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The location and function of respiratory fibres in the second cervical spinal cord segment: respiratory dysfunction syndrome after cervical cordotomy

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Abstract

After high cervical percutaneous cordotomy for pain in malignant disease, 12 patients died during sleep at postoperative intervals between 1 and 8 days. Nine died after a first cordotomy and three after a second (contralateral) procedure. All except one had known pulmonary disease before operation. The operated segment of the spinal cord (C2) was studied histologically after death. Superposition of lesion outlines made it possible to determine those parts of the lesioned areas common to all unilateral and bilateral cases respectively. All cases dying of presumed respiratory dysfunction syndrome had lesions involving the region of the anterolateral funiculus in the C2 segment containing "pain" fibres activated from the second to fifth thoracic dermatomes. The fibres whose destruction appeared to be responsible for respiratory dysfunction syndrome were completely intermingled with ascending "pain" fibres. The possibility of these fibres being afferent in function is discussed.

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Respiratory dysfunction has been recognised as a potentially fatal complication of cervical cordotomy since the operation was first introduced.[1–3] The condition, characterised by prolonged periods of apnoea, particularly during sleep, is sometimes referred to as "Ondine's Curse". Although more common after a bilateral procedure, it also occurs following unilateral cordotomy, and is as much to be feared after percutaneous as after open operation.[4 5]

Post-cordotomy respiratory dysfunction syndrome has been explained in terms of disruption of descending pathways controlling motor respiratory function. The nature of the responsible fibres which are anatomically interrupted in the anterolateral funiculus of the cervical spinal cord has been debated.

We studied the anatomical pathology of 38 cordotomies in 30 patients who died following percutaneous cervical cordotomy performed by us.[6] We report the results of anatomo-clinical correlations in 12 cases who died of presumed respiratory dysfunction syndrome.

Material and methods

Nine patients died within one to four days after unilateral cordotomy, and three within two to eight days after a second cordotomy. (table)

The spinal cords were removed into 10% formalin within 36 hours of death. Blocks were cut from the cervical cord (C1–C2) and included in paraffin, and sections cut at 3 or 4 μm for staining by haematoxylin and eosin or cresyl violet (Nissl), and at 15 μm for staining by the Heidenhahn method for myelin or by the Luxol Fast Blue method. Photographs were taken of those sections containing the most extensive lesions. The extent of the latter was determined by planimetry with a milli-

Table *Patients dying of respiratory dysfunction syndrome following percutaneous cervical cordotomy*

A UNILATERAL CASES

Patient	*Age at cordotomy*	*Diagnosis*	*Distribution of pain*	*Dermatomes showing pinprick deficit*	*Survival (Days)*
1 male	71	L pancoast	L arm	C3–T4	2
2 male	56	L bronchial ca	L thorax	T4–S5	2
3 male	62	Ca thyroid, extending to lung	Right upper limb	Not known	1
4 female	74	Bilateral Ca breast	L arm and thorax	Not known	2*
5 male	59	R pancoast	C3–T6	C5–S5	1
6 female	72	Postherpetic neuralgia, emphysema	C3–T2	C4–S5	2
7 male	71	Ca prostate, with metastatic carcinomatosis	Both legs	T2–S5	4
8 male	76	Pleural mesothelioma	L chest	C4–S5	4
9 female	63	R pancoast	R upper quadrant	C3–T9	2*

* This patient had had a previous cordotomy on the same side 265 days earlier, giving pinprick deficit from C4 to S5.

B BILATERAL CASES

Patient	*Age at cordotomy*	*Diagnosis*	*Distribution of pain*	*Dermatomes showing pinprick deficit* *First cordotomy*	*Second cordotomy*	*Survival (Days) after 2nd operation*
10 male	62	R pancoast	T2-T9 bilaterally	C6–S5	T2–S5	2
11 male	68	L pancoast	R shoulder + L thorax	C5–S5	C5–L1	5
12 female	52	Ovarian ca	T11–L2 bilaterally	C5–S5	Not known	8

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metre grid, whereby the percentage of damaged tissue as a proportion of the whole cord could be calculated.

