Chronic daily headache- one disease or two.? Diagnostic role of serum ionized magnesium

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The entity of chronic daily headache (CDH) is well documented, but is not included in the current classification. We divided patients with CDH into groups with and without migrainous features. This division resulted in clearly distinguishable syndromes of daily migrainous headaches (DMH) and daily tension-type headaches (DTH). Family history of headaches was more common in patients with DMH. Patients in both groups had a high incidence of caffeine or drug overuse. The clinical division into DMH and DTH was supported by our finding of a higher incidence of disturbed magnesium (Mg) metabolism in patients with DMH. Of 26 patients with DMH, 8 (30.8%) had low serum ionized, but not total, Mg levels, and 16 (61.5%) had high ionized calcium/magnesium ratios. The corresponding numbers for the 22 patients with DTH were 1 (4.5%) and 8 (30.4%). These new laboratory measurements offer possible biological markers for the diagnosis of different headache syndromes. • *Calcium, chronic daily headache, headache, headache classification, magnesium*

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The International Headache Society (IHS) classification of headaches (1) has provided a much needed impetus for the study of various headache types. The classification committee recognized the preliminary nature of this classification and called for further testing and modifications that are sure to continue for many years. An additional category, chronic daily headache (CDH), has been widely reported (2-6) and seems to deserve an entry in the classification. However, great confusion exists about its definition (7). Some authors exclude chronic tension-type headaches from this category because such headaches have an entry in the current classification. This leaves, in the CDH group, patients with migraines that were transformed into a continuous headache and those with an acute onset of daily headaches with migrainous features. These subdivisions and the entire IHS classification relies on clinical descriptions which have obvious limitations.

Attempts to find a biological marker for various types of headaches have proven to be very difficult. Whole brain p31 NMR spectroscopy (8) showed low Mg levels between migraine attacks with further reduction during an attack in a limited number of patients. Low serum and tissue levels of Mg have been reported with headaches (9-11). The number of such studies has been small and they have reported inconsistent results. For example, both normal and low total Mg (TMg) levels have been reported in the serum and red cells of patients with headaches. We postulated that the biologically active ionized Mg (IMg^{2+}) rather than TMg may be deficient in some headache patients. In our previous study (12), using a newly developed ion-selective electrode for Mg (13, 14), we reported that a higher proportion of patients with an acute migraine than with CDH have a low IMg^{2+}. We proposed using serum IMg^{2+} for classification of various headache syndromes (15), and in this study examined clinical features and $IMg2^{+}$ of 48 patients with daily headaches.

Methods

Forty-eight subjects were selected from approximately 270 consecutive patients who consented to participate in the study. We included in this analysis patients who had daily, but not necessarily continuous headaches. Thus, patients could have headache-free periods lasting for hours and on a rare occasion for a day. We divided patients arbitrarily into two groups, depending on the number of clinical features typical of a migraine headache, These included the following six features: presence of nausea, unilateral pain, pulsatile quality of pain, worsening of pain by light physical activity, photophobia and phonophobia. Family history of headaches, caffeine and medi-cation use were also recorded. It has been previously noted that many patients find it difficult to estimate the duration of their daily headaches (6), because the transition from intermittent to daily headaches is often gradual. Considering that memory for pain and headaches is very unreliable, no attempt was made to establish the duration of the continuous period of headaches. We recorded only the total duration of all types of headaches each patient experienced. Average severity of headaches and the severity of headache at the time of sampling were assessed on a l to

10 verbal scale. The number and type of headache drugs taken at the time were recorded along with caffeine intake. The patient was considered to abuse medications (medications containing caffeine, ergots or narcotics) or caffeine if more than one dose was taken on a daily basis. We did not include patients taking acetaminophen or non-steroidal anti-inflammatory drugs because little evidence exists that these drugs induce or worsen headache.

