

High incidence of endogenous depression in migraine: confirmation by tyramine test

Joan Jarman, Margaret Fernandez, P T G Davies, Vivette Glover, T J Steiner, C Thompson, F Clifford Rose, M Sandler

Abstract

Forty patients with migraine who were attending a specialist clinic were interviewed with the Schedule for Affective Disorders and Schizophrenia - Lifetime version. Sixteen (40%) had a history of major depression which was of endogenous type in 15, according to Research Diagnostic Criteria. The tyramine test, a previously established trait marker for endogenous depression, showed that the migraine group as a whole had significantly low values compared with 14 normal controls, due almost entirely to low values in the endogenous depressive subgroup; there were no differences between diet-sensitive and non-diet-sensitive migraine patients. Thus depression in patients with migraine seems unlikely to be secondary to migraine per se. A substantial subgroup of patients with migraine may possess an inherent predisposition to endogenous depression.

It has often been suggested that migraine is linked to personality traits such as obsessionality, over-conscientiousness, rigidity and excessive drive,^{1,2} but these associations are uncertain and controversial.³ Connections between depression and migraine are better established. An increased prevalence of depression among migraine patients,^{4,5} as well as a raised incidence of migraine among patients receiving treatment for depression⁶ have been reported. There is evidence to suggest that this association is not solely a hospital outpatient clinic phenomenon; two studies^{3,7} have shown that depression, and also anxiety, are migraine accompaniments in the general population. Furthermore, an association between major depression and migraine has recently been shown in subjects selected at random from a community sample.⁶

There may well be biochemical features common to both migraine and depression. There is evidence of a disturbance in 5-hydroxytryptaminergic systems in each,^{8,9} while both respond to tricyclic antidepressants.¹⁰ A further biochemical deficit, recorded in both, is in tyramine sulphoconjugation. In 1971 we and others, observed a deficit in urinary excretion of tyramine-O-sulphate following an oral tyramine load, in a group of psychiatrically unclassified patients with so-called dietary migraine,^{11,12} although we later had difficulty in replicating this find-

ing (unpublished data). Subsequently, we identified a similar sulphoconjugation deficit present as a trait marker in depression^{13,14} which later proved specific for endogenous depression.^{15,16} Its biochemical basis remains unclear.

In this study we have obtained detailed psychiatric histories from a group of patients attending a specialist headache clinic, and measured tyramine sulphate excretion in them, to clarify whether low tyramine sulphoconjugation is a characteristic of migraine patients in general, or of a depressed subgroup only.

Methods

From 176 patients seen consecutively in the Princess Margaret Migraine Clinic, Charing Cross Hospital, for treatment of common or classical migraine, diagnosed according to Vahlquist's criteria,¹⁷ 40 agreed to return to participate in the study. All the patients that were approached to take part in the study completed the self-rating Hospital Anxiety and Depression Scale,¹⁸ which provided a crude estimate of their current anxiety and depression. Control subjects (n=14) not regularly suffering from any form of headache and otherwise healthy, were recruited from laboratory personnel. The mean ages (SD) for controls and patients were 34.2 (11.8) years and 39.9 (10.6) years, respectively. The patient group comprised eight males and 32 females and the controls four males and 10 females.

In the 48 hours preceding oral tyramine challenge, patients and controls refrained from paracetamol or ascorbic acid ingestion and followed a low tyramine diet. They fasted overnight with only water to drink and, at the start of the test, emptied their bladders and swallowed a capsule containing 125 mg tyramine hydrochloride. All urine was then collected for exactly 3 hours and its volume determined. An aliquot was stored frozen at -20°C before measurement of tyramine-O-sulphate by a gas chromatographic method.¹⁹ Although patients were asked to refrain from paracetamol in the 48 hours before the oral tyramine challenge, a number of them had taken medication in the previous week (table 1). Only two patients were taking antidepressants, and both of these were diagnosed as having a history of endogenous depression.

