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BRIEF COMMUNICATION

Establishment of an Italian chronic migraine database: a multicenter pilot study

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Abstract

To optimize chronic migraine (CM) ascertainment and phenotype definition, provide adequate clinical management and health care procedures, and rationalize economic resources allocation, we performed an exploratory multicenter pilot study aimed at establishing a CM database, the first step for developing a future Italian CM registry. We enrolled 63 consecutive CM patients in four tertiary headache centers screened with face-to-face interviews using an ad hoc dedicated semi-structured questionnaire gathering detailed information on life-style, behavioral and socio-demographic factors, comorbidities, and migraine features before and after chronicization and healthcare resource use. Our pilot study provided useful insights revealing that CM patients (1) presented in most cases symptoms of peripheral trigeminal sensitization, a relatively unexpected feature which could be useful to unravel different CM endophenotypes and to predict trigeminal-targeted treatments' responsiveness; (2) had been frequently admitted to emergency departments; (3) had undergone, sometime repeatedly, unnecessary or inappropriate investigations; (4) got rarely illness benefit exemption or disability allowance only. We deem that the expansion of the database—shortly including many other Italian headache centers—will contribute to more precisely outline CM endophenotypes, hence improving management, treatment, and economic resource allocation, ultimately reducing CM burden on both patients and health system.

Keywords Chronic migraine · Migraine burden · Database · Disability · Epidemiology · Registry

Introduction

Chronic migraine (CM) is a headache disorder on ≥ 15 days/month for ≥ 3 months with migraine features on ≥ 8 days/month, affecting 3–4% of general population [1, 2]. CM is an extremely disabling and difficult-to-treat disorder condition for its unclear pathophysiology, complex comorbidities, and disappointing response to conventional pharmacological treatments [1].

The recent indication of onabotulinum toxin A for its treatment and the promising results with monoclonal antibodies to calcitonin gene-related peptide (CGRP) or its receptor [3] seems to open new therapeutic horizons, but their cost may represent an issue for the treatment of CM, a disease with still unsatisfying diagnostic criteria [4].

Thus, there is a need to optimize CM ascertainment, disentangle its endophenotypes, warrant specific clinical management and health care procedures, rationalize economic resources allocation, and provide adequate illness benefit exemption or disability allowance.

To address these points, we performed an exploratory multicenter pilot study coordinated by the Italian National Institute of Health aimed to establish a CM database, the first step for developing a future Italian CM registry.

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Methods

We enrolled all consecutive patients affected by CM [1] referring to four Italian tertiary headache centers (San Raffaele, Rome; Institute of Neurological Sciences, Bologna; University of Parma; C. Besta, Milan) from 1st June to 15th July 2017.

Specifically trained neurologists screened all patients with face-to-face interviews using a dedicated semi-structured questionnaire to gather detailed information on (1) life-style, (2) behavioral and socio-demographic factors, (3) comorbidities, (4) migraine features before and after chronicization (family history, disease duration, location, quality and intensity of pain, attack duration and frequency, presence, type and duration of aura, prodromes, accompanying symptoms, postdromes, triggers, alleviating factors, allodynia, unilateral cranial parasympathetic symptoms, triptan efficacy, previous/current acute and preventive treatments), (5) healthcare resource use (diagnostic procedures, hospitalizations), and (6) socio-economic benefits (disease status recognition and invalidity allowances).

The protocol was approved by the institutional review board at IRCCS San Raffaele Pisana and all patients gave their informed consent before enrollment.

We reported frequency for each variable applying the *t* test to compare means and standard deviations and performing a regression analysis considering monthly migraine days as dependent variable. Statistical analyses were conducted using SPSS software. A p value < 0.05 was considered statistically significant.

Results

Sixty-three patients affected by CM, mostly with medication overuse (MO, 60.3%) and frequently coming from other Italian regions (33.3%) were enrolled. One out of 4 patients (22.2%) referred a self-pharmacological management of CM. Socio-demographic and clinical characteristics of patients are detailed in Table 1. Notably, the majority of patients affected by CM referred symptoms linked to peripheral trigeminal sensitization: unilateral pain location (42.8%), pulsating quality (63.5%), severe intensity (62%), association with vegetative symptom (84.1%), and cranial parasympathetic autonomic symptoms (23.8%).

