Evidence-Based Guidelines in the Primary Care Setting: Neuroimaging in Patients with Nonacute Headache

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*Endorsement by ACEP means that ACEP agrees with the general concepts in the guidelines and believes that the developers have begun to define a process of care that considers the best interests of patients with migraine headache.

Neuroimaging in Patients with Nonacute Headache

A. Introduction

Headache is a common disorder with many potential causes. The primary headache disorders, which include migraine, cluster, and tension-type headaches, account for the majority of headaches, while secondary headaches, which are those with underlying pathology (e.g., tumor, aneurysm, or giant cell arteritis) are far less common.[1] Most patients presenting with headache in the primary care setting do not have serious underlying conditions.[2,3] The relative rarity of secondary headaches, compared with the large number of patients with primary headache, raises concern about the wisdom of routine neuroimaging studies, either computerized tomography (CT) or magnetic resonance imaging (MRI), to exclude underlying causes of headache.

While detection of significant and treatable lesions that impact quality of life remains the primary reason to obtain a neuroimaging study, there are other important considerations. Neuroimaging may relieve the patient's anxiety about having an underlying pathologic condition; therefore, neuroimaging may improve patient overall satisfaction and medical care. In a British study of patient expectations and satisfaction after visiting a regional headache clinic, 60% of 109 patients polled indicated having significant fears of serious illness.[4] Of these patients, 40% left the clinic still fearful, with some requesting imaging studies. Other reasons for obtaining a neuroimaging study in patients with headache include litigation concerns and the patient's or the family's request. Also, there are potential risks with neuroimaging, which include “false positive studies” that will worry the patient, false reassurance from an inadequate study, the risks of an allergic reaction to iodine contrast media with CT scanning, and the risk of over-sedation in claustrophobic patients having MRI scans.

Guidelines are developed to assist the physician in making appropriate choices in work-up and treatment of patients. They are not designed to supersede clinical judgment when dealing with individual patients, nor are they designed to prevent imaging in any given situation. The realities of our medical-legal climate are such that many physicians feel compelled to conduct neuroimaging studies on patients with headache even though the likelihood of finding pathology is about the same as in the general population. These studies are generally done to avoid the possibility of a lawsuit based on failure to diagnose a lesion, unrelated to the headache, which is an incidental finding during a headache evaluation. The Consortium recognized these realities when developing the Guidelines, but they did not alter the intention or direction of the Guideline's recommendations, which are based on the available evidence. Understanding that individual physicians have their own risk tolerance, some will find these Guidelines useful, while others will continue to image patients based on risk management strategies.

Aims of the Guideline

The objective of the US Headache Consortium is to develop scientifically sound, clinically relevant practice guidelines on chronic headache in the primary care setting. The specific aim of the Diagnostic Guideline is to provide recommendations for diagnostic testing in nonacute headache patients (encompassing all headache syndromes that have occurred for at least four weeks during a patient's lifetime) based on a comprehensive review and meta-analysis of scientific evidence.[‡] Specifically, the evidenced-based Guideline focuses on three questions:

‡This statement is provided as an educational service of the US Headache Consortium member organizations. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. These organizations recognize that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

(1) Are particular findings in the history and on the physical examination helpful in identifying which patients have significant intracranial abnormalities?

(2) What is the frequency of significant secondary causes of nonacute headache, as detected by CT or MRI, in patients presenting with nonacute headache and a normal neurological examination?

(3) What evidence exists concerning the relative ability of CT and MRI to detect significant intracranial lesions among patients with nonacute headache?

The results of the literature review and analysis showed that there is insufficient published clinical research to support evidence-based Guidelines for any diagnostic testing other than neuroimaging. Previous reports that reviewed the evidence on the role of electroencephalography (EEG) found that EEG is not indicated in the routine evaluation of headache.[5]

Methods

Review of the published clinical evidence available in the medical literature (from January 1966 through August 1998) included English-language studies that estimated the sensitivity, specificity, or predictive value of a neuroimaging test used in patients presenting with nonacute headache.[6] Studies that assessed observer variation or reproducibility of diagnostic tests for patients with nonacute headache were included. (A complete overview of methodology is presented elsewhere.[7])

Identified studies were reviewed with the assistance of two board-certified neurologists. Neuroimaging results were recorded and classified as either “significant abnormalities,” “abnormalities possibly related to headache,” “insignificant abnormalities,” (defined in Table 3 of the "Evidence-based guidelines for migraine headache: overview of program description and

methodology"[7]) or “normal”. To evaluate the medical aspects of neuroimaging, we focused exclusively on significant abnormalities (defined as abnormalities related to headache that may require further action [e.g., acute cerebral infarct, neoplastic disease, hydrocephalus, and vascular abnormalities, e.g., aneurysm or arteriovenous malformation]).

