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Plasma serotonin in patients with chronic tension headaches

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SUMMARY Previous reports have suggested that platelet level of serotonin in chronic tension headache (CTH) is lower than in normal control subjects, and that there is continuous activation of platelets both in migraine and in CTH. In this study we compared platelet serotonin concentration in 95 patients with CTH, 166 patients with migraine and 35 normal control subjects. Mean platelet serotonin (ng/10^9 platelets) was 310 for the CTH group, 384 during migraine headache, 474 for normal control subjects and 514 in headache-free migrainous patients. There was significant statistical difference of values between CTH patients and those of normal control subjects as well as headache-free migrainous patients, but not of those of migrainous patients during headache. It is suggested that CTH is a low serotonin syndrome, representing one end of the spectrum of idiopathic headache, the other end being represented by migraine.

It does not appear that muscle contraction plays a significant part in tension headache, as there are many reports failing to demonstrate increased muscle tension in patients with this complaint.[1–4] In fact, muscle contraction is at least as prominent in migraine as it is in tension headache.[5–8] Increasing tension by 10 μV in the frontalis muscle through biofeedback, for periods of 2 to 5 minutes, produced pain in patients with tension headache, during the period of contraction and 10 minutes after the contraction was stopped, whilst the control group experienced no pain at any stage. The inference of such an observation is that patients with tension headache experience pain at a lower level of nociceptive stimulation than non-headache subjects.[9]

On the other hand, tension headache may on occasions encompass some migrainous features, such as nausea, a throbbing quality, or mild photophobia. There is evidence of vasodilatation in some patients with tension headache, as shown by the rapid clearance of radioisotope from neck muscles during occipital headache,[10] increased severity of tension headache following inhalation of amyl nitrite,[11] and a pulsating headache in about 50% of patients, but not in normal controls during histamine infusion.[12]

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The outstanding biochemical change during migraine headache is a fall in plasma serotonin,[13] which has been considered to predispose to vasodilatation, particularly of the cranial vessels, and to increased perception of nociceptive stimuli by opening the pain gate.[14]

Rolf *et al*[15] have reported that platelet serotonin content in patients with tension headache is significantly lower than that of normal controls, and that the changes are similar to those observed in migrainous patients during attacks of headache. If this is correct, the weight of the pendulum would tend to swing in favour of those who feel that migraine and tension headache are not necessarily separate nosological activities, but represent the two extremes of the spectrum of the condition now recognised as idiopathic headache.

The purpose of this study was to expand the observations of Rolf *et al*,[15] by studying plasma levels of serotonin in a larger group of patients with tension headache and comparing them with a group of normal controls and another of migrainous subjects, both during headache and periods of headache freedom.

Patients and methods

Ninety five patients diagnosed as suffering from chronic tension headache (CTH), were seen by the authors at their Hospital outpatient or private practice clinics, between 1983 and 1987. The diagnosis was made on the clinical characteristics and duration of the headache, as outlined in table 1. Only patients with daily attacks, were accepted into the

Table 1 *Diagnostic criteria of chronic tension headache of patients admitted to the study*

The pain has the following characteristics:
1. Present for more than one year.
2. Daily or almost daily occurrence.
3. Generalised or poorly localised.
4. Constant, dull, aching, constricting or pressure-like.
5. Intensity mild to moderate, but rarely severe.
6. Few or no associated symptoms.
7. Only temporary relief from analgesics.
8. Poor or no response to antimigrainous drugs.

study, so as to avoid confusion with the periodic headache of migraine. Patients on preventive or analgesic medication were asked to suspend treatment for one week before the blood was collected, although most were on no treatment at all at the time of the initial interview when the procedure was performed.

Blood for estimation of plasma serotonin was collected in the morning, between 9 am and 12 midday, to minimise the effect of diurnal variations. Whole plasma serotonin was assessed fluorimetrically by a modification of the method of Crawford and Rudd.[16] All estimations were performed in duplicate. If the difference between the two aliquots was greater than 5%, the estimation was repeated. Plasma serotonin was expressed as ng/10^9 platelets, since they contain about 98% of serotonin in the blood.[17]

Comparison was made with 35 healthy (non-headache) control subjects and 166 migrainous patients, both during headache and periods of headache freedom. Statistical comparison of plasma serotonin values among the three groups of patients was made by analysis of variance, using the Student-Newman-Keyls procedure.

Results

The clinical profiles of the three groups of patients are shown in table 2. In the migraine group, about one fifth of patients (18%) were males, whilst in that with CTH, just over half of the group (55%) were males.