To compare cords and lesions in different individuals, the planimetrically recorded lesions were transferred to a diagram of the second cervical segment in the atlas of Riley.[7] Figure 1 shows the schematic diagram used, in which reference points were standardised. The grid pattern (fig 1) enabled us to trace all lesions and other features in every cord onto an identical, and therefore comparable, diagram.

Results

Clinical

Respiratory dysfunction appeared very early following uni- or bi-lateral cordotomy in these cases; survival ranged from a few hours to 8 days (table), most dying within 48 hours of operation. Virtually all patients subjected to unilateral cordotomy had pulmonary pathology before operation; and so did two of the bilaterally operated cases. The third patient undergoing bilateral cordotomy had disseminated carcinomatosis. All patients had diaphragmatic and intercostal respiratory movement on the cordotomised side postoperatively, and died in sleep.

The extent of post-cordotomy pinprick deficit is shown in the table for those patients in whom it could be determined. In two unilateral and one bilateral case, the patient's deteriorating condition made it impossible to perform this examination. In the 8 cases in which pinprick deficit was accurately determined, the T4/5 dermatomes were common to every case.

Histological

Figure 2 is a composite diagram showing the extent of the common lesion at C2 in all unilaterally- (A) and bi-laterally (B) operated cases. Three unilateral cases (4, 6, and 7) exhibited a bilateral lesion of the anterolateral cord quadrant following operation on one side. Figure 3a shows the preoperative distribution of pain and postoperative pinprick deficit in case 8; figure 3b is a photograph of the stained cord, and fig 3c shows the tracing of the lesion onto a standardised diagram (see fig 1).

Data from our series of 30 cases clinically studied after percutaneous cordotomy at C2,[6] in which the cervical cord was anatomically examined, indicates that the stippled area in fig 2 corresponds to the position of ascending fibres representing dermatomes C7–T4; while that in fig 3 corresponds to fibres representing dermatomes T2–L1.

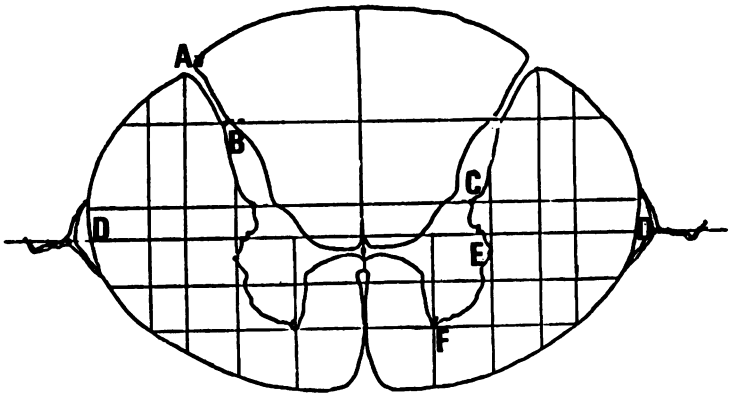

Figure 1 Reference points on transverse section through spinal cord in C2 segment used to allow standardisation of projections: (A) Entry of dorsal root; (B) Apex of dorsal horn; (C) Lateral limit of neck of dorsal horn; (D) Midpoint of attachment of dentate ligament; (E) Most prominent point of lateral border of ventral horn; (F) Anteriormost point of ventral horn.

Discussion

Respiratory dysfunction as a sequel of high cervical cordotomy was first brought to attention by Peet *et al.*[1] Since that time, results from large series of cases performed by open surgery[2 3 8–10] or by transcutaneous techniques[4 5 11–15 17–22] have continued to underline the risk. A study of the literature confirms our experience that apnoea following cervical cordotomy occurs almost exclusively in patients with coexisting pulmonary pathology (particularly neoplasm).

