Improving the Classification of Migraine Subtypes: An Empirical Approach Based on Factor Mixture Models

Richard B. Lipton, MD[1,2]; Daniel Serrano PhD[3]; Jelena M. Pavlovic, MD, PhD[1,2];
Aubrey N. Manack[4], PhD; Catherine C. Turkel, PhD, PharmD[4]; Michael L. Reed, PhD[3]; Dawn C. Buse, PhD[1,2]

1. Albert Einstein College of Medicine, Bronx, NY; 2. Montefiore Headache Center, Bronx, NY; 3. Vedanta Research, Chapel Hill, NC; 4. Allergan Inc., Irvine, CA

BACKGROUND

Chronic Migraine (CM) is generally defined as headache on ≥15 days per month for at least 3 months in individuals with ICHD-2 defined migraine. Even in the absence of treatment, diagnosis of CM based primarily on headache day frequency is unreliable with fluid movements into and out of the diagnosis over time within subject.

OBJECTIVE

To explore alternative approaches to classification using a statistical approach, factor mixture models (FMM), to define natural subgroups.

METHODS

- The American Migraine Prevalence and Prevention (AMPP) Study is a longitudinal, US-population-based study of individuals with self-identified "severe" headache in 2004. Annual surveys were mailed to a sample of 24,000 respondents with "severe" headache from 2005-2009.
- Persons with episodic migraine (EM, divided into low-moderate frequency [LM= 0-9 HA days/month] and high frequency [HF= 10-14 HA days/month]), probable migraine (PM, similarly stratified on frequency) and CM were combined into a migraine pool in the 2005 data.
- FMMs were fit to identify natural migraine subgroups.
- A two factor FMM with correlated factors was defined.
- The first factor was disease severity with indicators: migraine symptom severity score (MSSS), average headache pain intensity, headache-related disability, cutaneous allodynia, and depression.
- The second factor was disease frequency with two indicators: monthly headache and migraine frequency (in days).
- Model fit (AIC and BIC) was used to determine the optimal number of latent classes (taxa).
- Validation of taxa was based on descriptive characterization and by modeling CM-free survival for the taxa (natural subgroups) over 5 years of AMPP follow-up surveys.

RESULTS

- Of 18,500 eligible study respondents to the 2005 AMPP survey, 12,860 were eligible for analysis with 10,162 LMEM, 601 HFEM, 1,302 PM, and 795 CM.
- The best fitting model contained 5 taxa which corresponded imperfectly with clinical groups (Table 1).
- At cross section, CM and HFEM were most heavily represented in Taxon 2 and Taxon 3. But Taxon 3 had high percentages of EM also.

Table 1: Distribution of Headache Categories Across Taxa (Column %)

TAXA	CM	HFEM	LMEM	HFPM	LMPM	Total
1	18.1%	18.3%	26%	38.9%	18.7%	3,152
2	38.4%	40.4%	4.8%	15.3%	2.7%	1,076
3	33.5%	21.1%	30.7%	30.5%	29.3%	3,896
4	10.1%	19.8%	18.9%	13.6%	9.6%	2,251
5	0%	0.3%	19.6%	1.7%	39.8%	2,485
Total	795	601	10,162	59	1,243	12,860

CM defined using S-L criteria; all other categories are ICHD-2. HFPM is probable migraine with 10-14 headache days/month.

