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Complications ischémiques cérébrovasculaires au cours de l'artérite à cellules géantes : une étude française rétrospective de 271 patients, revue systématique de la littérature et méta-analyse.

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AVERTISSEMENT

La Faculté n'entend donner aucune approbation aux opinions émises dans les thèses : celles-ci sont propres à leurs auteurs.

LISTE DES ABREVIATIONS

ACG : artérite à cellules géantes

NOIAA : neuropathie optique ischémique antérieure aiguë

EIC : évènements ischémique cérébrovasculaire

IC 95% : intervalle de confiance à 95%

AngioTDM : angio-tomodensitométrie

ARM : angio-imagerie par résonance magnétique

TEP : tomographie par émission de positrons

18-FDG : 18 Fluorodeoxyglucose

GCA: giant cell arteritis

AAION: acute anterior ischemic optic neuropathy

CIE: cerebrovascular ischemic events

ACR-EULAR: American College of Rheumatology – European Ligue Against Rheumatism

ICD-10: International Classification of Diseases, 10th Edition

MOOSE: Meta-analysis of Observational Studies in Epidemiology

JBI: Joanna Briggs Institute

SD: standard deviation

IQR: interquartile range

Doppler US: doppler ultra-sound

PET/CT: positron emission computed tomography

CTA: computed tomography angiography

3T MRI: 3 Tesla magnetic resonance imaging

MRA: magnetic resonance angiography

CRP: C-reactive protein

BMI: body mass index

TIA: transient ischemic attack

TAB: temporal artery biopsy

ESR: erythrocyte sedimentation rate

95% CI: 95% confidence interval

INTRODUCTION GENERALE

L'artérite à cellules géantes (ACG) est la vascularite la plus fréquente chez les patients de plus de 50 ans, avec un âge moyen d'apparition de la maladie de 75 ans. Cette vascularite granulomateuse des gros et moyens vaisseaux touche l'aorte et ses principales branches, avec une prédilection pour les branches de l'artère carotide externe et l'artère ophtalmique, et dans une moindre mesure les artères vertébrales. Cette maladie touche deux fois plus les femmes que les hommes, survient préférentiellement dans les populations d'origine européenne et est beaucoup plus rare dans les populations d'origine africaine, asiatique ou arabe. En France, l'incidence de l'ACG a été estimée à 9 pour 100 000 habitants (1–3).

Les accidents ischémiques représentent les complications les plus graves de l'ACG, principalement les complications ophtalmologiques, notamment la neuropathie optique ischémique antérieure aiguë (NOIAA), qui peut entraîner une cécité irréversible, et les complications ischémiques cérébrales. Ces complications ischémiques ophtalmiques et cérébrales surviennent surtout au début de l'évolution de l'ACG et peuvent survenir malgré l'instauration d'une corticothérapie (4). Les études réalisées avant l'utilisation des corticoïdes pour traiter l'ACG retrouvaient une prévalence élevée de complications ischémiques ophtalmologiques (35 à 60%), tandis que leur prévalence est plus faible (12 à 20%) dans les études menées depuis l'utilisation des corticoïdes (2,3).

Les événements ischémiques cérébrovasculaires (EIC) sont plus rares dans l'ACG, avec une prévalence de 1,5-7% rapportée dans la littérature, en ne considérant que les études ayant défini un EIC lié à l'ACG s'il survenait entre le début des symptômes et jusqu'à 4 semaines après le début de la corticothérapie (2,5–12). L'incidence des EIC dans l'ACG a été estimée à 0,76/100 000 patients-années dans une étude

française de 2015 par Samson *et al.* (9). Cependant, il existe une hétérogénéité considérable concernant la définition des EIC lié à l'ACG entre les différentes études, ce qui conduit à une incertitude sur leur prévalence réelle, qui peut atteindre 14% dans certaines études (13). En 2016, Ungprasert *et al*. ont réalisé une méta-analyse retrouvant un risque relatif combiné d'EIC de 1,40 (IC 95% 1,27-1,56) chez les patients atteints d'ACG par rapport à la population générale (14). Il s'agit, à notre connaissance, de la seule méta-analyse réalisée sur les EIC liés à l'ACG.

Les EIC liés à l'ACG touchent plus souvent le territoire vertébrobasilaire (40-60%) que le territoire carotidien, alors que les événements cérébrovasculaires d'étiologie athéromateuse ne surviennent dans le territoire vertébrobasilaire que dans 15-20% des cas (2,15). Les EIC dans l'ACG sont la conséquence d'une sténose inflammatoire des artères carotides ou vertébrales, principalement dans leur portion extradurale. Les vaisseaux intracrâniens sont exceptionnellement touchés. Une explication ayant été apportée repose sur le fait que les vaisseaux intracrâniens ne contiennent que peu ou pas de limitante élastique interne, et ne contiennent pas de vasa vasorum, par lesquels les cellules inflammatoires pénètrent dans la paroi du vaisseau. Ainsi, le mécanisme d'un EIC liée à l'ACG est généralement une hypoperfusion cérébrale due à une sténose sévère voire une occlusion complète des artères carotides ou vertébrales extradurales, ou l'embolisation d'un thrombus s'étant formé sur une artère inflammatoire (16).

La prévalence et les facteurs de risque des complications ischémiques ophtalmiques ont été bien étudiés, mais ceux des EIC liés à l'ACG sont moins bien connus. Certaines études ont utilisé les complications ischémiques ophtalmiques et cérébrales comme critère combiné, tandis que d'autres ont évalué spécifiquement les facteurs de risque d'EIC, ce qui conduit à des résultats variables.

Les objectifs de notre étude étaient d'évaluer la prévalence des EIC liés à l'ACG, et de caractériser ces patients dans notre cohorte monocentrique française, puis de réaliser une revue systématique de la littérature et une méta-analyse sur la prévalence des EIC liés à l'ACG.

DISCUSSION GENERALE

Prévalence des EIC liés à l'ACG

Notre méta-analyse, synthétisant les données de prévalence à partir de 12 études incluant la nôtre, a retrouvé une prévalence combinée d'EIC liés à l'ACG de 4% (IC 95% 3-6%, I^2 = 70%). L'hétérogénéité diminuait à 55% après avoir identifié l'étude de Pariente *et al.* comme *outlier* (17). Notre méta-régression n'a pas permis d'expliquer l'hétérogénéité par l'utilisation d'un délai de survenue de l'EIC limité à 4 semaines après le diagnostic/la rechute de l'ACG (p=0,66), comme définition d'un EIC lié à l'ACG. Dans notre expérience, pour retenir l'ACG comme étiologie d'un EIC, l'analyse de tous les paramètres cliniques, biologiques et d'imagerie est nécessaire pour évaluer l'activité de la vascularite, et éliminer les autres causes plus fréquentes d'EIC.

Facteurs de risque d'EIC liés à l'ACG

Notre revue systématique de la littérature a permis de faire la synthèse des différents facteurs de risques d'EIC liés à l'ACG ayant déjà été identifiés, et notre étude a mis en évidence de nouvelles associations avec des paramètres d'imagerie.

