EXTENDED REPORTS

Neuropathology of the brainstem and spinal cord in end stage rheumatoid arthritis: implications for treatment

Fraser C Henderson, Jennian F Geddes, H Alan Crockard

Abstract

Objective—To study the detailed histopathological changes in the brainstem and spinal cord in nine patients with severe end stage rheumatoid arthritis, all with clinical myelopathy and craniocervical compression.

Methods—At necropsy the sites of bony pathology were related exactly to cord segments and histological changes, and correlated with clinical and radiological findings.

Results—Cranial nerve and brainstem pathology was rare. In addition to the obvious craniocervical compression, there were widespread subaxial changes in the spinal cord. Pathology was localised primarily to the dorsal white matter and there was no evidence of vasculitis or ischaemic changes.

Conclusions—Myelopathy in rheumatoid arthritis is probably caused by the effects of compression, stretch, and movement, not ischaemia. The additional subaxial compression may be an important component in the clinical picture, and may explain why craniocervical decompression alone may not alleviate neurological signs.

(*Ann Rheum Dis* 1993; 52: 629–637)

Rheumatoid arthritis is a systemic disease affecting the cervical spine in 16–88% of patients.^{1–6} Progressive subluxation is common,^{7–9} associated with increasing compression of the spinal cord and brain stem,^{5 10–15} and may cause clinical myelopathy and even sudden death.^{3 16 17} Despite these clinical effects, the pathophysiology and histopathology of cord and brain stem injury due to this type of compression are poorly understood, and there are only two studies available in which changes in the cord are described in any detail.^{4 18} As part of our wider study of cervical myelopathy in over 250 patients with rheumatoid arthritis we performed a detailed histopathological study of the spinal cord and brain stem in nine patients, and compared the findings with clinical and radiological features.

Methods

This study includes nine patients with seropositive rheumatoid arthritis (eight women, one man) from our ongoing prospective study, who underwent necropsy at the National Hospitals for Neurology and Neurosurgery between 1987 and 1991. All patients were evaluated by rheumatologists, a neurosurgeon (HAC), two neuroradiologists, a physiotherapist, and a research nurse. The clinical assessment included a full neurological examination and a detailed questionnaire about neurological symptoms. In addition, all patients were graded according to Ranawat *et al*¹⁹ and Steinbrocker *et al*.²⁰ The radiological assessment included plain lateral films of the cervical spine and high definition computed myelotomography with multiplanar reformatting.²¹ All operations were carried out by or under the direction of the same surgeon (HAC). Necropsies were performed by or under the supervision of the same neuropathologist (JFG). The necropsy technique used to remove the foramen magnum and cervical spine with the cord and medulla intact has been described previously.²²

Multiple transverse blocks of the cord were taken, and sections stained with haematoxylin and eosin, luxol fast blue, Woelche, Heidenhain, and modified Bielchowsky stains. Reticulin, Nissl, van Gieson, periodic acid-Schiff, and glial fibrillary acidic protein (Dako; 1:400) stains were performed on selected blocks.

Pre-operative results

CLINICAL FINDINGS

The table gives a summary of the principal clinical details.

The nine patients presented in this study were all white with longstanding seropositive rheumatoid arthritis, aged 47–72 years (average age 60 years, median age 64 years). The only man in the study was the youngest patient.

All patients had been treated with steroids during the course of the disease, three with gold and one with the addition of azathioprine. One other patient had azathioprine without gold.

Department of
Neurosurgery,
National Naval
Medical Center,
Bethesda,
MD 20814-5011, USA
F C Henderson

Department of
Morbidity Anatomy,
London Hospital
Medical College,
Turner Street,
London E1 1BB,
United Kingdom
J F Geddes

Department of
Surgical Neurology,
The National Hospital
for Neurology and
Neurosurgery,
Queen Square,
London WC1N 3BG,
United Kingdom
H A Crockard

Correspondence to:
Dr Crockard.

Accepted for publication
20 May 1993

Six of the nine patients presented with rapid neurological deterioration over three to 32 weeks (average 11 weeks, median 12 weeks). Patients 1, 6, and 9 had longstanding myelopathy.

Symptoms on presentation included neck pain (8/9), occipital neuralgia (8/9), hand numbness (7/9), weakness—usually arms weaker than legs—(8/9), incontinence or urinary retention (4/9), dysphagia (3/9), and dyspnoea (2/9).

Cranial nerve examination was normal in all patients. A corneal ulcer was found in patient 5, but the trigeminal nerve function was normal.

Somatosensory evoked potentials and motor evoked potentials were attempted in six patients and results obtained in four. Sleep studies of respiratory function were obtained in three. These are the subject of another study.

RADIOLOGICAL FINDINGS

The atlantodental interval varied from 1 to 11 mm (average 4.7 mm, median 3 mm). There was, however, marked vertical subluxation of the axis in all nine patients, measuring 9–26 mm using the technique described by Redlung-Johnell and Pettersson.²³ The tip of the odontoid process impinged on the upper medulla in patients 1, 8, and 9. Prominent backward tilting of the dens was present in patients 2 and 5 with compression of the medulla and upper cord at the level of C1. Patient 6 had medullospinal compression only during flexion (fig 1). The remaining patients showed cord compression by the dens at the C1 level. Major posterior compression from the neural arch of C1 was apparent only in patient 7.

Subaxial bony changes were present in 8/9 patients. Only patient 6 had a normal subaxial spine (see table).