Univariate analysis revealed that patients affected by more severe CM forms (≥ 21 headache days/month) had more often MO ($p = 0.01$) and family history of MO ($p = 0.01$), insomnia ($p = 0.05$), and ipsilateral ocular parasympathetic symptoms ($p = 0.03$) and had been more frequently treated with pharmacological prophylaxis ($p = 0.05$) than those with milder CM (≤ 20 headache days/month).

When considering monthly migraine days as dependent variable, regression analysis showed that patients with severe CM had more frequent insomnia ($p = 0.017$) and analgesic overuse ($p = 0.018$), and lower alcohol intake ($p = 0.033$) than those with milder CM.

Discussion

Reducing the burden of CM, the second largest cause of disability [5], requires accurate diagnosis, increased disease awareness, patient education, improved adherence to diagnostic and therapeutic guidelines, appropriate treatments in selected individuals, and recognition of adequate socio-economic benefits to patients with more severe CM forms. The present pilot study, representing the initial step for the establishment of a national CM registry, is the first Italian multicenter CM investigation involving four third-level headache centers thoroughly assessing life-style, socio-demographic and headache features, and public health implications using face-to-face interviews with a semi-structured questionnaire.

Our exploratory database findings outline some noteworthy aspects. First, the majority of patients affected by CM—a headache characterized by central *sensitization*—referred symptoms linked to peripheral trigeminal sensitization. Our simple clinical observation, based on easily obtainable patient-reported symptoms, is not trivial because it might help not only to unravel different CM endophenotypes but also to predict the responsiveness to costly trigeminal-targeted treatments such as onabotulinum toxin A, supraorbital nerve stimulation and antiCGRP monoclonal antibodies [6–8]. Second, a considerable proportion of CM patients had been admitted to emergency departments (36.5%), an unexpected finding in a disease known to decrease in intensity when frequency increases. In addition, many migraineurs not only had undergone unnecessary or inappropriate investigations such as electroencefalography (26.9%) and cervical spine imaging (26.9%) but, in some cases, had also repeated the diagnostic procedures over time without any reliable reason. Lastly, only very few patients got illness benefit exemption (6.3%) or disability allowance (4.7%).

The availability of targeted therapies prompts to reconsider CM management in terms of customized healthcare in the new precision medicine era [9], not only empowering scientific research but also implementing data digitization and electronic database creation. Much work is thus needed in CM, given its heterogeneity and unsatisfying diagnostic criteria [4]. Its name notwithstanding, CM is not as *chronic* because it may spontaneously remit to the episodic form in 26.1% of patients and fluctuate from EC to episodic migraine and vice versa in 40% of cases [10]. Furthermore, current CM diagnostic criteria embodies diverse endophenotypes with different outcomes: (a) never treated or not properly treated previously

Table 1 Synopsis of socio-demographic and clinical features of CM patients, health resource utilization, and socio-economic benefits

