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NASAL MUCOSA IN CLUSTER HEADACHE: MORPHOLOGICAL CHANGES AND CONTENT OF VASOACTIVE SUBSTANCES

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SUMMARY

Cluster Headache (CH) is a primary headache characterised by peculiar pattern of activity and symptom profile of attacks. The mechanisms underlying nasal congestion and rhinorrhea, symptoms most frequently experienced during the attacks, are still poorly understood. We evaluated the morphological aspects of nasal mucosa obtained from either side in 5 drug-free male patients suffering from CH, namely 2 episodic CH (active phase) and 3 chronic CH, according to the criteria of the International Headache Society (IHS). Tissue content of substance P and the vasoactive peptides neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP) and vasoactive intestinal polypeptide (VIP) was also measured using immunohistochemistry. The morphological study revealed a reduced glandular component, due to hypotrophy and fibrosis of serosal glands on both sides. We found no change in VIP and CGRP content, whereas a clear decrease in SP and NPY content in the nerve endings was observed in all CH patients. This was seen to be more pronounced on the side of the usual pain attacks. These data suggest that in CH the occurrence of rhinorrhea may not reflect increased activity of serosal glands, but rather oedemal/vasomotor phenomena located in the turbinate. The functional significance of changes in mediators within nasal mucosa is also discussed.

INTRODUCTION

Nasal congestion and rhinorrhea are common symptoms of pain attacks in cluster headache (CH), and occur with a prevalence of 47.8% and 37.8% of patients, respectively (1). These clinical features are usually bilateral, but tend to be more pronounced on the pain side. While in nasal congestion hyperemia and edema of nasal turbinates are thought to play a role, rhinorrhea has been ascribed to the passage of tears in the nasal cavity through the naso-lacrimal duct, or, more likely, to the direct activity of the glandular component of nasal mucosa and/or vasomotor phenomena with edema of turbinates (2). In order to elucidate the anatomo-functional

basis of such phenomena, in this study we have evaluated the morphological aspects of nasal mucosa from CH patients; moreover, we have performed a immunohistochemical determination of neuropeptides and mediators involved in the mechanisms of pain and vascular reactivity, i.e. substance P, neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP), and vasoactive intestinal polypeptide (VIP).

SUBJECT AND METHODS

Five CH patients were studied, 2 suffering from episodic CH, and 3 from chronic CH, according to the IHS criteria. The mean age of patients was 34.2 $\pm$ 2.6 years, while the duration of the disease was 6.4 $\pm$ 4.3 years. The clinical features of patients are reported in Table 1. Patients were not on prophylactic treatment, nor they had taken instant-relief drugs over 8 hours preceding evaluation. Five healthy subjects, sex and age-matched, served as controls. Accurate anterior rhinoscopy was performed, in order to: 1. rule out possible concomitant endonasal pathology or malformations; 2. define the exact position of the middle turbinate. Nasal mucosa was then obtained under rhinoscopy, without local anaesthesia, from the antero-superior region of the middle turbinate. The procedure caused little discomfort, with no further consequence (in no case tamponade was required).

Table 1. Features of cluster headache patients.

Case n.	Gender	Age (yrs)	Diagnosis (IHS)	Symptom Duration (yrs)	Symptomatic Side	Nasal Congestion	Rhinorrhea
1	M	35	Episodic CH (active phase)	6	sx	+	+
2	M	32	Episodic CH (active phase)	4	dx	+	+
3	M	36	Chronic CH	14	sx	+	+
4	M	31	Chronic CH	6	sx	+	+/-
5	M	37	Chronic CH	2	dx	+	+

Indirect immunostaining was performed on 5 μm paraffin and cryostat sections (fixed in 10% calcium-acetate-formalin, pH 7.0), using the ABC (Avidine-Biotine Complex) method (3). Each series of preparates had its own positive and negative control sections. Antisera for the different peptides (rabbit IgG) were obtained from Amersham International.

RESULTS

In all patients, the morphological study revealed the presence of edema, slightly more pronounced in episodic CH patients, along with reduced glandular component of nasal mucosa, in part due to hypotrophy and fibrosis, particularly in the 3 chronic CH patients. Figure 1 (chronic CH patient) also shows areas of mucosal cells with a pattern of hypertrophy and hyperfunction.