During the three hour period of the test, patients were interviewed by a trained clinical rater (MF), using the Schedule for Affective Disorders and Schizophrenia Lifetime Version

Department of
Chemical Pathology,
Queen Charlotte's and
Chelsea Hospital,
London

J Jarman
V Glover
M Sandler

Department of
Psychiatry, Charing
Cross Hospital,
London

M Fernandez
C Thompson*

Princess Margaret
Migraine Clinic,
Charing Cross
Hospital, London
PTG Davies
TJ Steiner
F Clifford Rose

*Present address:
Department of Psychiatry,
Royal South Hampshire
Hospital, Southampton

Correspondence to:
Professor M Sandler,
Department of Chemical
Pathology, Queen
Charlotte's and Chelsea
Hospital, Goldhawk Road,
London W6 0XG, United
Kingdom

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Table 1 Drug intake by patients in the week preceding oral tyramine challenge

Drug	n	Tyramine-O-sulphate excretion (mg/3h) median (range)
Drug-free	11	4.4 (2.0-9.1)
Propranolol/atenolol	18	4.4 (1.9-8.1)
Non-steroidal anti-inflammatory drugs	9	4.5 (2.2-8.1)
Others†	8	4.6 (2.6-6.2)
Pizotifen	3	4.7 (2.2-6.2)
Antidepressants	2	3.1 (3.8-4.4)
<i>Drug-free patients only</i>		
History of endogenous depression	5	2.9 (2.0-3.4)*
No history of endogenous depression	6	5.1 (4.3-9.1)

* $p < 0.02$ compared with patients with no history of endogenous depression (Mann-Whitney U-test, two tailed).

†"Others" includes ergotamine, benzodiazepines, and oral contraceptives. Patients taking more than one category of drug were placed in both categories.

(SADS-L)²⁰ to assess current and previous incidence of psychiatric disorder. Endogenous depression was diagnosed according to Research Diagnostic Criteria.²¹

Results

Prevalence of psychiatric disorder

To assess whether patients who had volunteered to have the oral tyramine test plus psychiatric interview were representative of the clinic population, anxiety and depression scores on the Hospital Anxiety and Depression Scale¹⁸ for the 40 participants and the 136 non-participants were compared. Scores greater than 11 indicated levels of anxiety or depression consistent with the presence of a clinical mood disorder. On the anxiety scale, scores >11 were obtained by 20% of the patients volunteering compared with 38% of non volunteers, and on the depression scale, by 8% of volunteers compared with 10% of non volunteers. Therefore, the patients participating in the study actually appeared to be less anxious and depressed than the rest of the patients attending the clinic.

Among the 40 volunteers, a lifetime history of major depression was by far the most prevalent psychiatric disorder (table 2), present in 40% of patients, with 15% being clinically depressed at the time of examination. All but one of the 40% also fulfilled Research Diagnostic Criteria for endogenous depression. This incidence of depression is in excess of literature estimates of lifetime occurrence of major depression in the general population (8-12% for males; 20-25% for females).²²

Tyramine sulphoconjugation

Mean urinary three hour tyramine-O-sulphate output was significantly lower in the 40 migraine patients compared with controls [4.69 (1.74) mg/3 hour and 6.12 (1.67) mg/3 hour; $p < 0.02$]. When the migraine patients were divided into those with a history of endogenous depression and those without, the former showed a significantly lower three hour excretion than the latter ($p < 0.02$) and the control group ($p < 0.001$). Those patients without a history of endogenous depression had excretion values not significantly different from control values (fig). Our earlier studies¹²

Table 2 Major psychiatric disorders in 40 migraine patients diagnosed using the SADS-L

	Lifetime incidence n	Present state n
Major depression (Endogenous depression)	16 (15)	6 (6)
Minor depression	2	1
Alcoholism	1	1
Labile personality	1	1
Antisocial personality	1	1
Generalised anxiety disorder	1	0
Agoraphobia	1	0
No psychiatric disorder	17	30

showed excretion levels for endogenous depressives to fall at or below 4.1 mg/3 hour, which was therefore proposed as the diagnostic cut-off point for the disorder. Our present data show that 73% of the endogenous depressives, as opposed to 12% of the non-depressive migraine group, fell into this "low conjugator" category, a highly significant difference ($p < 0.0003$, Fisher's Exact Test, two-tailed).

A number of patients had taken medication in the week preceding oral tyramine challenge. To check that these forms of medication were not responsible for the differences in tyramine conjugation noted between patients with and without a history of endogenous depression, output values in patients who had taken different categories of drugs were compared (table 1). No significant differences between patients taking any type of drug and drug-free patients were observed and the significant difference in conjugated-tyramine output between depressed and non-depressed groups persisted even when only drug-free patients were considered.

