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CLUSTER ANALYSIS TO DETERMINE HEADACHE TYPES*

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Abstract—Cluster analysis was used to separate 726 headache patients into clusters of patients with similar symptoms. This was done to answer two questions: what 'naturally occurring' groups of patients can be found? And how do these groups correspond to traditional headache types? When only two clusters were required, the best two clusters were tension and migraine-like. However, eight clusters could also be distinguished, and the migraine group then became very small. The clusters were tested for clinical interpretability by having 12 physicians name and prescribe treatment for the clusters. The suggested treatment was similar to what patients had actually received in about 2/3 of the cases but was rather different for the remainder. Further, the outcomes associated with different treatments appeared to vary by cluster. This suggests that the current method for classifying and treating headaches may not be optimal.

INTRODUCTION

A MAJOR problem in the study of headache has been the difficulty of defining homogeneous patient groupings. The *Ad Hoc* Committee of the National Institute of Neurological Diseases and Blindness summarized the consensus in 1962 by naming several symptom patterns of recurrent headache not due to specific local causes: classic migraine, common migraine, cluster headache, hemiplegic and ophthalmoplegic migraine, lower-half headache, muscle contraction (tension) headache, and combined headache (vascular and muscular contraction) [1]. These groupings are, however, defined ambiguously. For instance, vascular headaches are *commonly* unilateral, *usually* associated with anorexia, *sometimes* associated with nausea and vomiting, *some* are preceded by a prodome and they are *often* familial. It is difficult to create operational definitions for headache types using such criteria.

These problems occur chiefly because, except for a few rarely occurring causes (brain tumor, abscess, hematomas, etc.) there are no objective findings which clearly identify headache cause or type. That is, there is no laboratory or X-ray test which will produce a definitive diagnosis. Rather, headache types have been defined by practitioners who saw large numbers of headache patients and observed patterns. In further research they described the disease and treatment of patients who fit those patterns [2–6].

One problem with this process is that (as in most medical care) the symptoms were not elicited in a uniform manner; different physicians collected information about different

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sets of symptoms or recorded information about the same symptoms in different ways [7]. In addition, even if all the symptoms had been collected in a uniform manner, their sheer numbers might have prevented physicians from seeing the best groupings of headache symptoms. Finally, research which focused on patients selected to conform to these headache types tended to perpetuate any existing biases in the traditional groupings.

In this study we attempt to search out clinical headache patterns by statistical methods. Standardized clinical data on a large number of patients presenting for acute headache care were subjected to cluster analysis, to search for homogeneous subgroups ('clusters') of headache patients having similar symptoms. We would expect a cluster of patients to have headaches with similar etiologies and thay they therefore might benefit from similar treatment. Since cluster analysis requires no advance specification of the number or nature of subgroups which may be present, this maneuver should effectively remove the individual physician's bias in headache classification, permitting subsequent comparison of new-found statistical clusters with the older or more accepted clinical categories.

If two major clusters are found which are consistent with current perceptions of tension and migraine headaches, this will validate to some extent the process of clinical pattern recognition, and will provide operational definitions of these headache types. If more clusters are found, and if these clusters are medically interpretable, this may provide a new definition of headache types. These clusters might then be used in subsequent investigations to achieve more consistent correlations between clinical symptom patterns and biochemical and/or physiological data.

METHODS

The data for this study consist of 57 symptoms collected on 726 patients presenting at the walk-in clinic of Brooke Army Medical Center with headaches. The clinic serves active duty military personnel, their families, and military retirees. (Patients who were drowsy, had altered mental function, could not touch their chins to their chests, or had head trauma in the last 72 hr were triaged elsewhere, and were not included in this study.) There was telephone follow-up after four weeks to determine the outcome for each headache. An internist read each patient's medical record and assigned a retrospective diagnosis: tension (38%), migraine (25%), no diagnosis (30%) and other (6%). Using discriminant analysis, we developed a rule based on seven of the symptoms which successfully classified the migraine and the tension headaches. In a previous analysis [7] we found that 4 of the symptoms were significantly related to the internist's diagnosis of tension headache, and 19 were significantly related to migraine headache. We also analyzed the symptoms to determine 'syndromes' of symptoms which tended to occur together [8].

