Short report

Platelet size: no correlation with migraine or monoamine oxidase activity

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SUMMARY A Coulter Model "S Plus" counter has been used to study platelets from 39 migrainous patients between attacks, six during attacks, eight with active cluster headache and 26 controls. None of the patient groups showed any abnormality in platelet size profile. There was no correlation between platelet monoamine oxidase activity and mean platelet volume in any of the groups.

One of the few reproducible physiochemical abnormalities in migraine is a reduction of platelet monoamine oxidase (MAO) activity both during¹⁻³ and outside²⁻⁶ a headache attack, with particularly low values in patients with cluster headache.^{5,6} There is much evidence that platelet function is abnormal in migraine.⁷⁻¹³ Whether such abnormalities of platelet function are the primary cause of migraine,¹⁰ or are secondary to some circulating platelet damaging agent¹⁴ is still unknown. Platelet senescence is associated with a reduction in size, and reduced size with lower specific activity of MAO.¹⁵⁻¹⁷ We therefore wondered if the lower mean MAO activity in male migrainous patients could be attributed to a preponderance of older, smaller, and less active platelets in the circulation.

Patients and methods

Blood was taken from patients attending Princess Margaret Migraine Clinic at Charing Cross Hospital, London. Thirty-nine patients were studied between attacks of migraine, classified according to the criteria of Vahlquist.¹⁸ Men and women with common and classical migraine were considered separately (table 1). Four male subjects, two

with common and two with classical migraine, were included specifically because they had been shown to possess very low MAO activity values in an earlier investigation.^{3,6} There were six additional female patients who were experiencing a migrainous headache at the time blood was drawn, and eight male patients with active cluster headache, diagnosed according to standard criteria.⁶ Twenty-six control samples were taken from members of the hospital staff and students. Venous blood was collected into EDTA: 5 ml for platelet sizing and a further 10 ml for MAO assay. The former were analysed within 6 h of collection using a Coulter model "S Plus" counter (Coulter Electronics, Luton, Beds, UK), calibrated according to the manufacturer's instructions and checked each day using a preventative maintenance scheme which incorporates checks with Coulter "4C Plus". This counter provides a platelet count, and calculates the mean platelet volume (MPV); it also gives a "platelet distribution width" (PDW)¹⁹ which is a numerical index of the width of the log-normal distribution curve, that is the heterogeneity of platelet distribution. Platelets were prepared from the second venous blood sample by methods previously described.⁶ MAO was assayed using ¹⁴C-tyramine as substrate as previously described²⁰ and protein concentration estimated using the Lowry method.²¹ All statistical evaluation was by Student's two-tailed *t* test unless stated otherwise.

Results

The mean values ($\pm$ SEM) for age, platelet count, mean platelet volume and platelet distribution width for the 53 headache patients and 26 controls are

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Table 1 Platelet parameters in headache patients

Group	n	Age $\pm$ SEM (yr)	Platelet count $\pm$ SEM $\times 10^9/\text{litre}$	Mean platelet vol $\pm$ SEM (fl)	PDW $\pm$ SEM	n	MAO $\pm$ SEM nmol tyramine /mg in 30 min
Female normals	5	24 $\pm$ 2	274 $\pm$ 18	8.3 $\pm$ 0.4	9.2 $\pm$ 0.1	5	17.3 $\pm$ 1.3
Male normals	21	27 $\pm$ 2	255 $\pm$ 12	8.0 $\pm$ 0.2	9.5 $\pm$ 0.07	19	15.7 $\pm$ 1.1
All normals	26	26 $\pm$ 2	259 $\pm$ 10	8.0 $\pm$ 0.2	9.4 $\pm$ 0.06	24	16.0 $\pm$ 0.9
<i>Migraine between attacks</i>							
Male classical	11	37 $\pm$ 4	272 $\pm$ 18	8.2 $\pm$ 0.3	9.6 $\pm$ 0.2	9	12.4 $\pm$ 1.4
Female classical	11	39 $\pm$ 5	274 $\pm$ 16	8.6 $\pm$ 0.2	9.5 $\pm$ 0.1	11	14.3 $\pm$ 1.5
Male common	7	43 $\pm$ 4	266 $\pm$ 17	7.5 $\pm$ 0.3	9.3 $\pm$ 0.1	5	13.4 $\pm$ 1.4
Female common	10	44 $\pm$ 5	244 $\pm$ 20	8.3 $\pm$ 0.3	9.5 $\pm$ 0.09	10	13.4 $\pm$ 1.9
All male	18	39 $\pm$ 3	270 $\pm$ 13	7.9 $\pm$ 0.2	9.5 $\pm$ 0.1	14	12.7 $\pm$ 1.0
All female	21	41 $\pm$ 3	260 $\pm$ 13	8.5 $\pm$ 0.2	9.5 $\pm$ 0.07	21	13.8 $\pm$ 1.2
All classical	22	38 $\pm$ 3	273 $\pm$ 12	8.4 $\pm$ 0.2	9.6 $\pm$ 0.09	20	13.4 $\pm$ 1.0
All common	17	43 $\pm$ 3	253 $\pm$ 13	7.9 $\pm$ 0.2	9.4 $\pm$ 0.07	15	13.4 $\pm$ 1.3
All	39	40 $\pm$ 2	265 $\pm$ 9	8.2 $\pm$ 0.2	9.5 $\pm$ 0.06	35	13.4 $\pm$ 0.8
<i>Migraine during attacks</i>							
All female	6	37 $\pm$ 4	290 $\pm$ 27	8.1 $\pm$ 0.4	9.4 $\pm$ 0.06	5	15.6 $\pm$ 3.0
<i>Cluster headache between attacks</i>							
All male	8	36 $\pm$ 2	303 $\pm$ 18	7.7 $\pm$ 0.2	9.3 $\pm$ 0.04	8	11.5 $\pm$ 1.7