The immunohistochemical study showed no difference in CGRP and VIP immunoreactivity between patients and controls, in nasal mucosa from either side. By contrast, a clear reduction in the staining for substance P, more marked on the pain side, was observed in the perivascular nerve endings of nasal mucosa from all CH patients, regardless of the clinical type (Figure 2). In one case of chronic CH, the staining for substance P was similar to that of control, but only on the non-symptomatic side. A reduction of NPY-immunoreactive fibers was seen in all CH patients on the pain side, and in 3 out of the 5 patients also on the non-symptomatic side (but still less intense than that on the pain side). A summary of the observed changes in NPY and substance P is reported in Table 2.

Table 2. NPY and substance P - imunoreactivity in nasal mucosa, compared to controls.

CASE No.	NPY		Substance P	
	SS	NSS	SS	NSS
1	↓↓	↓	↓	↓
2	↓↓↓	↓	↓↓	↓
3	↓↓	↓	↓↓	↓
4	↓↓	–	↓	–
5	↓↓↓	↓	↓	–

DISCUSSION

The morphological findings of this study suggest that the typical rhinorrhea of CH may be related to vasomotor phenomena with edema of turbinates, rather than to hyperactivity of nasal mucosal glands. The immunohistochemical changes appear to be almost invariably consistent with the pain side, and even though data concern a limited number of cases, they do not suggest significant differences between the clinical forms

(episodic and chronic) of CH. While the content of the vasodilator peptides CGRP and VIP does not appear to be altered in nasal mucosa from CH patients, the finding of reduced substance P immunoreactivity in nerve fibers suggests depletion of this mediator, possibly due to increased release. It is indeed known that substance P is importantly involved in the modulation of both pain and vasoactive phenomena within the trigemino-vascular system (4). NPY, a vasoconstrictor peptide, is often co-stored with noradrenaline, as well as co-released under conditions of sympathetic activation. Although in this study patients were obviously not examined during the attacks, the reduced number of NPY-immunoreactive fibers, particularly on the pain side, may be compatible with the hypothesis of a sympathetic dysfunction of vascular control in CH, also observable at the nasal site.
These findings are still preliminary, and the data obtained suggest to investigate a larger number of patients, as well as to measure in nasal mucosa other mediators relevant to vasoactive processes (e.g. endothelins). There is little doubt that the multidisciplinary approach to the study of CH can provide useful information to clarify the nature of phenomena, such as nasal congestion and rhinorrhea, intimately related to the pathophysiology of CH.