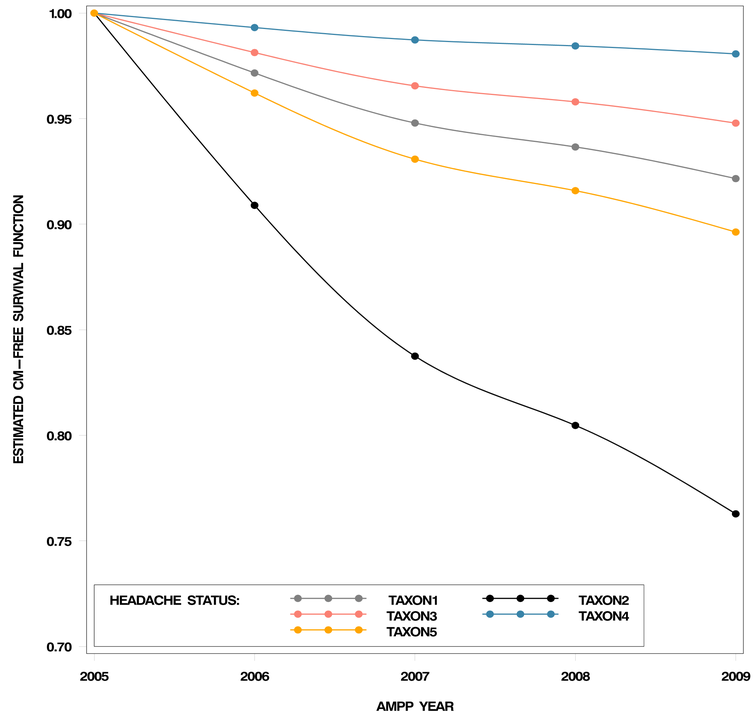
- Taxon 2 had the highest monthly headache and migraine frequency, headache-related disability levels, symptom severity scores, headache pain intensity, depression scores, and BMI scores.
- Taxon 2 had the second highest allodynia score and second youngest age of onset.

Table 2: Distribution of Disease Severity Indicators Across Taxa [Mean (SD)]

Variable	TAXON1	TAXON2	TAXON3	TAXON4	TAXON5
HA Days/Month	3.7(5.2)	11.2(7.5)	4.0(5.7)	1.5 (1.2)	4.6(4.3)
Migraine Days/Month	1.2(2.0)	3.7(3.6)	1.2(2.1)	0.2(0.8)	1.6(2.0)
HA Disability (MIDAS Score)	2.7(2.5)	44.1(15.0)	15.6(30.9)	1.8(2.1)	16.7(18.4)
MSSS	12.8(3.8)	14.6(3.9)	12.4(3.8)	10.9(4.0)	14.3(3.9)
HA Pain/Intensity	6.5(1.9)	7.4(1.8)	6.7(1.9)	5.9(2.0)	7.2(1.8)
Allodynia (ASC-12 Score)	5.2(4.3)	6.4(5.1)	2.5(2.9)	3.1(4.2)	7.1(5.0)
Depression (PHQ-9 Score)	8.2(5.7)	9.5(6.4)	3.8(4.0)	3.2(3.8)	8.7(6.2)
Age of Onset	23.4(12.5)	22.1(12.9)	23.1(12.3)	24.3(12.9)	21.7(11.5)
BMI Score	29.9(8.2)	30.3(8.5)	28.5(7.3)	28.3(7.2)	29.9 (8.5)

- We examined rates of CM free survival in each taxon among persons with EM at baseline.
- CM-free survival rates were lowest for Taxon 2.

Figure 1. CM-Free Survival for Estimated Taxa



CONCLUSIONS

- Stable and homogeneous subtypes (taxa) of migraine are identifiable using FMM.
- These taxa exhibit greater phenotypic similarity and more predictable longitudinal disease courses than do ICHD-defined migraine subtypes.
- This is largely due to the fact that FMMs are probabilistic classification models which can quantify similarity of diseases and symptom profiles within large sets of information, whereas ICHD can only consider limited sets.

The American Migraine Prevalence and Prevention Study was funded through a research grant to the National Headache Foundation from McNeil-Janssen Scientific Affairs LLC, Raritan, NJ.
The AMPP database was donated by McNeil-Janssen Scientific Affairs LLC to the National Headache Foundation for use in various projects. Additional analyses were supported by a grant from Allergan Inc., Irvine, CA, to the National Headache Foundation.