B. Summary of the Evidence

The literature search identified 28 studies that met the inclusion criteria.[2,8-33] These studies varied in setting, design, and other methodological features, as well as in the level of detail in reporting results.[6] Twenty-two of the 28 studies were retrospective; the six prospective studies all lacked blinding. All 28 studies were reviewed and assigned a quality grade of I through IV (Level I evidence: independent, blind comparison with a “gold standard” of anatomy, physiology, diagnosis, or prognosis among a large number of consecutive patients suspected of having the target condition. Level II evidence: independent, blind comparison with a “gold standard” among a small number of consecutive patients suspected of having the target condition. Level III evidence: independent, blind comparison with a “gold standard” among non-consecutive patients suspected of having the target condition. Level IV evidence: included studies that did not meet criteria for at least Level III evidence. Additional details are presented elsewhere.[6,7]) All of the studies identified received a quality Grade IV. Most of the studies identified did not characterize the study population in terms of duration of headache disorder. Most included a discussion of the neurological examination, but did not comment on symptoms. Several studies used populations having a mix of subjects with both acute and nonacute headaches.

Historical and Physical Examination Findings

Eight of the 28 studies reported sufficient information to construct tables relating specific historical or physical examination findings to the occurrence of significant abnormalities on CT or MRI (Table 1).[2,8-13,15]

Neurological Findings: Five studies described neuroimaging abnormalities in patients with neurological findings on examination.[8-12] This permitted the calculation of likelihood ratios for abnormal and normal neurological examination. In four of the five studies, an abnormal neurological examination (not described consistently in the individual study reports) significantly increased the likelihood of finding a significant abnormality on neuroimaging. Conversely, the absence of findings on the neurological examination led to a decreased likelihood of finding a significant lesion on neuroimaging in all five studies. This reduction approached statistical significance in two studies.

To describe the efficiency of the screening tests, sensitivity and specificity were combined to create likelihood ratios. Likelihood ratios are useful because they express the change in odds of disease for a given finding. As shown in Table 1, values greater than one increase the odds of disease, while values less than one diminish the odds. Values approaching one have an increasingly small impact on changing the odds of disease beyond the baseline prevalence. A calculated combined likelihood ratio of 3.0 (95% confidence interval, 2.3 to 4.0) suggests that abnormal findings on the neurological examination tripled the odds of finding a significant intracranial abnormality on neuroimaging.[††] Since the prior odds of significant intracranial abnormality is low (less than 1 in 100), the odds of such an abnormality in the face of an abnormal neurological examination is still low (i.e., less than 3 in 100). A combined negative likelihood ratio

[††] A likelihood ratio greater than one indicates that the diagnostic test results increase the post-test probability of disease.

of 0.7 (95% confidence interval, 0.52 to 0.93) suggests that a normal neurological examination reduced the odds of finding a significant intracranial abnormality on neuroimaging by 30%.

In two studies, the presence of abnormal neurological signs or symptoms (not just signs as described earlier) significantly increased the likelihood of finding a significant abnormality on neuroimaging.[12,13] The absence of neurological signs and symptoms was associated with a significantly decreased likelihood of a significant abnormality in one of the two studies. Two studies related several individual neurological signs and symptoms to the presence of significant abnormalities on imaging.[10,12] The small number of patients with any individual symptoms resulted in wide confidence intervals (low precision) around the likelihood ratios, which makes interpretation difficult. In at least one of these studies, the following symptoms were shown to increase significantly the odds of finding a significant abnormality on neuroimaging:

- rapidly increasing headache frequency,
- history of dizziness or lack of coordination,
- history of subjective numbness or tingling, and
- history of headache causing awakening from sleep.

The absence of these features did not significantly lower the odds of finding a neuroimaging abnormality.

The same two studies[10,12] found that a history of syncope, headache accompanied by nausea, or the experience of the "worst headache" of one's life did not significantly increase the likelihood of finding a significant abnormality on neuroimaging. Similarly, the absence of these findings did not significantly alter the likelihood of finding an abnormality. For each of the findings, the studies did not have sufficient power to exclude the possibility of a clinically important effect.

