Yield of CT angiography in patients with acute headache, normal neurological examination and normal non-contrast CT: a meta-analysis

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Yield of Computed Tomography (CT) Angiography in Patients with Acute Headache, Normal Neurological Examination, and Normal Non Contrast CT: A Meta-Analysis

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Background: Patients with acute severe headache, normal neurological examination, and a normal noncontrast head computed tomography (NCCT) may still have subarachnoid hemorrhage, cerebral venous thrombosis (CVT), cervical arterial dissection, or reversible cerebral vasoconstriction syndrome (RCVS). Computed tomography angiography (CTA) is used increasingly in the emergency department for evaluating this, but its added value remains controversial. *Methods:* We retrospectively collected data on the diagnostic yield of CTA in patients with acute severe headache, normal neurological examination, and normal NCCT who received additional CTA in the acute phase in 2 secondary referral centers for vascular neurology. We combined data of our patients with those from the literature and performed a meta-analysis. *Results:* We included 88 patients from our hospital files and 641 patients after literature search. Of 729 patients 54 had a vascular abnormality on CTA (7.4%; 95% confidence interval [CI] 5.5%-9.3%). Abnormalities consisted of aneurysms (n = 42; 5.4%; 95% CI 3.8%-7.0%), CVT (n = 3, .5%), RCVS (n = 4, .5%), Moyamoya syndrome (n = 2, .3%), arterial dissection (n = 2, .3%), and ischemia (n = 1, .1%). Because most of the aneurysms were probably incidental findings, only 12 (1.6%) patients had a clear relation between the headache and CTA findings. The number needed to scan to find an abnormality was 14 overall, and 61 for an abnormality other than an aneurysm. *Conclusion:* Diagnostic yield of CTA in patients with acute headache, normal neurological examination, and normal NCCT is low, but because of the possible therapeutic consequences, its use might be justified in the emergency setting. Prospective studies

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confirming these results including cost-effectiveness analyses are needed. **Key Words:** Computed tomography angiography—neuroimaging—acute headache—thunderclap headache—meta-analysis.

Introduction

Acute headache may be the only presenting symptom of life-threatening secondary headache syndromes. Patients with acute severe headache and a normal neurological examination may have not only subarachnoid hemorrhage (SAH), but also cerebral venous thrombosis (CVT), cervical arterial dissection, or reversible cerebral vasoconstriction syndrome (RCVS).[1-8]

Computed tomography angiography (CTA) is increasingly used in the emergency setting for evaluating these important causes of secondary headache. CTA has been proven sensitive in determining the presence of aneurysms and CVT, and, to a lesser extent, RCVS and dissections.[9,10] CTA has higher accessibility than magnetic resonance imaging (MRI) in most hospitals. Also cost and time reductions compared with MRI make it a possible valuable modality in evaluating emergency department (ED) patients, although CTA is more expensive than noncontrast head computed tomography (NCCT) alone. There are other drawbacks of CTA. First, there is an added radiation exposure of approximately 2.5 mSV after the NCCT which is also 2.5 mSV, with a total of 5 mSV.[11] Second, intravenous iodinated contrast media may, rarely, cause allergic reactions and contrast nephropathy, particularly in patients with known nephropathy.[11-13]

The diagnostic yield of CTA in patients with acute headache and normal neurological examination and NCCT is unclear. A pooled analysis of follow-up studies in patients with acute severe headache reported that in the group with normal noncontrast computed tomography (CT) and normal lumbar puncture (LP), none had subsequent SAH. Based on these findings the authors advocated that CTA should not be used on a standard basis in these patients.[14] However, the included studies had a limited follow-up period and in most patients CTA was not performed. Two large series of patients with acute headache concluded that if an NCCT is normal when performed within 6 hours of the start of the headache, an LP is no longer needed due to the highly sensitive nature of third-generation CT scanners.[15,16] This strategy is applicable to the exclusion of SAH, but because CTA was not performed in most patients, other diagnoses such as CVT, RCVS, or cervical arterial dissection might have been missed. Two studies report percentages of vascular abnormalities ranging from 6.6% to 19%, in patients with acute severe headache, normal neurological examination, and normal NCCT.[17,18] This is higher than may be expected in the general population. The first study was a large prospective study of 512 patients, but it was unknown whether LPs had been performed in these patients. In this study a large number of aneurysms were found, but it was not clear whether these were ruptured or unruptured intracranial aneurysms.[17] The second study from our own group had a limited size and patients were selected based on a normal LP. This may have caused selection bias.[18]