The mean value of plasma serotonin (ng/10^9 platelets) was 310 for the CTH group and 384 during migraine headache. In contrast, the mean value in headache-free migrainous patients was 514 and in normal controls 474 (table 3, fig). The difference between values for the group of CTH patients and normal controls, as well as headache-free migrainous subjects was statistically significant, whilst that between tension headache and migrainous patients during headache was not significant (fig). Of the 95 patients with CTH, 23 had a mean serotonin value of 503 ng/10^9 platelets, which was similar to that of normal controls and headache-free migraineurs.

Discussion

This study demonstrates that patients with CTH have mean levels of circulating plasma serotonin that are lower than those found in control non-headache subjects, in migrainous patients when headache-free

Table 2 *Plasma serotonin in chronic tension headache. Clinical profile of the three groups of patients compared*

		Sex		*Age (yr)*		*Duration of HA (yr)*
	No	*M*	*F*	*range*	*mean*	
Control	35	16	19	23–52	34	—
Migraine	166	30	136	21–76	39	1–42
Tension	95	52	43	16–81	42	1–26

Table 3 *Plasma serotonin in chronic tension headache. Plasma levels of serotonin (ng/10 platelets) of the three groups of patients investigated in this study*

	Range	*Mean*
Control subjects	125–872	474
Migraine h.a. free	100–1620	514
headache	70–1120	384
Tension headache	92–823	310*

*p = <0·001 Analysis of variance Student-Newman-Keyls Procedure.

and are of the same order as in migrainous patients during headache. Such observations appear to suggest that CTH, like migraine, is a low serotonin syndrome. The low level of circulating serotonin reflects the low content of the amine in platelets.[17]

The loss of serotonin from platelets in migraine has been attributed to their activation in vivo during attacks of headache, which are associated with raised levels of beta-thromboglobulin (BTG)[18] and platelet factor 4 (PT4),[19] both of which are released by alpha granules, whilst serotonin itself is lost from dense bodies in association with ATP and calcium. Similar activation of platelets has been reported to occur in patients with CTH,[20] in that, in addition to raised plasma BTG and PF4, the concentration of free plasma serotonin increases, almost certainly reflecting escape of serotonin from the platelet cell. Whilst in migraine, platelet activation and loss of serotonin are episodic, in the case of CTH these appear to be continuous.

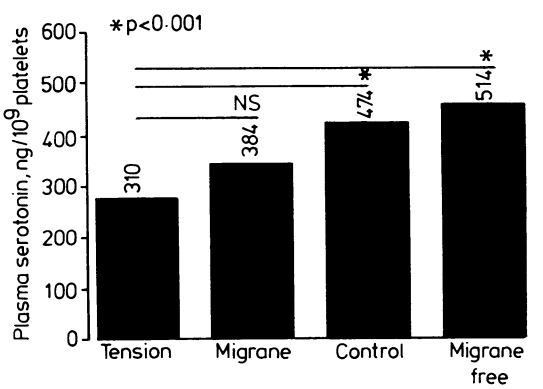

Fig *Plasma serotonin in tension headache (Statistical comparison between groups)*

The low platelet serotonin in migraine almost certainly reflects reduced concentrations of the amine in other parts of the body, and in particular the brainstem, where its depletion leads to increased perception of nociceptive stimuli from various head and neck structures, and possibly leads to cranial vasodilatation. Such neural and vascular influences may produce headache through an interplay of mechanisms as suggested by Lance *et al.*[14]

In a recent study,[21] serotonin uptake was found to be greater by platelets of patients with CTH than by those of migraineurs or normal controls, whilst mean platelet serotonin content (ng/10^9 platelets) was 533 in patients with CTH, 531 in normal controls and 332 in migraineurs. Unfortunately, there was no statement as to the frequency of headaches or whether headache was present at the time of collecting the specimens. In our own studies of serotonin metabolism in migraine,[13] it was found that platelet serotonin content fell during headache, but incubation of platelets from headache-free and headache periods with excess serotonin, produced equal concentrations of the amine in both sets of platelets. It is therefore highly probable, that the increased uptake of serotonin by platelets of patients with CTH found in the study by Shukla *et al*,[21] may in fact be an indication of the low initial serotonin content of the substance in the platelets of such patients. The authors' assumption that CTH is a high serotonin syndrome does not appear to be compatible with current concepts of serotonin physiology, namely peripheral vasoconstriction and central modulation of pain by closing the pain gate.[17]

On balance, the evidence available so far appears to favour the view that CTH resembles migraine biochemically, and can be regarded as one end of the spectrum of idiopathic headache, consisting of unremitting headache with a few, if any, migrainous characteristics, whilst the other end is made up of episodic headache with many associated features, the symptom-complex referred to as migraine.

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