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Diagnostic tests and headache misdiagnoses in individuals with resistant and refractory migraine – data from the REFINE study

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Abstract

Background: Individuals with difficult-to-treat migraine, including resistant migraine (ResM) and refractory migraine (RefM), might experience treatment delays, undergo unnecessary diagnostic tests and receive misdiagnoses, which might influence treatment outcomes. For this reason, we hypothesized that individuals with ResM and RefM might report more diagnostic tests and misdiagnoses in their medical history compared with those with non-resistant/non-refractory migraine (NRNRM).

Methods: This analysis used baseline, cross-sectional data from the REFINE study, a multicenter, prospective observational study conducted in 15 European tertiary headache centers. Adults with episodic or chronic migraine were classified into RefM, ResM, or NRNRM groups. Baseline data were analyzed to assess the frequency of previous diagnostic tests and misdiagnoses.

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Results: Overall, 689 participants were included with a median age of 46 years (interquartile range 36–53); 570 participants (82.7%) were female; 355 (51.5%) had NRNRM, 261 (37.9%) ResM, and 73 (10.9%) RefM. Referring to diagnostic tests, 335 participants (48.7%) had one and 237 (34.4%) multiple brain magnetic resonance imaging scans. ResM and RefM participants underwent more diagnostic tests than NRNRM. Overall, 193 participants (28.0%) had at least one prior headache misdiagnosis, most commonly cervical spine disorders and sinusitis; misdiagnoses were more frequent in NRNRM and ResM than in RefM (31.1%, 28.5%, and 15.1%, respectively; $p = 0.025$). Misdiagnosis rates were not influenced by age, sex, disease duration, or comorbidities.

Conclusions: Diagnostic tests use and misdiagnoses are highly prevalent in all the three groups of individuals with ResM, RefM, and NRNRM with some differences across the three groups that may depend on multiple factors. Our findings emphasize a need for better diagnostic accuracy and care pathway across the entire spectrum of migraine, to avoid unnecessary diagnostic tests and misdiagnoses.

Keywords

headache, chronic migraine, disability, misdiagnosis, headache diagnosis

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Introduction

Migraine is a neurological disorder associated with high levels of disability worldwide.[1] Despite the availability of highly effective migraine-specific drugs, a subgroup of individuals with migraine fails to respond adequately to preventive treatments, bearing most of the migraine burden.[2] These individuals fulfill the European Headache Federation (EHF) criteria for resistant (ResM) and refractory migraine (RefM),[3] which identify different degrees of difficult-to-treat migraine. ResM is characterized by a lack of efficacy, tolerability, or contraindication to at least three preventive treatment classes, whereas RefM is characterized by a lack of efficacy, tolerability, or contraindication to all pharmacological preventive classes.[3] Initiating highly effective treatments can often reverse the condition in individuals with ResM, but RefM is probably characterized by pathophysiological mechanisms that differ from those targeted by current preventive therapies.[2]

Migraine remains underdiagnosed and undertreated[4,5] and a delay in diagnosis and treatment of the condition might lead to poor treatment effectiveness. The clinical journey of individuals with migraine is often marked by delayed or incorrect diagnoses, unnecessary and costly diagnostic investigation[6] and inappropriate treatments.[7] Such delays can lead to progression from episodic to chronic migraine[8,9] and may potentially result in decreased response to preventive treatments.

Unnecessary diagnostic tests and misdiagnoses can delay proper treatment for migraine; however, on the other hand, additional diagnostic tests might be prescribed to individuals that do not respond to migraine treatments, to revise the diagnosis of migraine or to exclude the presence of exacerbating comorbidities. Additionally, diagnostic tests might be performed to confirm the diagnosis of migraine for the purposes of medical insurance. Instrumental diagnostic tests should not be performed routinely in all patients but should be reserved for cases with clinical "red flags" suggestive of secondary headache.[10,11] However, in some cases, diagnostic uncertainty due to atypical presentations and/or anxiety of individuals with migraine might justify diagnostic tests even in the absence of clear red flags.

Given those potential links between inappropriate diagnostic tests or misdiagnoses and failure of migraine preventive medications, we hypothesized that individuals with ResM and RefM might report more diagnostic tests and misdiagnoses in their medical history compared with those with non-resistant/non-refractory migraine (NRNRM). We tested this hypothesis in a large observational cohort.