The aim of our study was to evaluate the yield of CTA in patients presenting with acute severe headache to the ED in whom neurological examination and NCCT was normal using both our own patient population and a meta-analysis of the literature.

Methods

Own Hospital Data

We retrospectively evaluated data on all patients who underwent a cerebral CTA between 2011 and 2014 in the ED of the Leiden University Medical Center (LUMC), a tertiary vascular neurology referral center and university teaching hospital, and the MC Haaglanden, a secondary vascular referral center and primary teaching hospital. We included all patients who presented with acute headache, defined as headache that developed within 5 minutes and lasted for at least 1 hour.

In the Leiden University Hospital patients were scanned from the aortic arch up using the Aquilion One (Aquilion ONE, Toshiba Medical Systems, Tokyo, Japan) and Aquilion 64 CT scanner (Aquilion 64, Toshiba Medical Systems, Otawara, Japan). In the MC Haaglanden patients were scanned from the aortic arch to the vertex with a GE Lightspeed 64-slice scanner.

We charted patient characteristics (age, sex, patient history and medication, seizures, loss of consciousness before admission, nausea, vomiting) and headache characteristics (location, duration, mode of onset, presence of aura, autonomous symptoms). We recorded results of CTA and other diagnostic procedures including LPs, digital subtraction angiography, and MRI when performed. Patients with focal neurological deficits, abnormalities on standard NCCT and, if performed, abnormal cerebrospinal fluid findings (raised pressure and cerebrospinal fluid chemistry showing hemorrhage or infection) were excluded. We recorded all adverse events that were possibly related to the CTA such as allergic reactions, kidney failure, or infections after intravenous catheter use.

The study was approved by the local ethics committee and hospital board of both the LUMC and MC Haaglanden.

Literature Search

The literature search was performed with PubMed. Reference lists of relevant articles were scanned for further usable articles. Search terms were "acute headache," "thunderclap headache," "CT angiography," "neuro-imaging," "subarachnoid hemorrhage," and combinations thereof. We evaluated all articles published up to and including 2015.

Articles were included in the meta-analysis if they consisted of original articles including consecutive patients with acute, severe, or worst ever headache who were evaluated by CTA. Case reports and case series were excluded to eliminate publication bias. Reviews and non-English articles were also excluded.

We charted CTA results and, when performed, results of MRI, LP, and digital subtraction angiography. We also recorded adverse events possibly related to CTA.

All articles were read extensively, and data were extracted with a data extraction form. If data were missing, authors were contacted with the request for additional information.

Results

Own Data

In the LUMC and MC Haaglanden, 391 patients with acute headache who received a CTA were identified. Of the 391 patients 88 had a normal neurological examination and a normal NCCT. In 31 of the 88 patients, an LP was performed with normal results, and 57 patients did not receive an LP. A large number of patients (64 [73%]) had a history of migraine. Eight patients had a history of SAH (9.5%). Four patients presented twice with acute headache. One presented twice within 3 months and was diagnosed with RCVS. The other 3 patients presented over a period of 1 year and were diagnosed with primary thunderclap headache. All other patients presented with first-ever headache. Overall, 5 patients (5.7%) had a vascular abnormality on CTA (Table 1). In 4 (4.5%) of these patients, the abnormality was considered to be the cause of the headache, whereas the other patient had a small unruptured aneurysm with a normal LP.