In the current analysis, we used cluster analysis to find groups (clusters) of patients who have similar symptoms. The technique makes no use of the diagnosis in creating the clusters. We examined a solution with patients divided into two clusters and with eight clusters. More details about the clustering process and the choice of eight clusters are provided in the Appendix.

After the clusters were formed, the frequency of each symptom in each cluster was tabulated. Twelve physicians (eight internists, a neurologist, a pediatrician, a cardiologist, and a pathologist) were then asked to use the symptom frequencies to give a name to each cluster and to prescribe a typical therapy for each cluster. The internist's original diagnoses were compared to the clusters. Finally the treatments the patients in each cluster received and their outcomes were examined by cluster. Analysis of variance was used to examine the statistical significance of differences in the clusters.

FINDINGS

The 19 clinical symptoms used are shown in Table 1. These measures were chosen from a larger set because they were present in at least 10% of the patients and were independent of past treatment or 'physician bias'. Other variables, such as "previous use

TABLE 1. FREQUENCIES OF 21 CLINICAL HEADACHE SYMPTOMS FOR 726 HEADACHE PATIENTS

	Symptom	% with symptom
T	Described as pressure or tightness	60.3
T	Pain worst in back of neck	31.3
T	Becomes more severe as day progresses	44.9
T	Preceded by or associated with anxiety or tension	31.8
M	Spots/circles/flashing/stars in eyes	18.6
M	Nausea or vomiting	37.3
M	Prodrome	9.8
	Onset to great severity within 5 min	14.9
	Duration less than 21 hr	14.5
M	Pain in or around eye(s)	44.9
M	Acute visual change	11.0
M	Flushing	12.9
	Rhinorrhea	14.2
M	Lacrimation	14.5
	Sinus tenderness present	16.5
	Headache is recurrent	63.1
M	Headache is unilateral	32.1
M	Headache wakes patient from sleep	27.7
M	Temperature above 99.5°F	11.2
	Mean age (years)	32.1
	Sex (% female)	70.8

T: Symptom is more prevalent in patients diagnosed 'tension' headache; M: Symptom is more prevalent in patients diagnosed 'migraine' headache.

of ergot" are dependent on past diagnoses, and so were not used in forming the clusters. Age and sex were not used in forming the clusters, since they are not 'headache symptoms' *per se*. They are, however, treated in the discussion. The per cent of patients with each symptom is shown in Table 1. The symptoms labeled with a T in the table were significantly more prevalent in patients whom the internist diagnosed as having tension headache; those marked M were significantly more prevalent in patients diagnosed as migraine.

Two-cluster solution

On the first step of the cluster analysis, the algorithm separated the 726 patients into two clusters of 457 and 269 patients. The per cent of patients having each symptom in each cluster is shown in Table 2, and significantly different frequencies are noted. It is not surprising that there are so many significant differences between the two clusters, since the goal of a clustering algorithm is to make the two clusters as different as possible. The clusters do not have significantly different frequencies of recurrent headaches. There is also no difference in the mean age or per cent female.

The first four symptoms are significantly more frequent in cluster 1, and the remaining symptoms are more frequent in cluster 2. Recall from Table 1 that the first four symptoms were correlated with the internist's diagnosis of tension headache, and that many of the remaining were migraine correlates. Thus, cluster 1 seems to consist of tension headache patients, while cluster 2 could be labeled migraine. This suggests that if patients were to be divided into only two clusters, the traditional tension and migraine labels appear to be appropriate.

Eight-cluster solution

When the patients were separated into eight clusters the largest cluster contained 227 patients (31.3%) and the smallest had 15 (2.1%). For convenience we have assigned names to the clusters which will be explained in the following discussion. These names are Tension, No, URI, Fast, Migraine, Yes, Eye, and Systemic. Twenty-six per cent of all patients fell in the Tension cluster, and 31% in the No cluster; the remaining clusters each accounted for fewer than 10% of the patients.