Le rôle des facteurs de risque cardiovasculaires dans la survenue d'EIC liés à l'ACG reste controversé. Une association significative a été retrouvée dans certaines études

(6,9,10,13,17,18), alors que d'autres n'ont retrouvé aucune association significative (8,19–22). L'interprétation de ces associations doit tenir compte de la prévalence élevée des facteurs de risque cardiovasculaire chez ces patients âgés, pouvant être un facteur de confusion. Notre étude n'a pas retrouvé d'association significative entre les EIC liés à l'ACG et les facteurs de risque cardiovasculaire.

Parmi les signes cliniques, seule la claudication de la mâchoire a été identifiée comme facteur de risque d'EIC dans l'ACG par González-Gay *et al.* (4) avec un OR de 3,49 (IC 95% 0,63-19,2, p=0,151), mais cette association n'a pas été retrouvée dans les études ultérieures. De plus, Gonzalez-Gay *et al*. ont retrouvé dans une autre étude un risque diminué d'EIC chez les patients qui se plaignaient de céphalées (OR 0,15, IC 95% 0,02-0,99, p=0,05) (10).

Une activité inflammatoire clinique et biologique intense (comprenant fièvre, signes généraux, pseudo-polyarthrite rhizomélique, taux élevés de CRP et de VS, faible taux d'hémoglobine) a été rapportée en tant que facteur protecteur contre le risque de complications ischémiques visuelles et cérébrovasculaires de manière constante dans de nombreuses études, que ces complications soient étudiées en tant que critère combiné (4–7,20,22–25), ou bien que seul les EIC soient étudiés (10,13,19). Une explication possible à cette association a été proposée par Hernández-Rodríguez *et al*., qui ont montré une plus faible expression tissulaire et un plus faible taux plasmatique d'IL-6 chez les patients atteints d'ACG avec des complications ischémiques, et que l'effet pro-angiogénique de l'IL-6 pourrait être un mécanisme compensateur de l'ischémie dans l'ACG (26). Cependant, notre étude n'a pas retrouvé d'association significative entre ces caractéristiques cliniques ou biologiques inflammatoires et la survenue d'EIC.

Les complications ischémiques ophtalmiques ont également été rapportées comme un facteur de risque de l'EIC par certains auteurs, tels que Gonzalez-Gay *et al.* (4,10) (OR 7,65, IC 95% 1,58-37,0, p=0,012), et De Boysson *et al.* (OR 5, IC 95% 2,14-12,33, p=0,0002) (19). Cependant, nous n'avons pas retrouvé dans notre étude d'association significative entre les complications ischémiques ophtalmologiques et cérébrovasculaires, de même que Zenone *et al.* (8), Lo Gullo *et al.* (21) et Pego-Reigosa *et al.* (13).

Les EIC liés à l'ACG touchent plus souvent le territoire vertébrobasilaire (40-60%) que le territoire carotidien, alors que parmi les EIC d'étiologie athéromateuse, seuls 15-20% se produisent dans le territoire vertébrobasilaire (2,15). Nos résultats étaient concordant avec ceux de la littérature, 8 (57,2%) de nos 14 EIC liés à l'ACG survenant dans le territoire vertébrobasilaire.

Pour ce qui est des résultats des examens d'imagerie morphologique, dans notre étude, nous avons trouvé une association entre les EIC liés à l'ACG et la présence d'une thrombose de l'artère vertébrale à l'échographie doppler (17% vs 0,8%, p=0,012), et d'une atteinte des artères vertébrales sur l'angio-tomodensitométrie (angioTDM) et/ou l'angiographie par résonance magnétique (ARM) (50% vs 3,4%, p<0,001). L'atteinte des artères vertébrales est fréquente dans l'ACG, et l'utilité de l'échographie doppler pour détecter l'atteinte vertébrale est déjà bien établie (27,28). Dans une revue systématique de la littérature, Elhfnawy *et al.* ont constaté que des sténoses/occlusions multiples dans le territoire vertébrobasilaire touchaient environ 70% des patients victimes d'EIC et atteints d'ACG (29).

L'atteinte des vaisseaux intracrâniens était historiquement considérée comme exceptionnelle dans l'ACG car ils ne contiennent que peu ou pas de limitante élastique interne, et ne contiennent pas de vasa vasorum (15,16). Mais la littérature récente a

montré que l'atteinte des vaisseaux intracrâniens est plus fréquente qu'on ne le pensait, grâce au développement de techniques d'imagerie plus avancées, notamment l'IRM 3 Tesla. Les artères intracrâniennes les plus touchées sont en premier la carotide interne, suivie de la portion intradurale des artères vertébrales (V4), et des artères cérébrales postérieures. Ces patients ont une incidence élevée d'EIC et un mauvais pronostic (30–32). Dans une étude prospective, en utilisant l'IRM 3 Tesla avec une séquence T1WI avec saturation de la graisse, avant et après injection de produit de contraste, optimisée pour l'évaluation du rehaussement de la paroi des vaisseaux intraduraux, Siemonsens *et al.* ont trouvé que, parmi 20 patients atteints d'ACG, 10 (50%) présentaient une atteinte de l'artère carotide interne dans sa portion intradurale, 9 présentaient une atteinte des artères vertébrales, dont 5 bilatérales. Un patient présentait une atteinte de l'artère cérébrale moyenne. Cependant l'atteinte des vaisseaux intraduraux n'était pas corrélée avec les lésions sténo-occlusives intracrâniennes, ni avec les infarctus cérébraux, par conséquent sa valeur pronostique restait incertaine (33). Notre étude confirme la prévalence élevée de l'atteinte des artères intracrânienne. En effet, 7 (50%) de nos 14 patients atteints d'EIC liés à l'ACG présentaient une atteinte des artères intracrâniennes sur l'ARM cérébrale et/ou l'angioTDM. De plus, nous avons identifié une association significative entre l'atteinte des artères intracrâniennes sur l'angioTDM et/ou l'ARM et la survenue d'un EIC lié à l'ACG (50% vs 1,8%, $p<0,001$). Des études ultérieures sont nécessaires pour mieux définir la valeur pronostique de l'atteinte des artères vertébrales et intracrâniennes, et son potentiel prédictif de la survenue d'EIC.