OPERATIVE FINDINGS AND COMPLICATIONS

All patients were referred for surgery because of craniocervical junction compression or instability, or both, and, according to criteria outlined elsewhere,²⁴ had transoral odontoidectomy and decompression of the dura. Under the same anaesthesia a posterior occipitocervical stabilisation with a Ransford loop and sublaminar wire fixation was carried out. One patient (patient 5) was so ill because of respiratory insufficiency that an operation was never considered. None of the patients in this study required only posterior stabilisation without anterior decompression. Thus our patients had the most severe atlantoaxial compression.

In three patients there were problems related to the passage of sublaminar wires. Two were weaker after the operation (patients 1 and 4), a third patient (patient 8) improved initially, but was readmitted six weeks later as a quadriplegic; radiographs revealed 'cut out' of the sublaminar wire at several levels and a severe subaxial cord compression at C5/6.

Other causes of death included haemorrhage (patients 2 and 7), abscess (patient 6), pneumomediastinitis (patient 3), and myocardial infarction (patient 9).

GROSS PATHOLOGICAL FINDINGS

The vertebral artery was patent in all specimens. In seven of the eight patients in whom an operation was performed, the odontoid process and variable amounts of C2 had been resected. In five of the nine patients the upper cervical cord was compressed and flattened by the residual body of C2, and the anteroposterior diameter of the upper two cervical segments was correspondingly much reduced. In patient 1 the arch of C1 was assimilated to the occiput. In patient 7 the foramen magnum diameter was reduced. In three patients there was a markedly reduced

Figure 1 Coronal and sagittal reformatting through the craniocervical junction in patient 6 after myelotomy. The broken line indicates the plane of coronal reformat on the sagittally reformatted image. (A) The odontoid process and lateral masses of the atlas and axis are eroded. (B) The brainstem is angulated and compressed by the subluxed axis. There is also mild neuraxial deformity caused by subluxation of the axis on the body of C3. (C) The neuraxis is compressed on the right by granulation tissue. (D) The neuraxis has 'telescoped' through the ring of C1. The posterior ring of the atlas is tilted upward, and the anterior arch tilted downward causing a 'pseudo-reduction' of the atlantodental interval.

Summary of clinical and radiological findings

Patient No	Age (years)/sex	Duration of disease (years)/drugs received	Findings before operation	Ranawat/American Rheumatism Association grades	mm Vertical axial subluxation/ADI (mm)/CSA cord (mm ²)*	Subaxial changes	Operative findings	Findings after operation	Time from operation to death (days)
1	47/M	25/gold	Normoreflexia, quadriparesis, normal sensation	IIIb/4	23/11/60	Fibrous, ankylosis C2–C6	Fibrous pannus, C1 fracture, anterior C1 fused to clivus	Neurologically unchanged, tetraplegic on day 2	56
2	58/F	11	Spastic quadriparesis, suspended sensory loss	IIIa/3	17/1/40	Subluxation C6–7 with stenosis	Florid pannus	Dysphagia, walking, day 29 haemoptysis, metabolic disturbance	30
3	72/F	16	Incontinence, spastic quadriparesis, weak triceps, dissociated sensory loss, L'Hermittes sign	IIIb/4	9/6/36	Severe spondylosis, C5–6 ventral osseous bar	Fibrous pannus, C1 fused to peg	Laryngeal oedema, tracheal perforation, mediastinitis	11
4	70/F	55	Urinary retention, spastic quadriparesis, sensory level C7	IIIb/4	12/11/40	C5–6 subluxation, severe kyphosis (45°), pannus, myelographic block at C7	Florid pannus	Left side weaker, respiratory arrest, SIADH	11
5	54/F	16/azathioprine	Dyspnoea, dysphagia, corneal ulcer, incontinence, spastic quadriparesis, hypoaesthesia below C4, incontinence, anaesthetic C4 down	IIIb/4	26/1	Subluxation C4 on C5 with ventral osseous bar	No operation performed (severe asthma)		31 days after admission
6	63/F	25/gold	Bilateral deltoids and triceps weakness, ankle clonus	IIIa/3	22/0/81	None	Fibrous pannus	Neurologically unchanged until day 28, abscess C5–6, quadriplegic	39
7	64/F	25	Dysphagia, urine retention, spastic quadriparesis, hemianaesthesia	IIIb/4	19/17/35	Subluxation C3–4	Florid pannus	Day 7 posterior pharyngeal haemorrhage	7
8	64/F	8/gold and azathioprine	Dyspnoea, mild leg weakness, normal sensation	II/3	24/3/68	Staircase spine C2–T1, marked subluxation C5–6	Fibrous pannus, wire pulled through laminae	Weak right arm day 42, quadriplegic with myelographic block C5–6	49
9	68/F	32	Dysphagia, spastic quadriparesis, diffuse sensory loss	IIIb/4	21/5/29	Subluxation C3–4, minor subluxation C5–6, C6–7, C8–T1	?Pannus	Lower gastrointestinal haemorrhage, cardiac arrest	18

*ADI=atlantodental interval; CSA=cross sectional area of spine at point of maximum compression (at foramen magnum) with neck in extension; SIADH=syndrome of inappropriate centidiuretic hormone.

clivoaxial angle with concomitant kyphus or flexion of the medulla (patients 6, 8, and 9).