This study compares IMg^{2+}, ionized calcium (ICa^{2+}) and ICa^{2+}/IMg^{2+} ratios in patients with CDH and [3]2 of those features. We measured IMg^{2+} and ICa^{2+} using ion selective electrodes for Mg^{2+} and Ca^{2+} with a NOVA Biomedical Star Profile 8 Analyzer (13, 14). The accuracy of these electrodes is *97-100%* (14-16). Specific details of the characteristics of these electrodes can be found elsewhere (14-16). Total Mg in the serum was determined by atomic absorption spectroscopy and a Kodak DT-60 Ektachem Analyzer, which yielded identical results. Percent IMg^{2+} (%IMg^{2+}) and ICa^{2+}/IMg^{2+} ratios were calculated. We chose the lower limit of normal for IMg^{2+} levels to be 0.55 mmol/l. The normal range for ICa^{2+}/IMg^{2+} ratio is 1.92-2.01. In 95% of our normal controls, IMg^{2+} was above 0.55 mmol/l, ICa^{2+}/IMg^{2+} within the above range and ICa^{2+} was between 1.15 and 1.23 mmol/1.

Mean values ± SEM were calculated and compared for statistical significance by a non-paired Student's *t*-test, ANOVA, chi-square, and Scheffe's contrast test, where appropriate. A p value of less than 0.05 was considered significant.

Results (Tables 1-3)

We had 26 patients with chronic migrainous headaches (i.e. with three or more migrainous features) and 22 with chronic tension-type headache (two migrainous features or fewer). There was little overlap between these two groups. Sixteen patients had 5-6 of these features and eighteen patients had none or one. The mean number of migrainous features (±SEM) was 4.65 ± 0.21 in the migrainous group and 0.72 ± 0.16 in the tension group ($p < 0.001$). Mean duration (±SEM) of headaches (not just daily, but including earlier periods of episodic headaches) was 157 ± 31 months in the migrainous group (range from 1 to 480 months) and 133 ± 46 in the tension group (range from I to 840 months) ($p > 0.05$). The mean severity of headaches was higher in the migrainous group. Mean age was similar in both groups and ranged from 20 to 82, except for one boy of 12. Many more men were present in the tension than in the migrainous head-

Table 1A. **Patients with daily tension headaches.**

N	Age	Sex	Sev.	Dur.	MF	FH	Dru.	IMg^{2+}	ICa^{2+}/IMg^{2+}	TMg
1	23	F	5	24	2	N	N	0.55	2.14	0.78
2	35	M	7	24	1	N	N	0.56	2.12	0.78
3	80	M	7	840	0	7	N	0.60	2.07	0.95
4	43	M	2.5	48	0	N	N	0.57	2.17	0.90
5	39	F	9.5	24	1	N	Y	0.60	2.17	0.82
6	43	F	8	42	1	N	Y	0.59	2.10	0.95
7	40	M	5	6	0	N	N	0.57	2.07	0.82
8	28	F	5	24	I	N	Y	0.58	2.07	0.86
9	45	F	2	60	0	N	N	0.56	2.21	0.82
10	20	F	6	2	0	N	N	0.63	1.90	0.90
11	78	F	6	240	1	N	Y	0.56	2.20	0.82
12	59	F	7	66	0	Y	Y	0.55	2.22	0.90
13	41	M	4.5	24	1	Y	Y	0.62	1.93	0.95
14	55	M	3	576	0	N	Y	0.51	2.27	0.74
15	55	F	8	480	0	N	N	0.50	2.20	0.90
16	28	M	8	1	2	?	N	0.55	2.22	0.78
17	42	F	8	120	2	N	N	0.58	2.07	0.82
18	28	M	5	48	1	Y	N	0.61	2.06	0.90
19	43	M	5	72	N	N	Y	0.58	2.03	0.90
20	32	F	9	60	1	Y	N	0.66	1.82	0.90
21	34	M	7	144	0	Y	Y	0.60	1.97	0.90
22	46	F	7	3	2	N	N	0.59	2.10	0.95

Sev.-average headache severity on 1-10 verbal scale; Dur.-duration of headaches in months; MF-number of migrainous features; FH-family history of headaches; Dru-drug overuse; IMg^{2+} and TMg values in mmol/l.

