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Stratification of Risk for Emergent Intracranial Abnormalities in Children with Headaches: A Pediatric Emergency Care Applied Research Network (PECARN) Study Protocol

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ABSTRACT

Introduction

Headache is a common chief complaint of children presenting to emergency departments (EDs). Approximately 0.5-1% will have emergent intracranial abnormalities (EIAs) such as brain tumors or strokes. However, more than one-third undergo emergent neuroimaging in the ED, resulting in a large number of children unnecessarily exposed to radiation. The overuse of neuroimaging in children with headaches in the ED is driven by clinician concern for life-threatening EIAs and lack of clarity regarding which clinical characteristics accurately identify children with EIAs. The study objective is to derive and internally validate a stratification model that accurately identifies the risk of EIA in children with headaches.

Methods and analysis

Prospective cohort study of 28,000 children with headaches presenting to any of 18 EDs in the Pediatric Emergency Care Applied Research Network (PECARN). We include children aged 2 to 17 years with a chief complaint of headache. We exclude children with a clear non-intracranial alternative diagnosis, fever, neuroimaging within previous year, neurological or developmental condition such that patient history or physical examination may be unreliable, Glasgow Coma Scale score < 14, intoxication, known pregnancy, history of intracranial surgery, known structural abnormality of the brain, pre-existing condition predisposing to an intracranial abnormality or intracranial hypertension, head injury within 14 days, or not speaking English or Spanish. Clinicians complete a standardized history and physical examination of all eligible patients. Primary outcome is presence of an EIA as determined by neuroimaging or clinical follow-up. We will use binary recursive partitioning and multiple regression analyses to create and internally validate the risk stratification model.

Ethics and dissemination

Ethics approval was obtained for all participating sites. A waiver of informed consent was granted for collection of ED data. Verbal consent is obtained for follow-up contact. Results will be disseminated through international conferences, peer-reviewed publications, and open-access materials.

Strengths and limitations of this study

- In this large, multicenter, prospective cohort study, we will derive and internally validate a stratification model for children with headaches presenting to a PECARN ED that identifies the specific risk of EIA based on clinically sensible and reliable variables.
- This study will be the largest prospective study of children with headaches, providing rigorous evidence to facilitate clinical decision-making.
- The results of this study will allow clinicians to accurately identify children with headaches who require emergent neuroimaging and those who do not.
- Study results may not be generalizable to children with pre-existing medical or neurosurgical conditions or those with neurological or developmental conditions for whom history or physical examination may be unreliable.

INTRODUCTION

More than 400,000 children present annually to emergency departments (EDs) in the U.S. with a chief complaint of headache.[1–3] Most of these children have headaches that are primary (e.g., migraines) or secondary to conditions such as respiratory infections. Approximately 0.5-1%, however, are associated with intracranial abnormalities requiring emergent identification, such as brain tumors, hemorrhages, or strokes.[2,4–7]

Although emergent neuroimaging has a role for a small subset of children, as many as 36% of children presenting to EDs in the U.S. with headaches or migraines receive neuroimaging in the ED.[1,3,4,8,9] Overuse of computed tomography (CT), the most commonly used emergent neuroimaging for headaches, exposes children to unnecessary radiation, with an estimated lifetime risk of inducing lethal malignancies between 1 per 1000 to 1 per 5000 CT scans, depending on radiation dose and patient age.[1,5,8,10–13] The main alternative, magnetic resonance imaging (MRI), is not always available in the ED, is not time efficient in the ED setting, and may require procedural sedation with its associated risks and time intensiveness.[14–16] Finally, neuroimaging of any type may identify inconsequential findings that lead to unnecessary testing and interventions and unwarranted patient and parental concerns.[17,18]

The overuse of ED neuroimaging for complaints of headaches reflects the concern among clinicians for life-threatening, intracranial abnormalities requiring emergent interventions. Neuroimaging overuse also reflects the lack of clarity regarding which clinical characteristics, or "red flag findings," can be used to accurately identify children with headaches who may have emergent intracranial abnormalities (EIAs). Red flag findings in current use were derived from

research studies that were methodologically limited (e.g. retrospective studies, biased study populations) and/or of insufficient sample size.[6,19–30] The current frequency of emergent neuroimaging and the relative lack and limitations of prior research highlight the clear need for well-designed, large prospective studies to identify the risk of EIAs in children with headaches based on specific clinical factors.

Younger children with headaches require special consideration. Prior studies suggest that young age is a risk factor for EIAs; the relationship between age and risk of EIA, however, is unclear and needs to be systematically defined.[8,14,29,31–36] In addition, risk factors for EIAs may differ based on age, partly due to challenges in eliciting signs and symptoms in younger children. These issues may lead to diagnostic uncertainty and increased rates of neuroimaging in younger children, who are at greater risk of radiation-induced lethal malignancies from CT and adverse events during sedation.[11,12,37,38]

Objectives

Emergency department clinicians require specific recommendations based on precise estimates of the risk of EIAs to facilitate appropriate use of emergent neuroimaging for children presenting with headaches. Therefore, the objective of the study is to generate the definitive evidence that will allow clinicians to identify the risk of EIAs in otherwise healthy children presenting to EDs with chief complaints of headaches. The aims of the study are: 1) to derive and internally validate a stratification model for children presenting to the ED with headaches that identifies the specific risk of EIAs based on clinically sensible and reliable variables, and 2) to determine whether the prevalence of EIAs and association between risk factors and EIAs differs by age.

METHODS AND ANALYSIS

Study overview

We are conducting a prospective, multicenter cohort study titled, "Headache Assessment of Children for Emergent Intracranial Abnormalities" (HEADACHE). This study is enrolling children with headaches evaluated in any of the EDs in the Pediatric Emergency Care Applied Research Network (PECARN). PECARN is a federally funded multi-institutional network consisting of 18 pediatric EDs with geographic representation across the United States. Collectively, the EDs in PECARN have approximately 1.1 million pediatric visits annually.[39] Enrollment started in February 2021 and is anticipated to end in 2024.

Study population

Inclusion criteria

Children are eligible for inclusion from the age of 2 to 17 years old (i.e., before their 18th birthday) if they present to the ED with headache as a chief complaint (or per parent or the clinician). Headache may be present either by itself or in conjunction with other chief complaints and includes patients who do not have a headache at the time of ED evaluation.