Other Clinical Findings: One study reported that a history of headache worsening with Valsalva maneuver significantly increased the odds of finding a significant intracranial abnormality on neuroimaging, most commonly a Chiari malformation.[10] However, the lack of this finding (history of headache worsening with Valsalva maneuver) did not significantly alter the likelihood of finding an abnormality.

Continuous Variables

The distribution of several continuous variables (age, duration of headache, headache frequency, and ergot consumption) was reported for subjects with normal versus abnormal neuroimaging results. One study reported a statistically significant difference in the duration of the headache disorder between those with and without a significant abnormality on neuroimaging (Table 2).[10] All the patients in this trial had experienced either the recent onset of headaches or a clear change in the character of their nonacute headaches within the last year. This suggests that the duration of a headache disorder may be a useful predictor of significant abnormalities among patients with recent-onset headache symptoms, but not among patients with longstanding headache disorders.

Two studies described differences in mean age among patients with and without an abnormality on neuroimaging.[10,14] One of these studies found increasing age to be strongly associated with finding an abnormality; however, the abnormalities considered were mostly atrophy and old cerebral infarctions.[14] The relationship between age and significant abnormalities in another study found a statistical trend toward older age among those with significant abnormalities (age 53 vs. 42; $p=0.07$).[10]

Other continuous variables (e.g., headache frequency) have not been studied sufficiently to

determine whether they might be useful in discriminating between patients likely to have normal results on imaging and those likely to have abnormal results.

Nonacute Headache and Normal Neurological Examination

The estimates of the rates of significant abnormalities were based on samples of patients who appeared to have nonacute or recurrent headaches. Candidate articles on this topic were carefully scrutinized to ensure that patients with acute or new-onset headache (less than four weeks duration) were excluded or that at least neuroimaging test results were reported separately for patients with acute versus nonacute headache.

Migraine headache: Among patients with normal neurological examinations and headaches diagnosed as migraine, the prevalence of significant intracranial abnormalities on neuroimaging ranged from 0% to 3.1% in 11 studies (Table 3).[2,8,15-23] The populations in these studies were reasonably similar. Results from these studies were combined in a meta-analysis to yield a summary prevalence of 0.0018 (approximately 0.2%), with an upper 95% confidence limit of 0.0059 (approximately 0.6%). (This represents a prevalence that is less than the 0.8% incidence of arteriovenous malformations and the 2.4% incidence of saccular aneurysms found in autopsy series.[34, 35])

Tension-type headache: Two studies reported no patient with significant intracranial abnormalities among those with normal neurological examinations and headaches diagnosed as tension-type headaches (one study[18] specified as chronic tension-type headache).[18,23] However, both studies were small and included a total of only 83 patients.

Unspecified type of headache: In patients with normal neurological examinations presenting with headache not described as migraine or tension-type, rates of significant

intracranial abnormalities were more variable than among patients with migraine. Among these patients, the probability of finding significant intracranial abnormalities ranged from 0% to 6.7% (Table 4).[9,11, 12,14,24-29.] These rates were not homogeneous; therefore, no combined rates were calculated.

Other headache types (not specifically described as migraine or tension type): One "outlier" study[10] found a high probability of significant intracranial abnormalities (22.5%) in patients with either a recent (within 12 months) onset of headache or a recent (within 12 months) clear change in character of previous headaches. In another study among 27 patients with cluster headache, no clinically significant findings were observed.[30] Another study reported a high prevalence of significant abnormalities in patients with cough headache, exertional headache, and sex-induced headache.[31] Twelve of 28 patients (43%) with exertional headache had structural pathology, with 10 having had subarachnoid hemorrhages. They all had new onset of severe headache. Seventeen of 30 patients with cough-induced headache had a Chiari malformation, and 1 of 14 patients with headache associated with sex had a ruptured aneurysm with explosive headache.[31] This study did not describe neurological examination findings in relation to the neuroimaging findings.

Relative Effectiveness of CT and MRI

Three studies described the similarities between CT and MRI among patients with headache.[18,20,25] Each study had fewer than 100 patients, and a relatively small fraction of these patients were imaged using both technologies. No significant abnormalities were detected in these patients, so the relative effectiveness of the two tests for detecting significant lesions cannot be determined.