Methods

Study cohort and study design

REFINE is a prospective, multicenter, observational study conducted from 2020 to 2022 across 15 European tertiary headache centers in Austria, Estonia, Germany, Greece, Italy, Lithuania, Poland, Portugal, Spain, and Turkey. The study methodology was previously described elsewhere.[12] The study included consecutive adult individuals with a diagnosis of episodic or chronic migraine according to the International Classification of Headache Disorders (ICHD)-III diagnostic criteria.[13] This study is reported in accordance with the STROBE guidelines for an observational study. Participants were classified according to the EHF criteria[3] into refractory migraine (RefM – failure of all classes of migraine preventives and ≥8 debilitating headache days/month for at least six months), resistant migraine (ResM – failure of ≥3 classes of migraine preventives and ≥8 debilitating headache days/month for at least three months, not fulfilling the RefM criteria), and non-refractory

non-resistant migraine (NRNRM) which included participants not meeting the definitions of either ResM or RefM. Recruitment was stratified according to those three categories to balance the final cohort and allow comparisons.

Clinical status and variables of interest were collected for each participant via structured interviews and review of clinical documentation at two time points, i.e., at baseline and after six months. Data collected included demographics, medical history, lifestyle, headache characteristics, associated disability, and migraine treatments. At follow-up, participants were re-classified into one of the three categories: NRNRM, ResM, or RefM, based on their response to preventive therapies over the previous six months. However, the present analysis exclusively refers to baseline data and only considered medical history before the inclusion in the study.

For the present study, we considered a set of diagnostic tests and misdiagnoses determined in advance by the study group. Diagnostic tests included all those tests performed to distinguish primary from secondary headache disorders, including brain Magnetic Resonance Imaging (MRI), cervical spine MRI, brain Computed Tomography (CT), cervical spine X-rays, and consultations for patent foramen ovale, food allergies, hormonal problems (defined as any concern related to female sex hormone cycles), eye disorders, and temporomandibular joint disorders. Misdiagnoses included cervical spine disorders (disc herniation, osteoarthritis, or cervical muscle contracture), sinusitis, temporomandibular joint disorders, and hormonal disturbances. All those conditions were defined as misdiagnoses if considered as a potential cause of participants' headache attacks. Information was retrieved at the baseline visit by the study investigators from all participants via previous medical records and/or clinical interviews. Coordination among the study centers was ensured via preliminary meetings; however, no central adjudication of cases was performed. The definitions for misdiagnoses were ascertained by the study investigators of each participating center according to their clinical experience, in the absence of specific definitions, during structured interviews with participants. For diagnostic tests and misdiagnoses, physicians had to collect any condition as present or absent, without leaving missing data.

Standard protocol approvals, registrations, and patient consents

Ethical approval was obtained from the Institutional Review Board and/or relevant Ethics Committees at all participating centers (protocol number from coordinating center: 45/2020-21). Participants or their authorized representatives provided written informed consent.

Objectives and outcomes

The primary objective of the study was to determine the number and proportions of participants who performed diagnostic tests and/or received headache misdiagnoses in their history. Secondarily, we assessed the differences in the performance of diagnostic tests and the occurrence of misdiagnoses among the NRNRM, ResM, and RefM groups.

Statistical analysis

Continuous variables were reported as medians and interquartile ranges (IQR), given their non-normal distribution assessed via the Kolmogorov-Smirnov test, while categorical variables were reported as counts and percentages. Demographics, medical history, and headache characteristics were reported as descriptive statistics. Comparisons among the RefM, ResM, and NRNRM groups were performed using the chi-squared test for categorical variables and the Kruskal-Wallis test for continuous variables. We also calculated the odds ratios of performing diagnostic tests or receiving misdiagnoses in individuals with ResM or RefM compared with those with NRNRM; we reported odds ratios as the only measures for comparisons across groups to maintain conservative estimates, given the low numbers of many comparisons. To test whether previous diagnostic tests for headache or previous misdiagnoses were influenced by age, disease duration, chronic migraine, or medication overuse, we compared these variables in the subgroups of participants with and without diagnostic tests or misdiagnoses.