Significant subaxial pathology was present in eight spines in keeping with the radiological findings: fibrous ankylosis, disc erosion with subluxation (often at multiple levels), vertebral body collapse, and ventral bars (hard discs). Figure 2 shows the appearances in a typical case (patient 8) once the fixed spine had been hemisected, and the cord replaced in the spinal canal. In two patients the Ransford loop sub-laminar wires had partially cut through the osteoporotic bone (patients 2 and 8).

NEUROPATHOLOGY

Figure 3 summarises the histological findings in four representative patients.

With the exception of gliosis of the trigeminal nucleus (patient 8), and mild unilateral changes in the hypoglossal and dorsal motor nuclei of the vagus (patient 2), the cranial nerve nuclei were normal.

Where the compression was most severe, the cord was fragmented and necrotic. At the levels where the cord was less severely compressed, the pathology was localised principally to the

dorsal white matter, which was oedematous and showed axonal disruption. In one cord (patient 1) a circumscribed area of columnar necrosis ('pencil heterotopia') was seen in the ventral part of the dorsal columns, extending some way below the site of maximum compression, with ependymal cells and a degenerated anterior horn cell from a higher cord segment being found in necrotic debris dorsal to the central canal in the lowest segment, suggesting that the necrotic debris had been mechanically extruded away from the site of compression.

Milder degrees of compression produced milder changes, notably oedema, axonal and myelin loss. The most consistent changes were in the dorsal columns, the cuneate fascicle usually being more severely affected than the gracile. At one level in one cord (patient 5) the anterior horns were necrotic; otherwise the only histological change seen in the grey matter was that of anterior horn cell chromatolysis. Although it was present at several levels in eight of the nine cords, this phenomenon was variable; in any one section from one cell to several cells were chromatolytic. There was no anterior horn cell loss.

Figure 2 Patient 8. The hemisected cervical spine with the cervical cord replaced in the canal. The odontoid process has been resected. There is cervical stenosis at most levels. The C3-4 and C4-5 discs are partly haemorrhagic. The C5-6 disc was obliterated, and C5 was mobile on C6, producing cord compression. Lesser degrees of subluxation were present at the C2-3 and C4-5 level. The hole in the body of T1 has been made for reference purposes.

In all the cords, the pia-arachnoid was focally thickened at points of compression with chronic inflammation in several instances. There was hyalinisation of intramedullary arterioles. No evidence of vasculitis or vascular thrombosis was seen in any patient, and apart from the grey matter infarction in patient 5, there were no changes that might be interpreted as ischaemic.

Discussion

NEUROPATHOLOGY

Ours is the largest study of the neuropathology of the brain stem and spinal cord in rheumatoid patients; only three similar cases have previously been reported in any detail.^{4 18} Although our patients clearly had exceptionally severe end stage disease, requiring surgical intervention, we consider that our clinical and

pathological findings throw light on the pathogenesis of cord damage in rheumatoid arthritis. The histopathological changes were localised principally to the dorsal white matter of the cord, and included oedema, axonal swellings or balloons (fig 4), and necrosis. The localisation of pathology in the dorsal half of the cord was, at first sight, surprising given that the compression was ventral in most patients, but this phenomenon has been demonstrated by Breig,²⁵ who in a series of careful and detailed cadaver experiments, showed that a ventral deforming force caused tearing and fissure formation in the dorsal half of the cord.

Another common finding was of central chromatolysis of the ventral horn cells at most cervical levels. We believe this to have resulted from mechanical injury to the axons at the root level, although other aetiologies have been suggested in experimental work.²⁶

Other workers have noted the same selective injury of the cuneate fascicles with relative sparing of the gracile fascicles in studies of atlantoaxial subluxation, cervical spondylosis, rheumatoid arthritis, and cervical radicular disease.^{4 18 27-31} This selective injury is not unique to rheumatoid arthritis. Nevertheless, no-one has yet offered an explanation as to why the cuneate fascicle should, in these disorders, suffer more injury than the gracile fascicle.

Could the changes we observed have been the result of surgical trauma? Trauma to the spinal cord typically results in central cord injury, red cell extravasation or frank haemorrhage, hyperaemia, and cellular reaction with the accumulation of polymorphs and later lymphocytes.³²⁻³⁶ None of our findings remotely resembles these descriptions and thus we are disinclined to attribute the findings to the operation.

PATHOLOGICAL MECHANISMS

We have considered various aetiologies to explain the preponderance of dorsal pathology, the selective injury of the cuneate fascicles, and the widespread central chromatolysis of ventral grey neurones. Some of the theories are considered in the following.

Vascular

Compression or disease of the vertebral and anterior spinal arteries are often cited as aetiological factors to spinal cord pathology in rheumatoid and other diseases.^{4 18 31 37-39} Others have implicated intraforaminal compression of important medullary feeding vessels.⁴⁰⁻⁴⁵ We observed no changes of acute or chronic ischaemia in the cord and no major extramedullary vessel compression or thrombosis.⁴⁶⁻⁴⁹

Vasculitis is characteristic of rheumatoid arthritis and affects the small and medium sized arterioles of the peripheral nerves of the upper arm and mid thigh, causing inflammatory epineurial disease in 93% of rheumatoid patients⁵⁰ with resulting nerve fibre changes and ganglion cell loss.⁵¹ It is, however, rare in the spinal cord,⁵⁰ and was not seen in any of our patients.

Figure 3 Principal neuropathological findings in patients 3, 5, 6, and 8, mapped onto tracings of cord sections. Solid shading (black) denotes necrosis, coarse stippling axonal swellings, and fine dots oedema. The shading in the cuneate fascicle in patient 3 is Wallerian degeneration. Crosses in the anterior horns represent chromatolytic neurones.