Concernant l'imagerie fonctionnelle par tomographie par émission de positrons (TEP) au 18-FDG, les artères axillaires font partie des artères les plus fréquemment touchées dans l'ACG. Blockmans *et al.* ont retrouvé que les artères les plus fréquemment

atteintes sur la TEP au diagnostic étaient les sous-clavières (74%), l'aorte abdominale (54%) et thoracique (51%), et les axillaires (40%), dans leur cohorte prospective de 35 patients (34). Dans notre étude, nous avons trouvé une association entre l'atteinte des artères axillaires sur la TEP et la survenue d'un EIC lié à l'ACG (55% vs 20%, p=0.016). Peu d'études ont évalué le risque de complications ischémiques en fonction des résultats de la TEP. Dans une étude prospective de Mestre-Torres *et al.*, 30 patients atteints d'ACG, dont 21 présentant des complications ischémiques au moment du diagnostic (principalement ophtalmologiques, un seul patient présentait un EIC) ont bénéficié d'une TEP durant les 10 premiers jours de corticothérapie. Les patients présentant des manifestations ischémiques avaient plus fréquemment un hypermétabolisme des artères vertébrales sur la TEP, ce résultat étant à la limite de la significativité (OR 5, IC 95% 0,99-24,86, p=0,051). L'atteinte de tous les autres territoires sur la TEP s'est avérée être protectrice contre les complications ischémiques (35). Ces résultats sont difficilement comparables aux nôtres car notre critère de jugement principal était exclusivement les EIC. De plus, dans notre cohorte, 171 patients ont eu une TEP avec un délai médian de 1 jour (-7-20) par rapport au début de la corticothérapie. D'autres études sont nécessaires pour préciser l'intérêt de la TEP pour évaluer le risque d'événements ischémiques, en particulier les EIC.

Traitements

Dans notre étude, les patients atteints d'EIC liés à l'ACG étaient plus souvent traités par tocilizumab que le groupe témoin (29% vs 12%, p=0,081). Chez 4 patients, l'EIC lié à l'ACG a motivé la prescription de tocilizumab. Il est intéressant de noter qu'aucun des patients à qui du tocilizumab a été prescrit n'a présenté de récidive d'EIC après son introduction, bien que l'un d'entre eux, atteint d'un AVC multifocal sévère, soit

décédé de complications d'AVC dans les 3 mois suivant le diagnostic. Cependant, le design de notre étude ne nous permet pas de tirer des conclusions sur un potentiel effet protecteur du tocilizumab contre la survenue d'EIC, et des travaux supplémentaires sont nécessaires pour préciser la place du tocilizumab pour les EIC liés à l'ACG.

Conclusion

En conclusion, les EIC font partie des complications ischémiques les plus graves de l'ACG. Selon notre méta-analyse de la littérature, la prévalence combinée d'EIC liés à l'ACG était de 4%. Etant donné que les EIC liés à l'ACG augmentent la morbidité et la mortalité, l'identification de leurs facteurs de risque est cruciale pour prévenir leur apparition et améliorer le pronostic des patients. Notre étude a mis en évidence de nouvelles associations entre des atteintes vasculaires sur divers types d'imagerie et la survenue d'EIC liés à l'ACG, telles qu'une thrombose de l'artère vertébrale sur l'échographie doppler, une atteinte des artères vertébrales et des artères intracrâniennes sur l'angioTDM et/ou l'ARM, et une atteinte des artères axillaires sur la TEP. Des études supplémentaires sont nécessaires pour confirmer ces associations comme étant des facteurs de risque. Enfin, bien que l'utilisation du tocilizumab ait été motivée par la survenue d'un EIC lié à l'ACG chez 4 de nos patients avec des résultats positifs, d'autres études sont nécessaires pour préciser son utilisation dans la prévention des EIC liés à l'ACG.

GIANT CELL ARTERITIS-RELATED CEREBROVASCULAR ISCHEMIC EVENTS: A FRENCH RETROSPECTIVE STUDY OF 271 PATIENTS, SYSTEMATIC REVIEW OF THE LITERATURE AND META-ANALYSIS

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ABSTRACT

Introduction

Cerebrovascular ischemic events (CIE) are among the most severe complications in giant cell arteritis (GCA). Heterogeneity between different studies in the definition of GCA-related CIE leads to uncertainty regarding their real prevalence. The aim of our study was to evaluate the prevalence of GCA-related CIE and characterize these patients in a well-phenotyped cohort, and to perform a meta-analysis of the prevalence of GCA-related CIE in the literature.

Materials and methods

This was a retrospective study from January 1, 2010 to December 31, 2020 at Lille University Hospital. All consecutive patients with GCA according to ACR-EULAR diagnostic criteria were included. A systematic review of the literature using MEDLINE and EMBASE was performed. Cohort studies of unselected GCA patients reporting CIE were included in the meta-analysis. We calculated the pooled summary estimate of GCA-related CIE prevalence.

Results

A total of 271 GCA patients (89 males) with mean age 72 ± 9 years were included in the study. Among them, 14 (5.2%) presented a GCA-related CIE. Patients with GCA-related CIE more frequently had vertebral artery thrombosis on Doppler US (17% vs 0.8%, p=0.012), vertebral arteries involvement (50% vs 3.4%, p<0.001) and intracranial arteries involvement (50% vs 1.8%, p<0.001) on computed tomography angiography (CTA) and/or magnetic resonance angiography (MRA), and axillary arteries involvement on positron emission computed tomography (PET/CT) (55% vs 20%, p=0.016).

Twelves studies, including ours, were included in the meta-analysis, representing a total population of 2870 patients. The pooled prevalence of GCA-related CIE was 4% (95%CI 3-6, I^2=70%).

Conclusion

The pooled prevalence of GCA-related CIE was 4%. Our cohort identifies an association between GCA-related CIE and vertebral, intracranial and axillary arteries involvement on various imaging modalities.

INTRODUCTION

Giant cell arteritis (GCA) is the most common form of vasculitis in patients over 50 years of age, with an average age of onset of 75 years. This granulomatous vasculitis of large and medium arteries affects the aorta and its major branches, with a predilection for the external carotid and ophthalmic arteries, and to a lesser extent the vertebral arteries. This disease occurs twice as frequently in women than in men, occurs preferentially in populations of European origin and is much rarer in populations of African, Asian, or Arab origin. In France, the incidence of GCA has been estimated at 9 per 100,000 inhabitants (1–3).

Among the most serious complications of GCA are ischemic events, mainly ophthalmologic complications, mainly acute anterior ischemic optic neuropathy (AAION), which can lead to irreversible blindness, and cerebral ischemic complications. Both ophthalmic and cerebral ischemic complications occur mostly early in the course of GCA, and can occur despite initiation of corticosteroid therapy (4). Studies conducted prior to the use of corticosteroids to treat GCA had found a high prevalence of ophthalmologic ischemic complications (35 – 60%), while the prevalence is lower (12-20%) in studies conducted since the use of corticosteroids (2,3).

Cerebrovascular ischemic events (CIE) are more rarely associated with GCA, with a prevalence of 1.5-7% reported in the literature, in studies that have limited the inclusion of such events if occurring concomitantly with GCA diagnosis up to 4 weeks after the start of glucocorticoid therapy (2,5–12). The incidence of CIE in GCA has been estimated at 0.76/100,000 patient-years in a 2015 French study by Samson *et al.* (9). However, there is considerable heterogeneity about the definition of a GCA-related CIE between the different studies, leading to an uncertainty regarding the real

prevalence of CIE, which may be as high as 14% in some studies (13). In a 2016 meta-analysis, Ungprasert *et al.* found a pooled risk ratio of cerebrovascular events of 1.40 (95% CI 1.27-1.56) in patients with GCA versus non-GCA comparators (14). This is, to our knowledge, the only meta-analysis conducted about GCA-related CIE.