As all our analyses were exploratory, without adjustment for multiple comparisons, no formal sample size calculation was performed for these analyses. All calculated P-values were two-tailed. Statistical significance was assumed at $p < 0.05$. The statistical analysis was performed with R (Version 4.2.2).

Results

We included 689 patients, of whom 570 (82.7%) were female. The median age in the overall group was 46 years (IQR 37-54). We identified 355 individuals (51.5%) with NRNRM, 261 (37.9%) with ResM, and 73 (10.9%) with RefM (Table 1).

Overall, participants with RefM and ResM were older than those with NRNRM (median age of 49 [IQR 39-57] and 51 [43–58] vs 43 [34–52] years, $p < 0.001$), had a longer disease duration (29 [18–39], 32 [24–36], and 23 [15–32] years, $p < 0.001$), higher prevalence of chronic migraine and medication overuse (all $p < 0.001$; Table 1).

At baseline, 335 participants (48.7%) had performed a brain MRI once and 237 (34.4%) more than once; 193 (28.1%) had performed a MRI of the cervical spine once and 61 (8.9%) more than once; 235 (34.3%) had performed a brain CT once and 125 (18.2%) more than once; 67 (9.8%) had performed X rays of the skull once and 17 (2.5%) more than once. Regarding consultations, 60 participants (8.8%) had performed one and 6 (0.9%) more than one for patent foramen ovale; 99 (14.4%) had performed

Table 1. Baseline characteristics of the study participants.

	All (n = 689)	NRNRM (n = 355)	ResM (n = 261)	RefM (n = 73)	p-value
Female, n (%)	570 (82.8)	292 (82.3)	223 (85.8)	55 (75.3)	0.244
Age, years (median – IQR)	46 (37–54)	43 (34–52)	49 (39–57)	51 (43–58)	**<0.001**
Disease years (median – IQR)	26 (16–36)	23 (15–32)	29 (18–39)	32 (24–36)	**<0.001**
Chronic migraine, n (%)	388 (56.3)	143 (40.3)	184 (70.5)	61 (83.6)	**<0.001**
Medication overuse headache, n (%)	230 (33.4	71 (20.0)	126 (48.5)	33 (45.2)	**<0.001**
BMI (median – IQR)	24 (21–27)	24 (21–27)	24 (21–27)	24 (23–26)	0.495
Smoking					0.097
Current	101 (14.7)	55 (15.5)	37 (14.2)	9 (12.3)	
Former	111 (16.1)	52 (14.6)	39 (15.0)	39 (15.0)	
Never	476 (69.2)	248 (69.9)	184 (70.8)	44 (60.3)	
Caffeine intake					0.214
None	100 (14.5)	43 (12.1)	43 (16.5)	14 (19.2)	
1–2 coffees per day	405 (58.9)	217 (61.1)	143 (55.0)	45 (61.6)	
3–5 coffees per day	169 (24.6)	89 (25.1)	66 (25.4)	14 (19.2)	
>5 coffees per day	14 (2.0)	6 (1.7)	8 (3.1)	-	
Alcohol intake					**0.037**
Habitual (≥1 alcohol unit per day)	11 (1.6)	9 (2.5)	1 (0.4)	1 (1.4)	
Occasional (<1 alcohol unit per day)	291 (42.3)	164 (46.2)	98 (37.7)	29 (39.7)	
None	386 (56.1)	182 (51.3)	6 (1.7)	43 (58.9)	

