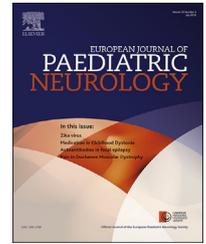




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## Original article

# Yield of brain imaging among neurologically normal children with headache on wakening or headache waking the patient from sleep

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## ABSTRACT

**Background:** Headache on wakening (HoW) or sleep interruption secondary to headache (SIH) has been commonly regarded as a potential sign of raised intracranial pressure and therefore a sign of significant underlying pathology that necessitates further investigation. Current recommendations for neuroimaging in patients with HoW/SIH are neither consistent nor clear across headache guidelines published both nationally and internationally.

**Aim:** The main aim of this study was to ascertain the relevance of HoW and/or SIH as an indication for routine neuroimaging.

**Methods:** This study focused on clinically well patients with normal neurological examinations who had experienced HoW or SIH. Demographic and neuroradiological data were collected prospectively and the headache diagnosis was based on the International Classification of Headache Disorders.

**Results:** 102/1065 patients reported either HoW and/or SIH. There were 57/102 (56%) females, 45/102 males (44%), and 33/102 (32%) of ethnic minority. Their age ranged between 5 and 17 years. 79/102 (77%) patients with HoW, 19/102 (19%) with SIH and 4/102 (4%) with both HoW and SIH. Headache diagnosis included migraine (n = 67; 66%), tension type headaches (n = 16; 16%), medication overuse headaches (n = 11; 11%), and sinusitis (n = 1; 1%). Neuroimaging was performed in 101/102 patients; imaging was normal for 97 scanned patients, and showed non-significant abnormality in the remaining 4 patients.

**Conclusion:** HoW or SIH among clinically well and neurologically normal paediatric patients was most likely to be caused by primary headaches, particularly migraine or tension type headaches. This symptom alone among healthy and clinically well children is not an indication for routine neuroimaging and is unlikely to be caused by sinister aetiologies.

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## 1. Section 1: Introduction

Headache on waking (HoW) or sleep interruption secondary to headache (SIH) have commonly been regarded as a potential sign of raised intracranial pressure. This symptom has been attributed to lying flat whilst sleeping which exacerbates raised intracranial pressure overnight.<sup>1</sup> Therefore HoW or SIH is often viewed as a “red-flag” symptom suggesting a sinister cause for the headache such as brain tumour or intracranial pathology. Due to the apparent connection between HoW/SIH and raised intracranial pressure, neuroimaging may be indicated to rule out underlying pathologies as a cause for the headache. However the current recommendation for neuroimaging in patients with HoW/SIH is neither consistent nor clear across published headache guidelines worldwide. This prospective study analyses hospital-based clinic data in children and adolescents to investigate the necessity of neuroimaging in reference to HoW/HWS as a red flag symptom. A review of current national and international guidelines was undertaken, looking at consensus on HoW/SIH as an indication for neuroimaging.

The International Headache society published an update of the International Classification of Headache Disorders in 2013 (ICHD-3 beta).<sup>2</sup> The ICHD-3 beta is not a clinical guideline per se but a definitive list of classifications which aid diagnosis and give specific direction for research. This guideline does however have some guidance regarding HoW/HWS or “hypnic headaches”: although the ICHD-3 beta does not go into detail it recommends ruling out any other causes that could be producing this symptom. Causes of headache on waking or headache waking an individual from asleep that need to be excluded include sleep apnoea, nocturnal hypertension, hypoglycaemia, medication overuse headache and intracranial disorders such as brain tumour or other space occupying lesions.

The European Headache Federation and the WHO (World Health Organisation) published a document for the management of common headache disorders in primary care in 2007, which includes warning features or “red flags” warranting referral from primary care and/or further investigation.<sup>3</sup> This guideline advises investigations, including neuroimaging, are indicated when the history or examination suggest headache may be secondary to another condition (i.e. warning feature present). It must be noted that headache on waking is not included in the list of warning features. The European collaboration with the WHO can be compared to the NICE (National Institute for Health and Care Excellence) guidelines for diagnosis and management of headache.<sup>4</sup> The NICE guidelines also have a list of “red flag features” in which headache on waking or headache waking patient from sleep is not included.<sup>4</sup> Looking more closely at the NICE guidelines it is noted that “early morning headache” was a symptom that was under debate as to its significance. The NICE guidelines conclude that the seriousness or significance of any underlying pathology indicated by early morning headache is “uncertain”. This conclusion was drawn by the NICE guidelines when a literature search was conducted to answer the clinical question: “For young people and adults presenting with early morning headache, how common are

serious intracranial abnormalities?” and did not uncover any significant data on this topic.

