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Prevalence of non-contrast CT abnormalities in adults with reversible cerebral vasoconstriction syndrome: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Reversible cerebral vasoconstriction syndrome (RCVS) is characterised by severe, recurrent thunderclap headaches (TCHs) and vasoconstriction of cerebral arteries that resolve within 3 months. Abnormalities on non-contrast CT (NCCT) such as ischaemic strokes, intracerebral haemorrhage and subarachnoid haemorrhages are frequently observed on brain imaging of patients with RCVS though their prevalence varies considerably between studies. The aim of this systematic review and meta-analysis is to estimate the prevalence of NCCT abnormalities seen on neuroimaging of adult patients with RCVS.

Methods and analysis We will search the Medline, Embase and the Cochrane Library databases for studies on the prevalence of NCCT abnormalities on neuroimaging of patients with RCVS. Search results will be screened for eligibility by title and abstract. Suitable studies will be fully reviewed and relevant data extracted using a data abstraction form. The studies will be assessed for methodological quality, risk of bias and heterogeneity. Prevalence estimates across studies will be pooled using a random-effects model and subgroup analysis will be performed to assess the impact of age, sex, publication year and study design on prevalence of vascular lesions. Sensitivity analysis will be used to investigate the robustness of the findings. This protocol has been devised using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 checklist.

Ethics and dissemination Formal ethics is not required as primary data will not be collected. The findings of this study will be disseminated through a peer-reviewed publication and conference presentations.

Trial registration number CRD42020190637.

Strengths and limitations of this study

► This study will be the first to provide an estimate of the prevalence of non-contrast CT abnormalities on imaging in patients with reversible cerebral vasoconstriction syndrome (RCVS).
► Risk of bias will be minimised by having two reviewers independently screen studies and extract data.
► The results of this study will help differentiate RCVS from illnesses that may present with similar symptoms.
► As this study will include several study designs, including case-series and observational studies, the results have a risk of heterogeneity.

INTRODUCTION

Reversible cerebral vasoconstriction syndrome (RCVS) is characterised by severe headaches, most often recurrent thunderclap headaches (TCHs), and segmental vasoconstriction of cerebral arteries that resolves within 3 months.[1] Patients are predominantly middle-aged females and may present with other focal neurological symptoms related to strokes, seizures or cerebral oedema.[1] RCVS has been linked to several precipitating factors including hypertension, pre-eclampsia and eclampsia, illicit substance use such as cannabis and cocaine and multiple medications including antidepressants, sympathomimetic drugs, triptans, immunosuppressant medications, among many others.[2] Current management for RCVS involves eliminating precipitating factors, analgesic therapy and use of a calcium channel blocker such as nimodipine or verapamil.[3]

RCVS is diagnosed based on characteristic clinical, imaging and angiographic features. Initial imaging modalities include non-invasive techniques such as non-contrast CT (NCCT) to assess the brain parenchyma, and either CT angiography

(CTA) or magnetic resonance angiography to assess the vasculature.[4] Digital subtraction angiography is typically reserved for circumstances where there is a high clinical suspicion of RCVS and normal non-invasive imaging.[4] Angiography typically demonstrates segmental narrowing and dilatation of the cerebral arteries with a classic string-of-beads appearance, though imaging may be normal in a third of patients if completed early in the course of disease.[5]

Imaging abnormalities such as acute ischaemic stroke, intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH) can frequently occur in RCVS making it a challenge to distinguish from other vascular conditions, such as aneurysmal SAH and primary angiitis of the central nervous system on imaging.[2] Current RCVS literature includes primarily small case series and the exact proportion of patients with RCVS presenting with these radiological lesions is therefore unclear. For instance, the prevalence of ischaemic stroke is estimated to range from 8% to 39% and estimates of ICH range from 6% to 20%.[2 6–9] We seek to better understand the imaging features of RCVS. The main objective of this systematic review is to estimate the prevalence of imaging findings consistent with ischaemic stroke, ICH and SAH on NCCT in adult patients with RCVS. We hope that the results of this review will help describe the initial imaging features of RCVS in order to increase diagnostic certainty at presentation and to better define the population of interest for future clinical trials.