TABLE 2. CLINICAL SYMPTOMS AND FREQUENCIES FOR TWO CLUSTERS (% HAVING EACH SYMPTOM)

Symptom	Cluster 1	Cluster 2
Pressure	67	49***
Back of neck	41	15***
Progressive	49	37**
Anxiety	35	27*
Spots/circles	9	35***
Nausea/vomiting	22	63***
Prodrome	2	23***
Rapid onset	8	27***
Short duration	12	19*
Eye pain	28	73***
Visual change	2	27***
Flushing	4	29***
Rhinorrhea	4	31***
Lacrimation	2	36***
Sinus tender	10	28***
Recurrent	62	65
Unilateral	23	48***
Awakens	18	45***
Fever (> 99.5)	12	9
Age	32	32
% Female	69	73
N	457	269

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 3 presents the per cent of patients in each cluster who have each symptom. For example, there are 188 people in cluster 1, labeled the Tension cluster. Of these, 89% described their headaches as pressure or tightness, and 3% had fever. All 19 symptoms had significantly different frequencies across the eight clusters, which is not surprising since the clusters were chosen to separate people with different symptoms.

Table 3 also shows additional variables which were not used in creating the clusters. These, too, are highly related to cluster type. Only age, 'clustering' of headaches in time, pulse, and respiratory rate were not significantly different across the clusters.

The eight clusters can be described by the relative frequencies of the symptoms. Twelve physicians read the data in Table 3, and assigned a probable diagnosis or label for each cluster. (The reader is invited to make his own comparisons.)

Based on this item-by-item analysis, cluster 1 is clearly a recurrent Tension headache, since it is more likely than the other clusters to have the four tension symptoms, and less likely than average to have any of the other symptoms. Women predominate in this group.

Cluster 2 is notably nondescript; nearly every symptom is least frequent in this cluster, and there was little previous treatment. This was called the No headache, and is the largest cluster.

In cluster 3, the URI cluster, there is a relatively high frequency of rhinorrhea, lacrimation, and sinus tenderness, but no flushing, and few other features. Patients had little previous treatment, and were more likely to have tender temporal arteries. There was some tendency to have clusters of headaches and eye pain. Overall this cluster seems to describe an upper respiratory infection or a sinus headache.

Cluster 4 headaches had rapid onset and short duration. We call them Fast headaches. They also tended to be recurrent, unilateral, and awakened the patient from sleep. Patients in the cluster had little previous treatment and were relatively more likely to be males. Many of these features are descriptive of a 'cluster' headache, but 'clusters' of headaches were not significantly more frequent among the Fast patients.

Cluster 5 is classic Migraine with spots and nausea; 100% of the patients had a prodrome. The cluster is associated with eye pain, acute visual change, and tends to be

recurrent, unilateral, awakening the patient from sleep, and associated with previous medication and procedures. Note that only 8% of all patients fell in this group.

Cluster 6 contains only 15 people, but is interesting because it consists of people who reported high frequencies of almost every symptom. The original 19 symptoms were less frequent than overall for only four symptoms: neck pain, acute visual change, sinus tenderness and unilaterality. The patients were more likely to be young and male, and had more problems speaking and walking, more extremity weakness, and more 'clusters' of headaches. They were relatively likely to have been treated with ergot and to have undergone EEG testing. Fully a third had been given sedatives and tranquilizers, and their pulse and respiration rates were somewhat above the mean. We called this the Yes headache. Several physicians suggested hypochondriasis as a diagnosis, and noted the high previous use of sedatives and tranquilizers.

Cluster 7 involves primarily Eye problems; 100% had acute visual change and 95% had eye pain. It was associated with spots, nausea, sinus tenderness, unilaterality, awakening from sleep, no prodrome and older females. Patients tended to have been treated previously with aspirin, and to have undergone lumbar puncture and/or EEG.