GCA-related CIE more often involve the vertebrobasilar territory (40-60%) rather than the carotid territory, whereas among atheromatous cerebrovascular events, only 15-20% occur in vertebrobasilar territory (2,15). This is the consequence of inflammatory stenosis of carotid or vertebral arteries, mainly in their extradural part. Intracranial vessels are exceptionally affected. One reported explanation is that intracranial vessels contain little or no internal elastic laminae, and do not contain vasa vasorum, through which inflammatory cells enter the vessel wall. Thus, the mechanism of GCA-related CIE is usually a cerebral hypoperfusion due to severe stenosis or even complete occlusion of extradural carotid or vertebral arteries, or embolization of a thrombus formed on the inflammatory artery (16).

Although prevalence and risk factors for ophthalmic ischemic complications have been well studied, these are less well known in the case of GCA-related CIE. Some studies have used both ophthalmic and cerebral ischemic complications as a combined endpoint, while others have specifically evaluated risk factors for CIE, which leads to variable results.

The aim of the present study was to fill these gaps by evaluating the prevalence of GCA-related CIE and characterize these patients in a well-phenotyped cohort, and perform a systematic review and meta-analysis of the prevalence of GCA-related CIE in the literature.

PATIENTS AND METHODS

French cohort study

Population

We conducted a retrospective observational study in the Internal Medicine Department of Lille University Hospital in France (National Center for Systemic Autoimmune Diseases). Medical Information Department was queried with relevant International Classification of Diseases, 10th Edition (ICD-10) codes, in order to screen all patients having been diagnosed with GCA between January 1, 2010 and December 31, 2020, and among them, those who presented with CIE (established or transient strokes). The ICD-10 codes used were M316 (Giant cell arteritis), I63 (Cerebral infarct), I64 (Stroke, not specified as hemorrhagic or infarct stroke), and G45 (Transient stroke and related syndromes). Patients identified with the ICD-10 codes were included if they met ACR-EULAR diagnostic criteria. Among the patients screened with GCA who presented one or more CIE, medical records were reviewed to assess whether the CIE were GCA-related or not.

A CIE was defined as GCA-related if it was clearly linked to GCA at diagnosis or relapse, within a delay of 4 weeks from diagnosis or relapse, after reviewing patient's medical records, in the absence of another well-identified etiology (mainly atherosclerosis, embolic or cerebral small vessel disease).

Cardiovascular events during follow-up were defined by the occurrence of non-GCA related CIE, myocardial infarction, or limb ischemia.

Data collection

Data collected at baseline were patient demographics, cardiovascular risk factors, cardiovascular history, atrial fibrillation, GCA symptoms, polymyalgia rheumatica symptoms, inflammatory biological markers, temporal artery biopsy findings, ischemic complications, inflammatory vascular involvement as diagnosed on Doppler ultrasound (mainly hypoechoic wall thickening and vertebral artery thrombosis), PET/CT (vascular hypermetabolism), CTA and MRA. Specific treatment was recorded as well as the occurrence of cardiovascular events during follow-up.

Systematic review of the literature and meta-analysis

The meta-analysis was conducted according to MOOSE guidelines. MEDLINE and EMBASE databases were queried by two of the authors (TP and MRP) using the following search terms: (giant cell arteritis, Horton [MeSH Terms]) AND (cerebrovascular accident [MeSH Terms]) and ‘giant cell arteritis’/exp AND ‘cerebrovascular accident’/exp". All records published before May 31, 2021, were included in the search. Language was restricted to English or French. Reference list of selected studies was hand-searched for additional relevant studies to be included in the meta-analysis.

Two of the authors (TP and MRP) independently screened the titles and abstracts of the retrieved records to identify eligible articles to be studied in full-text. The two reviewers then read the full-text of eligible articles for inclusion in the meta-analysis. Selected articles were compared and in case of disagreement, decisions were made by consensus. Studies of unselected adult GCA patients cohort, assessing a CIE

prevalence, were included in the analysis. Studies from same centers were included if their respective study periods were different. If for a same center, two studies covered an overlapping study period, data from the largest cohort were kept.

Quality of the studies was assessed using the JBI Critical Appraisal Checklist for studies reporting prevalence data (36).

Data were extracted and entered into a predefined spreadsheet table which included the following items: name of the first author, title of the study, year of publication, country, study design, study period, GCA diagnosis criteria, ischemic complications studied, study population, the definition, number and prevalence of GCA-related CIE.

Ethical statement

This study was conducted in compliance with the good clinical practices protocol and the Declaration of Helsinki principles. French legislation on non-interventional studies requires collecting the non-opposition of patients but does not require written consent. As such, non-opposition was obtained from each patient included in the study for the use of their de-identified medical record data.

Statistical analysis

Continuous variables are expressed as means ± standard deviation (SD) or medians (interquartile range (IQR)). Categorical variables were expressed as number (%). Comparisons between groups were conducted using Fisher's exact test or Pearson's Chi-squared test, as appropriate, for categorical variables, and Wilcoxon rank-sum test for continuous variables. A p value of ≤ 0.05 defined statistical significance.

For the meta-analysis, we calculated a weighted pooled summary estimate of proportion of GCA-related CIE. Proportions of individual studies was transformed using Freeman-Tukey double arcsine method for normalizing and variance-stabilizing the sampling distribution. For the meta-analysis, a random-effects model estimated with the DerSimonian and Laird method was used. Accordingly, studies were considered to be a random sample from a population of studies. Heterogeneity was assessed using an I^2 statistic and a chi-square heterogeneity statistic. The overall effect was estimated using a weighted average of individual effects, with weights inversely proportional to variance in observed effects.

Meta-regression was used to assess the impact of delay from diagnosis to define a CIE to be GCA-related.

All analyses were performed using R with meta and metafor packages, p values less than 0.05 were considered significant.

RESULTS

French cohort study

Baseline characteristics

Of the 339 patients screened, 271 (89 (33%) men) met the ACR-EULAR diagnostic criteria and were therefore included in the present study (Table 1). Mean age at the diagnosis was 72 ± 9 years. Median follow-up time was 48 months (21-81). Temporal artery biopsy was positive in 137 (55%) patients. Cardiovascular risk factors were present in 207 (76.4%) patients, mainly hypertension (56%), and 35 (13%) patients

had atrial fibrillation. The most frequent symptom at diagnosis was headache (71%). The median CRP level was 70 mg/l (35–120).

GCA-related cerebrovascular ischemic events

Among these 271 patients, 14 (5.2%) presented a GCA-related CIE at diagnosis or relapse (10 constituted and 4 transient), with a median delay between the GCA-related CIE and diagnosis or relapse of GCA of 5 days (-22-0). Regarding the territory of these 14 CIE, 8 (57.2%) occurred in the vertebrobasilar territory, 5 (35.7%) in the carotidal territory, and the remaining one associated multifocal ischemic and hemorrhagic strokes related to intra-cranial vasculitis. A detailed description of these GCA-related CIE is shown in Supplementary table 1. Two of these patients presented a recurrent GCA-related CIE.