Severe hyalinosis of intramedullary arterioles may cause ischaemia of the cord. The moderate hyalinosis seen in this necropsy series, however, was consistent with senile involutionary change.^{52 53} Hyalinosis increases with age, and is negatively associated with arteriosclerosis.⁵³ Arteriosclerotic myelopathy, characterised by focal rarefactive necrosis primarily in the grey matter, atrophy of neurones, gliosis, and spongiform degeneration^{49 53} was significantly absent in this necropsy series. Indeed, the incidence of spinal arteriosclerosis is low,⁴⁹ even in the presence of cerebrovascular changes.⁵³

Abnormalities of venous drainage have been implicated in cervical myelopathy.⁵⁴⁻⁵⁷ Although mild venous congestion was noted in four of our patients, there was no evidence of venous thrombosis or occlusion, no haemorrhagic change in the ventral grey matter and, except for the pencillar heterotopia in one patient, no central cord lesion.

Intermittent cord ischaemia may result from systemic atherosclerotic changes,^{49 53} and spinal cord ischaemia compromises the ability of the cord to tolerate compression.^{45 58} Prolonged hypotension is known to provoke central necrosis of the cord.³⁶ Could intraoperative ischaemia have produced some of the pathology observed in this series? Again, the absence of central necrosis and of grey matter

change argues against intraoperative hypotension being a factor.

Although clearly some degree of ischaemia occurs in the presence of any mechanical deformation of the spinal cord or brain stem, there was no histological evidence of it in this series of patients with severe end stage rheumatoid arthritis. Thus we consider ischaemia unlikely as a primary pathological mechanism.

Neurotoxicity

Rarely, gold has neurological side effects, including acute, predominantly distal, symmetrical, mixed sensory, and motor polyneuropathy.⁵⁹ A Guillain-Barré pattern of demyelination has been described.⁶⁰ Azathioprine has almost no side effects. It is improbable, therefore, that the white matter changes we have noted were pharmacologically induced.

Stretch and motion

The cord lengthens and becomes thinner on flexion of the neck, and shortens and thickens on extension.^{43 61} Between full extension and full flexion the contour of the dorsal canal increases up to 5 cm.⁶² Through the dentate ligaments this increased excursion of the spine imparts a stretching force to the cord.⁶³ The amount of stretch is surprisingly great: 1.3 cm

Figure 4 Pathological changes seen in many of the cords. (A) Cross section of the rostral part of the first cervical segment, showing long tract degeneration in the cuneate fascicle (patient 3, Woelche). (B) Axonal swellings at the level of compression (patient 6, Bielschowsky silver impregnation, bar=20 μ m). (C) A chromatolytic anterior horn cell (patient 8, haematoxylin and eosin, bar=20 μ m).

in cadaver studies.⁶⁴ Cord elongation, in primates at least, occurs maximally at levels where cord motion is greatest—namely, the lower cervical levels.⁶⁵ In human studies, Reid⁶⁶ found only 1 mm of movement at the C5 level, but 18 mm of cord movement at the C8 to T3 levels during flexion and extension. Change in length of the cervical canal is normally accompanied by stretching of the dura and spinal cord and movement of the cord within the dura, although this is limited by the dural root sleeves and the dentate ligaments respectively.^{64–66} Marked leptomeningeal fibrosis such as we observed may tether nerve roots as they enter the neural foramina,^{40–45} making them more susceptible to trauma³⁰ and stretching injury. Furthermore, tethering of the dura to the posterior longitudinal ligament^{27–30} results in variability of dural sac tension in the elderly.⁶⁶ Meningeal tethering may thus impart additional local shear and stress forces on the spinal cord and roots, with resultant axon injury, manifest histologically by chromatolysis and—in time—Wallerian degeneration in the dorsal columns. The presence of a mass ventral to the cord, such as a subluxed dens or spondylotic bar, may increase further the excursion of the spinal cord, thus generating increased axial tension along the neuraxis.^{25–63} Motion may cause repeated trauma over spondylotic protrusions causing myelorrhadiculopathy,^{30–61–62–64–69} and in our patients there was a great deal of subaxial spondylosis with associated histopathological changes.

Compression

Although stretch and motion contribute to the final pathology, we have considered compression at the craniocervical junction and subaxial sites to be the principal pathological factor in these patients, though we cannot

exclude completely some ischaemia. For the most part, the compression was ventral to the cord. At the foramen magnum, necrosis of the dorsal two thirds of the cord in the first two patients was reasonably explained by the posterior dislocation of the axis. In all but the one patient who did not have an operation (patient 5), compression by the odontoid process was the main cause of cord injury. In all of these, the territory of the anterior spinal artery was spared. Similarly, in the subaxial levels, compression appeared to be responsible for the observed pathology. Dorsal necrosis at the C4 level in patient 6 was probably secondary to a ventral mass—an abscess within the posterior longitudinal ligament. Sparing of the territory of the anterior spinal artery and the absence of ischaemic neuronal changes is against the hypothesis that dynamic compression of the anterior spinal artery was significant.⁷⁰

Cord pathology was always related to compression from degenerative spinal changes: a C6–7 subluxation (patient 2), a ventral osseous bar at C5–6 (patient 3) and at C3–4 (patient 7), a C5–6 kyphosis (patient 4), and staircase spines (patients 8 and 9). Interestingly, the patient presenting with the least neurological deficit (patient 6) had no subaxial spinal changes before the operation; spinal cord pathology after the operation was, however, related to compression from the abscess. Thus compression was present in all patients with cord pathology.