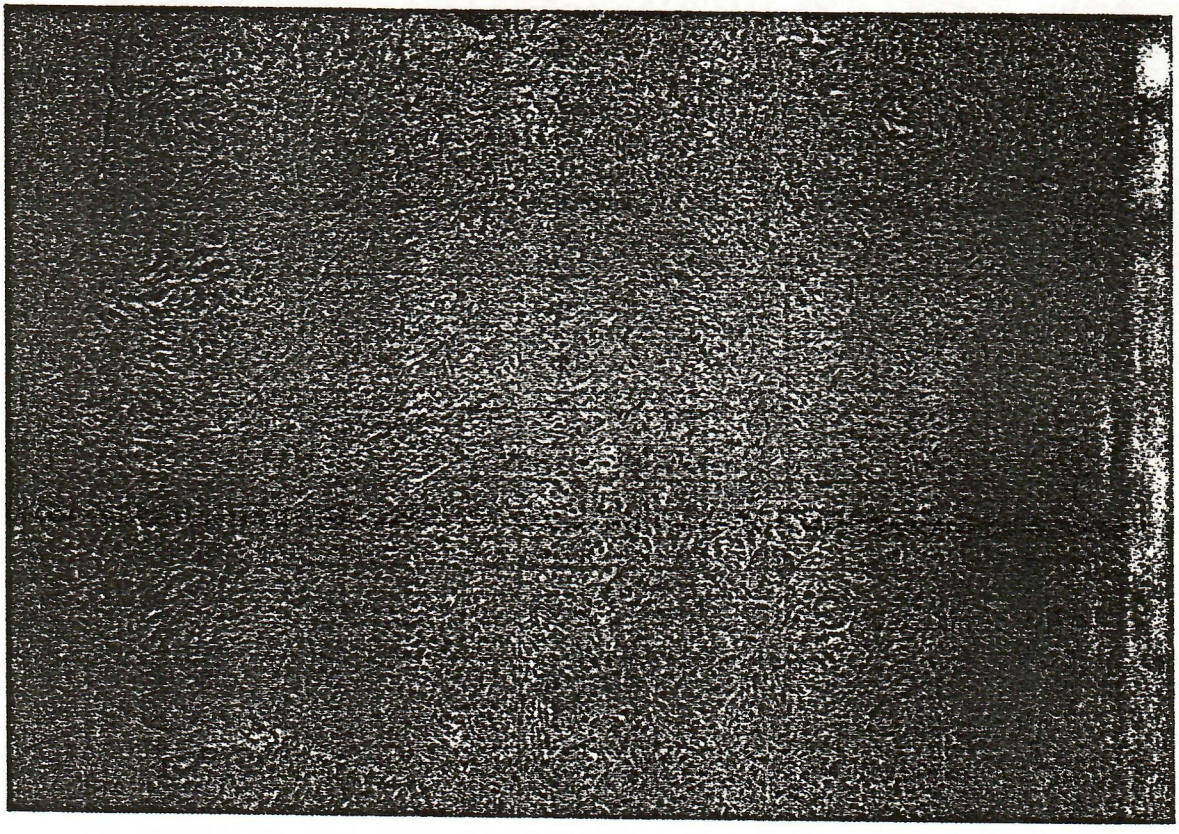

Figure 1. Chronic cluster headache (patient n. 3): hypotrophy and fibrosis of nasal mucosa on the pain side (E.E. x 125).

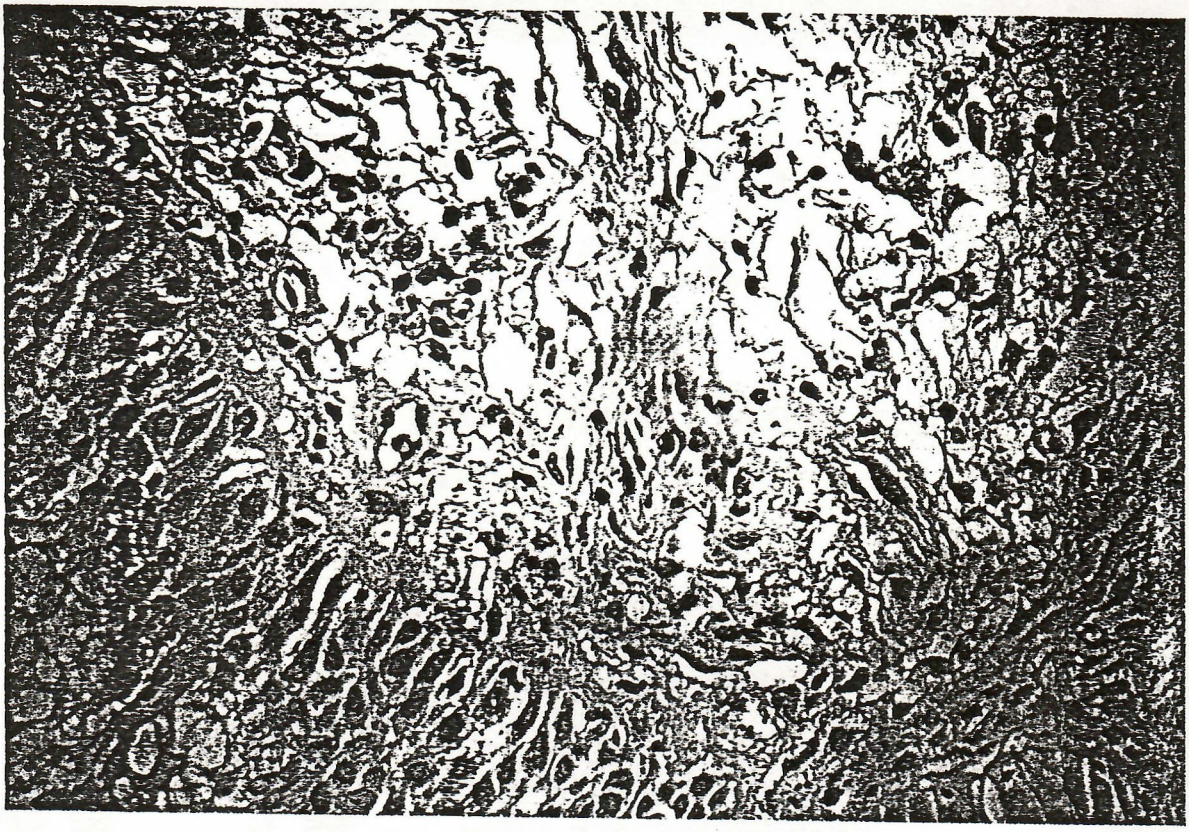

Figure 2. Episodic cluster headache (patient n. 2), nasal mucosa from the pain side: the immunoreactivity for substance P in nerve fibers is diffusely low. The pattern is compatible with previous discharge of the mediator (ABC x 540).

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