Table 1. *Patient characteristics own series*

Characteristics	Patients (n = 88)
Age (mean ± SD)	45.9 ± 14.9
Women	63 (72%)
Neurological history	
Migraine	64 (73%)
Tension type headache	14 (15.6%)
SAH	8 (9.5%)
Nausea	63 (72%)
Vomiting	33 (37.5%)
Aura	8 (9%)
<6 h presentation at ER	23 (26%)
6-24 h	30 (34%)
>24 h	35 (40%)
CTA including cervical arteries	88 (100%)
Location headache	
Whole head	32 (36%)
Half-sided	5 (6%)
Localized	57 (65%)
Missing	3 (3%)
Type of headache	
Throbbing	15 (17%)
Stabbing	25 (28%)
Pressing	27 (31%)
Nagging	4 (4.5%)
Other	11 (12.5%)
Missing	15 (17%)
Adverse events CTA	1 (1%)
Abnormal CTA	5 (6%)
Aneurysm	1 (1%)
CVT	1 (1%)
RCVS	2 (2%)
Cervical Dissection	1 (1%)
MRI/MRA	
Normal	6 (7%)
Dissection	1 (1%)
Ischemia	1 (1%)
Not performed	80 (91%)
Lumbar puncture	
Normal	31 (35%)
Not performed	57 (65%)

Abbreviations: CTA, computed tomography angiography; CVT, cerebral venous thrombosis; ER, emergency room; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; RCVS, reversible cerebral vasoconstriction syndrome; SAH, subarachnoid hemorrhage; SD, standard deviation.

Literature

Through the PubMed search a potential 1533 articles were identified. After elimination of duplicates, non-English articles, case reports, case series, and reviews, 482 articles remained. After scanning of titles and abstracts, 12 potential articles were selected for further reading.[9,17-26] Six articles met the inclusion criteria,[17-22] but only 3 articles gave sufficient information in order to ascertain the presence of a combination of a normal neurological examination, normal standard head CT, and, if performed, an LP without signs of hemorrhage.[17,18,20] Authors of the remaining 3 articles were contacted for additional information; however, none of them responded.

A total of 641 patients were identified through literature search. Of these patients 49 had an abnormality on CTA (7.3%) (Table 2).

Table 2. *Results of meta-analysis, sex, and age of patients*

Study	Study type	No.	LP normal	CTA including cervical arteries	CTA abnormal	CT <6 h after peak headache*	Sex (male)	Age, y (mean)	MRI	DSA	Adverse events	Diagnoses
Han et al[15]	Prospective	512	Not performed	0	34	Unknown	251 (49%)	46.2	—	15	0	31 Aneurysms 1 Dissection 2 Moyamoya
Rizk et al[18]	Prospective	59	Unknown	59	2	Unknown	—	—	—	—	—	2 UIAs
Alons et al[16]	Retrospective	70	70	35	13	0	20 (29%)	45	15	4	0	8 Aneurysms 2 CVT 2 RCVS 1 Ischemia
Current study	Retrospective	88	31	88	5	2	32 (36%)	46	8	0	1	1 Aneurysm 1 CVT 2 RCVS 1 Dissection
Total		729	101	182	54	2	303 (45.2%)	46	23	19	1	42 Aneurysms 2 Dissections 2 Moyamoya 4 RCVS 3 CVT 1 Ischemia

Abbreviations: CT, computed tomography; CTA, computed tomography angiography; CVT, cerebral venous thrombosis; DSA, digital subtraction angiography; LP, lumbar puncture; MRI, magnetic resonance imaging; RCVS, reversible cerebral vasoconstriction syndrome; UIA, unruptured intracranial aneurysm.

*Of patients with abnormal CTA.