Exclusion criteria

The eligibility criteria identify a spectrum of children with headaches for whom clinicians have greater uncertainty regarding the presence of EIAs. As such, we exclude patients for whom there are very low concerns for EIAs, predisposing conditions that would potentially render the study results less generalizable, or substantial concerns based on pre-existing conditions such that ED neuroimaging is more clearly necessary (Box 1).

Box 1: Eligibility criteria

Inclusion Criteria
Age 2 to 17 years old Headache is a chief complaint of the patient/parent or per clinician
Exclusion Criteria
Clear, non-intracranial alternative diagnosis or etiology at presentation Documented temperature of ≥38°C within prior 24 hours Neuroimaging performed within previous year Neurological or developmental condition such that patient history or examination may be unreliable Glasgow Coma Scale score < 14 Intoxication Known pregnancy History of intracranial surgery Known structural abnormality of the brain Known pre-existing condition predisposing to an intracranial abnormality or intracranial hypertension Head injury within previous 14 days Prior enrolment in study Foster child or ward of the state Patient and/or the parent/legal guardian do not speak English or Spanish

STUDY PROCEDURES

Participant screening and consent

Participants are screened for eligibility at all hours of the day at all participating sites. Screening criteria include any patient meeting age and chief complaint criteria. We have a waiver of informed consent from the University of Utah single Institutional Review Board (IRB) to collect information related to the patient history and physical examination. Verbal consent is obtained from the parent/legal guardian to conduct text messaging and/or telephone follow-up.

Data collection

Eligible participants undergo a standard evaluation that includes a medical history and physical examination. The attending physician, fellow, nurse practitioner, or physician assistant caring for the patient completes a standard case report form prior to knowledge of neuroimaging results (if

performed). Participants are considered enrolled if any part of the case report form is completed. For a subset of participants, a second attending physician, fellow, nurse practitioner, or physician assistant performs an independent medical history evaluation and physical examination and completes the same standard case report form within 60 minutes of the primary evaluation to determine the inter-rater reliability of predictors that will be considered for use in the risk stratification model.[40]

Data are collected to characterize the enrolled population, their clinical course and symptom severity. These data include patient demographics, vital signs, weight, Emergency Severity Index, neuroimaging performed, treatments administered, procedures performed, consultations obtained, ED disposition, return ED visits within 72 hours, and diagnoses. We are collecting data to evaluate reasons clinicians ordered neuroimaging (if applicable) and the clinician's assessment of risk of EIA for each child.

Participant follow-up

Follow-up procedures depend on whether participants undergo neuroimaging in the ED, the type of neuroimaging they receive, and the results of the neuroimaging (when applicable). Participants who receive a regular cranial MRI that is interpretable - irrespective of findings - do not undergo follow-up because outcome determination has been completed. Participants who receive a cranial CT or rapid MRI that identifies an EIA do not undergo follow-up. However, if CT or rapid MRI from the ED reveals normal findings, sinus findings, or any other non-EIA intracranial abnormality.

For participants who consent to follow-up and do not have neuroimaging performed in the ED or have neuroimaging with only limited or uninterpretable results, we perform follow-up using monthly text messaging for up to 6 months after the index ED visit and a telephone call, if needed, based on the results of the texting. The text messages sent during months 1 to 5 ask a single question assessing whether the participant underwent neuroimaging after the index ED visit. The text message sent at month 6 asks two questions: one assessing whether the participant underwent neuroimaging after the index ED visit, and the second assessing if the participant had a healthcare visit for headache-related reasons after the index ED visit. If the parent/legal guardian answers "no" to both 6-month text message questions, no further follow-up is conducted. If the parent/legal guardian answers "yes" to any of the monthly text messages, or if either of the 6-month text messages are unanswered, study personnel perform a medical record review. If any new neuroimaging, or treatment or intervention indicative of an intracranial abnormality, is identified in the medical record, no further follow-up will be conducted. If no such record is identified, a telephone follow-up is performed to ascertain if the patient received any neuroimaging, or underwent any treatments or interventions indicative of an intracranial abnormality. We consider patients lost to follow-up if a telephone call was indicated but unable to be completed. Patients who did not consent to follow-up procedures undergo 6-month medical record reviews and are considered lost to follow-up if no medical record is identified. The primary analysis considers patients with an unknown outcome (i.e., did not respond to both 6-month text message questions, could not complete telephone call and no medical record identified) as being negative for the primary outcome. A sensitivity analysis will be performed that considers patients with unknown outcomes as missing.

Missed eligible patients

An assessment of patients who were eligible but not enrolled (i.e., missed eligible) is being performed to evaluate for biased patient enrollment. We perform medical record reviews for patients presenting to participating EDs on two randomly selected days per week to assess for missed eligibility. Data collected for these patients include demographics, disposition, and any neuroimaging (and associated findings), neurosurgical procedures or interventions performed during index ED visit, hospitalization directly from index ED visit, and/or within 6 months after the index ED visit. These patients will be compared to enrolled patients to assess for biased enrollment.

Potential predictor variables

Potential predictors of EIA to be evaluated were selected through extensive literature review and expert consensus. Box 2 lists examples of potential predictors; a full list of the variables collected is found in the Supplemental Table.

Box 2: Examples of potential predictors of emergent intracranial abnormalities in children with headaches

History Finding	Physical Examination Finding
Headache awakens from sleep	Abnormal gait and/or tandem gait
Worst headache of their life	Abnormal cranial nerve function
Early morning vomiting	Abnormal deep tendon reflexes
Positional headache	Abnormal motor function
Increasing frequency and/or severity of headaches	Papilledema

Outcome measures

The primary outcome is the presence of an EIA, defined as an intracranial finding for which one of the following interventions is indicated at the index ED visit: 1) neurosurgical intervention; 2)

directed medical intervention (e.g. chemotherapy); 3) interventional radiological procedure (e.g. endovascular thrombectomy); or 4) hospital admission to monitor for potential clinical deterioration, obtain additional diagnostic evaluation, or perform another intervention specifically targeting the intracranial abnormality. Based on these criteria, the specific diagnoses included as EIAs are listed in Box 3. This definition and the diagnoses included were determined by an expert consensus group consisting of pediatric emergency medicine physicians, neurologists, neuro-oncologists, and neurosurgeons.