This uncertainty surrounding headache on waking continues when looking at the British Association for the Study of Headache (BASH) guidelines from 2010.<sup>5</sup> Morning headache is discussed in the warning features for this guideline and therefore warrants investigation however this includes “persistent morning headache with nausea” suggesting that morning headache in isolation is not a warning feature. Again these guidelines do not specify when neuroimaging is indicated but suggest when a patient needs a specialist referral or further investigation (which may include neuroimaging). Another set of headache guidelines originating from the UK is from the Scottish Intercollegiate Guidelines Network (SIGN).<sup>6</sup> Headache on waking is a red flag in this guideline and specialist referral and further assessment is indicated if this symptom is present. As with other guidelines discussed, no specific imaging is mentioned as part of this further assessment. This guideline specifically states that neuroimaging is not indicated in patients with a clear history of migraine without red flag features for potential secondary headache and a normal neurological exam. One of the red flag features included is headache waking the patient but it is noted that migraine is the most frequent cause of morning headache. This could cause some confusion but it is presumably to make sure unnecessary neuroimaging in a clear migraine history is avoided.

The Journal of Headache and Pain published revised French guidelines for diagnosis and management of migraine.<sup>7</sup> It is interesting to note that there are no references to headache on waking. The Croatian society for neurovascular disorders published updated primary headache guidelines in 2012.<sup>8</sup> It may also be of note that headache on waking is mentioned in these guidelines in the general principles of migraine management and that migraine sometimes has the feature of headache on waking.

The search for US headache guidelines proved difficult. There were guidelines published in 2005 by the US Headache consortium for neuroimaging in patients with non-acute headache.<sup>9</sup> This guideline does not, like other guidelines, include a list of red flag symptoms as it is specifically for non-acute headache. It therefore does not include in its remit headache presentations in emergency scenarios. In this guideline neuroimaging is indicated for non-acute headache and an unexplained abnormal finding on neurological examination. Neuroimaging is specifically not indicated in patients with migraine and normal neurological examination. Headache causing waking from sleep is mentioned in these guidelines and it is stated that this may indicate a higher likelihood of significant intracranial pathology. This is based on several small studies and the recommendation is that evidence is insufficient in order to draw any conclusion and give any indication for neuroimaging.

One of the most recent updates of headache guidelines comes from the Canadian Family Physician in 2015.<sup>10</sup> This guideline is for primary care management of headache. It has a list of red flags and as with other national guidelines headache on waking is not included.

The Japanese headache guidelines<sup>11</sup> states that secondary headache should be suspected in the presence of specific symptoms and/or signs such as headache with sudden onset or headache never experienced before. “Intensive investigations are required” if a secondary cause is suspected. As with the ICHD-3 beta classification the main reference to a headache that awakens the patient from sleep is regarding hypnic headaches. In this guideline, in conjunction with ICHD-3 beta, hypnic headache is grouped under “other primary headache disorders” and careful evaluation using neuroimaging and other tests are necessary. This guideline reiterates the idea that migraine pain can start during sleep and awaken the patient with pain – this is mentioned in the therapeutic subsection regarding sumatriptan treatment but nothing in specific was mentioned regarding headache on waking.

The Headache in Primary Care guidelines from New Zealand<sup>12</sup> are adapted from the BASH guidelines, which as previously discussed mention early morning headache coupled with nausea as a red flag sign. The New Zealand guidelines however do not include this in their red flags. Similarly to other guidelines mentioned, if any red flags indicating secondary headache are present, a more detailed examination is needed. No modality of examination or imaging is specified. It is important to note that this article does not provide as much detail as others. It states that it cannot cover all issues associated with headache presentation and is mainly focussing on secondary headache presentation, diagnosis, management of primary headaches and medication overuse headache. This means neuroimaging, when and what modality should be used, and the challenges these decisions pose are not included in this article.