Experimental studies on animals as well as respiratory measurements in humans have been performed to determine the type of respiratory disturbance induced by anterolateral cordotomy. Most authors have emphasised the interruption of descending pathways controlling respiration as the aetiopathological mechanism responsible for this condition.[23]

Krieger and Rosomoff[15] described 10 patients with respiratory dysfunction syndrome developing within 24–48 hours of cervical cordotomy. They noted that the patients initially manifested a subjective sensation of panic and respiration with frequent sighing before any objective signs became evident. Later, the patients hypoventilated and characteristically exhibited sleep apnoea. If the patient awoke during apnoea, normal respiration resumed, though hypoventilation continued and apnoea recurred if (when) the patient fell asleep again.

A diminution in tidal volume following anterolateral cord lesions 4–5 mm deep was recorded by Belmusto *et al*[11] in patients with lung cancer who had cordotomy. The immediate decrease was very profound; and although it recovered within a few minutes, it never regained preoperative values. Nathan[16] also observed a two thirds reduction in vital capacity following cordotomy in a patient without pulmonary pathology, but noted that respiratory movements on the affected side were not completely eliminated. Both Nathan[16] and Belmusto *et al*[11] observed that the degree of pain relief produced by cordotomy in patients with lung cancer could be predicted from the extent of reduction of tidal volume.

Tenicela *et al*,[4] reporting their observations of 41 patients, found that Forced Vital Capacity and Maximum Voluntary Ventilatory Capacity, although reduced preoperatively in patients subsequently developing postoperative dyspnoea, were not significantly changed as a result of cordotomy. On the other hand, Rosomoff *et al*[12] observed that the parameter most sensitive to cordotomy was tidal volume.

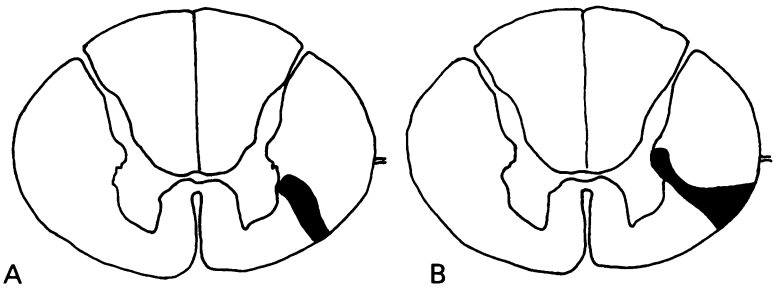

Figure 2 Outlines of lesioned areas at C2 common to all subjects in unilateral cases (A) and following the second operation in bilateral (B) cases.

Its reduction was compensated, when possible, by an increase in respiratory rate. Following bilateral cordotomy, tidal volume was reduced by 36%, and was not compensated by a 32% increase in respiration rate; but inhalation of 5% CO_2 brought about a return to baseline conditions.

Patients with sleep apnoea, while awake, exhibit both diaphragmatic and intercostal movements; and are able to take a deep(er) breath to command. It may be that sleep apnoea could represent a disturbance of the afferent rather than the efferent control of respiration. The notion that breathing is under "voluntary" control while awake and not while asleep seems to us to involve semantic and perhaps philosophical considerations which cannot be resolved by purely scientific observations.

In experimental work on the dog, Belmusto *et al*[11] found that the spinal pathways controlling respiratory function were intermingled with the "ventral and lateral spinothalamic tracts". As our results on humans indicate, there also seems to be an intimate association between "pain" fibres ascending from upper thoracic segments and fibres controlling ventilation.

The topographical location of these latter fibres in the transverse plane in the C2 segment (figs 2, 3) confirms other reports. As a result of his study of eight cases of open high cordotomy, Nathan[3] produced a diagram illustrating the area common to two cases with respiratory dysfunction and considered to be critical for the control of respiration. Our own composite diagrams (figs 2, 3) defines a smaller area which is included in the dorsal part of Nathan's diagram.