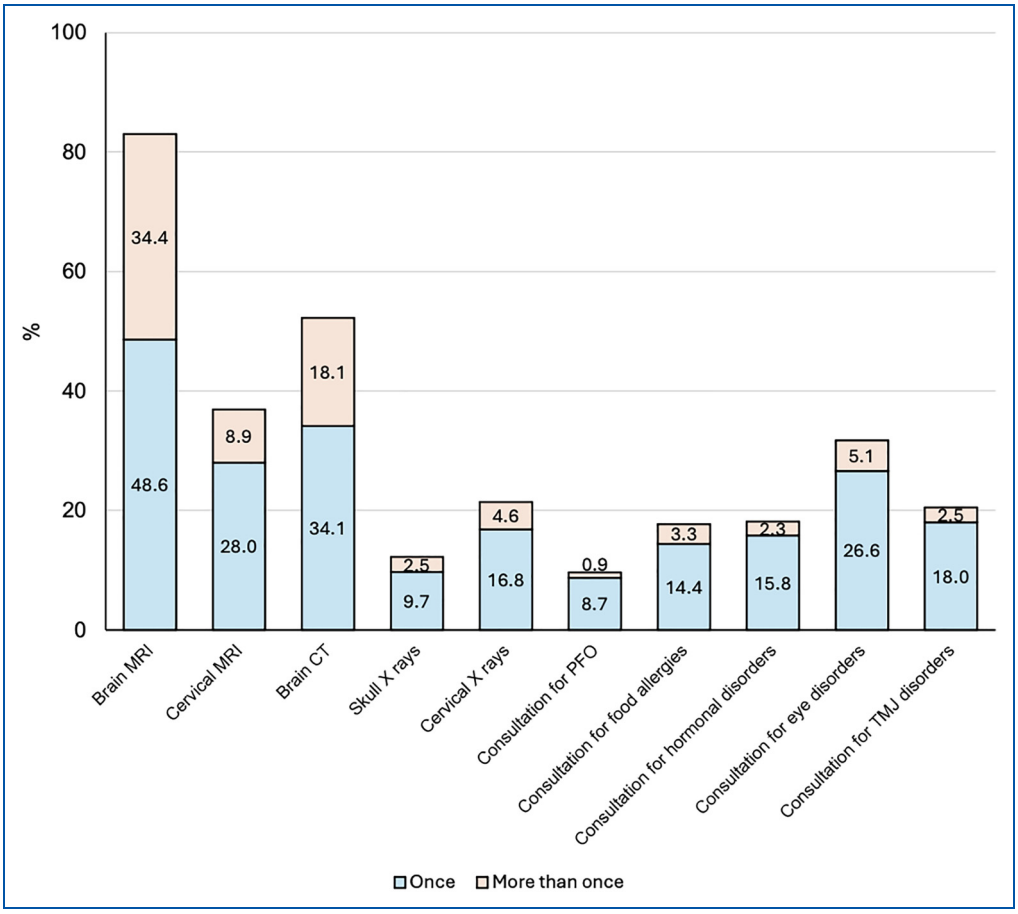

Figure 1. Proportion of participants with previous diagnostic tests in the overall population.
MRI: Magnetic resonance imaging, CT: Computed tomography, PFO: Patent foramen ovale, TMJ: temporomandibular joint.

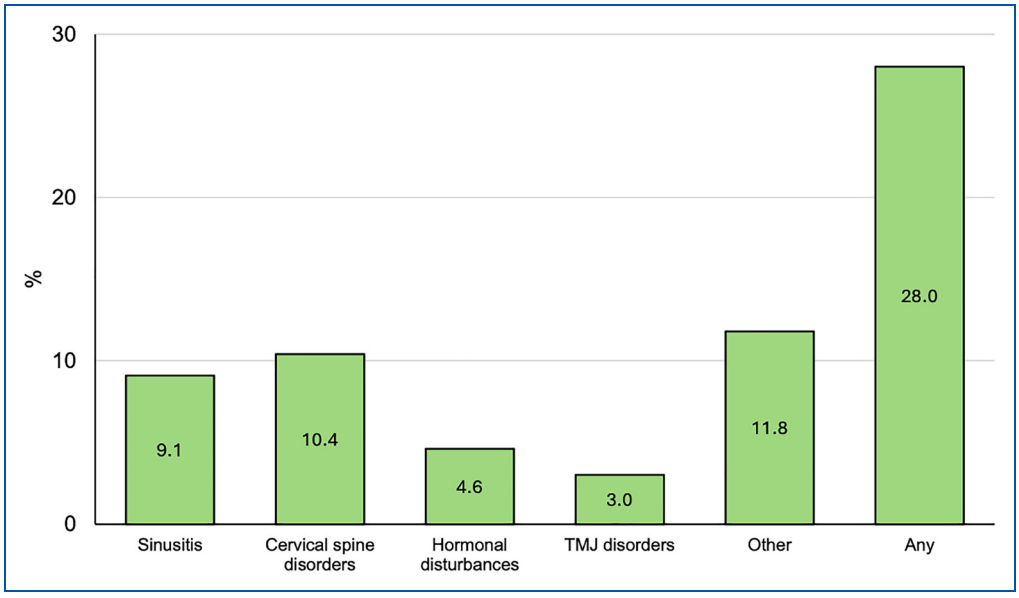

Figure 2. Proportion of participants with misdiagnoses at baseline in the overall population.
TMJ: temporomandibular joint.