An Australian review article published in 2014 on the management of chronic headaches includes a set of red flag symptoms that does not specifically mention HoW or SIH but discusses urgent investigation if there are concerns about raised intracranial pressure as indicated by headaches worsening with coughing, straining, sneezing or stooping/posture.<sup>13</sup> Finally, HeadSmart campaign UK raises awareness of the most common signs and symptoms of brain tumour in children and teenagers. As in other guidance headache on waking and/or sleep interruption secondary to headaches are particularly not included.<sup>14</sup>

Overall, there is no consistent guidance as to whether HoW or SIH should be considered a “red flag” when looking across all the guidelines discussed. The ICHD-3 beta does recommend that if a headache wakes a patient from sleep other serious causes should be ruled out. This could be done by using the diagnostic criteria or by other means for example neuroimaging. In the comparison of guidelines, only 3 out of the 12 guidelines included headache on waking, headache awakening the patient from sleep or early morning headache as a warning feature or red flag symptom. Despite this, HoW/SIH is often interpreted by clinicians as a potential sign of raised intracranial pressure. This lack of consensus suggests that the clinical implications of headache on waking are not necessarily fully understood and further research on the subject would be useful, particularly as primary headaches (in particular migraines) can often present with these features. It is also important to note that the guidelines that have been

reviewed are primarily adult guidelines; there is a scarcity of guidance out there in specific reference to the paediatric population. This opens up a whole area of research that needs addressing to reduce unnecessary neuroimaging in children and adolescents.

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## 2. Section 2

### 2.1. Aim

The main objective of this study is to examine the yield of brain imaging among neurologically normal, healthy children and adolescents with headache on waking or headache awakening the patient from sleep. This is to determine whether HoW and/or SIH alone are red flags suggesting a significant underlying intracranial pathology requiring further evaluation by neuroimaging.

### 2.2. Methods

In this non-interventional prospective single centre hospital-based study, demographic and clinical data were obtained from 1065 (680 migraineurs) patients who were referred to the paediatric headache clinic between August 2012 and August 2016. There were 612 (57.5%) females and 570 (39%) patients were from ethnic minorities. The average patient age was 11.7 years. Ethical approval was granted by the Research Health Authority, England and the Research and Development Department at Barking, Havering, and Redbridge University Hospitals NHS Trust. Formal consent from the parents and/or patients was not needed.

In this study, neuroimaging (Magnetic Resonance Imaging (MRI) or Computed Tomographic (CT) Scan) was arranged for all patients with HoW or SIH. Other investigations were arranged as clinically appropriate. Hospital based follow-up was arranged for all 102 patients included in the study, but 6 patients were lost to follow – up and the parents of 23 patients requested no further follow up. All these patients had neuroimaging. We previously examined the development of decision rule and brain imaging of neurologically normal children with headache. The current prospective cohort was not included in the previous study.

#### 2.2.1. Inclusion and exclusion criteria

To achieve relatively stable results, the following inclusion and exclusion criteria were used. Inclusion criteria: i- Well and healthy child; ii- Normal neurological examination; iii - Age 17 years or less; iv-Headache on waking; iv- Headache waking a patient from a sleep.

We have not measured the occurrence of HoW or SIH in terms of percentage (e.g. < 10%; > 50%) but we included patients when HoW and/or SIH embraced all or most of their headache attacks and caused concerns to the patients and their parents. Exclusion criteria: diagnosis of epilepsy, specific learning difficulties, sleep related problems, psychiatric disorders, systemic illnesses and lack of relevant information.

### 2.2.2. Diagnosis and definition

Headache diagnosis was made according to the criteria of the ICHD (3 beta).<sup>2</sup> Primary headaches were categorised into migraine, tension type headache (TTH) and others. Unclassified headaches were considered ‘not yet specified’ headaches. Headache course is defined as the duration between age at headache onset and age at last assessment. Headache attacks need to be separated by at least 24 h of pain-free intervals. Headache frequency is defined as the average number of headache attacks per month. On the basis of frequency, headaches are classified as episodic (<1 attack/month), frequent (>1 to <15 attacks/month), and chronic daily headaches (15 headache days or more/month for at least 3 months). In this study, headache intensity is categorised into mild, moderate or severe. Moderate and severe intensity were defined as a headache that inhibits or prohibits daily life activity respectively.