In cluster 8 all of the patients experienced flushing, and rhinorrhea, lacrimation, and sinus tenderness were frequent. No patients had prodrome, but nausea, rapid onset, eye pain, sinus tenderness, being awakened by pain, and fever were more frequent than for the average patient. These patients tended to be older and female, with tender temporal

TABLE 3. CLINICAL SYMPTOMS AND FREQUENCIES BY CLUSTER† (% HAVING EACH SYMPTOM)

	Cluster number									
Symptom	1 Tens	2 No	3 URI	4 Fast	5 MIG	6 Yes	7 Eye	8 System	All	Significance level
Pressure	89	38	58	60	47	73	64	61	60	**
Back of neck	72	7	16	34	18	20	27	25	31	**
Progressive	76	26	30	37	40	53	40	49	45	**
Anxiety	62	10	23	31	35	67	25	25	32	**
Spots/circles	9	13	12	21	47	53	38	21	19	**
Nausea/vomiting	23	33	33	32	69	67	56	52	37	**
Prodrome	1	0	0	0	100	100	0	0	10	**
Rapid onset	0	0	2	98	18	47	16	30	15	**
Short duration	10	11	12	45	16	20	7	18	14	**
Eye pain	31	36	56	37	58	73	95	54	45	**
Visual change	0	0	0	2	33	0	100	9	11	**
Flushing	1	0	0	6	2	100	11	100	13	**
Rhinorrhea	1	0	98	5	4	47	15	37	14	**
Lacrimation	2	7	44	11	13	47	18	45	14	**
Sinus tender	9	15	39	5	11	7	24	36	17	**
Recurrent	77	49	49	77	80	87	58	55	63	**
Unilateral	14	37	35	37	58	20	45	28	32	**
Awakens	19	24	25	35	45	33	33	40	28	**
Fever (>99.5)	3	15	5	8	5	13	5	24	10	**
Age	33	31	32	32	30	28	34	34	32	
% Female	81	65	67	59	67	60	76	76	71	**
Speaking prblm	0	1	0	2	7	13	4	0	2	**
Walking prblm	1	1	0	5	4	20	7	12	3	**
Extremity weak	3	7	4	11	11	33	11	9	7	**
Clusters of ha's	6	7	12	11	5	13	5	4	7	
Prev aspirin	49	40	42	50	51	47	53	64	48	*
Prev ergot	4	7	4	5	25	13	7	12	8	**
Prev sed/tranq	14	10	12	8	27	33	15	9	13	**
Curr vasc tx	5	6	7	2	29	0	7	9	7	**
Prev lumbar pct	2	4	0	3	4	0	11	10	4	**
Prev EEG	5	8	9	8	18	13	16	13	9	*
Tender temp arts	2	4	11	5	4	0	5	15	5	**
Pulse (mean)	81.7	81.4	82.1	80.7	83.2	82.3	83.0	87.1	82.2	
Respir (mean)	17.8	17.7	18.2	17.7	17.9	21.2	18.2	17.5	17.9	
N	188	227	57	62	55	15	55	67	726	
%	26	31	8	9	8	2	8	9	100	

*$p < 0.05$; **$p < 0.005$; †The first 19 symptoms were used to define the clusters.

TABLE 4. CLUSTER BY DIAGNOSTIC GROUPING (NUMBER OF PATIENTS)

Cluster	Internist's diagnosis No DX	Tension	Migraine*	Other	Total
1. Tension	15	156	16	1	188
2. No	117	41	48	21	227
3. URI	26	16	10	5	57
4. Fast	23	24	11	4	62
5. Migraine	5	8	41	1	55
6. Yes	4	1	8	2	15
7. Eye	15	12	23	5	55
8. System	16	21	24	6	67
Total	221	279	181	45	726

*Patients with combined tension/migraine headaches are included in the migraine category.

arteries, previous use of aspirin, walking problems, and the highest pulse and lowest respiration rates. We call this the Systemic cluster.

DIAGNOSIS

The internist who assigned the initial retrospective diagnosis had the advantage of seeing each patient's chart separately, rather than having to diagnose for clusters of patients. Table 4 shows the distribution of patients by his diagnostic groupings and by cluster. The no-diagnosis patients are primarily in the No cluster, tension in the Tension cluster, migraine in the No and Migraine clusters, and patients with 'other' diagnoses tend to be in the No cluster. Although there is a statistically significant relationship between cluster and diagnosis, there is far from a perfect correspondence. For example, only 41 of the 55 patients in the Migraine cluster were diagnosed as migraine by the internist.