The extent of compression at the subaxial levels and the related neurological deficits have previously been insufficiently emphasised. Again, the effects of compression are increased with traction.^{25–69} Subaxial bone changes occur late in only 20–40% of rheumatoid spines.^{5–12–15–18–71–75}

CLINICAL FINDINGS

We found no evidence before the operations of cranial nerve palsy, nystagmus, or internuclear ophthalmoplegia in any of the nine patients in this series. The absence of cranial nerve findings in this series and our other study⁷⁶ is at variance with other series.^{4 5 10 12 72 77 78} We consider that dysphagia in our patients was due to fixed flexion of the neck, xerostomia, or cricoarytenoid arthritis.⁷⁹ There was only one cranial nerve deficit in this series, and that occurred after the operation (patient 2). In two other series of rheumatoid patients⁹ and congenital atlantoaxial subluxation,³¹ no cranial nerve nuclei changes were noted.

Although there were no major areas of brainstem damage, there may be ultrastructural changes which we did not observe. Subclinical problems such as sleep disturbances do occur in these patients. Howard R S, Henderson F, Hirsch N P, *et al* (unpublished data) have shown that even in the rheumatoid patient who does not report symptoms there may be central alterations in the respiratory pattern, which may be due to dorsal and dorsolateral column injury.

RADIOLOGICAL FINDINGS

Atlantoaxial subluxation due to ligament laxity is the most common cervical spine deformity in rheumatoid arthritis. The incidence varies between 25 and 71% of rheumatoid patients^{7 15} and was present in seven of our nine patients. Approximately 27% of patients with atlantoaxial subluxation show radiological progression.⁹ Basilar invagination or vertical subluxation of the dens follows atlantoaxial subluxation in 13% of patients,¹ and occurs due to erosion of the lateral masses (primarily of the axis) late in the disease process.^{12 13} Vertical subluxation, unlike atlantoaxial subluxation, is related to the age of the patient and the duration of the disease.⁹ The average vertical subluxation in this series was 19 mm (range 9–26 mm). Vertical subluxation causes a pseudoreduction in the atlantodental interval, and may in fact signal the onset of vertical subluxation of the dens.^{1 8 9 12} Interpretation of the atlantodental interval must therefore be made in conjunction with measurement of the vertical axial subluxation. It is clear, however, that this bony abnormality is only one aspect of the disease process.

Another factor we studied was the cross sectional area of the spinal cord at the point of maximum compression and the degree of neurological disability. We noted marked decreases in cord cross sectional area in six patients. In general terms our most severely affected patients had the greatest reduction in cord cross sectional area. This is consistent with the finding that cord cross sectional area is predictive of surgical outcome,⁸⁰ and that myelopathy due to repeated microtrauma, such as occurs with undetected odontoid fractures, increases with time.⁸¹ Chronic cord compression has been shown to cause flattening of the cord,⁶¹ which is presumably due to

demyelination.^{82 83} The ability of the nerves to conduct in the peripheral nervous system with only 3% of the normal myelin thickness⁸⁴ would explain why there is no consistent relation between cross sectional area and clinical disability.⁶¹

SURGICAL COMPLICATIONS

There are many lessons to be learnt from our experience, beginning with the degree of disability. Most were Ranawat IIIb and, in our wider study, it is this group that has the greatest mortality and morbidity. Indeed, most of our deaths after the operation presented in this disability category,²⁴ and most of the survivors did not achieve self caring status after the operation. Is it poor selection for an operation, or too late referral? Secondly, although all had longstanding disease, their neurological deterioration was rapid (between three and 32 weeks). The question arises as to how best to manage these patients: frequent outpatient assessment, or pre-emptive surgery while they are still comparatively fit?

There are also technical lessons to be learnt, such as the importance of adequate decompression, and in two patients (patients 1 and 8) the anterior surgery was inadequate. Sublaminar wire passage for posterior fixation is hazardous, particularly where there is cord compression^{85 86}; it is hoped that the new stainless steel and titanium cables (Sofwire, Codman and Shurtleff, Randolph, MA, USA) will cause less intradural damage. Pharyngeal wound infection has occurred in 2.1% of all our transoral operations. The delayed haemorrhages and abscesses are considered to be due to infection. Although tragic when it occurs, it is much less than might have been expected in such ill patients and, in our opinion, less of a hazard than posterior fusion alone in the presence of anterior compression.

Conclusions

The pathological findings in our series of patients suggest that: (a) cranial nerve and brain stem pathology is uncommon; (b) subaxial degenerative changes of the cervical spine often occur in end stage rheumatoid disease; (c) cord pathology may be caused by subaxial degeneration; (d) cord pathology occurs predominantly in the dorsal half of the cord, despite the ventral compression; (e) cuneate fascicle changes and anterior horn cell chromatolysis suggest diffuse injury throughout the cervical spine; (f) mechanical deformation, stretch and motion, rather than ischaemia appear to have played the primary part in the pathological changes observed.

Thus, in terms of treatment, (a) widespread subaxial cord involvement with myelopathy may not respond to surgical decompression at the craniocervical junction and (b) focal cord compression due to deformity or instability, even in the relatively asymptomatic patient should be treated surgically before neurological deterioration occurs.