Combined Data

We identified 729 patients with acute severe headache who met inclusion criteria. Average age was 46 years, and there were 54.8% women. A CTA including the cervical arteries was performed in 182 patients. Fifty-four had an abnormality on CTA (7.4%; 95% confidence interval [CI] 5.5%-9.3%); Table 3 provides an overview of abnormalities found. The patients with an abnormality on CTA had an average age of 50 years and 31 were women (57%). The abnormalities consisted of 1 patient with right occipital ischemia (.1%), 2 with cervical dissection (.2%), 2 with abnormalities suspected for Moyamoya syndrome (.3%), 3 with CVT (.4%), 4 with RCVS (.5%), and 42 cases with aneurysms (5.8%; 95% CI 4.1%-7.5%). In 9 out of 42 patients with an aneurysm an LP was performed, which showed no signs of hemorrhage in none of these patients. Of the remaining 33 patients, no data on whether an LP was performed or outcome of LP were found. Of the 42 patients with an aneurysm, 25 patients received either coiling or clipping of an aneurysm.

Four patients received altered medical treatment concerning CVT or stroke. Of the remaining patients, 23 received either clinical or imaging follow-up. The number needed to scan for finding an abnormality likely causative of the acute headache was 61. In 12 patients (1.6%), there was a clear relation with the acute headache. When one considers unruptured aneurysms to be clinically relevant, the number needed to scan is 14 (n = 54).

One patient in this series had an adverse event, an allergic reaction to contrast iodinated contrast media, with reversible effect and short-term harmful effects for the patient.

Discussion

In our meta-analysis, a vascular abnormality was identified with CTA in 7.4% of patients with acute severe headache and a normal neurological examination and NCCT of the head. In 12 (1.6%) patients this abnormality was presumably the cause of the headache.

The number of aneurysms found is slightly higher than might be expected in the general population. This number is dependent on the percentage of women and the average age. For all patients described here the expected percentage would be 3.2%.[27]

The question remains whether these aneurysms are of clinical significance. If an aneurysm has not actively bled, it is probably not the cause of the acute headache, but an incidental finding. An LP is necessary to rule out hemorrhage. However, in a large proportion of patients with an aneurysm in this series the outcome of the LP was unknown, and, therefore, we cannot determine if the aneurysm had ruptured or not. Radiological follow-up may be offered to patients with an unruptured intracranial aneurysm; however, it is unknown if such a follow-up strategy is cost-effective. The necessity to treat an aneurysm depends on the estimated risk of rupture, which in turn depends on patient factors such as age, hypertension, location of the aneurysm, previous SAH, and ethnicity of the patient.[28] As not all factors were known to us in this patient group, the necessity of treatment of the detected aneurysms could not be determined. A considerable number of patients with aneurysms in this series have been treated, but because we were unaware of the indication of treatment, we cannot confirm that they are clinically relevant.

We found a surprisingly low number of patients with RCVS. In a recent paper, RCVS was found in 8.8% of the patients using MRI/magnetic resonance angiography. It is likely that CTA is not the ideal modality for diagnosing this condition. Also it is postulated that RCVS may only be seen on imaging in a later stage, and repeated imaging improves sensitivity.[9] Cervical artery dissection is often suspected in patients with acute headache. In this series only 2 of the 182 patients who received CTA, including the carotid and vertebral arteries, had a cervical artery dissection (1.1%; 95% CI –.4% to 2.6%). Our data suggest that it is a relatively rare cause of secondary headache, but because not all patients had a CTA from the aortic arch, this may be an underestimation.