When patients were classified as diet-sensitive, that is, those who observed improvement in their migraine attacks when avoiding supposedly responsible foods and deterioration when they were reintroduced, and non-diet-sensitive, no differences in tyramine sulphoconjugation were observed between the two groups, whether or not the endogenous depressives were included in the analysis. Three of the diet-sensitive patients believed that cheese specifically would initiate their attacks; we therefore scrutinised them

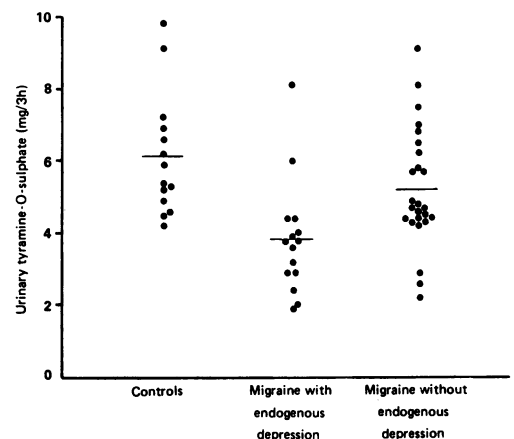


Figure Urinary tyramine-O-sulphate excretion in 14 controls (CON), 15 migraine patients with a history of endogenous depression (M+D) and 25 migraine patients with no history of endogenous depression (M). Controls versus M+D, $p < 0.001$; versus M, $p < 0.02$; Controls versus M, not significant; Student's *t* test, two-tailed.

separately but were unable to demonstrate any difference in sulphoconjugation in these patients compared with the control group.

Discussion

This study demonstrates a high lifetime incidence of endogenous depression in migraine patients, a finding confirmed by the tyramine test, a sensitive biochemical trait marker.¹⁵ In any investigation of patients attending a specialist clinic, the question arises as to whether the patients, to some extent self-selected, are representative of those in the community. In this study there was some evidence from a self-rating Hospital Anxiety and Depression Scale¹⁸ to suggest that the patients volunteering for further psychiatric and biochemical evaluation were actually somewhat less anxious and depressed than the non-volunteers. Although not investigated here, it would be of interest to extend these findings by comparing other aspects of personality and also of migraine severity in volunteers and non-volunteers. An overall link between migraine and depression has previously been noted in community studies,⁶ suggesting that the findings in our volunteers may have a wider validity.

A striking and unexpected characteristic of the depressive illness observed in the migraine volunteers was its almost completely endogenous nature, confirmed by tyramine test. Low tyramine conjugation is a trait marker for the endogenous variant of the disorder and is thus independent of present state; it manifests in approximately half the first degree relatives of endogenous depressives, whether or not they have yet experienced an episode of the illness.¹⁵ It therefore appears likely that the conjugation deficit represents an inborn error of metabolism which can be employed to pinpoint objectively those individuals with a predisposition towards this particular form of depressive illness. The presence of the trait in this group seems to rule out that depression was a secondary reaction to migraine, as had previously been suggested.⁶ It appears more likely that an individual may have a predisposition to both migraine and endogenous depression, which have their basis in a shared set of biochemical abnormalities.

Recently, Hale *et al*²³ have shown that possession of the tyramine conjugation deficit by depressives is a predictor for a favourable response to tricyclic antidepressant therapy. It will be interesting to see whether it is similarly a predictor of tricyclic treatment response in migraine.

The sulphoconjugation of tyramine is catalysed by phenolsulphotransferase (PST). Although activity of PST has previously been found to be deficient in the platelets of dietary migraine patients,^{24,25} we have found no significant correlation between either platelet PST M or PST P and urinary excretion of tyramine-O-sulphate in subjects participating in this study (Jarman *et al* in preparation). This confirms previous work in which no differences were found in platelet PST M or P activity in depressed patients of a type characterised by low excretion of tyramine-O-sulphate compared with controls.²⁶

Despite earlier indications to the contrary,^{11,12} the present investigation has failed to demonstrate any correlation between diet sensitivity per se and the tyramine sulphoconjugation deficit. It is only when a lifetime history of endogenous depression is present in the same individual that the conjugation deficit is observed. The original patients with dietary migraine and tyramine conjugation deficiency^{11,12} were psychiatrically unclassified. In the light of our findings, it seems likely that the group investigated had included a significant number of patients with the endogenous depression trait.

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