TREATMENT

When the 12 physicians were asked how they would have treated patients in each cluster, there was a fair amount of agreement. The Tension and No headache patients would have received aspirin and reassurance. The URI patients would have received decongestants and antihistamines in addition to aspirin and reassurance. The Systemic cluster might also have received antibiotics. The Migraine patients would have received ergotamine, and the Eye patients would have been given a vision examination. There was disagreement on the treatment of the Fast and Yes headaches, with suggestions including ergotamine, a neurology consultation, counselling, and "a good long talk".

Table 5 shows the actual treatment received by patients. The most usual treatments were the tension (non-specific) protocol of aspirin or acetaminophen; the vascular protocol which gave Fiorinal or an ergot preparation; and the sinusitus protocol which included an antibiotic and a decongestant. All three protocols were used at rates which differed significantly across the clusters.

The treatments suggested by the 12 physicians can be compared to the treatment actually received. In the Tension cluster, only 83% received the tension headache proto-

TABLE 5. COMPARISON OF TREATMENT AND CLUSTER (% WITH EACH TREATMENT)

Treatment (%)	Cluster number 1 Tens	2 No	3 URI	4 Fast	5 Migr	6 Yes	7 Eye	8 System	Total
Tension headache protocol	83	30	39	40	22	33	36	33	46*
Vascular h/a tx protocol	20	28	26	37	58	73	47	51	33*
Acute sinusitus protocol	9	15	35	5	11	13	16	30	15*

*Significant difference across clusters ($p < 0.05$).

TABLE 6. COMPARISON OF OUTCOME AND CLUSTER

	Cluster number								
	1 Tens	2 No	3 URI	4 Fast	5 Migr	6 Yes	7 Eye	8 System	Total
Number followed	153	183	45	50	50	14	49	56	600
Status (% same or worse)	24	20	22	24	18	36	20	9	21
Days lost from work (mean)	1.48	1.75	1.33	1.16	1.10	2.79	3.12	2.09	1.71*
New symptoms (% of patients)	16	10	20	20	6	21	20	11	14
Went to another MD (%)	13	11	11	14	18	14	12	14	13
Dissatisfied (%)	10	11	11	6	2	7	10	5	9
Number of return visits (mean)	0.74	0.73	0.73	0.60	0.69	0.93	1.04	0.77	0.75

*Significant difference across clusters ($p < 0.05$).

col. Those in the URI cluster might be expected to have received decongestants; however, only 35% received the sinusitus protocol. The Fast cluster might have received vascular treatment, but only 37% received that protocol. In the Migraine cluster, only 58% received the vascular protocol. However, among the Yes headache patients, 73% received the vascular protocol! Finally, patients in the Systemic cluster were more likely to receive vascular treatment than any other treatment. The Eye and Systemic clusters were thought by the 12 physicians to have problems ranging from refraction error to glaucoma to viral infections, but half of each were treated for vascular headache. This raises the possibility that not all patients received optimal treatment for their problems. Alternatively, it could be that the care givers and the physician panelists differed as to the diagnostic implications of a particular set of findings, or about the optimal therapy for a given headache syndrome.