Microphotographs from 3 patients dying of respiratory dysfunction syndrome following bilateral percutaneous cordotomy illustrated by Rosomoff *et al*[12] show anterolateral quadrant lesions within the area shown in fig 3. Tranmer *et al*[21] published microphotographs and diagrams of the cords of 3 patients who died of respiratory dysfunction syndrome following cordotomy. Their composite diagram depicting a common lesion area coincides almost exactly with the area deemed critical for the development of respiratory dysfunction in this study.

Our study does give a definite conclusion about the laterality of fibres, damage to which gives rise to fatal respiratory dysfunction syndrome, as in most instances a bilateral cord lesion was found. In those cases in which the cord lesion was strictly unilateral, it was on the side opposite the lung with abnormal preoperative function. This indicates that the lesion would affect a pathway subserving the ipsilateral lung (shown at necropsy to be unaffected in most cases), responsible for maintaining adequate ventilation in these patients. However, the likelihood of the existence of a bilateral pathway, the lesion of which produces respiratory dysfunction syndrome, is supported by the absence of this syndrome after unilateral cordotomy in patients with no pulmonary pathology, and its occurrence in the same patients after bilateral procedure.

Why do most patients survive after bilateral high cervical cordotomy? We agree with one of Nathan's[16] theories that the critical area is not damaged on at least one side, with a concomitantly low level of pinprick deficit on that side. Tenicela *et al*[4] described 10 patients who apparently did not develop respiratory dysfunction syndrome after bilateral cervical cordotomy; eight had an upper level of analgesia below T4 on one side.

What is the nature of the neural messages conveyed by the pathway in the anterolateral quadrant which is destroyed by cordotomy at C2 to produce respiratory dysfunction syndrome? It is well recognised that impulses from both low- and high- threshold receptors ascend in the anterolateral quadrant;[25] but it is not known for certain whether respiratory afferents are included in this pathway. Remmers,[26] however, showed that proprioceptive information from intercostal muscles and tendons in cats reaches supraspinal levels. Another possibility is that the responsible anterolateral fibres carry information from broncho-pulmonary afferents. Such information is bilaterally represented in the nucleus of the solitary tract, with approximately one third coming from the contralateral side. This has also been described in cats.[27] These messages travel peripherally in the vagus nerve. However, Adams and Victor[28] suggest that in humans some afferents may enter the spinal cord via sympathetic rather than parasympathetic peripheral afferents; and in the cat, Foreman *et al*[29] elicited activity in ascending anterolateral axons of spinothalamic and spinoreticular pathways by stimulating the sympathetic chain between the 2nd and 3rd thoracic ganglia, as did Ammons *et al*[30] by stimulating the stellate ganglion. It is thus relevant that sympathetic afferents from the lungs and bronchi enter the cord between T2 and T7,[31] and that the "pain fibres" representing these segments are precisely those whose destruction is critical for the development of the respiratory dysfunction syndrome. The vast majority of fibres ascending in the anterolateral funiculus of the spinal cord which are destroyed by cordotomy are spinoreticular,[32] and could be expected to participate in the arousal mechanism, including arousal of brainstem respiratory centres.[15] These mechanisms are greatly attenuated, if not dormant, during sleep but reactivated during wakefulness.

The clinical and anatomical results of this study clearly indicate that the fibres whose