Box 3: Emergent intracranial abnormalities

Brain tumor	Hydrocephalus, obstructive	Venous or cavernous angioma, bleeding
Cerebral infarction	Hydrocephalus, non-obstructive	Aneurysm, bleeding
Cerebral venous sinus thrombosis	Shift of midline structures	Arteriovenous malformation, bleeding
Intracranial hemorrhage	Brain abscess	
Cerebral edema	Cysticercosis with edema	

Secondary outcomes include the presence of serious intracranial abnormalities (SIA) or incidental intracranial abnormalities (IIA). We defined SIAs as intracranial findings that the consensus panel did not consider emergent but have the potential to be the cause of the headache (depending on characteristics such as size or location of the finding) and potentially require an intervention as above. We defined an IIA as a finding that is neither an EIA nor SIA, may or may not require outpatient follow-up, and is unlikely to be the cause of the headache. Although termed incidental in accordance with prior literature, these findings may still be concerning to patients and families and elicit further evaluation. Diagnoses assigned to the categories of SIA and IIA are listed in Box 4.

Box 4: Serious and incidental intracranial abnormalities

Serious intracranial abnormalities	
Aneurysm, non-bleeding	Finding suggestive of increased intracranial pressure without anatomical explanation
Arachnoid cyst (concerning due to size or location)	Perfusion abnormality without acute infarction
Arteriovenous malformation, non-bleeding	Pituitary adenoma
Chiari I malformation	Venous or cavernous angioma, non-bleeding
Cysticercosis without edema	
Incidental intracranial abnormalities	
Abnormal myelination	Hippocampal shape abnormality
Anatomical variant	Increased pineal gland signal
Arachnoid cyst (not concerning due to size or location)	Mesial temporal sclerosis
Cerebral atrophy	Migration abnormality
Cortical or subcortical hyperintensity	Peri-ventricular leukomalacia
Developmental abnormality	Pineal cyst
Empty sella syndrome	Prominent subarachnoid space
Focal calcification	Ventricular abnormality, without hydrocephalus
Focal encephalomalacia	White matter increased signal
Gliosis	

A centralized review by the lead study investigators (DST, PSD, NK) and neurologist co-investigator (LR) makes the initial determination by consensus of whether an abnormality is an EIA, SIA, or IIA. This review is based on available radiology reports, medical records, follow-up text message responses, and information gathered from telephone calls. It is conducted without any knowledge of associated clinical variables. If the classification of the abnormality cannot be

determined by this centralized review process, the case is referred to an independent adjudication panel, who determines the classification of the abnormality by consensus.

Data analysis

Sample size and power

The derivation of the risk stratification rule will be conducted in two parts with two goals: a near-zero risk classification and a risk stratification model for patients not at near-zero risk. The sample size was determined based on the desired sensitivity of the near-zero risk classification model. We used the presence of an EIA as the main outcome to determine the sample size, because a risk stratification model for EIA must have a nearly perfect sensitivity to identify those at near-zero risk of EIAs. Specifically, we aim to enroll at least 140 patients with EIAs, such that a model with a minimum 99.3% sensitivity (i.e., at most one missed EIA of the 140) will have a lower boundary of the 95% CI for sensitivity greater than 95%. After univariable screening ($p<0.1$), the number of variables we will consider for inclusion in a multivariable logistic regression analysis to derive a risk score without needing to employ lasso penalization is 15 (approximately one-tenth of the expected 139 patients with observed EIAs who do not meet near-zero risk criteria).

To enroll 140 patients with EIAs, we aim to enroll 28,000 eligible patients with headaches over a period of at least 3.5 years. Using the PECARN clinical registry, we estimated that 1-1.5% of ED visits met eligibility criteria across all sites between 2012 and 2014.[41] With 1.1 million annual visits to PECARN EDs and expected enrolment of 80% of eligible patients, we estimated enrolling 8000 eligible patients with headaches annually. We expected to have outcome data

(i.e., neuroimaging or follow-up results) for at least 80% of the 28,000 patients enrolled (i.e., 22,400 patients). Based on prior literature describing children presenting to EDs with headaches, we conservatively assumed that 0.7% of enrolled patients in whom follow-up is completed will have EIAs.[2,4–7] This would result in having 156 patients with EIAs in 3.5 years, which is greater than our desired 140 patients.

Statistical analysis plan

To derive the near-zero risk component of the risk stratification model, we will use binary recursive partitioning.[42] Patients with missing predictors will be included by substituting surrogate variables that partition patients in a way similar to the missing variables. However, if more than 20% of the data for any variable are missing across all sites, that variable will be excluded. We will also exclude variables with kappa statistics less than 0.5, calculated on those patients with two assessments.

In the construction of the decision tree, we will assign misclassification costs to specific misclassification errors. We will vary the assigned value of the relative misclassification cost of not identifying a patient with an EIA from 100 to 1000 relative to misclassifying a patient who is at low risk for having an EIA and assess how this impacts tree creation. We will use classification and regression tree software (CART; SPM Salford Predictive Modeler®; Minitab®) to perform the recursive partitioning analysis and will internally validate the risk stratification model using 10-fold cross validation. We will also enter each PECARN site as a dummy variable into the analysis to explore whether any site exerts disproportionate influence in model generation. For the primary analysis, patients lost to follow-up will be considered not to

have an EIA. Sensitivity analyses will be performed by excluding patients for whom the primary outcome could not be determined.

To complement the near-zero risk component of the risk stratification model created by recursive partitioning, we will use the same candidate variables to perform multiple logistic regression analyses to derive a risk score model for those patients who do not meet near-zero risk criteria. We will first conduct single variable logistic regression to identify all variables with associations ($p<0.1$) with EIAs and include these for consideration in the multivariable model. The multivariable model will be based on a combination of best subsets and bidirectional stepwise selection at $p<0.1$ if there are at most 15 candidate variables; otherwise, we intend to use lasso estimation but may use forward selection ($p<0.1$) if lasso estimation is unwieldy given the multiple imputation of missing data.

We will also perform the multivariable logistic regression approach on the entire cohort (including near-zero risk patients) and compare the performance (i.e., concordance-statistic) and prediction calibration with the model that best assesses near-zero risk. We will conduct these analyses for our primary outcome (i.e., presence of EIA) and our secondary outcomes of presence of an EIA or SIA. We will use SAS software version 9.4 or higher (SAS Institute, Cary, NC) or other statistical software to perform all regression analyses. As an exploratory analysis, we will also use random forests (and possibly other machine learning algorithms) to derive a prediction algorithm for EIA. We will use SPM Salford Predictive Modeler and R software (www.R-project.org) to perform the random forests analyses.