The authors are grateful to Dr J T Hughes, Dr J M Stevens, Dr B E Kendall, and Professor Alf Breig for their help and encouragement. Dr Fraser C Henderson was sponsored by the United States Navy as the International Spinal Fellow at the National Hospitals for Neurology and Neurosurgery. This work has been supported, in part, by a generous donation from His Highness the Aga Khan. The authors are grateful to Michelle Green for her assistance with the preparation of the manuscript.

- 1 Smith P H, Benn R T, Sharp J. Natural history of rheumatoid cervical luxations. *Ann Rheum Dis* 1972; **31**: 431-9.
- 2 Conlon P W, Isdale I C, Rose B S. Rheumatoid arthritis of the cervical spine. An analysis of 33 cases. *Ann Rheum Dis* 1966; **25**: 120-6.
- 3 Bland J H. Rheumatoid arthritis of the cervical spine. *J Rheumatol* 1974; **1**: 319-41.
- 4 Nakano K K, Schoene W C, Baker R A, Dawson D M. The cervical myelopathy associated with rheumatoid arthritis: analysis of 32 patients with two postmortem cases. *Ann Neurol* 1978; **3**: 144-51.
- 5 Menezes A H, van Gilder J C, Clark C R, El-Khoury G. Odontoid upward migration in rheumatoid arthritis. An analysis of 45 patients with cranial settling. *J Neurosurg* 1985; **63**: 500-9.
- 6 van Gilder J C, Menezes A H, Dolan K D. *The cranio-vertebral junction and its abnormalities*. New York: Futura, 1987: 167-93.
- 7 Mathews J A. Atlanto-axial subluxation in rheumatoid arthritis. A five year follow up study. *Ann Rheum Dis* 1974; **33**: 526-31.
- 8 Pellici P M, Ranawat C S, Tsairis P, Bryan W J. A prospective study of the progression of rheumatoid arthritis of the cervical spine. *J Bone Joint Surg [Am]* 1981; **63**: 342-50.
- 9 Rana N A. Natural history of atlanto-axial subluxation in rheumatoid arthritis. *Spine* 1989; **14**: 1054-6.
- 10 Marks J S, Sharp J. Rheumatoid cervical myelopathy. *Q J Med* 1981; **50**: 307-19.
- 11 Crockard H A, Essigman W K, Stevens J M, Pozo J L, Ransford A O, Kendall B E. Surgical treatment of cervical cord compression in rheumatoid arthritis. *Ann Rheum Dis* 1985; **44**: 809-16.
- 12 Santavirta S, Kakaapää U, Sandelin J, Laasonen E, Kontinen Y T, Slätis P. Evaluation of patients with rheumatoid cervical spine: a review. *Scand J Rheumatol* 1987; **16**: 9-16.
- 13 Agarwal A K, Kraus D R, Eisenbeis C H Jr, Stolzer B L, Balk P M, Barkley T A. Anatomical and neurological characteristics of cervical spine involvement in rheumatoid arthritis. *J Orthop Rheumatol* 1989; **2**: 77-89.
- 14 Dvorak J, Grob D, Baumgartner H, Gschwend N, Grauer W, Larsson S. Functional evaluation of the spinal cord by magnetic resonance imaging in patients with rheumatoid arthritis and instability of upper cervical spine. *Spine* 1989; **14**: 1057-64.
- 15 Papadopoulos S M, Dickman C A, Sonntag V K H. Atlantoaxial stabilization in rheumatoid arthritis. *J Neurosurg* 1991; **74**: 1-7.
- 16 Davis F W, Markley H E. Rheumatoid arthritis with death from medullary compression. *Ann Intern Med* 1951; **35**: 451-4.
- 17 Mikulowski P, Wollheim F A, Rotmil P, Olsen I. Sudden death in rheumatoid arthritis with atlanto-axial dislocation. *Acta Med Scand* 1975; **198**: 445-51.
- 18 Hughes J T. Spinal cord involvement by C4-C5 vertebral subluxation in rheumatoid arthritis: a description of two cases examined at necropsy. *Ann Neurol* 1977; **1**: 575-82.
- 19 Ranawat C S, O'Leary P, Pellici P, Tsairis P, Marchisello P, Dorr L. Cervical spine fusion in rheumatoid arthritis. *J Bone Joint Surg [Am]* 1979; **61**: 1003-10.
- 20 Steinbrocker O, Traeger C H, Batterman R C. Therapeutic criteria in rheumatoid arthritis. *JAMA* 1949; **140**: 659-62.
- 21 Stevens J M, Kendall B E, Crockard H A. The spinal cord in rheumatoid arthritis with clinical myelopathy: a computed myelographic study. *J Neurol Neurosurg Psychiatry* 1986; **49**: 140-51.
- 22 Geddes J F, Gonzalez A G. Examination of spinal cord in diseases of the craniovertebral junction and high cervical spine. *J Clin Pathol* 1991; **44**: 170-2.
- 23 Redlund-Johnell I, Pettersson H. Radiographic measurements of the craniovertebral region, designed for evaluation of abnormalities in rheumatoid arthritis. In: Redlund-Johnell I, ed. *Dislocations of the cervical spine in rheumatoid arthritis*. Malmö: University of Lund; 1984: 55-67.
- 24 Crockard H A, Calder I, Ransford A O. One-stage transoral decompression and posterior fixation in rheumatoid atlanto-axial subluxation. *J Bone Joint Surg [Br]* 1990; **72**: 682-5.
- 25 Breig A. *Adverse mechanical tension in the central nervous system*. New York: Wiley, 1978: 61-83.
- 26 Shimomura Y, Hukuda S, Mizuno S. Experimental study of ischemic damage to the cervical spinal cord. *J Neurosurg* 1968; **28**: 565-81.
- 27 Bedford P D, Bosanquet F D, Russell W R. Degeneration of the spinal cord associated with cervical spondylosis. *Lancet* 1952; **2**: 55-9.
- 28 Mair W G P, Druckman R. The pathology of spinal cord lesions and their relation to the clinical features in protrusion of cervical intervertebral discs. *Brain* 1953; **76**: 70-91.