One study found that, of 15 patients imaged with both CT and MRI, 11 received the same diagnosis with the two technologies.[18] In the remaining four patients, abnormalities (including white matter changes) were seen on MRI but not on CT. In a second study, 17 patients were imaged with both CT and MRI, and 14 of them received identical diagnoses with the two procedures.[25] Differences in the remaining three patients related to the imaging of developmental venous anomalies. These findings were seen on MRI but not on CT in one case, and were suspected on CT, but not confirmed on MRI, in the remaining two cases. In the third study, MRI appeared to be more sensitive than CT in identifying white matter lesions.[20] In summary, the limited number of studies identified and reviewed here suggest that MRI may be more sensitive than CT for identifying clinically insignificant abnormalities. However, MRI may not be more sensitive for identifying clinically significant pathology that is relevant to the cause of headache. Only one study compared the sensitivity of CT with and without enhancement; however, this study excluded patients with migraine.[25]

C. Transition from Evidence to Guidelines

While the studies selected for this analysis were rigorously screened for quality, many failed to define headache duration, specify headache type, or adequately detail the history and examination of the patients. Studies differed in their size, methods, and endpoints, making it difficult to perform a meta-analysis. In addition, significant biasing effects were encountered in this review. In patients presenting with nonacute headache and a normal neurological examination, most of the studies included in this analysis shared two significant biases that may cause overestimation of the prevalence of significant abnormalities in the primary care population. First, because most were conducted at referral centers, the study populations could possibly be

skewed toward a higher frequency of pathology (referral filter bias). Second, most studies were assembled from a series of patients selected for neuroimaging, but provided no description of the criteria used to select patients. That is, no explanation was given for why some patients and not others were chosen for scanning, from the larger population of headache patients with normal neurological examinations. Therefore, the findings summarized above may not be generalizable to all populations of patients. The evidence gathered is all Level IV and lacks the strength preferred when making evidence-based guidelines.

D. General Principles of Management

In making decisions about neuroimaging in headache, the US Headache Consortium identified three consensus-based (not evidence-based) general principles of management:

(1) Testing should be avoided if it will not lead to a change in management.

(2) Testing is not recommended if the individual is not significantly more likely than anyone else in the general population to have a significant abnormality.

(3) Testing that normally may not be recommended as a population-policy may make sense at an individual level, resources notwithstanding. For example, exceptions can be considered for patients who are disabled by their fear of serious pathology, or for whom the provider is suspicious even in the absence of known predictors of abnormalities on neuroimaging studies (red flags).

E. Specific Testing Recommendations

The consortium considered the available evidence, and through a consensus process arrived at the following treatment recommendations listed below. Importantly, this list of recommendations is not all-inclusive, and there are other reasons for performing neuroimaging studies that are not detailed below due to the lack of published studies in the literature.

Neurological Examination

Finding: An abnormal neurological examination increases the likelihood of finding significant intracranial pathology (e.g., brain tumor, arteriovenous malformation, hydrocephalus) on neuroimaging. The absence of any abnormalities on neurological examination reduces the odds of finding a significant abnormality on imaging.

Recommendation: Neuroimaging should be considered in patients with nonacute headache and an unexplained abnormal finding on the neurological examination (Grade B[‡‡]).

Neurological Symptoms

Finding: Headache worsened by Valsalva maneuver, headache causing awakening from sleep, new headache in the older population, or progressively worsening headache may indicate a higher likelihood of significant

[‡‡]Grade A. Multiple well-designed randomized clinical trials, directly relevant to the recommendation, yielded a consistent pattern of findings.[36]
Grade B. Some evidence from randomized clinical trials supported the recommendation, but the scientific support was not optimal. For instance, either few randomized trials existed, the trials that did exist were somewhat inconsistent, or the trials were not directly relevant to the recommendation. An example of the last point would be the case where trials were conducted using a study group that differed from the target group for the recommendation.
Grade C. The US Headache Consortium achieved consensus on the recommendation in the absence of relevant randomized controlled trials.

intracranial pathology, as reported in several small studies. (One study reported that a history of headache worsening with Valsalva maneuver significantly increased the odds of finding a significant intracranial abnormality on neuroimaging, most commonly a Chiari malformation. In general, however, the absence of signs and symptoms is less reliable and informative than their presence.