one and 23 (3.4%) more than one consultation for food allergies; 109 (15.9%) had performed one and 16 (2.3%) more than one consultation for hormonal problems; 183 (26.6%) had undergone one and 35 (5.1%) more than one consultation for eye disorders; 124 (18.1%) had performed one and 17 (2.5%) more than one consultation for temporomandibular joint disorders (Figure 1).

Among the 689 study participants, 193 (28.0%) received at least one misdiagnosis of headache; the most common one was cervical spine disorders (72, 10.4%) followed by sinusitis (62, 9.1%), hormonal disorders (32, 4.6%), and temporomandibular joint disorders (21, 3.0%; Figure 2). Notably, 23 participants (3.4%) had surgical treatments performed for sinusitis, and 11 (1.6%) surgical treatments for the cervical spine.

Referring to subgroup differences, participants with ResM and RefM performed more diagnostic tests and consultations than those with NRNRM; this applied to all the assessed tests (Figure 3). Participants with ResM had the highest proportion of misdiagnoses (81, 31.2%), followed by those with NRNRM (101, 28.5%) and by those with RefM (11, 15.1%; $p = 0.025$; Figure 4). Focusing on specific misdiagnoses, there was a significant difference across groups for sinusitis only ($p = 0.047$; Figure 4). Online Supplementary Table A1 reports the odds ratios for diagnostic tests and misdiagnoses in individuals with ResM or RefM compared with those with NRNRM.

Participants' age, sex, disease duration, or prevalence of chronic migraine or medication overuse did not differ according to the prevalence of misdiagnoses (Online Supplementary Table A2). However, age, disease duration, and the prevalence of chronic migraine and medication overuse presented some differences when comparing participants with and without previous diagnostic tests (Online Supplementary Table A2).

Discussion

Performing unnecessary diagnostic tests can delay the diagnosis and treatment of migraine and contribute to increasing the costs of the disease, which are already high, especially for chronic migraine.[14] In the REFINE cohort, many participants underwent numerous diagnostic tests, with a particular emphasis on neuroimaging. Specifically, four out of five had a brain MRI, and one-third of participants had more than one brain MRI (Figure 1). Misdiagnoses of migraine were also very common at 28.0% (Figure 2), within the range of comparable observational data, where misdiagnoses ranged from 106 to 72%.[15,16] Consistent with existing literature, the most frequent misdiagnoses involved sinusitis and cervical spine disorders.[16–18]

When comparing participants with ResM, RefM, and NRNRM, those with ResM and RefM performed more diagnostic tests for headache compared to those with NRNRM. The higher prevalence of diagnostic tests in participants with ResM or RefM compared with those with NRNRM might be explained by the clinicians' or individuals' concerns about the correctness of the migraine diagnosis, given the failure of preventive treatments. However, the performance of diagnostic tests could have been influenced by participants' age, migraine duration, or the presence of chronic migraine or medication overuse, as these characteristics presented some associations with the performance of diagnostic tests in our population (Online Supplementary Table A2).