OUTCOME

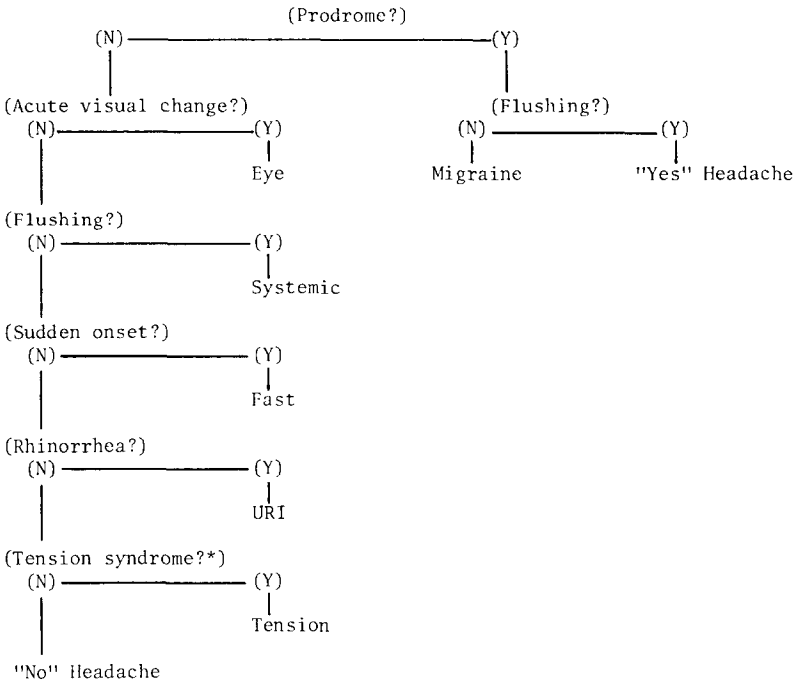
Another issue of interest is whether membership in a particular cluster has prognostic implications. Table 6 shows the outcome measures which were obtained by chart review and telephone interview four weeks after the initial visit for 600 patients (83%). Only the number of days lost from work differs significantly across the clusters ($p < 0.05$), which ranged from 0 to 30 days. The Yes and Eye headaches lost the most days, and the Fast and Migraine lost the fewest. In general, the Yes and Eye clusters had the worst outcomes on every measure, although most outcomes were quite good. Differences in the treatment received by patients in different clusters could, of course, also have contributed to these results.

TREATMENT AND OUTCOME

To see if treatments had different effects for patients in different clusters, the number of days lost were examined for people with and without the tension, vascular, and sinus treatments. Several transformations of the data were used to reduce the effect of a few people who lost excessive amounts of time. Based on this analysis, and reporting only significant findings ($p < 0.05$) we found that the tension protocol was significantly associated with worse results for the Fast headache patients (0.6 vs 2.1 days lost on the average) and better results for Yes and headache patients (4.0 vs 0.6 days). The patients in the No and URI clusters who received the vascular protocol had worse outcomes (1.4 vs 2.6 days and 0.7 vs 2.6 days, respectively). And, the sinus protocol appeared to have good effects in the Migraine cluster (1.22 vs 0 days lost).

These findings were based on fairly small numbers of patients who were not randomly assigned to treatment. Further, since three treatment protocols were compared in eight cluster groups, some significant results could be expected by chance alone. Thus, these findings should be considered to be only tentative. They do, however, suggest that a

TABLE 7. ASSIGNING PATIENTS TO CLUSTERS



*Two or more of: Pressure or tightness; worst at back of neck worsens as day progresses; preceded by or associated with anxiety or tension. (See reference 8).

treatment may have different efficacy in different clusters. They might also suggest changes in treatment for the 40% of Fast headaches who received the tension protocol, the two-thirds of Yes patients who did not receive the tension protocol, the quarter of No and URI patients who received the vascular protocol, and the 89% of migraine patients who did not receive the sinus protocol.

ASSIGNING PATIENTS TO CLUSTERS

A new patient could be assigned to a cluster (diagnosed) by comparing his symptom pattern to the patterns shown in Table 3. A simpler algorithm which was developed by inspection is shown in Table 7. This rule puts 92% of the people in the currect cluster. Of the 56 people misclassified, 38 No were called Tension, four Fast were called Systemic, and 6 Systemic were classified as Eye. The simplicity of this rule suggests that it could be used to assign patients to clusters. A more complex rule could reproduce the cluster assignments perfectly. The key role of 'flushing' in this algorithm is somewhat puzzling, and is discussed further in the Appendix.