To assess how age relates to prevalence of EIA among children presenting to the ED with headaches as chief complaints, a logistic regression model will be fit to the primary outcome with only age as a predictor. In one model, age will be categorized using thresholds determined by Schwarz's Bayesian Information Criterion from among candidates deemed clinically relevant by study PIs. In another model, age will be entered with linear trends (and if warranted, higher order polynomial trends or even cubic splines with up to two interior knots). In the event anything more than a quadratic trend is included, graphical depiction with 95% pointwise confidence bands will be used to summarize the relationship between age and log-odds of presence of EIA.

To explore the effect of age on risk stratification, we will include age as a potential predictor in all stages of model derivation. We will also examine the performance characteristics (e.g., sensitivity, specificity) of our final risk stratification model as a function of age and will perform multivariable logistic regression analyses using our derived risk score and age as predictors. We will consider age as both a continuous variable (possibly including a quadratic term) and a categorical variable. If we suspect an age-specific relationship, we will explore the derivation of separate risk stratification models in different age groups. Furthermore, recognizing that it may be more difficult for clinicians to ascertain some assessments in younger patients, we will examine missingness of potential predictors by age category (with the age categories not necessarily prespecified). If key predictors from the primary analysis have widely variable missingness rates across age groups, we will consider deriving age-specific rules.

Patient and public involvement

This research was planned without patient involvement. Patients did not comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Ethics and dissemination

This study poses minimal risk to participating children and their families. Ethics approval was obtained at all participating sites. The University of Utah Institutional Review Board (IRB) is serving as the single IRB for all participating sites. Patients receive standard care in the ED. There is no change in the ED care provided for study purposes, and patients are not subjected to any interventions. In particular, neuroimaging performed in the ED is at the discretion of the clinician caring for the patient. Children are enrolled irrespective of whether ED neuroimaging is obtained. The only possible risk is a minor risk of loss of confidentiality. Local sites store identified data necessary for participant tracking and follow-up procedures in locked filing cabinets and/or in secured electronic data systems in locked offices. A waiver of informed consent was granted for collection of ED data. Verbal consent is required for follow-up text and/or telephone contact. Families can withdraw at any time without explanation.

Results will be disseminated at regional, national and international conferences and through peer-reviewed research publications. PECARN social media and creation of free open-access materials will also be used for dissemination of results.

Limitations

We anticipate several limitations of this study. First, study results may not be generalizable to children with pre-existing medical or neurosurgical conditions who have increased risk of EIA or those with neurological or developmental conditions for whom history or physical examination may be unreliable. Similarly, study results may not be applicable to children with headaches for whom clinicians may have a lower suspicion for an EIA (e.g., children with documented fever or a clear non-intracranial alternative diagnosis or etiology). However, our rule will provide important information for the cohort of children with headaches who pose the greatest degree of diagnostic uncertainty for clinicians. Second, we will not be obtaining definitive neuroimaging on all participants because we could not ethically justify exposing children to the risks associated with neuroimaging if the clinician did not think it was indicated. However, we have an extensive follow-up plan that accounts for symptom intervals (i.e., duration of symptoms before diagnosis) for EIAs such as brain tumors. This type of follow-up is an acceptable alternative for outcome determination when definitive testing is not feasible or ethical.

CONCLUSIONS

This study will create a robust and precise stratification model that will enable clinicians to accurately determine the risk of EIAs in children with headaches based on clinical findings. The data will fundamentally improve how children with headaches presenting to the ED are managed by providing definitive evidence to facilitate the clinician's decision to obtain or forgo emergent neuroimaging. Future implementation of this risk stratification tool will facilitate the safe reduction of unnecessary emergent CT and MRI scans and decrease exposure to risks associated with neuroimaging in children with headaches.

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Authors' Contributions

DST, NK and PSD conceived the study and wrote the initial draft of the manuscript. TCC and BJB are the methodologists that contributed to study design and plan and will execute the statistical analysis plan. LPR contributed substantive intellectual input into the design of the study. DST, DBL, PJO, CRM, SRM, JKS, RDM, LB, SPS, MDJ, EJK, KSQ, DWS, ATC, AJR, DGT, JMG, and TJJ are the initial site investigators for this study. All authors contributed to study design and execution, critically reviewed and edited the initial protocol draft and approve of the final manuscript. DST takes responsibility for this manuscript as a whole.

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Competing interests

None.

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Supplemental Table: Complete list of variables assessed in children with headaches.

Characteristics of presenting headache	
Duration Daily headache (i.e. consecutive days) Constant or intermittent ("comes and goes") Location Laterality/distribution Quality Headache pain intensity at time of assessment Maximum headache pain intensity this episode Instantly peaking severe pain	Time it took for headache to become most painful Worse with routine or light physical activity Worse with or caused by physical exertion Positional headache Improves or resolves with rest or sleep Improves with medication taken at home Awakens from sleep Early morning headache
Associated symptoms with presenting headache	
Upper respiratory infection symptoms Neck pain or stiffness Nausea Vomiting Phonophobia Photophobia Seeing abnormal patterns Problems or changes with vision	Dizziness Unsteadiness Focal motor weakness Sensory changes Abnormal speech Loss of consciousness Seizure Other neurological symptoms
Questions related to headaches prior to presenting headache	
First headache episode of their life Time since onset of (lifetime) headaches Number of days per month with headaches Increase in frequency or severity of headaches Change in location or quality of headaches Worst headache of patient's life	Prior headaches wake from sleep Prior early morning headaches Early morning vomiting or vomiting waking from sleep with prior headaches Unsteadiness with prior headaches
Family history	
First- or second-degree relatives with migraines	
General physical examination	
General appearance Glasgow Coma Scale score Neck stiffness Head tilt	Abnormal speech Skin findings associated with neurological conditions
Neurological exam	
Pupil reactivity to light Extra-ocular movements Nystagmus Cranial nerves (not incl. extraocular movements) Motor function Sensory function Deep tendon reflexes Babinski/extensor plantar response	Dysmetria or dysdiadochokinesia Stance Romberg Pronator drift Gait Tandem gait Visual fields Papilledema

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Stratification of Risk for Emergent Intracranial Abnormalities in Children with Headaches: A Pediatric Emergency Care Applied Research Network (PECARN) Study Protocol

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ABSTRACT

Introduction

Headache is a common chief complaint of children presenting to emergency departments (EDs). Approximately 0.5-1% will have emergent intracranial abnormalities (EIAs) such as brain tumors or strokes. However, more than one-third undergo emergent neuroimaging in the ED, resulting in a large number of children unnecessarily exposed to radiation. The overuse of neuroimaging in children with headaches in the ED is driven by clinician concern for life-threatening EIAs and lack of clarity regarding which clinical characteristics accurately identify children with EIAs. The study objective is to derive and internally validate a stratification model that accurately identifies the risk of EIA in children with headaches.