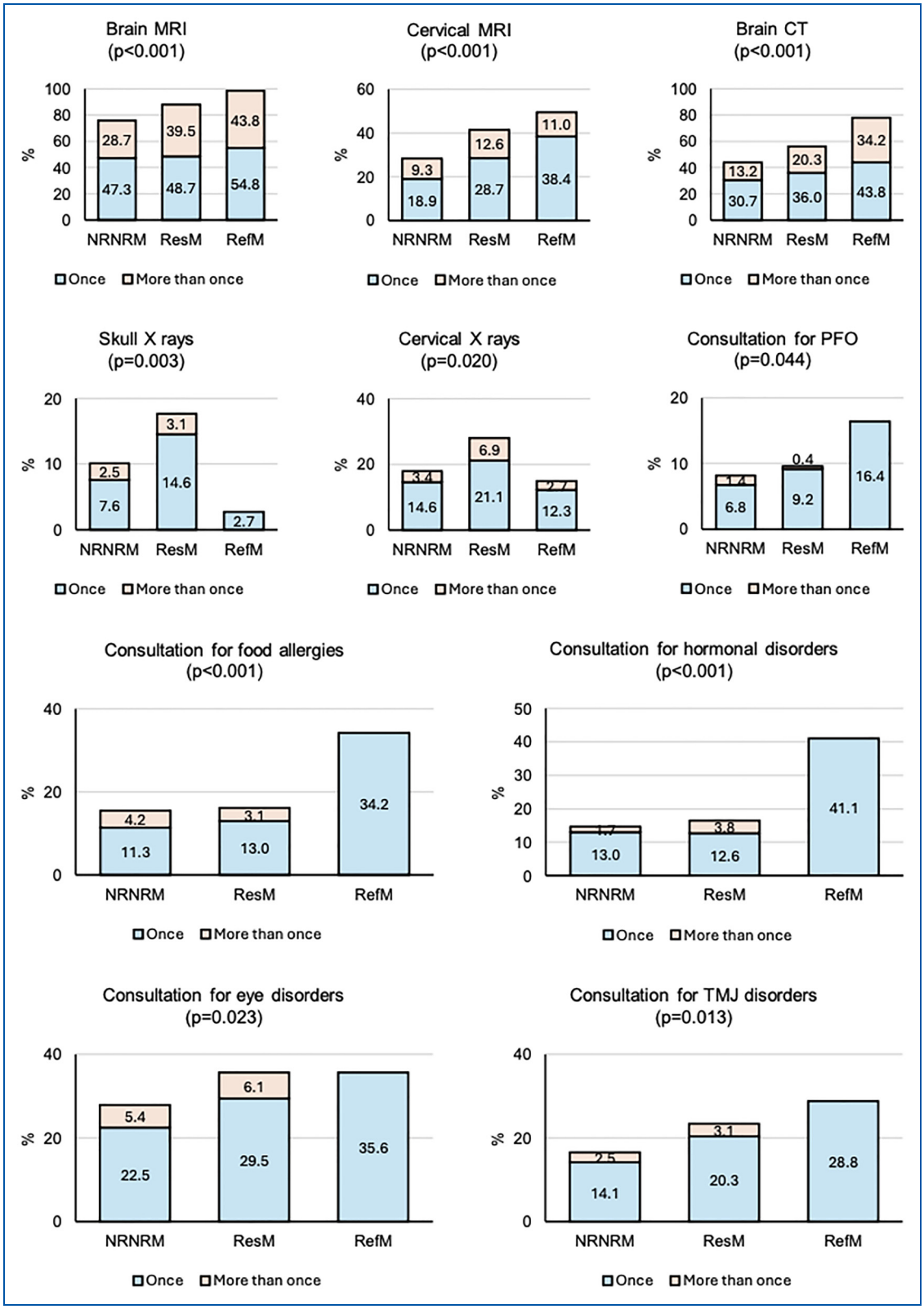

Figure 3. Proportion of participants who had performed diagnostic examinations at baseline according to their status of non-resistant non-refractory, resistant, or refractory migraine.
NRNRM: non-resistant non-refractory, ResM: resistant migraine, RefM: refractory migraine, MRI: Magnetic resonance imaging, CT: Computed tomography, PFO: Patent foramen ovale, TMJ: temporomandibular joint.
p-value represent the difference across the three groups: NRNRM, ResM and RefM.