Headache on waking was defined as head pain reported after waking up from sleep and before getting up from supine position. To distinguish headache on waking from headaches occurring after getting up the patients were asked: “Does your headache wake you from sleep or does it only occur after you get out of bed?” Headache causing sleep interruption was defined as head pain leading to sleep disturbance and therefore, the patient wakes from sleep because of head pain. To distinguish sleep disturbances associated with attacks of specific headache types (e.g. migraine), the patients were asked: “Do you wake up from sleep because of the headache that you have had before you falling asleep? Therefore, in this study, sleep interruption secondary to headache is strictly defined as head pain causing sleep disturbances in a patient who had no headache prior to falling asleep.

## 3. Section 3: Results

Of the 1065 patients with headaches, 102 (9.5%) patients reported HoW and/or SIH during attacks of their headaches. Of these 102 patients, 79 (77%) reported HoW and 19 (19%) patients reported SIH. The remaining 4 (4%) reported both HoW and SIH. There were 57 (56%) females and 45 (44%) males; 33/102 (32%) were from ethnic minorities. Their average age was 11.7 years (range 5–17.2 years). Headaches were mild (n = 7; 7%), mild to moderate (n = 6; 6%), moderate (n = 25; 24.5%), moderate to severe (n = 16, 16%) or severe (n = 48; 47%). Headaches were episodic (n = 1; 1%); frequent (n = 44; 43.5%); or chronic daily headaches (n = 57, 56%). Specific triggers of headaches were identified among 30/102 (30%) patients. Positive family history of headaches was reported by 42/102 (41%) patients. Table 1 illustrates epidemiological data, clinical characteristics and headache diagnoses in our cohort comprise three groups. As migraine is the most common type of headache among the 1065 patients (680/1065; 64%), it is not surprising migraine is the commonest headache type among our cohort of the 102 patients. Interestingly, HoW and/or SIH reported by just 67 (10%) of the 680 patients.

101 out of 102 patients had brain imaging (96 MRI; 5 CT) – see Table 2. Brain imaging showed no intracranial

abnormality in n = 97 (95%). Brain imaging was abnormal among the remaining 4 (4%) patients. Abnormalities included arachnoid cyst (n = 1; 1%); cerebellar tonsillar descent to C2 (n = 1, 1%); periventricular leukomalacia (n = 1, 1%) and non-specific high signal in the right temporal region (n = 1, 1%). The parents of the remaining patient decided against imaging. This patient was a seven-year-old healthy girl who presented with frequent headaches that reported on waking. Headaches were triggered by stress at school and were consistent with migraine without aura. Her headaches disappeared completely during the study period and she remained fit and well. 72/102 (71%) patients were followed up in our clinic for a mean period of 9.5 months (range = 4–24 months). Of these, headaches disappeared or considerably improved among 60 (83%) of patients, while 12 (17%) reported ongoing headaches at the same frequency. 24/102 (23.5%) patients were discharged from the follow up and 6/102 (6%) patients were lost to follow up. All 24 patients that were discharged and the 6 patients lost to follow up had normal brain imaging.

## 4. Section 4: Discussion

A comprehensive search of national and international guidelines on the management of headache on waking or sleep interruption secondary to headaches in childhood and adolescence revealed little clear guidance. Although controversy exists, brain imaging is recommended by some experts to exclude secondary causes of HoW/SIH. The concept of secondary headaches (e.g. brain tumour) as a cause of HoW or SIH, therefore indicating a need for neuroimaging, is common belief among clinicians. Whether primary headaches (e.g. migraine, tension type headache) could also cause HoW or SIH is not yet formally established.