Methods and analysis

Prospective cohort study of 28,000 children with headaches presenting to any of 18 EDs in the Pediatric Emergency Care Applied Research Network (PECARN). We include children aged 2 to 17 years with a chief complaint of headache. We exclude children with a clear non-intracranial alternative diagnosis, fever, neuroimaging within previous year, neurological or developmental condition such that patient history or physical examination may be unreliable, Glasgow Coma Scale score < 14, intoxication, known pregnancy, history of intracranial surgery, known structural abnormality of the brain, pre-existing condition predisposing to an intracranial abnormality or intracranial hypertension, head injury within 14 days, or not speaking English or Spanish. Clinicians complete a standardized history and physical examination of all eligible patients. Primary outcome is presence of an EIA as determined by neuroimaging or clinical follow-up. We will use binary recursive partitioning and multiple regression analyses to create and internally validate the risk stratification model.

Ethics and dissemination

Ethics approval was obtained for all participating sites from the University of Utah single Institutional Review Board. A waiver of informed consent was granted for collection of ED data. Verbal consent is obtained for follow-up contact. Results will be disseminated through international conferences, peer-reviewed publications, and open-access materials.

Strengths and limitations of this study

- We are prospectively enrolling a diverse group of children with headaches from one of 18 pediatric emergency departments participating in the Pediatric Emergency Care Applied Research Network (PECARN), which collectively sees more than 1.1 million patients annually and has geographic representation across the United States.
- The eligibility criteria identify a spectrum of children with chief complaints of headaches for whom clinicians have greater uncertainty regarding the presence of emergent intracranial abnormalities.
- Clinicians perform standard evaluations to prospectively collect patient history and physical examination findings that are potential predictors of emergent intracranial abnormalities.
- We will analyze the data using binary recursive partitioning and multiple logistic regression analyses to derive the risk stratification model.
- Study results may not be generalizable to children with pre-existing medical or neurosurgical conditions or those with neurological or developmental conditions for whom history or physical examination may be unreliable.

INTRODUCTION

More than 400,000 children present annually to emergency departments (EDs) in the U.S. with a chief complaint of headache.[1–3] Most of these children have headaches that are primary (e.g., migraines) or secondary to conditions such as respiratory infections. Approximately 0.5-1%, however, are associated with intracranial abnormalities requiring emergent identification, such as brain tumors, hemorrhages, or strokes.[2,4–7]

Although emergent neuroimaging has a role for a small subset of children, as many as 36% of children presenting to EDs in the U.S. with headaches or migraines receive neuroimaging in the ED.[1,3,4,8,9] Overuse of computed tomography (CT), the most commonly used emergent neuroimaging for headaches, exposes children to unnecessary radiation, with an estimated lifetime risk of inducing lethal malignancies between 1 per 1000 to 1 per 5000 CT scans, depending on radiation dose and patient age.[1,5,8,10–13] The main alternative, magnetic resonance imaging (MRI), is not always available in the ED, is not time efficient in the ED setting, and may require procedural sedation with its associated risks and time intensiveness.[14–16] Finally, neuroimaging of any type may identify inconsequential findings that lead to unnecessary testing and interventions and unwarranted patient and parental concerns.[17,18]

The overuse of ED neuroimaging for complaints of headaches reflects the concern among clinicians for life-threatening, intracranial abnormalities requiring emergent interventions. Neuroimaging overuse also reflects the lack of clarity regarding which clinical characteristics, or "red flag findings," can be used to accurately identify children with headaches who may have emergent intracranial abnormalities (EIAs). Red flag findings in current use were derived from research studies that were methodologically limited (e.g. retrospective studies, biased study

populations) and/or of insufficient sample size.[6,19–30] The current frequency of emergent neuroimaging and the relative lack and limitations of prior research highlight the clear need for well-designed, large prospective studies to identify the risk of EIAs in children with headaches based on specific clinical factors.

Younger children with headaches require special consideration. Prior studies suggest that young age is a risk factor for EIAs; the relationship between age and risk of EIA, however, is unclear and needs to be systematically defined.[8,14,29,31–36] In addition, risk factors for EIAs may differ based on age, partly due to challenges in eliciting signs and symptoms in younger children. These issues may lead to diagnostic uncertainty and increased rates of neuroimaging in younger children, who are at greater risk of radiation-induced lethal malignancies from CT and adverse events during sedation.[11,12,37,38]

Objectives

Emergency department clinicians require specific recommendations based on precise estimates of the risk of EIAs to facilitate appropriate use of emergent neuroimaging for children presenting with headaches. Therefore, the objective of the study is to generate the definitive evidence that will allow clinicians to identify the risk of EIAs in otherwise healthy children presenting to EDs with chief complaints of headaches. The aims of the study are: 1) to derive and internally validate a stratification model for children presenting to the ED with headaches that identifies the specific risk of EIAs based on clinically sensible and reliable variables, and 2) to determine whether the prevalence of EIAs and association between risk factors and EIAs differs by age.

METHODS AND ANALYSIS

Study overview

We are conducting a prospective, multicenter cohort study titled, "Headache Assessment of Children for Emergent Intracranial Abnormalities" (HEADACHE). This study is enrolling children with headaches evaluated in any of the EDs in the Pediatric Emergency Care Applied Research Network (PECARN). PECARN is a federally funded multi-institutional network consisting of 18 pediatric EDs with geographic representation across the United States. Collectively, the EDs in PECARN have approximately 1.1 million pediatric visits annually.[39] Enrollment started in February 2021 and is anticipated to end in 2024.

Study population

Inclusion criteria

Children are eligible for inclusion from the age of 2 to 17 years old (i.e., before their 18th birthday) if they present to the ED with headache as a chief complaint (or per parent or the clinician). Headache may be present either by itself or in conjunction with other chief complaints and includes patients who do not have a headache at the time of ED evaluation.