Socio-demographic and anamnestic data					
Patients n	63				
Sex (F/M)	51/12				
Age (years)	47.4 ± 14.6				
Years of education	≤ 5: 3 (4.8%)	6–8: 15 (23.8%)	9–13: 24 (38.1%)	≥ 14: 15 (23.8%)	
Employment status	Employed 34 (54%)	Housewife 10 (16%)	Unemployed 8 (12.6%)	Retired 7 (11.1%)	Student 4 (6.3%)
Civil status	Married/living common-law 43 (68.3%)		Single 13 (20.7%)	Divorced 6 (9.5%)	Widow 1 (1.5%)
Body mass index (mean ± SD)	23.8 ± 3.7				
Coffee, cups/day (mean ± SD)	2.29 ± 2.01				
Smoking habits	Nonsmoker 44 (69.8%)	Previous smoker 8 (12.7%)		Current smoker 11(17.5%)	
Alcohol users	16 (25.4%)				
Sport participants	16 (25.4%)				
Menopause, pts	16 (25.39%)				
Hormonal replacement therapy, pts	2 (3.2%)				
Oral contraceptives, pts	5 (9.8%)				
Comorbidities	Psychiatric 31 (49.2%)	Hypertension 8 (12.7%)	Neurological 4 (6.3%)		Others 8 (12.7%)
	Sleep disturbances 25 (39.7%)	Gynecological 7 (11.2%)	Diabetes 2 (3.2%)		
	Gastrointestinal 12 (19%)	Dyslipidemia 7 (11.1%)	Other cardiovascular 1 (1.6%)		
	Endocrinological 11 (17.5%)	Trauma 6 (9.5%)	Respiratory 1 (1.6%)		
Characteristics of previous EM					
Age at EM onset, years	15.2 ± 6.6				
Family history of EM	47 (74.6%)				
Migraine	Without aura 58 (92.1%)		Without aura + with aura 5 (7.9%)		
Concomitant headaches	Tension-type headache 3 (4.7%)				
Attack frequency, days/month	5.6 ± 5.4				
Acute treatments	NSAIDs 42 (66.7%)		Triptans 26 (41.3%)	Analgesic combinations 20 (31.7%)	
Prophylaxis	Ca^{++} antagonists 13 (20.6%)	Antidepressants 11 (17.5%)	Antiepileptics 8 (12.7%)	Acupuncture 8 (12.7%)	Nutraceuticals 4 (6.3%)
	- Flunarizine 12 (19%)	*- Amitriptyline 10 (15.9%)*	*- Topiramate 6 (9.5%)*	Beta-blockers 7 (11.1%)	*- Riboflavin 6 (9.5%)*
	- Cinnarizine 2 (3.2%)	*- Venlafaxine 3 (4.8%)*	*- Sodium valproate 4(6.3%)*	*- Propanolol 5 (7.9%)*	*- Magnesium 2 (3.2%)*
		- Duloxetine 3 (4.8%)	*- Pregabalin 3 (4.8%)*	*- Atenolol 2 (3.2%)*	Osteopathy 2 (3.2%)
		- Fluoxetine 1 (1.6%)	*- Gabapentin 1 (1.6%)*	Anti-serotoninergics:	
		- Paroxetine 1 (1.6%)		*- Pizotifen 6 (7.9%)*	
Characteristics of current CM					
Age at CM onset	36.6 ± 14.1 years				
Putative chronicization factors (based on patient opinion)	- None 72 (55.6%)			- Physiological events 5 (7.9%)	
	- Life events 21 (33.3%)			- Comorbidities 2 (3.2%)	
Family history of MO	10 (15.8%)				
Headache frequency, days/month	24.5 ± 30.4				
Pain location	Unilateral 27 (42.8%)		Bilateral 14 (22.2%)	Unilateral or bilateral 22 (35%)	
Pain quality	Pulsating 40 (63.5%)		Pressing 17 (27%)	Other 8 (12.7%)	
Intensity	Mild 3 (4.7%)		Moderate 21 (33.3%)	Severe 39 (62%)	
Disability	Mild 1 (1.6%)		Moderate 21 (33.3%)	Severe 37 (58.7%)	
Associated symptoms	Vegetative 53 (84.1%)		Cranial parasympathetic 15 (23.8%)		
Allodynia	32 (50.7%)				
Acute treatment	NSAIDs 32 (50.8%)		Triptans 46 (73%)	Analgesic combinations 19 (30.2%)	
Acute treatment, mean monthly dose	NSAIDs 18.6 ± 9.2		Triptans 40 ± 7.3	Analgesic combinations 31 ± 7.2	
Medication overuse	38 (60.3%)				

Table 1 (continued)