DISCUSSION

We have examined the symptoms of 726 headache patients presenting to an acute minor illness clinic, to look for naturally occurring clusters of patients, and to see if the clusters thus formed bear any resemblance to traditional headache types. When the data were separated into two clusters, they appeared to reflect the traditional tension/migraine dichotomy. However, we also found eight clusters which could be interpreted reasonably. A cluster of patients with systemic or upper respiratory infection, a cluster with potential eye problems, and a cluster with a wide variety of positive symptoms were detected in the eight clusters but would not have been included in the usual headache definitions. Fifty-

seven per cent of the patients were in the Tension or the No clusters, for which no specific therapy is suggested. Only 8% of all patients fell into the cluster named Migraine, about equal to the number in the URI, Fast, Eye, or System clusters. This suggests that the diagnosis of migraine headaches may be too broadly used, since the labels of some of the other headache types suggest specific alternative therapies (eye examinations, counselling, or antibiotics) for patients who might have been classified as having migraine headaches.

Physicians who saw the information presented in this way tended to prescribe different treatment for the patients than many of them actually received, and the clusters were somewhat different from diagnoses made by an internist who read the entire medical record for each patient. Outcomes appeared somewhat worse in the clusters where the treatments did not agree with the 12 physicians' 'ideal' treatment. For example, the Eye and Yes patients might have benefitted more from visual testing or counselling than from the vascular treatment most received. Thus, diagnosis and treatment based on the usual tension-migraine-nonspecific breakdown may not be optimal.

From a clinical standpoint, there are some interesting implications to looking at the data in this way. The Yes syndrome, for example, is not mentioned in the headache literature but seemed familiar to several clinicians. One suspects that the common denominator among these patients is either heightened awareness of body sensations in general or perhaps heightned suggestibility: they are asked about a particular symptom and, sure enough, they remember having experienced it (or think they have). Clinicians are often guided by positive responses toward a diagnosis [11]. When faced with this wealth of 'diagnostic leads' the clinician may feel obligated to pursue them with tests or therapeutic trials, some of which may in fact be rather risky or costly. Perhaps the Yes syndrome is instead a particular pattern of verbal behavior in response to illness, rather than a coherent set of clinical manifestations with a common pathophysiologic basis. If so, it is interesting to speculate that the No syndrome is its mirror image—a stoic pattern of symptom reporting. In either case, the clinician might be led into an overly interventionist or an overly complacent position if unaware of the phenomenon.

The Fast syndrome is a curious but consistent pattern, suggesting further work to see if its existence can be verified elsewhere and its cause found. The prominence of the flushing syndrome in denoting the Migraine, Yes, and Systemic clusters is unexpected, and may suggest other lines of investigation. It might also be an artifact, as mentioned in the Appendix.

The National Ambulatory Medical Care Survey [9] has released statistics showing the principal diagnoses in a random sample of headache visits across the nation. Of 18,342 visits, the most frequent final diagnoses were: neurosis, tension, migraine, refractive errors, hypertension, acute URI, chronic sinusitis, hay fever, headache (not nonorganic, tension, or migraine), concussion, and other diagnoses. Note that many of the categories are similar to the clusters determined in our analysis. Only the Fast cluster does not match any of the categories. Further, of the NAMCS categories, only two do not appear among our clusters: trauma and hypertension. Since the triage system screened out head trauma cases, and less than 1% in our patients had severe hypertension, these differences are acceptable. This is further evidence that the clusters represent meaningful groupings.

We have suggested that headache patients could easily be placed into eight groups, and that this might change the treatment and outcome for patients. These conclusions must be regarded as tentative, however, for several reasons. First, our analysis involved only 19 symptoms, chosen because the literature suggested that they were related to headache differential diagnosis. A more complete analysis of the types of headaches would require us to sample the domain of all symptoms more systematically, including symptoms not traditionally associated with headache.

The use of different variables to form the clusters might change their nature somewhat. Subtle changes in the wording or definitions of the symptoms may also cause a difference in the type of clusters formed. Although a standard data base was collected, the methods of eliciting the symptoms may have varied in response to provider bias. A brief sensitivity

analysis, shown in the Appendix, suggests that the choice of variables or of eight clusters did not make a major impact on the findings.

