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Ganglion Cells in Achalasia of the Cardia

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Summary. The histopathology of 40 cases of achalasia of the cardia, 6 cases of oesophageal spasm-incoordination and 4 cases of scleroderma was examined. Three cases of carcinoma and 6 cases of reflux oesophagitis were used as a control group. A nearly complete loss of myenteric ganglion cells was found in the upper thickened segment in achalasia. Some surviving ganglion cells were found in the lower segments in half the cases of achalasia; in two cases counts were normal in this segment. The occurrence of neuronal chromatolysis in 9 biopsies of achalasia supports the view that an active disease process was involved. The preganglionic parasympathetic fibres in two cases of achalasia were normal in appearance and number; this somewhat limited evidence tends to count against a primary disorder of the preganglionic neurone in this condition. The 6 cases of oesophageal spasm-incoordination showed similar neuronal loss to that in the lower segment in achalasia. Possibly "oesophageal spasm" represents an early stage or incomplete expression of achalasia. One case of scleroderma showed loss of ganglion cells, but the myenteric plexus was here involved by the disease process. None of the 9 cases in the control group showed any loss of ganglion cells or chromatolysis. Acute and chronic inflammation was not convincingly associated with loss of ganglion cells in either achalasia or oesophageal spasm.

Key words: Ganglion cells – Achalasia – Oesophagus – Innervation.

Introduction

In previous studies we found a small number of residual myenteric ganglion cells in the lower narrowed segment of the oesophagus in achalasia (Adams et al., 1960, 1961). This contrasts with reports varying from near-complete disappearance of all ganglion cells (Hurst and Rake, 1929; Lendrum, 1937; Cross, 1952; Cassella et al., 1964; Smith, 1970) to reports of a nearly normal neuronal

population in this lower zone of the achalasic oesophagus (Trounce et al., 1957). Most would agree that the upper thickened segment of the oesophagus in this disease is almost bereft of ganglion cells, but Misiewicz et al. (1969) found ganglion cells were absent in 9 out of 14 of their patients with achalasia, scanty in 3 and numerically normal in 2.

The purpose of this brief report is to summarise the histological findings in a large series of 42 patients treated surgically for achalasia; to comment on the normality of the vagus nerve and its branches in two cases of achalasia; to present limited evidence that achalasia is a progressive aquired lesion and is not developmental in origin; and to compare the pathology of this disease with that of 6 cases of oesophageal spasm and 4 cases of scleroderma.

Materials and Methods

Clinical

Forty-two patients were subjected to oesophageal biopsy during surgery for achalasia of the cardia. Biopsies were taken from the hypertrophied muscle of the body of the oesophagus about 4–6 cm above the cardia (henceforth termed "upper segment") and also from the zone just below when it had become narrowed and thin ("lower segment"). In many cases only the upper segment was biopsied. Biopsies were also obtained from 6 subjects with oesophageal spasm and from 4 with histologically-proven scleroderma. Oesophageal spasm was diagnosed on the finding of a clinical syndrome consisting of periodic attacks of severe oesophageal pain with dysphagia, together with the radiological appearance of a corkscrew-type deformity. Biopsies were taken from normal areas of the oesophagus in 3 subjects with carcinoma of the oesophagus, and from 6 with reflux oesophagitis associated with hiatus hernia; these formed the 9 controls.

Histological

The biopsies (1.0–1.5 cm long) were fixed in formol-saline, orientated in their longitudinal and radial axes during paraffin embedding, sectioned and stained with haematoxylin and eosin or by Van Gieson's method. The length of the biopsy in the stained section was measured, and ganglion cells in the myenteric plexus were counted and expressed as mean number per cm length of biopsy. One biopsy of achalasia was rejected as it was incorrectly orientated and ganglion regions could not be seen, while another was rejected as it was too superficial. No attempt was made in this study to demonstrate the myenteric ganglion cells with cholinesterase and carboxyesterase histochemical techniques, as used before (Adams, 1965a). In two surgically-treated cases of achalasia, vagal branches to the affected lower oesophagus were excised, and cross- and longitudinal sections were stained by the above-mentioned methods together with Loyez's myelin technique.

Results and Comment

The histological results on the 59 cases and controls are summarized in Table 1. The ganglion cell count in the myenteric plexus shows a near-complete loss of neurons from the upper dilated segment in achalasia, whilst the lower segment usually has a much reduced number. However, in 3 out of 15 cases the number of ganglion cells in the lower segment was normal (8, 5 and 5 cells/cm; for normal values see Table 2). We have previously noted this more severe loss

Table 1. Ganglion cell counts and other pathological features in oesophageal biopsies

Clinical diagnosis	Total cases	Biopsies[a]	Myenteric ganglion cells/cm				Chromatolysis	Nerve fibres	Acute inflammation	Chronic inflammation	Fibrosis
			>3	1–3	<1	0					
Achalasia[a]											
upper segment	40	31	0[b]	0	7	24	5	29	2	12	13
lower segment		15	3	4	1	7	4	13	1	4	2
Oesophageal spasm	6	8	0	6[d]	1	1	1	6	1	2	1
Scleroderma	4	4	3	0	0	1[e]	0	3	0	3	3
Controls[c]											
Carcinoma	3	3	3	0	0	0	0	2	0	1	1
Reflux oesophagitis	6	6	6	0	0	0	0	6	2	2	0