Table 1B. **Patients with daily migrainous headaches.**

N	Age	Sex	Sev.	Dur.	MF	FH	Dru.	IMg^{2+}	ICa^{2+}/IMg^{2+}	TMg
1	28	F	4	120	6	Y	Y	0.67	1.82	0.99
2	22	F	10	6	5	?	N	0.57	2.19	0.82
3	28	F	10	156	3	N	Y	0.53	2.34	0.78
4	*55*	F	5.5	480	5	Y	N	0.56	2.18	0.90
5	33	F	9	360	6	N	N	0.58	2.02	0.78
6	36	F	I0	36	6	Y	Y	0.54	2.18	*0.78*
7	41	F	10	1	3	N	N	0.50	2.48	0.82
8	32	M	5	36	6	Y	Y	0.57	2.09	0.82
9	12	M	6	6	5	Y	N	0.56	2.11	0.82
10	27	F	8	168	5	N	Y	0.52	2.40	0.86
11	42	F	6	480	6	Y	Y	0.51	2.39	0.78
12	35	F	7	120	3	Y	N	0.55	2.22	0.82
13	28	F	9	1	5	Y	N	0.57	2.21	0.80
14	32	F	10	312	6	Y	Y	0.61	2.00	0.82
15	33	F	10	168	5	Y	N	0.64	1.84	0.90
16	25	F	10	1	4	N	Y	0.55	2.20	0.86
17	24	F	7	48	3	Y	Y	0.54	2.09	0.74
18	82	F	5.5	360	3	Y	N	0.72	1.94	1.03
19	22	F	10	84	5	Y	Y	0.57	2.37	0.82
20	29	M	9	2	4	N	N	0.58	2.17	0.82
21	59	M	9	96	5	N	N	0.55	2.18	0.80
22	41	F	8	240	5	N	N	0.55	2.31	0.78
23	35	F	8	36	5	N	N	0.51	2.29	0.82
24	49	F	10	360	5	N	Y	0.55	2.14	0.78
25	62	F	6	336	5	Y	Y	0.73	1.57	1.23
26	23	F	6.5	60	3	N	N	0.53	2.49	0.82

Sev.-average headache severity on 1- 10 verbal scale; Dur.-duration of headaches in months; MF-number of migrainous features; FH-family history of headaches; Dru-drug overuse; IMg^{2+} and TMg values in mmol/l.

Table 2. **Clinical features of daily migrainous (DMH) and daily tension-type (DTH) headaches.**

N	DMH	DTH	All
	26	22	48
Unilateral	12146%*	4/18%	16/34%
Pulsatile	19/73%*	4/18%	23/48%
Worse on activity	24/92%*	2/12%	26/54%
Nausea	22/85 %*	1/5 %	23/48%
Photophobia	23/88%*	2/12%	27/56%
Phonophobia	21/81%*	3/14%	24/50%
Family history	12/46%**	6/27%	18/38%
Drug overuse	12/46%	10/45%	22/46%
Female	22/85%	12/55%	34/71%
Mean age ± SEM	36.8 ± 2.9	42.6 ± 3.3	39.1 ± 2.2
Mean duration (months)	157 ± 31	133 ± 46	146 ± 27
Mean average severity ± SEM	8.02 ± 0.38	6.11 ± 0.50	7.15 ± 0.31
Mean severity at testing ± SEM	7.33 ± 0.49	5.14 ± 0.55	6.32 ± 0.91

SEM = Standard Error of Mean.

* Significantly different from DTH, $p < 0.01$.

** Significantly different from DTH, $p < 0.02$.

ache group (45% vs 15%, $p < 0.01$). A family history of headaches was reported by 15 patients (58%) in the first group and by 6 patients (27%) in the second group ($p < 0.02$). Patients in both groups had an equally high incidence of caffeine or medication

Table 3. **Ionized Mg, total Mg and ICa^{2+}/IMg^{2+} ratios in daily migrainous (DMH) and daily tension-type (DTH) headaches.**

	IMg^{2+}	ICa^{2+}/IMg^{2+}	TMg
Controls (n = 66)	0.60 ± 0.004	1.95 ± 0.006	0.84 ± 0.008
DMH (n = 26)			
Mean	0.57 ± 0.011	2.15 ± 0.04*	0.85 ± 0.019
% abnormal	30.8**	61.5**	
DTH (n = 22)			
Mean	0.58 ± 0.006	2.09 ± 0.024*	0.865 ± 0.006
% abnormal	4.5	36.4	

Values are means in mmol/1 ± SEM.