Recommendation: Evidence is insufficient to make specific recommendations regarding neuroimaging in the presence or absence of neurological symptoms (Grade C[‡‡]).

Migraine and a Normal Neurological Examination

Finding: Meta-analysis of patients with migraine and a normal neurological examination found a rate of significant intracranial lesions of 0.18% (2/1000; previously reported rates of finding intracranial lesions with CT and MRI ranged from 0.3% to 0.4%[37]). Neuroimaging is thus unlikely to reveal an abnormality on MRI or CT scanning in patients with migraine and a normal neurological examination.

Recommendation: Neuroimaging is not usually warranted for patients with migraine and normal neurological examination. (Grade B[‡‡]). For patients with atypical headache features or patients who do not fulfill the strict definition of migraine (or have some additional risk factor), a lower threshold for

neuroimaging may be applied (Grade C‡‡).

Tension-type Headache and Normal Neurological Examination

Finding: In two studies of imaging in patients with tension-type headache (one study specified as chronic tension-type headache[18]) and normal neurological examinations, no significant lesions were demonstrated.

Recommendation: Data were insufficient to make an evidence-based recommendation regarding the use of neuroimaging for tension-type headache (Grade C‡‡).

Effectiveness of CT vs. MRI

Finding: Based on the limited data in the studies reviewed here, MRI appears to be more sensitive in finding white matter lesions and developmental venous anomalies than CT, a result that could be expected based upon the characteristics of the two technologies. The greater resolution and discrimination of MRI, however, appears to be of little clinical importance in the evaluation of patients with nonacute headache. Data were lacking comparing enhanced with unenhanced CT scans.

Recommendation: Data were insufficient to make any evidence-based recommendations regarding the relative sensitivity of MRI compared with CT in the evaluation of migraine or other nonacute headache (Grade C‡‡).

F. Future Research

In the studies reviewed in this report, sufficient evidence was available in the literature to evaluate the rate of significant intracranial lesions among patients with migraine and a normal neurological examination. However, for patients with tension-type headache and a normal neurological examination, information was not sufficient to estimate the probability of important intracranial pathology. Among patients with nonacute headache of an unspecified type and no neurological signs or symptoms, rates of significant abnormalities were statistically heterogeneous. Available studies are not sufficient to permit definitive recommendations about neuroimaging in these groups of patients. Review of the literature on diagnostic imaging in headache patients does provide a reasonable estimate of the prevalence of significant intracranial lesions in patients with migraine and normal neurological exam. However, additional research is needed to determine the prevalence of significant intracranial lesions for patients with tension-type headache and normal neurologic exam, and for the prognostic importance of various findings on the headache and neurologic exam for headaches of all types. These include history of syncope, nausea, history of "worst headache of life," headache frequency, the presence of risk factors (e.g., diabetes mellitus, multiple sclerosis, hypertension, collagen disease, valvular heart disease) and significant laboratory abnormality (e.g., anticardiolipin antibody, polycythemia, hyperlipidemia).

Additional comparative, well-controlled studies are needed to better understand the significant differences in sensitivities between MRI and CT neuroimaging for patients with nonacute headache.

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Table 1: Evidence for historical or physical examination findings changing the odds of detecting a significant abnormality on neuroimaging.