Comparison of GCA patients with and without GCA-related cerebrovascular ischemic events

Patients with GCA-related CIE presented a lower BMI (22.5 vs 24.9 kg/m², p=0.02). Imaging studies showed that patients with GCA-related CIE more frequently had vertebral artery thrombosis on Doppler US (17% vs 0.8%, p=0.012), vertebral artery involvement (50% vs 3.4%, p<0.001) and intracranial artery involvement (50% vs 1.8%, p<0.001) on CTA and/or MRA. There was also a trend towards more frequent involvement of carotid artery on CTA and/or MRA with borderline significance (36% vs 15%, p=0.053). Patients with GCA-related CIE more frequently had axillary artery involvement on PET/CT (55% vs 20%, p=0.016).

There was a trend towards less cranial symptoms in patients with GCA-related CIE (headache: 54% vs 72%, p=0.2; scalp tenderness 15% vs 39%, p=0.087). Patients with GCA-related CIE were also more frequently men (57% vs 32%, p=0.075) and smokers (54% vs 30%, p=0.12) but it was not statistically significant. We observed a trend towards less visual complications in patients with GCA-related CIE (7.1% vs 30%, p=0.12).

Regarding the treatments received, patients with GCA-related CIE had more frequently been treated by glucocorticoids pulses (69% vs 25%, p=0.001). They also tended to receive tocilizumab more often than the control group, but this result did not reach significance (29% vs 12%, p=0.081). Mortality tended to be higher in patients with GCA-related CIE, but with borderline significance (29% vs 11%, p=0.075).

Table 1. Comparison of baseline characteristics according to GCA-related CIE

Characteristic	N	Overall, N = 271	No GCA-related CIE, N = 257	GCA-related CIE, N = 14	p-value
Age at diagnosis (years)	271	72 ± 9	72 ± 9	70 ± 9	0.3
Follow up (months)	271	48 (21-81)	50 (22-84)	24 (9-31)	**0.02**
Cardiovascular risk factors	271	207 (76.4%)	197 (76.6%)	10 (71.4%)	NS
Male	271	89 (33%)	81 (32%)	8 (57%)	0.075
Hypertension	271	151 (56%)	145 (56%)	6 (43%)	0.3
Diabetes	271	54 (20%)	51 (20%)	3 (21%)	>0.9
Dyslipidemia	271	99 (37%)	94 (37%)	5 (36%)	>0.9
Obesity	190	77 (41%)	75 (42%)	2 (18%)	0.2
Smoking	267	83 (31%)	76 (30%)	7 (54%)	0.12
BMI (kg/m2)	147	24.8 (22.1-28.4)	24.9 (22.3-28.6)	22.5 (18.0-24.1)	**0.02**
Cardiovascular history					
Coronary heart disease	271	11 (4.1%)	11 (4.3%)	0 (0%)	>0.9
Stroke history	271	24 (8.9%)	23 (8.9%)	1 (7.1%)	>0.9
Peripheral artery disease	271	20 (7.4%)	19 (7.4%)	1 (7.1%)	>0.9
Atrial fibrillation	271	35 (13%)	33 (13%)	2 (14%)	0.7
Positive temporal artery biopsy	248	137 (55%)	129 (55%)	8 (57%)	0.9
Clinical features					
Constitutional symptoms	263	150 (57%)	141 (56%)	9 (69%)	0.4
Fever	263	53 (20%)	51 (20%)	2 (15%)	>0.9
Headache	264	188 (71%)	181 (72%)	7 (54%)	0.2
Jaw claudication	263	104 (40%)	98 (39%)	6 (46%)	0.6
Scalp tenderness	262	99 (38%)	97 (39%)	2 (15%)	0.087
Limb claudication	262	27 (10%)	27 (11%)	0 (0%)	0.4
Non palpable temporal pulse	262	46 (18%)	44 (18%)	2 (15%)	>0.9
Polymyalgia rheumatica	270	93 (34%)	89 (35%)	4 (29%)	0.8
Ischemic complications					
Visual involvement	271	77 (28%)	76 (30%)	1 (7.1%)	0.12
AAION	271	41 (15%)	40 (16%)	1 (7.1%)	0.7
Time from diagnosis to AAION (days)	41	-4 (-11-0)	-4 (-10-0)	-128 (-128--128)	0.11
Other visual involvement	271	38 (14%)	38 (15%)	0 (0%)	0.2