METHODS AND ANALYSIS
This a priori protocol for a systematic review and meta-analysis was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols checklist.[10]

Eligibility criteria
In order to be eligible for inclusion in this systematic review, the study must meet the following criteria:

Population
The study population will be all adult patients (≥18 years old) with CTA or equivalent (conventional angiogram or MR-angiogram) confirmed RCVS. Studies that report on other illnesses apart from RCVS will be included if they also independently report on imaging findings in RCVS.

Outcome
The primary outcomes will be prevalence of imaging findings consistent with ischaemic strokes, ICH and SAH on NCCT. Prevalence will be reported as the proportion of cases to the number of evaluated participants.

Study design
All case-series, observational studies and clinical trials that report on prevalence of imaging findings in patients with RCVS will be included.

Publication type
All case reports, abstracts, conference proceedings, letters and duplicate publications will be excluded, as will literature not published in the English language.

Information sources
Electronic searches will be conducted in Medline, Embase and the Cochrane Register of Clinical Trials from inception to 1 May 2020. References of identified studies will be manually reviewed to identify relevant papers missed in the database searches. Full search strategies for all databases are included in the online supplemental file.

Search strategy
The search will be performed by combining terms related to RCVS, neuroimaging and vascular imaging abnormalities. The full search strategy can be found in the online supplemental file.

Study selection
Covidence will be used to screen articles for inclusion. Two trained reviewers will independently screen titles and abstracts for inclusion based on predefined criteria. The reviewers will meet after 10% of the sample has been screened to identify, resolve and codify areas of ambiguity when screening the rest of the sample. Conflicts will be resolved by consensus of a third independent reviewer. Full-texts will then be reviewed by two independent reviewers and final inclusion will be based on the criteria mentioned above. Reasons for exclusion of eligible studies will be documented and a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram will be used to describe the study screening and selection process.

Data extraction
Two reviewers will independently extract information from the selected studies using a data extraction form. The form will be pilot tested on a small sample of included studies and modified if it fails to capture all pertinent information. Areas of disagreement between extractors will be identified and clarified. Any remaining disagreements of extracted data will be resolved through consensus or an independent third reviewer.

Study characteristics that will be collected include:
► General study information: title, name of the journal and authors, year of publication, number of sites and location of the central site.
► Study design: study duration, study design (case-series, observational or randomised trial), number of patients with RCVS, mean age of patients with RCVS and male-female distribution of patients with RCVS.
► Primary outcomes of interest: prevalence of imaging findings diagnostic of acute ischaemic stroke on NCCT in patients with RCVS, prevalence of imaging findings diagnostic of ICH on NCCT in patients with

RCVS and prevalence of imaging findings diagnostic of SAH on NCCT in patients with RCVS. We will also extract and report the criteria used by each study to diagnose RCVS, ischaemic stroke, ICH and SAH on NCCT as well as the timing of imaging with respect to symptom onset.

Risk of bias assessment

The methodological quality of case series and observational studies shall be assessed using Newcastle-Ottawa based scales that account for selection, ascertainment, causality and reporting.[11 12] The Cochrane Risk of Bias Tool for Randomized Controlled Trials will be used to assess included randomised trials.[13]

Data synthesis

Key study characteristics and clinical findings will be synthesised and presented in tables.

Pooled prevalence of imaging features will be calculated using the inverse variance-weighted method. Random-effects meta-analysis models will be used over fixed effect models to take into account variability both within and between studies. The Q statistic and I^2 statistic will be used as measures of heterogeneity among studies.

Subgroup analysis will be done to assess the impact of specific variables on prevalence of vascular lesions. When enough data are available, we will consider age, sex, publication year and study design as grouping variables.

Sensitivity analysis will be performed to assess the robustness of the findings. We will perform sensitivity analysis by removing studies with an outlying prevalence, excluding high bias studies as well as removing by study design.

Meta-bias(es)

We will attempt to minimise publication bias by generating and examining funnel plots. Duplicate publication bias will be minimised during the study screening phase by carefully screening publications to ensure duplications do not enter the analysis.

Patient and public involvement

There will be no involvement of patients or the public in this review.

ETHICS AND DISSEMINATION

Formal ethics is not required as primary data will not be collected. The findings of this study will be disseminated through a peer-reviewed publication and conference presentations.

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