Exclusion criteria

The eligibility criteria identify a spectrum of children with headaches for whom clinicians have greater uncertainty regarding the presence of EIAs. As such, we exclude patients for whom there are very low concerns for EIAs, predisposing conditions that would potentially render the study results less generalizable, or substantial concerns based on pre-existing conditions such that ED neuroimaging is more clearly necessary (Box 1).

Box 1: Eligibility criteria

Inclusion Criteria
Age 2 to 17 years old Headache is a chief complaint of the patient/parent or per clinician
Exclusion Criteria
Clear, non-intracranial alternative diagnosis or etiology at presentation Documented temperature of ≥38°C within prior 24 hours Neuroimaging performed within previous year Neurological or developmental condition such that patient history or examination may be unreliable Glasgow Coma Scale score < 14 Intoxication Known pregnancy History of intracranial surgery Known structural abnormality of the brain Known pre-existing condition predisposing to an intracranial abnormality or intracranial hypertension Head injury within previous 14 days Prior enrolment in study Foster child or ward of the state Patient and/or the parent/legal guardian do not speak English or Spanish

STUDY PROCEDURES

Participant screening and consent

Participants are screened for eligibility at all hours of the day at all participating sites. Screening criteria include any patient meeting age and chief complaint criteria. We have a waiver of informed consent from the University of Utah single Institutional Review Board (IRB) to collect information related to the patient history and physical examination. Verbal consent is obtained from the parent/legal guardian to conduct text messaging and/or telephone follow-up.

Data collection

Eligible participants undergo a standard evaluation that includes a medical history and physical examination. The attending physician, fellow, nurse practitioner, or physician assistant caring for the patient completes a standardized case report form prior to knowledge of neuroimaging results

(if performed). Participants are considered enrolled if any part of the case report form is completed. For a subset of participants, a second attending physician, fellow, nurse practitioner, or physician assistant performs an independent medical history evaluation and physical examination and completes the same standard case report form within 60 minutes of the primary evaluation to determine the inter-rater reliability of predictors that will be considered for use in the risk stratification model.[40]

Data are collected to characterize the enrolled population, their clinical course and symptom severity. These data include patient demographics, vital signs, weight, Emergency Severity Index, neuroimaging performed, treatments administered, procedures performed, consultations obtained, ED disposition, return ED visits within 72 hours, and diagnoses. We are collecting data to evaluate reasons clinicians ordered neuroimaging (if applicable) and the clinician's assessment of risk of EIA for each child.

Participant follow-up

Follow-up procedures depend on whether participants undergo neuroimaging in the ED, the type of neuroimaging they receive, and the results of the neuroimaging (when applicable). Participants who receive a regular cranial MRI that is interpretable - irrespective of findings - do not undergo follow-up because outcome determination has been completed. Participants who receive a cranial CT or rapid MRI that identifies an EIA do not undergo follow-up. However, if CT or rapid MRI from the ED reveals normal findings, sinus findings, or any other non-EIA intracranial abnormality.

For participants who consent to follow-up and do not have neuroimaging performed in the ED or have neuroimaging with only limited or uninterpretable results, we perform follow-up using monthly text messaging for up to 6 months after the index ED visit and a telephone call, if needed, based on the results of the texting. The text messages sent during months 1 to 5 ask a single question assessing whether the participant underwent neuroimaging after the index ED visit. The text message sent at month 6 asks two questions: one assessing whether the participant underwent neuroimaging after the index ED visit, and the second assessing if the participant had a healthcare visit for headache-related reasons after the index ED visit. If the parent/legal guardian answers "no" to both 6-month text message questions, no further follow-up is conducted. If the parent/legal guardian answers "yes" to any of the monthly text messages, or if either of the 6-month text messages are unanswered, study personnel perform a medical record review. If any new neuroimaging, or treatment or intervention indicative of an intracranial abnormality, is identified in the medical record, no further follow-up will be conducted. If no such record is identified, a telephone follow-up is performed to ascertain if the patient received any neuroimaging, or underwent any treatments or interventions indicative of an intracranial abnormality. We consider patients lost to follow-up if a telephone call was indicated but unable to be completed. Patients who did not consent to follow-up procedures undergo 6-month medical record reviews and are considered lost to follow-up if no medical record is identified. The primary analysis considers patients with an unknown outcome (i.e., did not respond to both 6-month text message questions, could not complete telephone call and no medical record identified) as being negative for the primary outcome. A sensitivity analysis will be performed that considers patients with unknown outcomes as missing.

Missed eligible patients

An assessment of patients who were eligible but not enrolled (i.e., missed eligible) is being performed to evaluate for biased patient enrollment. We perform medical record reviews for patients presenting to participating EDs on two randomly selected days per week to assess for missed eligibility. Data collected for these patients include demographics, disposition, and any neuroimaging (and associated findings), neurosurgical procedures or interventions performed during index ED visit, hospitalization directly from index ED visit, and/or within 6 months after the index ED visit. These patients will be compared to enrolled patients to assess for biased enrollment.

Potential predictor variables

Potential predictors of EIA to be evaluated were selected through extensive literature review and expert consensus. Box 2 lists examples of potential predictors; a full list of the variables collected is found in the Supplemental Table.

Box 2: Examples of potential predictors of emergent intracranial abnormalities in children with headaches

History Finding	Physical Examination Finding
Headache awakens from sleep	Abnormal gait and/or tandem gait
Worst headache of their life	Abnormal cranial nerve function
Early morning vomiting	Abnormal deep tendon reflexes
Positional headache	Abnormal motor function
Increasing frequency and/or severity of headaches	Papilledema

Outcome measures

The primary outcome is the presence of an EIA, defined as an intracranial finding for which one of the following interventions is indicated at the index ED visit: 1) neurosurgical intervention; 2)

directed medical intervention (e.g. chemotherapy); 3) interventional radiological procedure (e.g. endovascular thrombectomy); or 4) hospital admission to monitor for potential clinical deterioration, obtain additional diagnostic evaluation, or perform another intervention specifically targeting the intracranial abnormality. Based on these criteria, the specific diagnoses included as EIAs are listed in Box 3. This definition and the diagnoses included were determined by an expert consensus group consisting of pediatric emergency medicine physicians, neurologists, neuro-oncologists, and neurosurgeons.

