PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The management of chronic headache with referral from primary care to direct access to Magnetic Resonance Imaging (MRI) compared to Neurology services: an observational prospective study in London.
AUTHORS	Rua, Tiago; Mazumder, Asif; Akande, Yvonne; Margariti, Charikleia; Ochulor, Juliana; Turville, Joanna; Razavi, Reza; Peacock, Janet; McCrone, Paul; Goh, Vicky; Shearer, James; Afridi, Shazia

VERSION 1 – REVIEW

REVIEWER	Paolo Martelletti Sapienza University of Rome, Italy
REVIEW RETURNED	12-Dec-2019

GENERAL COMMENTS	This interesting study has focused on a topic extremely important in the headache management, the necessity, the numerousness, at what level brain MRI must be requested in headache patients. The context in which the study has been carried out is national, by general practitioners with special interest in headache and hospital neurologists, avoiding one important access point in healthcare: the emergency department. Everything has been evaluated in terms of costs and patients' satisfaction. Results support those who since many years indicate the general practitioner as the first embankment towards this huge number of migraine patients. In this context I suggest to include the following refs: PMID: 29392600 PMID: 26969188 PMID: 21744225 PMID: 31113373

REVIEWER	Sait Ashina Harvard Medical School, Beth Israel Deaconess Medical Center Consulting fees from Novartis, Amgen, Allergan, Elly Lilly, Supernus, Satsuma, Percept, Promius , Cowen, Theranica.
REVIEW RETURNED	16-Feb-2020

GENERAL COMMENTS	The aims of this prospective, single-center study were to evaluate the 6-month health care costs (primary outcome), accessibility and patient satisfaction implications of two clinical pathways used in the management of chronic headache in UK: a referral from Primary Care to either a Neurology appointment or an MRI brain scan. Authors demonstrated that direct referral to brain MRI from Primary Care led to cost savings and quicker access to care but lower satisfaction rates when compared with referral to Neurology

	appointment. The study is important and may have clinical implications. However, as stated by authors, these results cannot be applied to general population/other populations. Nevertheless, this pilot study warrants the publication. I agree with authors that a multi-center study is needed (including urban and non-urban populations). Other limitations of the study include the over-representation of females in Neurology group. More patients in Neurology group were started on preventative medications which may imply that these patients might have more severe headaches. Authors also state that "the allocation was decided a priori, i.e. the referrer (in this case the GP) decided which referral route would suit each participant". Since GPs decide the referral path, the "confounding by indication", may be an issue. In that case the clinical indication for selecting a treatment/referral path may affect the outcomes of the study. This needs to be discussed in the manuscript. This also needs to be addressed in the suggested future study. Minor comments: 1. Were headache cases classified according to ICHD-3 criteria (International Headache Society diagnostic criteria? Or were diagnoses ICD based? Please specify in Methods. 2. Were the comorbidities (including other pain, psychiatric comorbidities) recorded? You may consider adjusting analyses for comorbidities, age, gender, headache-related disability, education and household income? These covariates may influence the results of the study.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Paolo Martelletti
Institution and Country: Sapienza University of Rome, Italy
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
This interesting study has focused on a topic extremely important in the headache management, the necessity, the numerousness, at what level brain MRI must be requested in headache patients.
The context in which the study has been carried out is national, by general practitioners with special interest in headache and hospital neurologists, avoiding one important access point in healthcare: the emergency department. Everything has been evaluated in terms of costs and patients' satisfaction.
Results support those who since many years indicate the general practitioner as the first embankment towards this huge number of migraine patients.
In this context I suggest to include the following refs:

PMID: 29392600
PMID: 26969188
PMID: 21744225
PMID: 31113373

Many thanks for your positive feedback.

We would like to highlight that the study was conducted in secondary care, following a GP (with or without special interest in headache) referral to either brain MRI or Neurology appointment. Some of these patients recruited had attended the emergency department prior to the GP referral.

The suggested references have been included in the manuscript. In fact, the main author of one of the references is a co-author in the present study.