In this patient group there was only 1 recorded adverse event; an allergic reaction to iodinated contrast media, with reversible effect and short-term harmful effects for the patient. Possible adverse events after CTA are nephrotoxicity and allergic reactions to iodinated contrast media.[12,13] It is likely that in this group of relatively young patients, with little comorbidity, renal function is good, thus reducing the risk of nephrotoxicity. The chance of contrast nephropathy in patients receiving CTA after acute stroke is low and is reported to be 2%-3.2%, including only mild, reversible nephropathy.[12,13] Underreporting may have also affected these numbers, as nephrotoxicity was not systematically checked in this retrospective series. The added radiation exposure after CTA is on average 2.5 mSv per patient. This is equal to 20 months of background radiation. There is a debate how radiation exposure due to head CT alters the risk of cancer. One study evaluating pediatric patients after 10 years of follow-up after head CT concluded that the risk of development of a malignant brain tumor was not raised. However, there was an increased risk of development of benign brain tumors.[29] In this study, the reason for the CT study was unknown. Therefore, "reverse causation" may blur results and give cause to a higher reporting of cancer rates than caused by added radiation exposure alone. Another large, recent study concluded that the risk of leukemia was tripled when doses exceeding 50 mSv were given.[30] Moreover, the risk of brain tumor was tripled when doses of more than 60 mSv were given. These doses are nowhere near the dose given for a single CTA. The risk of cancer induction from a single combined brain/cervical CTA seems

Table 3. *Characteristics of patients with an abnormality on CTA*

Number	Sex	Age	Study	Abnormality	Follow-up
1	F	30	Han et al	Aneurysm, ICA 3.4 mm	Clinical follow-up
2	M	56	Han et al	Aneurysm, ICA 2.7 mm	Clinical follow-up
3	F	35	Han et al	Aneurysm, ICA, 4.2 mm	Clinical follow-up
4	M	52	Han et al	Aneurysm, ICA, 3.5 mm	Clinical follow-up
5	F	71	Han et al	Aneurysm, ICA, 9.4 mm	Refused treatment
6	F	70	Han et al	Aneurysm, ICA, 3.3 mm	Clip ligation
7	F	27	Han et al	Aneurysm, ICA, 3.8 mm	Follow-up with CTA
8	F	50	Han et al	Aneurysm, ICA, 2.0 mm	Clinical follow-up
9	M	56	Han et al	Aneurysm, ICA, 2.6 mm	Follow-up with CTA
10	F	67	Han et al	Aneurysm, ICA, 2.0 mm	Clinical follow-up
11	F	40	Han et al	Aneurysm, ICA, 2.9 mm	Clinical follow-up
12	F	42	Han et al	Aneurysm, ICA, 2.8 mm	Clinical follow-up
13	M	47	Han et al	Aneurysm, AcomA, 3.0 mm	Clip ligation
14	F	41	Han et al	Aneurysm, AcomA, 13.1 mm	Coil insertion
15	M	37	Han et al	Aneurysm, AcomA, 3.5 mm	Refused treatment
16	F	57	Han et al	Aneurysm, AcomA, 5.6 mm	Clip ligation
17	F	68	Han et al	Aneurysm, AcomA, 2.5 mm	Clinical follow-up
18	M	61	Han et al	Aneurysm, AcomA, 2.7 mm	Clinical follow-up
19	M	48	Han et al	Aneurysm, AcomA, 4.6 mm	Coil insertion
20	M	80	Han et al	Aneurysm, MCA, 6.9 mm	Clip ligation
21	M	64	Han et al	Aneurysm, MCA, 2.5 mm	Clinical follow-up
22	F	55	Han et al	Aneurysm, MCA, 2.1 mm	Follow up with CTA
23	M	46	Han et al	Aneurysm, MCA, 2.0 mm	Clinical follow-up
24	F	55	Han et al	Aneurysm, MCA, 2.1 mm	Clinical follow-up
25	F	65	Han et al	Aneurysm, MCA, 3.0 mm/ACA, 2.5 mm	Clinical follow-up
26	M	33	Han et al	Aneurysm, PcomA, 3.5 mm	Coil insertion
27	F	23	Han et al	Aneurysm, PcomA, 4.0 mm	Coil insertion
28	M	49	Han et al	Aneurysm, PcomA, 2.7 mm	Follow-up with CTA
29	F	51	Han et al	Aneurysm, PcomA, 3.0 mm	Clinical follow-up
30	M	54	Han et al	Aneurysm, PcomA, 11.0 mm/MCA, 3.0 mm	Coil insertion
31	F	53	Han et al	Aneurysm, BA, 3.3 mm	Refused treatment
32	M	37	Han et al	Dissection, VA	Medication change
33	F	50	Han et al	Moyamoya disease	Follow-up with MRA
34	M	32	Han et al	Moyamoya disease	Follow-up with MRA
35	F	31	Alons et al	Aneurysm, MCA, 2 mm	Clip ligation*
36	F	67	Alons et al	Aneurysm, AcomA, 3 mm	Follow-up with CTA*
37	M	62	Alons et al	Aneurysm, MCA, 3 mm	Clip ligation*
38	F	54	Alons et al	Aneurysm, MCA, 8 mm	Coil insertion*
39	F	61	Alons et al	Aneurysm, AcomA, 7.5 mm	Coil insertion*
40	F	58	Alons et al	Aneurysm, PcomA, 2 mm	Follow-up with CTA*
41	F	38	Alons et al	Aneurysm, ICA, 7.5 mm	Coil insertion*
42	F	48	Alons et al	Aneurysm, Pcom, 12 mm	Coil insertion*
43	M	37	Alons et al	CVT transverse and sagittal sinus	Anticoagulant therapy
44	F	53	Alons et al	Cortical vein thrombosis	None
45	M	48	Alons et al	RCVS	None
46	F	30	Alons et al	RCVS	One recurrent episode
47	M	73	Alons et al	Ischemia right occipital lobe	Medication change
48	-	-	Rizk et al	UIA	Follow-up with imaging
49	-	-	Rizk et al	UIA	Follow-up with imaging
50	F	51	Current study	Aneurysm, MCA,10 mm	Clip ligation*
51	M	42	Current study	RCVS	Clinical follow-up†
52	M	42	Current study	RCVS	Clinical follow-up†
53	F	36	Current study	CVT	Medication change
54	M	46	Current study	Dissection left ICA	Medication change