Box 3: Emergent intracranial abnormalities

Brain tumor	Hydrocephalus, obstructive	Venous or cavernous angioma, bleeding
Cerebral infarction	Hydrocephalus, non-obstructive	Aneurysm, bleeding
Cerebral venous sinus thrombosis	Shift of midline structures	Arteriovenous malformation, bleeding
Intracranial hemorrhage	Brain abscess	
Cerebral edema	Cysticercosis with edema	

Secondary outcomes include the presence of serious intracranial abnormalities (SIA) or incidental intracranial abnormalities (IIA). We defined SIAs as intracranial findings that the consensus panel did not consider emergent but have the potential to be the cause of the headache (depending on characteristics such as size or location of the finding) and potentially require an intervention as above. We defined an IIA as a finding that is neither an EIA nor SIA, may or may not require outpatient follow-up, and is unlikely to be the cause of the headache. Although termed incidental in accordance with prior literature, these findings may still be concerning to patients and families and elicit further evaluation. Diagnoses assigned to the categories of SIA and IIA are listed in Box 4.

Box 4: Serious and incidental intracranial abnormalities

Serious intracranial abnormalities	
Aneurysm, non-bleeding	Finding suggestive of increased intracranial pressure without anatomical explanation
Arachnoid cyst (concerning due to size or location)	Perfusion abnormality without acute infarction
Arteriovenous malformation, non-bleeding	Pituitary adenoma
Chiari I malformation	Venous or cavernous angioma, non-bleeding
Cysticercosis without edema	
Incidental intracranial abnormalities	
Abnormal myelination	Hippocampal shape abnormality
Anatomical variant	Increased pineal gland signal
Arachnoid cyst (not concerning due to size or location)	Mesial temporal sclerosis
Cerebral atrophy	Migration abnormality
Cortical or subcortical hyperintensity	Peri-ventricular leukomalacia
Developmental abnormality	Pineal cyst
Empty sella syndrome	Prominent subarachnoid space
Focal calcification	Ventricular abnormality, without hydrocephalus
Focal encephalomalacia	White matter increased signal
Gliosis	

A centralized review by the lead study investigators (DST, PSD, NK) and neurologist co-investigator (LR) makes the initial determination by consensus of whether an abnormality is an EIA, SIA, or IIA. This review is based on available radiology reports, medical records, follow-up text message responses, and information gathered from telephone calls. It is conducted without any knowledge of associated clinical variables. If the classification of the abnormality cannot be

determined by this centralized review process, the case is referred to an independent adjudication panel, who determines the classification of the abnormality by consensus.

Data analysis

Sample size and power

The derivation of the risk stratification rule will be conducted in two parts with two goals: a near-zero risk classification and a risk stratification model for patients not at near-zero risk. The sample size was determined based on the desired sensitivity of the near-zero risk classification model. We used the presence of an EIA as the main outcome to determine the sample size, because a risk stratification model for EIA must have a nearly perfect sensitivity to identify those at near-zero risk of EIAs. Specifically, we aim to enroll at least 140 patients with EIAs, such that a model with a minimum 99.3% sensitivity (i.e., at most one missed EIA of the 140) will have a lower boundary of the 95% CI for sensitivity greater than 95%. After univariable screening ($p<0.1$), the number of variables we will consider for inclusion in a multivariable logistic regression analysis to derive a risk score without needing to employ lasso penalization is 15 (approximately one-tenth of the expected 139 patients with observed EIAs who do not meet near-zero risk criteria).

To enroll 140 patients with EIAs, we aim to enroll 28,000 eligible patients with headaches over a period of at least 3.5 years. Using the PECARN clinical registry, we estimated that 1-1.5% of ED visits met eligibility criteria across all sites between 2012 and 2014.[41] With 1.1 million annual visits to PECARN EDs and expected enrolment of 80% of eligible patients, we estimated enrolling 8000 eligible patients with headaches annually. We expected to have outcome data

(i.e., neuroimaging or follow-up results) for at least 80% of the 28,000 patients enrolled (i.e., 22,400 patients). Based on prior literature describing children presenting to EDs with headaches, we conservatively assumed that 0.7% of enrolled patients in whom follow-up is completed will have EIAs.[2,4–7] This would result in having 156 patients with EIAs in 3.5 years, which is greater than our desired 140 patients.

Statistical analysis plan

To derive the near-zero risk component of the risk stratification model, we will use binary recursive partitioning.[42] Patients with missing predictors will be included by substituting surrogate variables that partition patients in a way similar to the missing variables. However, if more than 20% of the data for any variable are missing across all sites, that variable will be excluded. We will also exclude variables with kappa statistics less than 0.5, calculated on those patients with two assessments.

In the construction of the decision tree, we will assign misclassification costs to specific misclassification errors. We will vary the assigned value of the relative misclassification cost of not identifying a patient with an EIA from 100 to 1000 relative to misclassifying a patient who is at low risk for having an EIA and assess how this impacts tree creation. We will use classification and regression tree software (CART; SPM Salford Predictive Modeler®; Minitab®) to perform the recursive partitioning analysis and will internally validate the risk stratification model using 10-fold cross validation. We will also enter each PECARN site as a dummy variable into the analysis to explore whether any site exerts disproportionate influence in model generation. For the primary analysis, patients lost to follow-up will be considered not to

have an EIA. Sensitivity analyses will be performed by excluding patients for whom the primary outcome could not be determined.

To complement the near-zero risk component of the risk stratification model created by recursive partitioning, we will use the same candidate variables to perform multiple logistic regression analyses to derive a risk score model for those patients who do not meet near-zero risk criteria. We will first conduct single variable logistic regression to identify all variables with associations ($p<0.1$) with EIAs and include these for consideration in the multivariable model. The multivariable model will be based on a combination of best subsets and bidirectional stepwise selection at $p<0.1$ if there are at most 15 candidate variables; otherwise, we intend to use lasso estimation but may use forward selection ($p<0.1$) if lasso estimation is unwieldy given the multiple imputation of missing data.

We will also perform the multivariable logistic regression approach on the entire cohort (including near-zero risk patients) and compare the performance (i.e., concordance-statistic) and prediction calibration with the model that best assesses near-zero risk. We will conduct these analyses for our primary outcome (i.e., presence of EIA) and our secondary outcomes of presence of an EIA or SIA. We will use SAS software version 9.4 or higher (SAS Institute, Cary, NC) or other statistical software to perform all regression analyses. As an exploratory analysis, we will also use random forests (and possibly other machine learning algorithms) to derive a prediction algorithm for EIA. We will use SPM Salford Predictive Modeler and R software (www.R-project.org) to perform the random forests analyses.