shown in table 1. MAO activity values for 48 patients and 24 controls are also shown, the four patients selected because of their previously low values having been excluded. The samples from patients and controls were not processed simultaneously, but there was no correlation ($r = 0.29$) of mean parameters and date of analysis of each batch.

MAO activity in the eight male patients with cluster headache was lower than that in the male controls ($p < 0.05$), confirming our previous finding.⁶ Values were similarly lower in the 11 male patients with classical migraine but, perhaps because of smaller numbers, the difference did not reach statistical significance ($0.1 < p < 0.05$). The four patients selected for their previously low MAO activity had a mean MAO activity of 6.7 ± 1.5 (SEM) nmol/mg

protein/30 min, a mean MPV of 7.5 ± 0.5 SEM fl, and a mean PDW of 9.3 ± 0.1 SEM.

It will be seen that none of the platelet values (count, mean volume or PDW) was different in any patient group from those of controls. Female control and migraine subjects, taken together, have slightly larger platelets than the males ($8.45 \text{ fl} \pm 0.16$ SEM in the females and $7.96 \text{ fl} \pm 0.16$ SEM in the males) but this difference was not statistically significant ($0.1 < p < 0.05$). There was no correlation between MAO activity and mean platelet volume nor between mean platelet volume or PDW and the time interval since the last attack. Although our control subjects were significantly younger than the migrainous patients, there was no correlation between age and mean platelet volume. The correlation coefficients are given in table 2.

Table 2 Correlation coefficients

	n	r	p
<i>Mean platelet volume vs MAO:</i>			
Control	24	0.182	NS
Migraine between attacks	39	0.021	NS
Migraine during attacks	5	0.111	NS
Cluster headaches	8	-0.458	NS
Total	76	0.048	NS
<i>Mean platelet volume vs days since last attack:</i>			
All migraine patients	39	0.080	NS
<i>Platelet distribution width vs days since last attack:</i>			
All migraine patients	39	-0.088	NS
<i>Age vs mean platelet volume:</i>			
Migraine between attacks	39	0.076	NS
Controls	26	-0.070	NS
Total	65	0.069	NS

Discussion

This study has failed to demonstrate any link between platelet size and migraine. Platelets were not significantly smaller in headache subjects outside an attack than in controls, nor were they smaller just after an attack. Platelet counts were not significantly different in these groups of patients: any balanced replacement of small, spent platelets by new large ones would influence the size distribution. Although there are increased numbers of platelet aggregates circulating in migraine patients,^{7,8,10} these break up when blood is anticoagulated with EDTA alone⁸ and would not have been found in this study. Nevertheless, the overall platelet count might have been altered if such aggregates, which would presumably be formed from the younger, more active platelets, were being removed from the circulation.

The Coulter sizing technique we employed is sensitive to changes in the shape of the particles as well as their size.²² There is, therefore, no evidence that the platelet aggregation has reached the point of irreversible microtubular reorientation during attacks of migraine. Our findings lend no support to the idea that the primary defect in migraine is a disproportion between different platelet subpopulations released from different ploidy classes of megakaryocytes.²³

This study also demonstrates that there is no link between specific MAO activity and platelet size in controls, migrainous patients, or those with cluster headache. Thus, although different subpopulations in a given individual may have widely different MAO activity values,¹⁵⁻¹⁷ it seems unlikely that the low values noted in some headache patients are explicable in terms of abnormally-sized platelets. The fact that the platelet protein in patients with low MAO activity is normal⁶ supports this conclusion. Whether low platelet MAO activity values found in some migraine patients are genetically linked, acquired, or both, and their relevance to the pathogenesis of migraine remain obscure.

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