Abbreviations: ACA, anterior cerebral artery; Acom, anterior communal artery; BA, basilar artery; CTA, computed tomography angiography; CVT, cerebral venous thrombosis; ICA, internal carotid artery; MCA, medial carotid artery; MRA, magnetic resonance angiography; PcomA, posterior communal artery; RCVS, reversible cerebral vasoconstriction syndrome; UIA, unruptured intracranial aneurysm; VA, vertebral artery.

*Lumbar puncture normal.

†CT < 6 hours after peak headache.

therefore negligible and to outweigh the risk of a missed vascular cause of acute headache.

This is the largest study on the yield of CTA in the group of patients with acute headache, normal neurological examination, and normal NCCT. By performing a meta-analysis we improved the generalizability and precision of our results.

Our study has limitations. First, we were dependent on studies of varying methodology and with varying diagnostic goals and thus the indication for performed CTA may not be completely clear and patient series may not have been consecutive. Secondly, not all patient data from studies eligible for inclusion could be retrieved, limiting the number of available patients. Unfortunately, despite repeated requests, additional information was not obtained from 3 studies. Our added data were collected retrospectively and therefore an indication bias for performing CTA might have occurred. We cannot deduce how many patients with acute headache did not receive a CTA.

The chance of a finding with clinical implications in the group of patients with acute headache, normal examination, and normal noncontrast CT is low. However, as any finding of CVT and dissection warrants medication change and follow-up, the finding of these diagnoses has high clinical relevance. RCVS is deemed self-limiting; however, consequences of this condition may be severe. The number needed to scan in our series to find a clinically relevant abnormality (e.g., the probable cause of headache) on CTA was 61, and the number needed to scan to find any abnormality was 14. There was only 1 recorded complication, and radiation from CTA is relatively low. We therefore conclude that the diagnostic yield of CTA in patients with acute headache, normal neurological examination, and normal NCCT is limited, but because of the consequences for treatment is high enough to justify the possible adverse events. However, prospective studies to confirm these findings are needed.

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