- 29 Wadia N H. Myelopathy complicating congenital atlanto-axial dislocation. *Brain* 1967; **90**: 449-70.
- 30 Wilkinson M. The morbid anatomy of cervical spondylosis and myelopathy. *Brain* 1960; **83**: 589-617.
- 31 Dastur D K, Wadia N H, Desai A D, Sinh G. Medullospinal compression due to atlanto-axial dislocation and sudden haematomyelia during decompression. *Brain* 1965; **88**: 897-927.
- 32 Ducker T B, Kindt G W, Kempe L G. Pathological findings in acute experimental spinal cord trauma. *J Neurosurg* 1971; **35**: 700-8.
- 33 Tarlov I M. Acute spinal cord compression paralysis. *J Neurosurg* 1972; **36**: 10-20.
- 34 Hughes J T. Pathology of spinal cord damage in spinal injuries. In: Feiring E H, ed. *Brock's injuries of the brain and spinal cord*. 5th ed. New York: Springer, 1974.
- 35 Gooding M R, Wilson C B, Hoff J T. Experimental cervical myelopathy. *J Neurosurg* 1975; **43**: 9-17.
- 36 Balentine J D. Impact injuries of the spine and spinal cord. In: Leestma J E, ed. *Forensic neuropathology*. New York: Raven Press, 1988: 254-75.
- 37 Elsberg C A, Strauss I. Tumors of the spinal cord which project into the posterior cranial fossa. *Arch Neurol Psychiatry* 1929; **21**: 261-73.
- 38 Symonds C P, Meadows S P. Compression of the spinal cord in the neighbourhood of the foramen magnum. *Brain* 1937; **60**: 52-84.
- 39 Taylor A R, Aberd M B. Vascular factors in the myelopathy associated with cervical spondylosis. *Neurology* 1964; **14**: 62-8.
- 40 Frykholm R. Cervical nerve root compression resulting from disc degeneration and root sleeve fibrosis. *Acta Chirurgica Scand* 1951; **160** (suppl): 24-33.
- 41 Brain W R, Northfield D, Wilkinson M. The neurological manifestations of cervical spondylosis. *Brain* 1952; **75**: 187-225.
- 42 Payne E E, Spillane J D. The cervical spine: an anatomicopathological study of 70 specimens (using a special technique) with particular reference to the problem of cervical spondylosis. *Brain* 1957; **80**: 571-616.
- 43 Breig A, Turnbull I, Hassler O. Effects of mechanical stresses on the spinal cord in cervical spondylosis. *J Neurosurg* 1966; **25**: 45-56.
- 44 Spillane J D, Lloyd G H T. The diagnosis of lesions of the spinal cord in association with osteoarthritic disease of the cervical spine. *Brain* 1952; **75**: 177-86.
- 45 Hoff J, Nishimura M, Pitts L, Vilnis V, Tauer K, Lagger R. The role of ischemia in the pathogenesis of cervical spondylotic myelopathy. *Spine* 1977; **2**: 100-8.
- 46 Webb F W S, Hickman J A, Brew S J. Death from vertebral artery thrombosis in rheumatoid arthritis. *BMJ* 1968; **2**: 537-8.
- 47 Hughes J T. *Pathology of the spinal cord*. 2nd ed. London: Lloyd-Luke, 1978: 176-9.
- 48 Zeitlin H, Lichtenstein B W. Occlusion of the anterior spinal artery. *Arch Neurol Psychiatry* 1936; **36**: 96-111.
- 49 Hughes J T, Brownell B. Spinal cord ischemia due to arteriosclerosis. *Arch Neurol* 1966; **15**: 189-202.
- 50 Kim R C, Collins G H. The neuropathology of rheumatoid disease. *Hum Pathol* 1981; **12**: 8-15.
- 51 Morrison L R, Short C L, Ludwig A O, Schwab R S. The neuromuscular system in rheumatoid arthritis. *Am J Med Sci* 1947; **214**: 33-9.
- 52 Morrison L R, Cobb S, Bauer W. *The effect of advancing age upon the human spinal cord*. Massachusetts: Harvard University Press, 1959: 55.
- 53 Jellinger K. Spinal cord arteriosclerosis and progressive vascular myelopathy. *J Neurol Neurosurg Psychiatry* 1967; **30**: 195-206.
- 54 Hughes J T. Venous infarction of the spinal cord. *Neurology* 1971; **21**: 794-800.
- 55 Taylor A R, Byrnes D P. Foramen magnum and high cervical cord compression. *Brain* 1974; **97**: 473-80.
- 56 Doppman J L. The mechanism of ischemia in antero-posterior compression of the spinal cord. *Invest Radiol* 1975; **10**: 543-51.
- 57 Henderson F C, Crockard H A, Stevens J M. Spinal cord oedema due to venous stasis. *Neuroradiology* 1993; **35**: 312-5.
- 58 Hukuda S, Wilson C B. Experimental cervical myelopathy: effects of compression and ischemia on the canine cervical cord. *J Neurosurg* 1972; **37**: 631-52.
- 59 Jacobs J A, Lequesne T M. Toxic disorders. In: Adams J H and Duchen L W, eds. *Greenfield's neuropathology*. 5th ed. London: Edward Arnold, 1992: 881-91.
- 60 Winderbank A J. Metal neuropathy. In: Dyck P J, Thomas P K eds. *Peripheral neuropathy*. 3rd ed. London: Saunders, 1993: 1563-6.
- 61 Yu Y L, Du Boulay G H, Stevens J M, Kendall B E. Computer-assisted myelography in cervical spondylotic myelopathy and radiculopathy. *Brain* 1986; **109**: 259-78.
- 62 O'Connell J E A. The place of surgery in the treatment of cervical spondylosis. *Proc Roy Soc Med* 1956; **49**: 202-12.
- 63 Breig A, El-Nadi A F. Biomechanics of the cervical spinal cord. *Acta Radiol* 1966; **4**: 602-24.
- 64 Adams C B T, Logue V. Studies in cervical spondylotic myelopathy. Parts I-III. *Brain* 1971; **94**: 557-94.
- 65 Smith C G. Changes in length and position of the segments of the spinal cord with changes in posture in the monkey. *Radiology* 1956; **66**: 259-65.