Medications overused	- Triptans 21 (55.3%) - NSAID 7 (18.5%) - Analgesic combinations 4 (10.5%)		- Triptans + NSAIDs 3 (7.8%) - Triptans + analgesic combinations 2 (5.3%) - NSAID + analgesic combination 1 (2.6%)		
Prophylaxis	Antiepileptics 42 (66.7%) *- Topiramate 39 (61.9%)* *- Sodium valproate 13 (20.6%)* *- Pregabalin 10 (15.9%)* *- Gabapentin 6 (9.5%)* Antidepressants 32 (50.8%) *- Amitriptyline 31 (49.2%)* *- Duloxetine 6 (9.5%)* *- Paroxetine 6 (9.5%)* *- Venlafaxine 1 (1.6%)* BoNT-A 26 (41.3%)	Beta-blockers 25 (39.7%) *- Propanolol 15 (23.8%)* *- Atenolol 13 (20.6%)* *- Timolol 3 (4.8%)* *- Metoprolol 1 (1.6%)* *- Nadolol 1 (1.6%)* *- Nebivol 1 (1.6%)* Calcium antagonists 23 (36.5%) *- Flunarizine 17 (27%)* *- Cinnarizine 6 (9.5%)*	Anti-serotoninergics 8 (12.7%) *- Pizotifen 7 (11.1%)* *- Methysergide 3 (4.8%)* Sartans 3 (4.8%) *- Cadesartan 3 (4.8%)* Nutraceuticals 12 (19.0%) *- Riboflavin 10 (15.9%)* *- Coenzyme Q10 3 (4.8%)* *- Magnesium 2 (3.2%)* *- Thenacetum partenium 1 (1.6%)*	Others *- Acupuncture 13 (20.6%)* *- Rehab/osteopathy 9 (14.3%)* *- Psychotherapy 5 (7.9%)* *- Vagus nerve stimolation 4 (6.3%)* *- Occipital nerve block 3 (4.8%)* *- Occipital nerve stimulation 1 (1.6%)*	
Health resource utilization					
Investigations, pts	Brain CT scan 24 (38.0%) *- Once 15 (62.5%)* *- Twice 5 (20.8%)* *- 3 times 2 (8.3%)* *- 4 times 1 (4.2%)* *- 5 times 1 (4.2%)*	Brain MRI 36 (57.1%) *- Once 27 (75%)* *- Twice 5 (13.9%)* *- 3 times 3 (8.4%)* *- 4 times 1 (2.7%)*	EEG 17 (26.9%) *- Once 14 (82.3%)* *- Twice 1 (5.9%)* *- 3 times 1 (5.9%)* *- 8 times 1 (5.9%)*	Cervical MRI 12 (19.0%) *- Once 9 (75%)* *- Twice 2 (16.7%)* *- 5 times 1 (8.3%)*	Cervical X-ray 5 (7.9%) *- Once 4 (80%)* *- Twice 1 (20%)*
Prescriptor of investigation, pts	Headache specialist 33 (52.4%) General practitioner 31 (49.2%) Other specialist 18 (28.6%) None 12 (19%) *- Self prescription 7 (11.1%)* *- Friend/relative advice 4 (6.3%)* *- Media suggestions 1 (1.6%)*				
Hospitalization, pts	Inpatient 17 (27%) *- Once 9 (53%)* *- Twice 3 (17.6%)* *- 3 times 4 (23.5%)* *- 4 times 1 (5.9%)*	DH 6 (9.5%) *- Once 4 (66.6%)* *- Twice 1 (16.7%)* *- 12 times 1 (16.7%)*		ED access 23 (36.5%) *- Once 5 (21.7%)* *- Twice 8 (34.8%)* *- 3 times 2 (8.8%)* *- 4 times 2 (8.8%)* *- 5 times 3 (13%)* *- 8 times1 (4.3%)* *- 10 times 1 (4.3%)* *- 20 times 1 (4.3%)*	
Socio-economic benefits					
Disability allowance	3 (4.7%)				
Illness benefit exemption	4 (6.3%)				

ITALIC, to differentiate from the principal category

EM, episodic migraine; *CM*, chronic migraine; *MO*, medication overuse; *NSAIDs*, non-steroidal anti-inflammatory drugs; *CT*, computerized tomography; *MRI*, magnetic resonance imaging; *EEG*, electroencefalography; *DH*, day hospital; *ED*, emergency department

episodic migraineurs, (b) *true* CM sufferers without MO, (c) CM patients with MO, (d) CM patients with prominent psychiatric disorders or other relevant comorbidities, and (e) drug-resistant CM patients.

Unfortunately, CM diagnosis relies entirely on clinical grounds, posing the issues of physician's individual expertise and reliability of patients' medical history. This underlines the urgent need for a shared patient management strategy among headache specialists. We deem that the expansion of the database—shortly including many other Italian headache centers—and its evolution toward a national registry, will contribute to unravel CM endophenotypes, minimizing the risk of misdiagnosis, shedding light on neglected clinical governance areas, offering proper treatments and social support to chronic migraineurs, and rationalizing economic resource allocation, ultimately reducing CM burden on both patients and health system.

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