To assess how age relates to prevalence of EIA among children presenting to the ED with headaches as chief complaints, a logistic regression model will be fit to the primary outcome with only age as a predictor. In one model, age will be categorized using thresholds determined by Schwarz's Bayesian Information Criterion from among candidates deemed clinically relevant by study PIs. In another model, age will be entered with linear trends (and if warranted, higher order polynomial trends or even cubic splines with up to two interior knots). In the event anything more than a quadratic trend is included, graphical depiction with 95% pointwise confidence bands will be used to summarize the relationship between age and log-odds of presence of EIA.

To explore the effect of age on risk stratification, we will include age as a potential predictor in all stages of model derivation. We will also examine the performance characteristics (e.g., sensitivity, specificity) of our final risk stratification model as a function of age and will perform multivariable logistic regression analyses using our derived risk score and age as predictors. We will consider age as both a continuous variable (possibly including a quadratic term) and a categorical variable. If we suspect an age-specific relationship, we will explore the derivation of separate risk stratification models in different age groups. Furthermore, recognizing that it may be more difficult for clinicians to ascertain some assessments in younger patients, we will examine missingness of potential predictors by age category (with the age categories not necessarily prespecified). If key predictors from the primary analysis have widely variable missingness rates across age groups, we will consider deriving age-specific rules.

Patient and public involvement

This research was planned without patient involvement. Patients did not comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Ethics and dissemination

This study poses minimal risk to participating children and their families. Ethics approval was obtained from the University of Utah single IRB, whose determination was reviewed and accepted by the local IRBs of participating sites. Patients receive standard care in the ED. There is no change in the ED care provided for study purposes, and patients are not subjected to any interventions. In particular, neuroimaging performed in the ED is at the discretion of the clinician caring for the patient. Children are enrolled irrespective of whether ED neuroimaging is obtained. The only possible risk is a minor risk of loss of confidentiality. Local sites store identified data necessary for participant tracking and follow-up procedures in locked filing cabinets and/or in secured electronic data systems in locked offices. A waiver of informed consent was granted for collection of ED data because the study is minimal risk, and to avoid patient enrollment bias from incomplete enrollment that would lead to invalid and non-generalizable results. Verbal consent is required for follow-up text and/or telephone contact. Written consent was not required because the study is minimal risk and does not involve any procedures for which written consent is normally required outside of the research context. Families can withdraw at any time without explanation.

Results will be disseminated at regional, national and international conferences and through peer-reviewed research publications. PECARN social media and creation of free open-access materials will also be used for dissemination of results.

Limitations

We anticipate several limitations of this study. First, study results may not be generalizable to children with pre-existing medical or neurosurgical conditions who have increased risk of EIA or those with neurological or developmental conditions for whom history or physical examination may be unreliable. Similarly, study results may not be applicable to children with headaches for whom clinicians may have a lower suspicion for an EIA (e.g., children with documented fever or a clear non-intracranial alternative diagnosis or etiology). However, our rule will provide important information for the cohort of children with headaches who pose the greatest degree of diagnostic uncertainty for clinicians. Second, we will not be obtaining definitive neuroimaging on all participants because we could not ethically justify exposing children to the risks associated with neuroimaging if the clinician did not think it was indicated. However, we have an extensive follow-up plan that accounts for symptom intervals (i.e., duration of symptoms before diagnosis) for EIAs such as brain tumors. This type of follow-up is an acceptable alternative for outcome determination when definitive testing is not feasible or ethical.

DISCUSSION

This study will create a robust and precise stratification model that will enable clinicians to accurately determine the risk of EIAs in children with headaches based on clinical findings. The data will fundamentally improve how children with headaches presenting to the ED are managed

by providing definitive evidence to facilitate the clinician's decision to obtain or forgo emergent neuroimaging. Future implementation of this risk stratification tool will facilitate the safe reduction of unnecessary emergent CT and MRI scans and decrease exposure to risks associated with neuroimaging in children with headaches.

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Authors' Contributions

DST, NK and PSD conceived the study and wrote the initial draft of the manuscript. TCC and BJB are the methodologists that contributed to study design and plan and will execute the statistical analysis plan. LPR contributed substantive intellectual input into the design of the study. DST, DBL, PJO, CRM, SRM, JKS, RDM, LB, SPS, MDJ, EJK, KSQ, DWS, ATC, AJR, DGT, JMG, and TJJ are the initial site investigators for this study. All authors contributed to study design and execution, critically reviewed and edited the initial protocol draft and approve of the final manuscript. DST takes responsibility for this manuscript as a whole.

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Competing interests

None.

Word count

3500

Supplemental Table: Complete list of variables assessed in children with headaches.

Characteristics of presenting headache	
Duration	Time it took for headache to become most painful
Daily headache (i.e. consecutive days)	Worse with routine or light physical activity
Constant or intermittent ("comes and goes")	Worse with or caused by physical exertion
Location	Positional headache
Laterality/distribution	Improves or resolves with rest or sleep
Quality	Improves with medication taken at home
Headache pain intensity at time of assessment	Awakens from sleep
Maximum headache pain intensity this episode	Early morning headache
Instantly peaking severe pain	
Associated symptoms with presenting headache	
Upper respiratory infection symptoms	Dizziness
Neck pain or stiffness	Unsteadiness
Nausea	Focal motor weakness
Vomiting	Sensory changes
Phonophobia	Abnormal speech
Photophobia	Loss of consciousness
Seeing abnormal patterns	Seizure
Problems or changes with vision	Other neurological symptoms
Questions related to headaches prior to presenting headache	
First headache episode of their life	Prior headaches wake from sleep
Time since onset of (lifetime) headaches	Prior early morning headaches
Number of days per month with headaches	Early morning vomiting or vomiting waking from sleep with prior headaches
Increase in frequency or severity of headaches	Unsteadiness with prior headaches
Change in location or quality of headaches	
Worst headache of patient's life	
Family history	
First- or second-degree relatives with migraines	
General physical examination	
General appearance	Abnormal speech
Glasgow Coma Scale score	Skin findings associated with neurological conditions
Neck stiffness	
Head tilt	
Neurological exam	
Pupil reactivity to light	Dysmetria or dysdiadochokinesia
Extra-ocular movements	Stance
Nystagmus	Romberg
Cranial nerves (not incl. extraocular movements)	Pronator drift
Motor function	Gait
Sensory function	Tandem gait
Deep tendon reflexes	Visual fields
Babinski/extensor plantar response	Papilledema