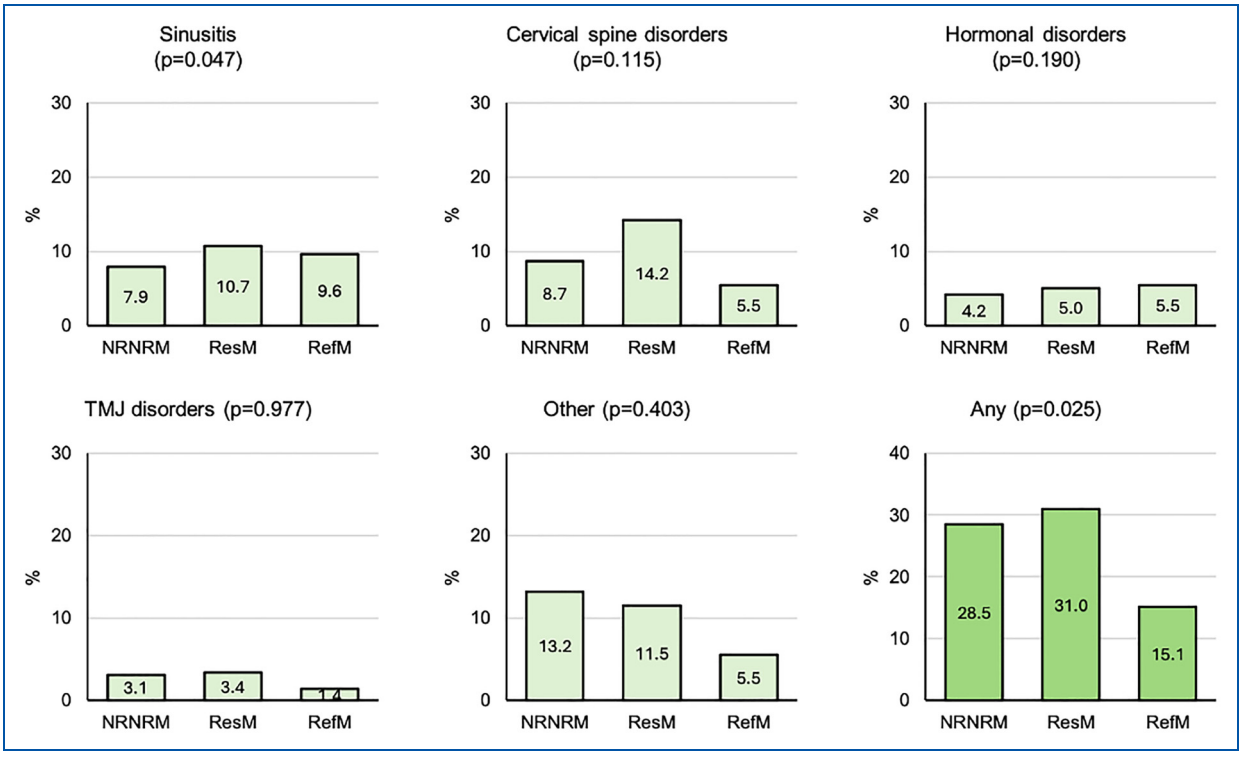

Figure 4. Proportion of participants with misdiagnoses at baseline according to their status of non-resistant non-refractory, resistant, or refractory migraine.
NRNR: non-resistant non-refractory, ResM: resistant migraine, RefM: refractory migraine, TMJ: temporomandibular joint.
p-value represent the difference across the three groups: NRNRM, ResM and RefM.

Contrary to the performance of diagnostic tests, prior misdiagnoses were fewer in individuals with RefM than in those with ResM or NRNRM (Figure 2). The higher prevalence of misdiagnoses in participants with NRNRM compared with those with ResM or RefM might be explained by the fact that individuals with ResM or RefM are mainly managed in tertiary headache centers for many years, while those with NRNRM are usually handled in general practice or in lower-level centers where migraine diagnosis can be less precise than in specialized centers. Notably, while misdiagnoses should be always considered inappropriate in individuals of our cohort with a confirmed diagnosis of migraine, diagnostic tests might have been appropriate in several cases of individuals with ResM or RefM to help differential diagnoses with secondary headache disorders or to evaluate the impact of possible comorbidities on the poor response to preventive treatments. Moreover, it remains to be clarified whether RefM itself could be considered a warning sign that needs to be monitored or investigated further to revise the diagnosis of migraine. To date, there are no guidelines on which tests are recommended in subjects with RefM or accounts on how many cases of RefM conceal non-migraine headache disorders.

As ResM or RefM may indicate the progression from treatable to difficult-to-treat forms of migraine, we can hypothesize that this progression was associated with a higher burden of misdiagnoses and of unnecessary diagnostic tests compared with NRNRM. Notably, despite the differences among subgroups, we observed a high prevalence of previous misdiagnoses across all individuals with migraine, regardless of their responsiveness to preventive treatment. Additionally, we found a lower prevalence of misdiagnoses in the RefM group compared with the ResM and NRNRM groups, suggesting that misdiagnoses and additional diagnostic tests do not necessarily affect the responsiveness of individuals with migraine to preventive treatments.