* Significantly different from controls ($p < 0.01$).

** Significantly different from DTH ($p < 0.01$).

abuse (46% vs 45%). IMg^{2+} was low in 30.7% of patients in the first group and only in 4.5% of the second ($p < 0.01$). The corresponding numbers for an elevated ICa^{2+}/IMg^{2+} ratio were 61.5% and 36.4% ($p < 0.02$). No correlation was found between age, sex, the overuse of drugs and ICa^{2+}/IMg^{2+} or IMg^{2+} in either subgroup or when all patients were analyzed together.

Discussion

Solomon et al. (6) have reported that the incidence of migrainous features in 100 patients with CDH

was somewhat lower than in our patients. Mathew et al. (5) found that 76% of patients with CDH had a prior history of episodic migraines, and 52% used excessive amounts of caffeine or medications. Lumping together patients with migrainous and tension-type daily headaches has some basis because of similar features that these patients exhibited. Daily occurrence, overuse of medications and resistance to treatment are some of such features. Many of these patients also consume excessive amounts of dietary caffeine, which is not emphasized in the literature on CDH. On the other hand, clinical features of headaches in these two groups of patients are different. We did divide patients into these groups on the basis of clinical features typical of migraine. We expected to find a continuous distribution of such features, while in fact most patients had either very few or very many of such symptoms, thus forming distinct clinical groups.

A good argument can be made for placing patients who overuse medications into a separate category. Most of these patients improve when the offending drug is stopped, although it can be speculated that the rate of improvement may be different for patients with different clinical features.

Thus, we propose dividing patients with daily headaches by clinical features into two categories, patients with daily migrainous headaches (DMH) and those with daily tension-type headaches (DTH). Our findings of a higher incidence of low IMg^{2+} in patients with DMH support this clinical differentiation. The difference of the mean IMg^{2+} values may not support the clinical differences in the two sub-groups, but the difference in the incidence of abnormalities does. Patients with low IMg^{2+} may represent a category of patients with a different pathophysiology from those with normal values.

A somewhat higher average severity of the headache may reflect a more severe metabolic disturbance that is manifested by the higher incidence of low IMg^{2+} levels. However, in a previous study we found no direct correlation between the severity of headaches and IMg^{2+} levels (17).

A decrease in serum IMg^{2+} levels and an increase of the ICa^{2+}/IMg^{2+} ratio would increase affinity for serotonin cerebral vascular muscle receptor sites (18-20), potentiate cerebral vasoconstriction induced by serotonin (21-25), and facilitate 5HT release from neuronal storage sites (26). A decrease in serum and tissue Mg may produce vascular vasodilatation of large arteries followed by a contraction mediated by endothelium-derived relaxant factors (27-29). Such a sequence of events would explain the biphasic vasomotor changes in cerebral vascular tone seen in migraine (30-32). These effects of lowered IMg^{2+} levels allow us to combine the most popular hypotheses of migraine pathogenesis, serotonin and vascular theories. Other multiple effects of magnesium deficiency may play a more important or an initialing role in headache pathogenesis. For example, magnesium is involved in glutamate metabolism, thus affecting N-methyl-D-aspartate (NMDA) receptors (33).

Mg supplementation has been reported to be effective in the prevention of migraines in many anecdotal reports (34-36) and in a double-blind trial (9). These reports do not offer sufficient evidence to recommend widespread Mg supplementation in headache patients. It is possible, however, that patients with low IMg^{2+} or high ICa^{2+}/IMg^{2+} ratios may be good candidates for the treatment with Mg salts.

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