- 66 Reid J D. Effects of flexion-extension movements of the head and spine upon the spinal cord and nerve roots. *J Neurol Neurosurg Psychiatry* 1960; **23**: 214–21.
- 67 Ono K, Ota H, Tada K, Yamamoto T. Cervical myelopathy secondary to multiple spondylotic protrusions. *Spine* 1977; **2**: 109–25.
- 68 Barnes M P, Saunders M. The effect of cervical mobility on the natural history of cervical spondylotic myelopathy. *J Neurol Neurosurg Psychiatry* 1984; **47**: 17–20.
- 69 Jellinger K. Neuropathology of cord injuries. In: Vinken P J and Bruyn G W, eds. *Handbook of clinical neurology*. Vol. 25. *Injuries of the spine and spinal cord, part I*. Amsterdam: North-Holland, 1976: 93.
- 70 Hughes J T, Brownell B. Cervical spondylosis complicated by anterior spinal artery thrombosis. *Neurology* 1964; **14**: 1073–7.
- 71 Ball J, Sharp J. Rheumatoid arthritis of the cervical spine. In: Hills A G S, ed. *Modern trends in rheumatology*. London: Butterworth, 1971.
- 72 Kontinen Y T, Santavirta S, Kauppi M, Moskovich R. The rheumatoid cervical spine. *Curr Opin Rheumatol* 1991; **3**: 429–40.
- 73 Hopkins J S. Lower cervical rheumatoid subluxation with tetraplegia. *J Bone Joint Surg [Br]* 1967; **49**: 46–50.
- 74 Eulerink F, Meijers K A E. Pathology of the cervical spine in rheumatoid arthritis: a controlled study of 44 spines. *J Pathol* 1976; **120**: 91–108.
- 75 Bland J H, Boushey D R. Anatomy and physiology of the surgical spine. *Semin Arthritis Rheum* 1990; **20**: 1–20.
- 76 Rogers M A, Crockard H A, Moskovich R, et al. Nystagmus and joint position sensation; their importance in posterior occipito-cervical fusion in rheumatoid arthritis. *Spine*. In press.
- 77 Rana N A, Hancock D O, Taylor A R, Hill A G S. Upward translocation of the dens in rheumatoid arthritis. *J Bone Joint Surg [Br]* 1973; **55**: 471–7.
- 78 Slatis P, Santavirta S, Sandelin J, Kontinen Y T. Cranial subluxation of the odontoid process in rheumatoid arthritis. *J Bone Joint Surg [Am]* 1989; **71**: 189–95.
- 79 Gall E P, Schumacher H R. Systematic features of rheumatoid arthritis. In: Schumacher E P and Gall E P, eds. *An illustrated guide to pathology, diagnosis and management*. Philadelphia: Lippincott, 1988: 14.78–80.
- 80 Hunter J V, Stevens J M, Kendall B E, Moskovich R, Crockard H A. Radiological assessment for transoral surgery in rheumatoid arthritis, using dynamic CT myelography. *Neuroradiology* 1991; **33** (suppl): 413–5.
- 81 Crockard H A, Heilman A E, Steven J M. Progressive myelopathy secondary to odontoid fractures: clinical, radiological and surgical features. *J Neurosurg* 1993; **78**: 579–86.
- 82 Holmes G. On the relation between loss of function and structural change in focal lesions of the central nervous system, with special reference to secondary degeneration. *Brain* 1906; **29**: 514–23.
- 83 Gledhill R F, Harrison B M, McDonald W I. Demyelination and remyelination after acute spinal cord compression. *Exp Neurol* 1973; **38**: 472–87.
- 84 Koles K J, Rasminsky M. A computer simulation of conduction in demyelinated nerve fibers. *J Physiol* 1972; **227**: 351–64.
- 85 Hamblen D L. *Postgraduate textbook of clinical orthopaedics*. Bristol: Wright, 1983: 487–97.
- 86 Wilber R G, Thompson G H, Shaffer J W, Brown R H, Nash C L. Post-operative neurological deficits in segmental spinal instrumentation. *J Bone Joint Surg [Am]* 1984; **66**: 1178–87.