Historical or physical exam findings	**Reference**	**Number of patients in the study**	**Likelihood ratio (LR) positive (95% confidence interval)**	**Likelihood ratio (LR) negative (95% confidence interval)**
Abnormal neurological exam	Cala, 1976[8]	46	1.7 (0.39 to 7.3)	0.71 (0.18 to 2.9)
	Carrera, 1977[9]	32	3.0* (2.2 to 4.2)	0 (0 to 11)
	Duarte, 1996[10]	100	2.5* (1.2 to 5.3)	0.73 (0.52 to 1.05)
	Larson, 1980[11]	40	4.4* (1.9 to 10)	0 (0 to 42)
	Mitchell, 1993[12]	350	5.4* (2.2 to 14)	0.62 (0.33 to 1.2)
	Combined LR; Test for homogeneity		***3.0* (2.3 to 4.0); X^2=2.3; d.f.=4; p=0.66***	***0.70* (0.52 to 0.93); X^2=2.5; d.f.=4; p=0.64***
Any neurological sign or symptom	Kahn, 1993[13]	1111	1.1* (1.05 to 1.2)	0.47* (0.25 to 0.89)
	Mitchell, 1993[12]	350	6.0* (4.7 to 7.8)	0 (0 to 7.9)
Rapidly increasing headache frequency	Mitchell, 1993[12]	350	12* (3.1 to 48)	0.73 (0.46 to 1.2)
History of syncope	Mitchell, 1993[12]	350	0.69 (0 to 340)	1.0 (0.92 to 1.1)
Nausea	Mitchell, 1993[12]	350	0 (0 to 260)	1.0 (0.93 to 1.1)
	Duarte, 1996[10]	100	1.4 (0.69 to 3.0)	0.87 (0.63 to 1.2)
History of headache causing awakening from sleep	Duarte, 1996[10]	100	1.7 (0.81 to 3.7)	0.78 (0.51 to 1.2)
	Mitchell, 1993[12]	350	98* (10 to 960)	0.72 (0.45 to 1.1)
History of dizziness or lack of coordination	Mitchell, 1993[12]	350	49.0* (3.4 to 710)	0.86 (0.64 to 1.2)
History of subjective numbness or tingling	Mitchell, 1993[12]	350	49.0* (3.4 to 710)	0.86 (0.64 to 1.2)
"Worst headache of life"	Mitchell, 1993[12]	350	1.9 (0.30 to 12)	0.93 (0.68 to 1.3)
Headache worse with Valsalva maneuver	Duarte, 1996[10]	100	2.3* (1.1 to 4.6)	0.67 (0.42 to 1.1)
Abnormal skull roentgenograph	Sargent, 1983[2]	88	0 (0 to 29)	1.1* (1.0 to 1.2)

* $p \leq 0.05$

Table 2: Potential predictors of abnormalities on imaging- continuous variables

Potential Predictors	**Reference**	**Number of patients in the study**	**Mean (SD) for patients with any abnormality on neuroimaging**	**Mean (SD) for patients with no abnormality on neuroimaging**
Age (years)	Duarte, 1996[10]	100	52.6†††	44.2
	Baker, 1983[14]	505	50.4(48.2)	47.5(140.0)
Duration of headache disorder (years)	Duarte, 1996[10]	100	0.68**	0.24

†††p=0.07

**p<0.001

Table 3: Rates of significant intracranial abnormalities in patients with migraine or tension-type headache and normal neurological examination.

Study	**Number of patients**	**Significant abnormality detected**	**Rate**	**Upper 95% CI**
MIGRAINE				
Cala, 1976[8]	32	1	0.031	0.141
Cuetter, 1983[16]	435	1	0.002	0.011
Cull, 1995[17]	69	0	0.000	0.043
De Benedittis, 1995[18]	28	0	0.000	0.103
Hungerford, 1976[19]	53	0	0.000	0.055
Igarashi, 1991[15]	91	0	0.000	0.033
Kuhn, 1990[20]	74	0	0.000	0.040
Osborn, 1991[21]	41	0	0.000	0.071
Robbins, 1992[22]	46	0	0.000	0.064
Sargent, 1979[23]	129	0	0.000	0.023
Sargent, 1983[2]	88	0	0.000	0.034
Combined			**0.0018**	**0.0059**
Test for homogeneity:			**X^2=6.1; d.f.=10; p=0.81**	
TENSION-TYPE HEADACHE				
De Benedittis, 1995[18]	35	0	0.000	0.083
Sargent, 1979[23]	48	0	0.000	0.061

Table 4: Rates of significant intracranial abnormalities in patients with chronic headache of an unspecified type (not new onset).

Study	Number of patients	Significant abnormality detected	Rate	Upper 95% CI
Normal neurological examination				
Akpek, 1995[24]	592	0	0.000	0.005
Baker, 1983[14]	505	34	0.067	0.093
Carrera, 1977[9]	53	0	0.000	0.055
Demaerel, 1996[25]	363	5	0.014	0.030
Dumas, 1994[26]	370	2	0.005	0.017
Knaus, 1978[27]	258	2	0.008	0.025
Larson, 1980[11]	31	0	0.000	0.094
Mitchell, 1993[12]	320	4	0.012	0.030
Sotaniemi, 1991[28]	207	2	0.010	0.031
Weingarten, 1992[29]	89	0	0.000	0.033
Normal neurological examination and no neurological signs or symptoms				
Kahn, 1993[13]	155	9	0.058	0.104
Mitchell, 1993[12]	287	0	0.000	0.010