[a] Biopsies not available from both upper and lower segments in all cases
[b] Number of biopsies falling in each category
[c] Present series 3.0–10.5 cells/cm; 5–6 cells/cm (Adams et al., 1961); 3–9 cells/cm (Lendrum, 1937)
[d] Biopsies from upper and lower regions in 2 cases
[e] Inflammation and fibrosis of ganglion region

of ganglion cells from the upper segment than the lower segment (Adams et al., 1961), and this observation has been confirmed by Cassella et al. (1964). In the present study the upper segment contained less than 1 ganglion cell/cm in all 31 biopsies. When upper and lower segments are taken together, our 40 cases of achalasia show an average density of 0.69 ganglion cells/cm, which is rather more than the 0.32 cells/cm recorded by Lendrum (1937) in his smaller series.

A modest chronic inflammation was a feature of ganglion areas in rather less than half of the achalasic thickened upper segments. Such inflammation was characterised by a moderate fibrosis in ganglion regions. The lower segment was less affected by inflammation. If the lower segment can be regarded as suffering from a less advanced state of the disease, this last observation tends to exonerate inflammation as the initiating factor in achalasia. Moreover, we cannot be certain that our so-called modest chronic inflammation in the upper segment was anything more than a proliferation of satellite cells (satellitosis) in the ganglion areas; we agree with Lendrum (1937) that these satellite or supporting cells can be mistaken for lymphocytes.

The occurrence of neuronal chromatolysis in 4 specimens from the lower segment and in 5 from the upper segment gives limited support to the view that achalasia is an active acquired process. Chromatolytic changes were absent in the control cases. Such evidence of progressive degeneration would not be expected if the disease were due to a developmental defect.

Cassella et al. (1964) found minimal ultrastructural evidence of Wallerian

Table 2. Statistical analysis of ganglion cell counts

Clinical diagnosis	Mean ± SD Mean ganglion cell count/cm	Range	*N*
Achalasia			
upper segment	0.14 ± 0.34	0.0 – 0.8	31[a]
lower segment	1.71 ± 2.37	0.0 – 8.0	15[a]
Oesophageal spasm	1.39 ± 0.79	0.0 – 2.2	8[b]
Scleroderma	6.15	0.0 – 9.0	4
Controls	6.63 ± 2.56	3.0 – 10.5	9

[a] From 40 cases
[b] From 6 cases (in 2 cases biopsies from both upper and lower regions)

Probability levels (Students T-Test)
achalasia upper segment vs. controls. $P < 0.0001$
achalasia lower segment vs. controls. $P \sim 0.0005$
achalasia upper segment vs. lower segment. Trend, $P = 0.138$
oesophageal spasm vs. controls. $P \sim 0.0002$
oesophageal spasm vs. achalasia (upper). $P \sim 0.0001$
oesophageal spasm vs. achalasia (lower). Not significant

degeneration in oesophageal branches of the vagus in their cases of achalasia, as well as some neuronal loss from the dorsal motor nucleus of the vagus. However, nothing was found in our material to suggest that the preganglionic nerve (vagal) fibres are abnormal in achalasia. Thus, the myelinated fibres coursing through the region of the myenteric plexus usually appeared normal in nature and number, and cross- and longitudinal sections of the vagal branches to the affected region of the lower oesophygus showed no abnormality, in 2 cases, as regards fibre-density and myelin-staining. Likewise, Lendrum (1937) and Smith (1970) both recorded that the vagus was normal in their cases. In parenthesis, it is likely that such vagal fibres in the myenteric plexus are the source of the persistent acetyl-cholinesterase activity that has been determined in the achalasic oesophagus (Trounce et al., 1957; Adams et al., 1960; Misiewicz et al., 1969; Cohen et al., 1972), for this enzyme is distributed along the length of both pre- and post-ganglionic parasympathetic fibres (see review, Adams, 1965b).

The occurrence of neuronal loss in the oesophagus in 7 out of 8 biopsies from 6 cases of oesophageal spasm or muscular incoordination might be a pertinent observation. Possibly such disordered function (e.g. "the corkscrew oesophagus") represents either an early phase or incomplete expression of achalasia. However, by contrast, ganglion cells were found to be normal in a series of patients with oesophageal spasm and muscular hyperplasia, but without the characteristic dilatation of achalasia (Sloper, 1954).

The absence of either acute or chronic inflammation in more than half these cases of oesophageal spasm or incoordination discourages the view that

an infective agent is a primary factor in their aetiology. Thus, in contrast to Hurst and Rake's (1929) conclusion, a direct cause-and-effect relationship cannot be easily established between oesophageal inflammation and achalasia.

One of our 4 cases of scleroderma showed marked fibrosis of ganglion areas and a corresponding complete absence of neurones: ganglion cells were normal in number and appearance in the other three cases where the plexus was relatively uninvolved by scleroderma. The loss of ganglion cells in the one case is not unexpected in view of the severity of oesophageal fibrosis that may occur in visceral scleroderma; it adds nothing to our understanding of the pathogenesis of achalasia.

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