In our study, all patients presenting with HoW and/or SIH were offered neuroimaging as a means of ruling out sinister secondary causes of headache. 101/102 (99%) of patients underwent neuroimaging and 96% (97/101) of those imaged showed no underlying intracranial abnormality. The most common cause of HoW/SIH identified by the data was migraine (n = 67; 66%) followed by TTH (n = 16; 16%). This is a total of 83% of patients whose HoW/SIH were in fact caused by primary headache which should not require any neuroimaging. Another 11% of the HoW/SIH was attributed to medication overuse headaches and a further 1% was caused by sinusitis. In our cohort, headache remained unclassified among seven patients. All these patients are healthy and well children and all had normal brain imaging (MRI). In our study, not only does this data show that a majority of the HoW/SIH were actually caused by primary headache but also that neuroimaging frequently revealed no intracranial pathology.

In our cohort, neuroimaging among 4% of patients revealed intracranial abnormalities that were unlikely to have caused HoW or SIH and none of these abnormalities required prompt intervention. Furthermore, in our cohort, none of the imaged patients had intracranial sinister causes that could be implicated in the pathogenesis of their headaches. This is where the debate lies; is it deemed necessary to scan every patient

presenting with HoW/SIH or is there a way the process can be further refined? Our findings show that HoW/SIH is predominantly associated with primary headaches and this need to be more widely recognised in order to avoid unnecessary brain imaging. The data that this study has revealed needs to be consolidated further by more studies of this nature giving further insight into the issue.

#### 4.1. Strengths and limitations

Our study has several strengths. This is the first study to focus on headache on wakening and/or headache as a symptom causing sleep interruption among healthy neurologically normal children and adolescents. The prospective setting, strict eligibility, study design and homogenous disease-specific evaluation are the main strength of the study. However, the study had some limitations. It is a clinic population study and the study subjects might not be representative of the general population, so our findings cannot be generalized. To reduce bias, we assessed all patients with headache who had been referred to the clinic; this means that our study does not just look at those patients where headache on wakening or sleep interruption secondary to headache were the primary reason for referral.

#### 4.2. Conclusion

From the data, it can be concluded that primary headaches, and in particular migraine, are common causes of HoW/SIH. It could also be argued that brain imaging should not be routinely arranged for healthy and neurologically normal young patients with HoW/SIH. The importance of a thorough headache history and neurological examination to prevent unnecessary brain imaging is highlighted.

#### Authors' contributions

MASA carried out the design of the study. RB, KT and MASA participated in the results discussion, manuscript draughting and revision. All authors read and approved the final manuscript.

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#### Competing interests

The authors declare that they have no competing interests.

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## Appendix A

**Table 1 – Epidemiological data and clinical characteristics among our patients.**

	HoW n = 79	SIH n = 19	HW and SIH n = 4
Age range (mean)	4–16.9 (11.8)	5.7–15 (10.2)	12.5–17.2 (14.6)
Female	46 (58%)	9 (47%)	2 (50%)
Male	33 (42%)	10 (53%)	2 (50%)
Ethnic minority	27 (34%)	6 (32%)	0 (–)
FH of headaches	32 (40.5%)	8 (42%)	2 (50%)
Headache triggers	23 (29%)	4 (21%)	2 (50%)
Headache intensity			
Mild	5 (6%)	2 (10.5%)	0 (–)
Moderate	20 (25%)	3 (16%)	2 (50%)
Severe	34 (43%)	12 (63%)	2 (50%)
Mild – moderate	6 (8%)	0 (–)	0 (–)
Moderate to severe	14 (18%)	2 (10.5)	0 (–)
Headache diagnosis			
Migraine	50 (63%)	15 (79%)	2 (50%)
TTH	14 (18%)	2 (10.5%)	0
MOH	9 (11%)	0	2 (50%)
Sinusitis	1 (1%)	0	0
UH	5 (6%)	2 (10.5%)	0 (20%)

Abbreviations: FH: family history of headaches; HoW: headache on wakening; SIH: sleep interruption secondary to headache; TTH: tension-type headache; MOH: medication over use headaches; UH: not yet specified headaches.

## Appendix B

**Table 2 – Yield of brain imaging.**

Patients	Normal	Abnormal
HoW	74/78 (95%)*	4/78 (5%)
SIH	19/19 (100%)	0
HoW & SIH	4/4 (100%)	0

Abbreviations: HoW: headache on wakening; SIH: sleep interruption secondary to headache. \*: the remaining patient did not have brain imaging.

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