Reviewer: 2
Reviewer Name: Sait Ashina
Institution and Country: Harvard Medical School, Beth Israel Deaconess Medical Center
Please state any competing interests or state 'None declared': Consulting fees from Novartis, Amgen, Allergan, Elly Lilly, Supernus, Satsuma, Percept, Promius , Cowen, Theranica.

Please leave your comments for the authors below
The aims of this prospective, single-center study were to evaluate the 6-month health care costs (primary outcome), accessibility and patient satisfaction implications of two clinical pathways used in the management of chronic headache in UK: a referral from Primary Care to either a Neurology appointment or an MRI brain scan. Authors demonstrated that direct referral to brain MRI from Primary Care led to cost savings and quicker access to care but lower satisfaction rates when compared with referral to Neurology appointment. The study is important and may have clinical implications. However, as stated by authors, these results cannot be applied to general population/other populations. Nevertheless, this pilot study warrants the publication. I agree with authors that a multi-center study is needed (including urban and non-urban populations). Other limitations of the study include the over-representation of females in Neurology group. More patients in Neurology group were started on preventative medications which may imply that these patients might have more severe headaches. Authors also state that "the allocation was decided a priori, i.e. the referrer (in this case the GP) decided which referral route would suit each participant". Since GPs decide the referral path, the "confounding by indication", may be an issue. In that case the clinical indication for selecting a treatment/referral path may affect the outcomes of the study. This needs to be discussed in the manuscript. This also needs to be addressed in the suggested future study.

Many thanks for your positive feedback and recommending the manuscript for publication.

With regards to your specific comments, the proportion of females was considered as a covariate in the adjustment of the 6-month cost analysis (primary outcome).

Patients in the Neurology group presented a higher headache burden at baseline (based on the EQ-5D-5L questionnaire and headache-specific questionnaires HIT-6 and MIDAS). The authors appreciate the reviewer's comment regarding the potential confounding by indication introduced by GPs. In order to mitigate this confounding factor, we have used multivariable regression analyses adjusted using covariates that were different at baseline using a conservative threshold ($p<0.1$). The authors have included the following sentences in the 'discussion', 'limitations' and 'implications for further research' sections to further clarify this confounding factor.

'Discussion' section:

In order to mitigate the potential confounding by indication introduced by GPs referring patients to both clinical pathways, adjusted GLMs were conducted.

'Limitations of this study' section:

In order to mitigate potential confounding factors, adjusted multivariate analyses showed that the primary outcome was hardly affected and remained statistically significant. Nevertheless, residual confounding factors remain a limitation of the study.

‘Implications for further research and clinical practice’ section:

Future study designs should consider the confounding by indication introduced by recruiting participants referred to the two pathways based on GP decision.

Minor comments:

1. Were headache cases classified according to ICHD-3 criteria (International Headache Society diagnostic criteria? Or were diagnoses ICD based? Please specify in Methods.

We have used the ICHD-3 classification once patients entered secondary care, i.e. chronic migraine as a headache occurring on 15 or more days/month for more than 3 months.

2. Were the comorbidities (including other pain, psychiatric comorbidities) recorded? You may consider adjusting analyses for comorbidities, age, gender, headache-related disability, education and household income? These covariates may influence the results of the study.

The baseline characteristics were summarised in Table 1. The presence/absence of mental health conditions (dichotomous variable) was considered, along with others, e.g. age, gender, headache disability or education. However, we have only adjusted the primary outcome with covariates that were statistically significant at baseline using a conservative thresholds ($p<0.1$).

VERSION 2 – REVIEW

REVIEWER	Sait Ashina Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA, USA
REVIEW RETURNED	10-Apr-2020

GENERAL COMMENTS	I would like to to thank authors for addressing my comments. I have one last comment. I would suggest to specify the type of chronic headache patient were diagnosed with. I assume patient were diagnosed with either chronic migraine or chronic tension-type headache.

VERSION 2 – AUTHOR RESPONSE

Many thanks for the positive comments. Reviewer 2 is correct as all patients were diagnosed with chronic migraine. We have update the ‘Methods’ section of the manuscript accordingly.