Cerebrovascular ischemic events					
GCA-related CIE		14 (5,2%)	0 (0%)	14 (100%)	
GCA-related recurrent CIE	271	2 (0.7%)	0 (0%)	2 (14%)	**0.002**
Time from diagnosis to GCA-related first CIE (days)	14	-5 (-22-0)	NA (NA-NA)	-5 (-22-0)	
Coronary artery involvement	271	3 (1.1%)	3 (1.2%)	0 (0%)	>0.9
Aortic involvement	271	9 (3.3%)	8 (3.1%)	1 (7.1%)	0.4
Other involvement	271	26 (9.6%)	25 (9.7%)	1 (7.1%)	>0.9
Biological parameters					
CRP (mg/l)	251	70 (35-120)	70 (35-120)	44 (24-98)	0.5
Hemoglobin level (g/dl)	169	11.70 (10.60-12.80)	11.65 (10.60-12.80)	12.10 (10.90-13.70)	0.5
Imagery					
Doppler US					
Hypoechoic wall thickening of temporal artery	250	74 (30%)	70 (29%)	4 (33%)	0.8
Hypoechoic wall thickening of carotid artery	251	43 (17%)	41 (17%)	2 (17%)	>0.9
Hypoechoic wall thickening of vertebral artery	250	6 (2.4%)	5 (2.1%)	1 (8.3%)	0.3
Thrombosis of vertebral artery	251	4 (1.6%)	2 (0.8%)	2 (17%)	**0.012**
Hypoechoic wall thickening of axillary artery	251	43 (17%)	43 (18%)	0 (0%)	0.2
Hypoechoic wall thickening of subclavian artery	251	37 (15%)	35 (15%)	2 (17%)	0.7
Hypoechoic wall thickening of femoral artery	250	15 (6.0%)	15 (6.3%)	0 (0%)	>0.9
PET/CT					
PET/CT delay from diagnosis (days)	171	1 (-7-20)	2 (-7-24)	0 (-9-0)	0.14
Temporal artery involvement	171	8 (4.7%)	8 (5.0%)	0 (0%)	>0.9
Carotid artery involvement	171	55 (32%)	51 (32%)	4 (36%)	0.7
Vertebral artery involvement	171	38 (22%)	35 (22%)	3 (27%)	0.7
Axillary artery involvement	171	38 (22%)	32 (20%)	6 (55%)	**0.016**
Subclavian artery involvement	171	85 (50%)	78 (49%)	7 (64%)	0.4
Femoral artery involvement	171	39 (23%)	37 (23%)	2 (18%)	>0.9
Aortitis	171	92 (54%)	86 (54%)	6 (55%)	>0.9
Polymyalgia rheumatica	171	36 (21%)	35 (22%)	1 (9.1%)	0.5
CTA/MRA					
CTA/MRA carotid artery involvement	193	31 (16%)	26 (15%)	5 (36%)	0.053
CTA/MRA vertebral artery involvement	193	13 (6.7%)	6 (3.4%)	7 (50%)	**<0.001**
CTA/MRA axillary artery involvement	172	12 (7.0%)	12 (7.5%)	0 (0%)	>0.9
CTA/MRA subclavian artery involvement	172	38 (22%)	36 (22%)	2 (17%)	>0.9
CTA/MRA aortitis	172	72 (42%)	68 (42%)	4 (33%)	0.8
CTA/MRA cerebral artery involvement	71	8 (11%)	1 (1.8%)	7 (50%)	**<0.001**
CTA cerebral artery involvement	13	4 (31%)	0 (0%)	4 (57%)	0.070
MRA cerebral artery involvement	69	7 (10%)	1 (1.8%)	6 (43%)	**<0.001**
Treatments					
Pulse glucocorticoids	265	71 (27%)	62 (25%)	9 (69%)	**0.001**
Initial oral glucocorticoid dosage (mg/day)	264	55 (45-60)	50 (45-60)	60 (55-80)	**0.017**
Aspirin	270	216 (80%)	204 (80%)	12 (86%)	0.7
Tocilizumab	265	33 (12%)	29 (12%)	4 (29%)	0.081
Methotrexate	270	74 (27%)	72 (28%)	2 (14%)	0.4
Cardiovascular events during follow-up	270	32 (12%)	30 (12%)	2 (14%)	0.7
Cardiovascular event type	32				>0.9
Non GCA-related CIE		19 (59%)	17 (57%)	2 (100%)	
Myocardial infarction		9 (28%)	9 (30%)	0 (0%)	
Limb ischemia		4 (12%)	4 (13%)	0 (0%)	
Time from diagnosis to non GCA-related CIE (days)	18	1,499 (717-1,723)	1,378 (626-1,636)	3,073 (2,830-3,316)	0.052
Non GCA-related CIE etiology	18				0.8
Atherosclerosis		2 (11%)	2 (12%)	0 (0%)	
Cardioembolism		6 (33%)	5 (31%)	1 (50%)	
Small vessel disease		3 (17%)	2 (12%)	1 (50%)	
Septic		1 (5.6%)	1 (6.2%)	0 (0%)	

Undetermined		6 (33%)	6 (38%)	0 (0%)	
Mortality	271	33 (12%)	29 (11%)	4 (29%)	0.075

Results are expressed as mean ± SD or median (IQR) for quantitative variables, n (%) for qualitative variables
N: number of patients with available data
GCA: giant cell arteritis, CIE: cerebrovascular ischemic event, BMI: body mass index, AAION: acute anterior ischemic optic neuropathy, CRP: C-reactive protein, Doppler US: doppler ultra-sound, PET/CT: positron emission computed tomography, CTA: computed tomography angiography, MRA: Magnetic resonance angiography, NS: non-significant

Cardiovascular events during follow-up

During follow-up, 32 (12%) patients presented a cardiovascular event, of which 19 (59%) were non GCA-related CIE, 9 (28%) myocardial infarction, and 4 (12%) limb ischemia. The etiology of the 19 non GCA-related CIE was available for 18 of them: 2 (11%) were atheromatous, 6 (33%) were cardioembolic, 3 (17%) related to small artery disease, 1 (5.6%) of septic cause (embolism of endocarditis), and 6 (33%) with no identified etiology.

Among the population of patients with GCA-related CIE, 2 of them presented a non GCA-related CIE during follow-up, but this complication occurred later than in the control group (3 073 vs 1 378 days, p=0.052).

Systematic review of the literature and meta-analysis

Study selection

A total of 564 potentially relevant articles were found from MEDLINE and EMBASE search, after exclusion of duplicated articles. After screening, 50 potentially eligible studies were selected, 4 relevant articles found in the reference list of selected studies were added, and full-text copies of these citations were obtained. Of these articles, 12 studies, including our cohort, were included in the meta-analysis, representing a total population of 2870 patients (Figure 1). The main characteristics of the included studies are summarized in Table 2.

Figure 1. Flow chart showing search strategy to identify studies in the meta-analysis