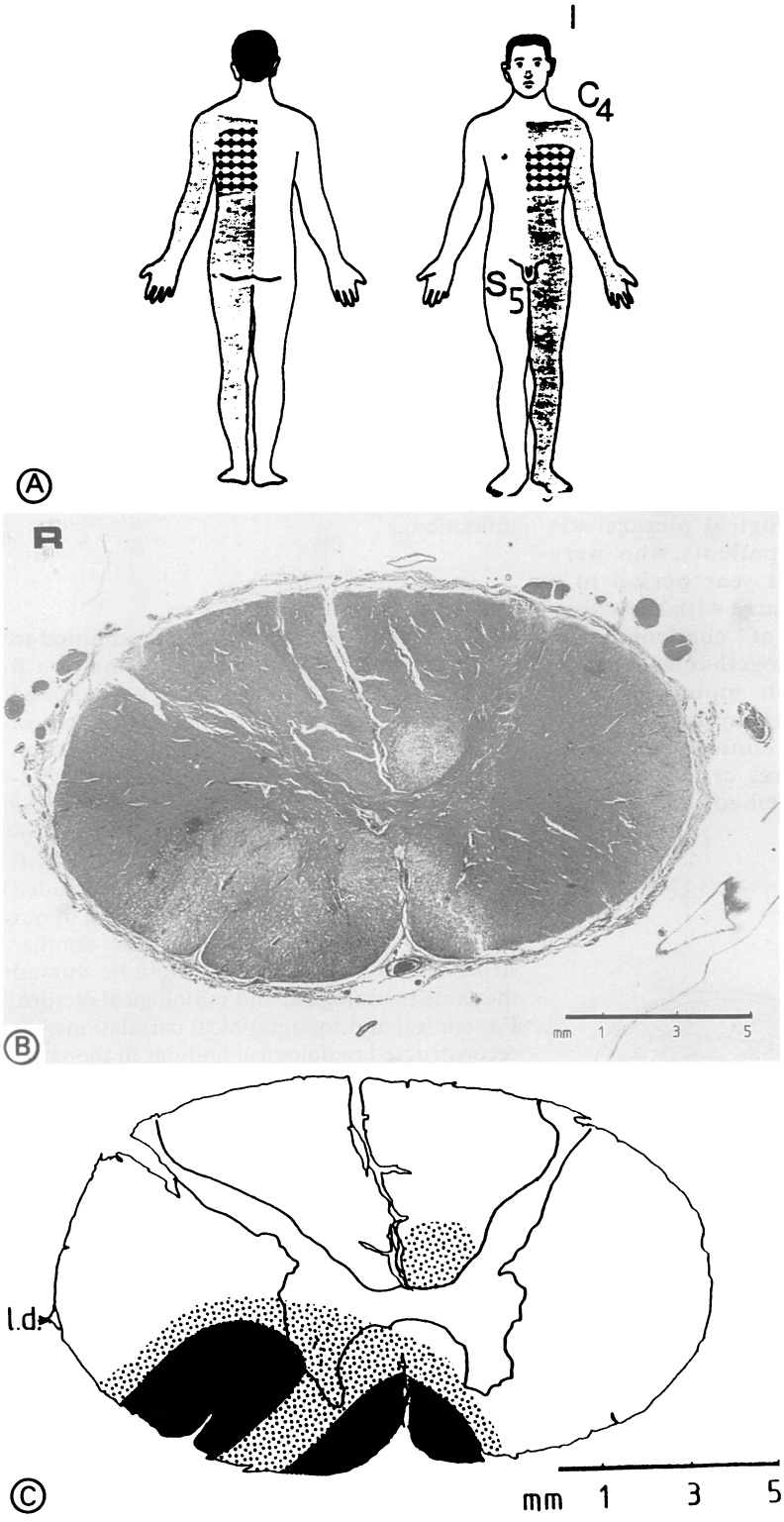

Figure 3 Case 8, male age 76 with bilateral asbestosis and left pleural mesothelioma; pain in left chest; cordotomy resulted in complete relief of pain, with absence of pinprick sensation from C4 to S5. postoperative survival 4 days: (A) Postoperative clinical diagram, showing region of original pain (crosses) and region of pinprick loss following cordotomy (shaded); (B) 15 µm paraffin section through C2 cord segment, stained with Holmes' Luxol Fast Blue, (R = right); (C) Standardised projection drawing of B (see fig 1).

destruction is responsible for the appearance of respiratory dysfunction syndrome are intimately related to fibres of the "pain pathway", particularly those representing the T2–T5 segments. While there is no proof that they are afferent in nature, we feel that this possibility should not be entirely dismissed.

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