The population of patients sampled may not be typical of all headache patients, although they do seem representative of acute headaches based on the frequency of female patients and nausea reported in the literature.

Perhaps the best test of validity and generalizability of our findings will come when others attempt to replicate them in another setting with different patients and possibly additional symptoms. But at a minimum, these findings suggest that further analysis of headache types could provide some new insights into the classification and treatment of headaches.

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APPENDIX

Cluster analysis and sensitivity analysis

There are a number of different clustering methods and a number of different ways of defining or measuring the similarity of the symptoms of two patients. The method used in this paper defines a dissimilarity between the two patients' symptoms as the sum of the squared differences in the measured symptom values. Symptom values are standardized so that each symptom has a standard deviation of 1, to give all symptoms approximately equal weight or influence over the cluster formation.

Generally the algorithm attempts to create a specified number of clusters so that the sum of the average within cluster distances is a minimum. This measure is the same as the "within group sum of squares" WGSS, of an analysis of variance. The approach first forms two clusters using a local optimization search to minimize the WGSS [10]. It then forms three clusters, then four, and so on up to the user specified maximum. The clusters are not hierarchical; even if patients A and B are in different clusters for the two cluster solution, they may later appear in the same cluster.

The choice of the number of clusters to analyze is a subjective decision. There is no known method to assure that the number selected is the 'true' number of clusters in the data. Therefore, we employed common rules of thumb to select a reasonable number of clusters. For example, if a clustering into three groups results in only a modest reduction in WGSS from the two group cluster then it would seem reasonable to select two clusters for analysis. We also looked for significant reductions in the variation of individual symptoms as the number of clusters increased. A significant reduction suggests the identification of 'natural clusters', at least for those symptoms. A further consideration was the size of the resulting clusters; if they contain too few patients, the generalizability of the results is more questionable. These considerations led us to select the two cluster and the eight-cluster solutions for analysis.

Clustering algorithms are capable of 'finding' structure where none exists. Further, decisions made in analysis may have affected the results. To examine the stability of the clustering process, we will discuss the outcome of stopping at a different number of clusters, and of using different variables in the analysis.

It is difficult to describe the clustering process, since patients who are together in one of five clusters may not be together in one of eight. However, an approximate summary of the clustering process is as follows. At step 1, there was one cluster. At step 2, the Tension and Migraine headaches separated out, as in Table 2. At the third step the URI cluster was formed, drawing from both of the others. The FAST cluster appeared on the fourth step. At step 5, the URI cluster broke into a URI cluster and the Systemic cluster (defined by flushing). On step

6 the Tension and Migraine clusters lost many members and the No group was formed. Until this step, more than half of the patients were in the Tension cluster; after this step only about one fourth were in the Tension cluster. It was this interesting finding that led us to consider more, rather than fewer clusters. On the seventh step the Migraine cluster lost all of its cases to the other clusters as the Yes group was formed. Finally, on step 8, a new Migraine group was formed in which all the patients had a prodrome. Thus, stopping earlier in the clustering would have provided fewer clusters, but the clusters remaining would have been similar to those on the eighth step.

We performed the cluster analysis with and without the fever symptom. The results were very similar at the eighth step, with the same interpretation for the eight clusters. However, the groups were not identical. The Yes group was about twice as big (4% of all patients) and not all members had both flushing and prodrome. In the Migraine cluster formed without the symptom 'fever', all patients had prodrome but 16% were flushed, while in the cluster obtained using fever no Migraine patient was flushed. The character of the Fast cluster also changed; when fever was used to form the clusters, 100% of the Fast headaches had rapid onset and 45% had short duration; without fever, 100% had short duration and 36% had rapid onset. Thus, the rules for cluster membership would change somewhat depending on which variables were used to create the clusters. However, the general interpretation of the clusters seemed quite stable. The major change introduced with the variable fever appeared to be in the variable flushing, which was correlated with fever and took on a greater role in variance reduction when fever was one of the symptoms than when it was not.

In this very limited sensitivity analysis, the broad conclusions of this study appear to be robust against small changes in the variables and the number of clusters chosen.