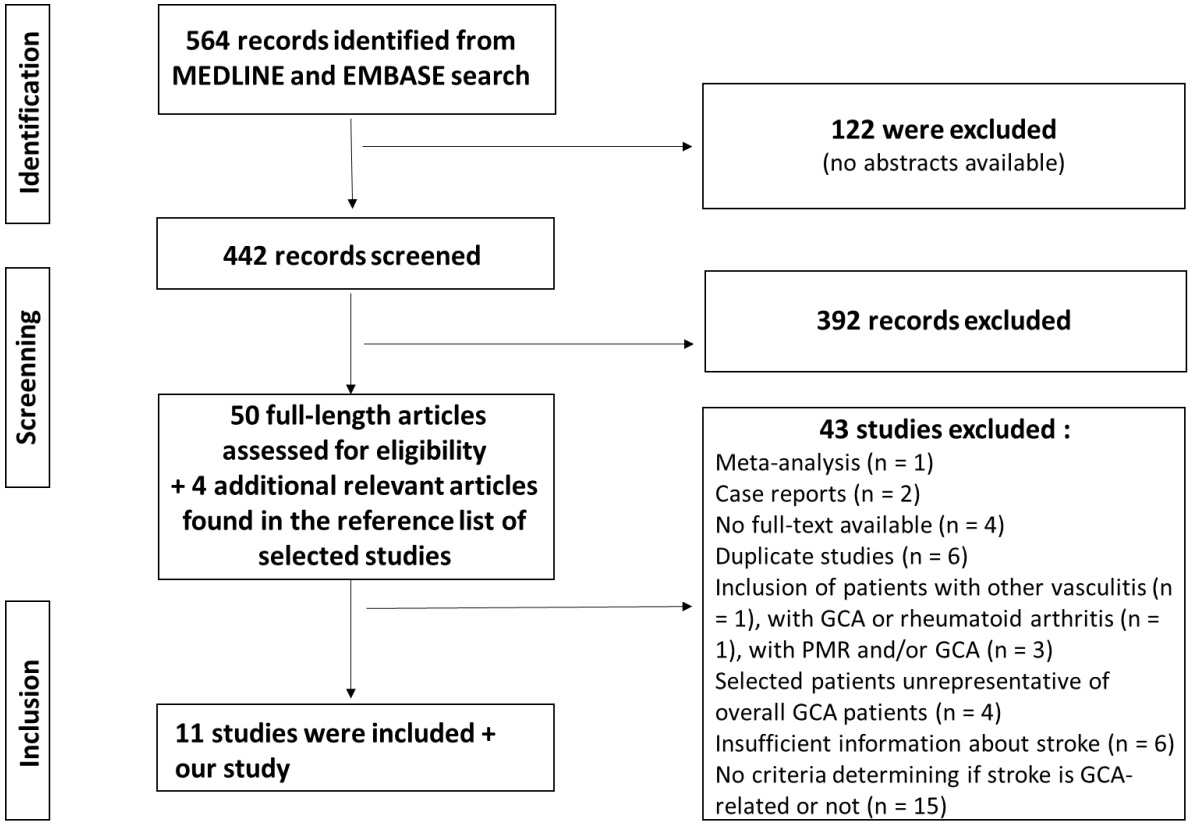


Table 2. Main characteristics of studies in the prevalence meta-analysis

First author	Country	Year	Study design	Study period	GCA diagnosis criteria	GCA-related cerebrovascular ischemic event (CIE) definition	Popul-ation	Number of CIE	Preval-ence
Berger (7)	Switzerland	2009	Retrospective	10 years (1997 - 2007)	Biopsy-proven GCA and/or ACR-EULAR criteria (≥3/5)	If occurring within 2 weeks of diagnosis. TIA were excluded.	85	2	2,35%
Cid (5)	Spain	1998	Retrospective	16 years	Biopsy-proven GCA	If they were concomitant with disease manifestations and in the absence of significant vascular risk factors such as heavy smoking, hypertension, hypercholesterolemia, or diabetes.	200	3	1,50%
De Boysson (19)	France	2017	Retrospective	20 years (1995 - 2015)	ACR-EULAR criteria (≥3/5)	If occurring at the time of diagnosis or within 4 weeks after starting GCA therapy. TIA were excluded.	876	35	4,00%
Gonzalez-Gay (10)	Spain	2009	Retrospective	27 years (1981 - 2008)	Biopsy-proven GCA	If occurring between the onset of symptoms of the disease and 4 weeks after the onset of steroid therapy. All patients in whom stroke was diagnosed had lesions on CTA and/or MRA that were read by a neuroradiologist and correlated clinically by a neurologist. TIA were excluded.	287	8	2,79%
Hočevar (25)	Slovenia	2020	Prospective	8 years (2011 - 2019)	Corresponding clinical and laboratory features, and a positive result of a TAB, or CDS or PET/CT	If occurring after the onset of GCA symptoms and up to 1 month after the initiation of glucocorticoid therapy. TIA were excluded.	295	9	3,05%
Lee (20)	USA	2006	Retrospective	15 years (1989 - 2004)	ACR-EULAR criteria (≥3/5)	If other signs, symptoms, or laboratory evidence of a recurrence was present. Hemispheric strokes only were included. TIA were excluded.	143	6	4,20%
Narváez (37)	Spain	2008	Retrospective	18 years (1986 - 2004)	Biopsy-proven GCA and/or ACR-EULAR criteria (≥3/5)	If occurring within the time between the onset of GCA symptoms and 4 weeks after the onset of corticosteroid therapy.	121	5	4,13%
Nesher (22)	Israel	2004	Retrospective	20 years (1980 - 2000)	Biopsy-proven GCA and/or ACR-EULAR criteria (≥3/5)	If occurring at presentation or within 2 weeks of GCA diagnosis. Strokes developing later were considered GCA related only when associated with at least 1 of the other GCA-related signs or symptoms, or laboratory evidence of acute-phase reaction. TIA were excluded.	175	19	10,86%

Pariente (17)	France	2019	Retrospective	8 years (2010 - 2018)	ACR-EULAR criteria (≥3/5)	If occurring within a delay between GCA diagnosis and stroke inferior to 12 months, and with no other etiology of stroke, notably the absence of atrial fibrillation at the time of stroke.	139	18	12,95%
Penet	France	2021	Retrospective	11 years (2010 - 2020)	ACR-EULAR criteria (≥3/5)	If it was clearly linked to GCA at diagnosis or relapse after reviewing patient's medical records, in the absence of another well identified etiology (mainly atherosclerosis, embolic or cerebral small vessel disease).	271	14	5,17%
Salvarani (6)	Italy	2009	Retrospective	19 years (1986 - 2005)	Biopsy-proven GCA	If occurring within the time between the onset of GCA symptoms and 4 weeks after the onset of corticosteroid therapy.	180	5	2,78%
Zenone (8)	France	2013	Retrospective	12 years (1999 - 2012)	ACR-EULAR criteria (≥3/5)	Doppler-US or MRA of the supra-aortic vessels performed in order to demonstrate concentric segmental narrowing, stenosis and/or occlusions suggestive of vasculitis.	98	6	6,12%

GCA: giant cell arteritis, CIE: cerebrovascular ischemic events, TIA: transient ischemic attack, TAB: temporal artery biopsy, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, CDS: color doppler ultra-sound, CTA: computed tomography angiography, MRA: magnetic resonance angiography, PET/CT: positron emission computed tomography

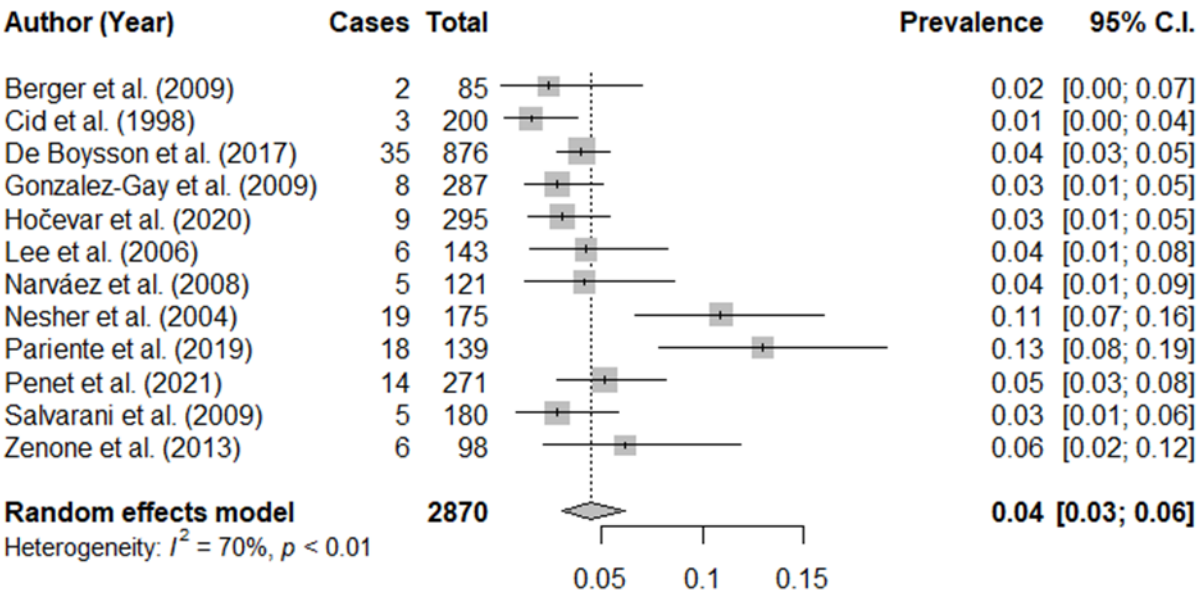
Cerebrovascular ischemic events prevalence meta-analysis

The pooled prevalence of GCA-related CIE for all studies was 0.04 [(95% CI 0.03-0.06); I^2 = 70%; p (het)<0.01] (Figure 2).

