al., 2004) to 57% (Neva et al., 2006).

Cervical spinal disorders should be diagnosed early and treated actively to prevent severe and potentially fatal complications (Neva et al., 2006). Early surgery corrects AS and prevents further instability (Grob et al., 1999; Hamilton et al., 2001; McRorie et al., 1996). Early surgery may also reduce mortality (Grob, 2000; Paus et al., 2008; Tanaka et al., 2005). Posterior fusion reduces pain and may improve neurological symptoms or signs (Eyres et

al., 1998; Matsunaga et al., 2003) as well as preventing progression of existing neural lesions without undue risk for the patient (Kim & Hilibrand, 2005; Santavirta et al., 1988).

When cervical neurological symptoms or signs have developed, the literature agrees that there is indication for operative treatment (Kim & Hilibrand, 2005). In addition to reducing pain, neurological recovery is more consistent with lower grade of preoperative myelopathy (Monsey, 1997). An autopsy study suggests that paralysis may be due to both mechanical neural compression and vascular impairment (Delamarter & Bohlman, 1994).

It is claimed that patients with no clear radiographic evidence of fusion following occipitocervical instrumentation seemed to do just as well as those who have obvious fusion (Moskovich et al., 2000). In our total series of patients (Paus et al., 2008) we came to the same conclusion. However, when we consider the most severely affected patients (i.e. those with neurological symptoms or signs as in the present study), we find a significant better prognosis if ankylosis is achieved. To obtain a higher proportion of bony ankylosis we have changed operative method from Brattstrøm and Granholm (1976) to transarticular screws (Claybrooks et al., 2007; Cornefjord et al., 2003; Haid, Jr. et al., 2001; Henriques et al., 2000; Praveen & Regis, 2005) after this study.

In our minds, based on the present findings, patients with relevant neurology are late for operation, their prognosis being worse, and we advise that operative treatment is initiated prior to the development of neurological symptoms or signs. We disagree with the routine of conservative treatment until neurological complications develop. Residual neurological deficit following operation also resulted in a reduced prognosis in the present study, indicating that delayed treatment may be hazardous.

The high incidence of neurological involvement in patients with SS is well described in the literature (Moskovich et al., 2000; Stirrat & Fyfe, 1993), and we find that this group of patients has a worse prognosis. Our conclusions regarding these patients are more cautious as the operative procedure is more elaborate and carries a higher risk of morbidity, but despite this these patients may benefit from operation prior to the development of neurological complications.

VS can be stopped by AA fixation (Grob, 2000) and patients with neurological symptoms or signs have a significantly more serious settling. In patients with VS, early fixation may reduce the danger of developing neurological complications.

AS is the most frequently occurring dislocation in the spinal neck with an increasing number with increasing severity in both operated groups. However, severe AS is significantly more frequent in the non-neurological group, while SS and VS are over-represented in the group with relevant neurology. This suggests a weak association between degree of AS per se and neurological phenomena. In the non-neurological group, the majority of patients are operated related to severe AS. As neurological symptoms or signs with indication for surgery may develop before severe AS occurs in patients with SS and VS, this may explain the reduced number with severe AS in the group with relevant neurological findings.

5. Conclusion

Development of neurological symptoms or signs in RA patients with cervical subluxations significantly increases the mortality rate. It is therefore important to diagnose these patients

early and if possible operate prior to the development of neurological complications. Early surgical intervention will reduce the patients' local symptoms as well as the danger of developing neurological complications which most likely will decrease their life-time expectancy.

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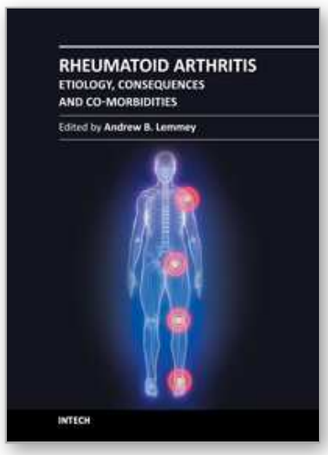

Rheumatoid Arthritis - Etiology, Consequences and Co-Morbidities
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The purpose of this book is to provide up-to-date, interesting, and thought-provoking perspectives on various aspects of research into current and potential treatments for rheumatoid arthritis (RA). This book features 16 chapters, with contributions from numerous countries (e.g. UK, USA, Japan, Sweden, Spain, Ireland, Poland, Norway), including chapters from internationally recognized leaders in rheumatology research. It is anticipated that Rheumatoid Arthritis - Etiology, Consequences and Co-Morbidities will provide both a useful reference and source of potential areas of investigation for research scientists working in the field of RA and other inflammatory arthropathies.

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