We included participants from a large, multicenter study carried out in centers with high activity levels and extensive clinical experience. However, the study also has limitations. We only analyzed cross-sectional data from baseline visits, which are susceptible to recall bias. Additionally, previous misdiagnoses and diagnostic tests were reported either as present or as absent, which contributed to completeness of data entry while on the other hand increasing the risk for underreporting. We did not use standardized definitions or central quality control on misdiagnoses; however, although classifications were based on clinical judgment supported by medical history and clinical records, the possibility of

classification bias cannot be excluded. We did not report data about invasive procedures such as lumbar puncture which can be performed for the differential diagnosis of migraine. We did not record the time from diagnostic tests or misdiagnoses to the baseline visit; unnecessary tests or misdiagnoses may have been made decades ago, when migraine treatments were non-specific and headache classifications differed from today's standards. Furthermore, due to the lack of temporal data regarding misdiagnoses and diagnostic tests, it was not possible to establish a clear causal link in the absence of a temporal sequence between the occurrence of misdiagnoses and repeated or unnecessary diagnostic tests. This limitation might also affect the low prevalence of misdiagnoses in RefM than in ResM or NRNRM, as it may reflect not only greater access to tertiary care, but also the fact that participants with misdiagnosis may never have made it to the level of care required to be classified as RefM. Besides, we could not retrieve whether the tests were performed before or after developing ResM or RefM; some tests might have been performed in individuals with ResM or RefM to revise their diagnosis of migraine. Additionally, since participants were recruited from tertiary headache centers, our data may not be representative of the entire migraine population. In fact, tertiary care centers manage individuals with migraine referred from lower levels of care, with a clinical history spanning several years, including many diagnostic tests and therapies. The number of participants with RefM was relatively small, potentially reducing the statistical power of some results. We also could not determine the setting of misdiagnoses or unnecessary diagnostic tests, whether conducted in general practices or specialized headache centers; knowing this would help to identify areas for public health interventions to improve migraine care and the timely diagnosis of ResM and RefM. Furthermore, we were unable to establish the timing of diagnostic tests, misdiagnoses, or the REFINE baseline visit. We also could not determine whether some conditions labeled as misdiagnoses, such as temporomandibular joint disorders or cervical spine disorders, might have been actually present in the participants' clinical history and thus aggravating migraine despite not being the cause of headache attacks. Finally, we lacked information on migraine symptoms; participants with atypical migraine phenotypes might have undergone more diagnostic tests and received more misdiagnoses than those with typical symptoms.

Conclusions

We observed a high rate of diagnostic tests and misdiagnoses in all the groups of individuals with ResM, RefM, and NRNRM, with a higher prevalence of diagnostic tests in the ResM and RefM groups compared with the NRNRM group. Our findings emphasize a need for better diagnostic accuracy and care pathway for all individuals with migraine and particularly for those most in need of effective prevention.

Article highlights

- A large proportion of individuals with migraine, especially those with resistant or refractory migraine, underwent multiple and unnecessary diagnostic procedures, mostly including neuroimaging studies.
- Among participants, 28% reported at least one previous headache misdiagnosis, most commonly cervical spine disorders and sinusitis.
- While diagnostic testing was more common in individuals with resistant or refractory migraine than in those with non-resistant, non-refractory migraine, misdiagnoses were not more frequent in refractory migraine.

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Ethical considerations

Ethical approval was obtained from the Institutional Review Board and/or relevant Ethics Committees at all participating centers (protocol number from coordinating center: 45/2020-21).

Consent to participate

Participants or their authorized representatives provided written informed consent.

Author contributions

S.S. conceived the study; R.O., C.R., and S.S. supervised the study; R.O. and F.d.S. performed the statistical analysis and wrote the original draft of the manuscript; all the Authors collected data for the present study and revised the manuscript for intellectual content.

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Declaration of conflicting interests

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Data availability statement

Data from the present study are available from the corresponding author upon reasonable request.

Supplemental material

Supplemental material for this article is available online.

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