Outlier and influential analyses were used to explain heterogeneity. After identification of Pariente *et al.* as outlier study, the resulting pooled prevalence was 0.04 (95% CI 0.03-0.05) with a decrease in heterogeneity (I^2 = 55%).

Moreover, we attempted to explain heterogeneity by distinguishing studies having used a delay cut-off of 4 weeks from diagnosis to define a CIE to be GCA-related. Meta-regression using as moderator this delay cut-off did not explain heterogeneity (p=0.66). Hence, no subgroup analysis was conducted.

Figure 2. Forest plot of GCA-related CIE prevalence in all studies



DISCUSSION

Relating a CIE to GCA can be challenging because of multiple other CIE causes that patients may present. The aim of our study was to evaluate the prevalence of GCA-related CIE in our cohort using strict criteria along with a systematic review and meta-analysis of the literature, to determine the pooled prevalence of CIE in GCA. We further characterized patients with GCA-related CIE in our well-phenotyped cohort with especially various imaging modalities available. The main results of our study are: (i) a prevalence of GCA-related CIE of 5.2% in our cohort, (ii) a pooled prevalence of GCA-related CIE of 4% (95% CI 3-6 %) in our meta-analysis of the literature, including our new cohort, (iii) an association between GCA-related CIE and lower BMI, vertebral artery thrombosis on Doppler US, vertebral and intracranial arteries involvement on CTA and/or MRA, and axillary arteries involvement on PET/CT.

GCA-related CIE prevalence

There is considerable heterogeneity about the definition of a GCA-related CIE between the different studies, leading to an uncertainty regarding the actual prevalence of CIE, which can range from 1.5% (5) to 12.95% (17). Thus, a meta-analysis was needed to provide a reliable prevalence of GCA-related CIE. Our meta-analysis found a pooled prevalence of GCA-related CIE of 4% (95% CI 3-6%, I^2 = 70%). The heterogeneity decreased to 55% after identifying Pariente *et al.* as an outlier study. The high prevalence of 13% in Pariente *et al.* could be partly explained by a long delay of up to 12 months from diagnosis in defining GCA-related CIE, although they had ensured that there was no other etiology of CIE (17). In 9 out of 12 studies included in our meta-analysis, a temporal criterion of up to 4 weeks delay from diagnosis/relapse of GCA to

CIE was used. However meta-regression using as moderator this delay cut-off did not explain heterogeneity (p=0.66). In our experience, to relate a CIE to GCA, a complete lookup of all clinical, laboratory and imaging data is needed to evaluate the activity of the vasculitis, in addition to eliminating other usual causes of CIE.

GCA-related CIE risk factors

Cardiovascular risk factors, clinical and biological features

The role of traditional cardiovascular risk factors in GCA-related CIE remains controversial. Some authors found an association with CIE (6,9,10,13,17,18), whereas others did not show any significant association (8,19–22). In our study, GCA-related CIE were not significantly associated with cardiovascular risk factors, except for BMI which was lower in GCA-related CIE patients and a trend towards more frequent men and smokers. However, interpretation of these associations must consider the high prevalence of cardiovascular risk factors in aged patients with GCA.

Regarding clinical features, only jaw claudication has been linked to CIE by González-Gay *et al.* (4) with an OR of 3.49 (95% CI 0.63-19.2, p=0.151), but this association was not found in subsequent studies. In a study by Hočevar *et al.*, jaw claudication was a risk factor for visual and cerebrovascular ischemic complications when studied as a combined endpoint (OR 3.43, 95% CI 1.84-6.42, p<0.001), but this remained a risk factor only for visual complications in multivariable logistic regression performed to determine predictors separately for vision complications and stroke (25). Moreover, Gonzalez-Gay *et al.* found in a 2009 study a reduced risk of stroke in patients who complained headache at the time of GCA diagnosis (OR 0.15, 95% CI 0.02-0.99,

p=0.05) (10). This is consistent with our results, showing a trend towards less cranial symptoms (headache and scalp tenderness) in patients with GCA-related CIE, although it did not reach statistical significance.

A high clinical and biological inflammatory activity as a protective factor against visual and cerebrovascular ischemic complications was first reported by Cid *et al.* (5), and then has been consistently found among different studies. Patients presenting fever, constitutional symptoms, polymyalgia rheumatica, high CRP and ESR levels, and low hemoglobin show a reduced risk of both visual and cerebrovascular complications, whether these complications are studied as a combined endpoint (4–7,20,22–25), or whether only CIE are studied (10,13,19). A possible explanation of this association was given by Hernández-Rodríguez *et al.*, who demonstrated a lower tissue expression and circulating level of the inflammatory cytokine IL-6 in GCA patients with ischemic complications, which have a pro-angiogenic effect that could be a compensatory mechanism for ischemia in GCA (26). However, our study, as well as Pariente *et al.* (17), did not show any significant association between these inflammatory clinical or biological characteristics and CIE.

Ophthalmologic ischemic complications

Ophthalmic ischemic complications have also been reported as a predictor of CIE in some studies. Gonzalez-Gay *et al.* (4,10) found that the best predictor for the occurrence of stroke was the presence of permanent visual loss (OR 7.65, 95% CI 1.58-37.0, p=0.012) as well as De Boysson *et al.* (OR 5, 95% CI 2.14-12.33, p=0.0002) (19). However, we did not find in our study a significant association between

ophthalmologic and cerebrovascular ischemic complications, as well as Zenone *et al.* (8), Lo Gullo *et al.* (21) and Pego-Reigosa *et al*. (13)

Morphological imaging (Doppler-US, CTA, MRA)

GCA-related CIE more often involve the vertebrobasilar territory (40-60%) rather than the carotid territory, whereas among atheromatous cerebrovascular events, only 15-20% occur in vertebrobasilar territory (2,15). Our results are consistent with the literature, 8 (57.2%) of our 14 GCA-related CIE occurring in the vertebrobasilar territory.

In our study, we found an association between GCA-related CIE and vertebral artery thrombosis on Doppler US (17% vs 0.8%, p=0.012), and vertebral arteries involvement on CTA and/or MRA (50% vs 3.4%, p<0.001). Vertebral arteries involvement is known to be frequent in GCA, and the usefulness of Doppler ultrasound for the detecting vertebral involvement is already well established (27,28). In a systematic review of the literature, Elhfnawy *et al.* found that multiple stenoses/occlusions in the vertebrobasilar territory affected around 70% of stroke patients with GCA (29).

Involvement of intracranial vessels has historically been considered exceptional because they contain few or no internal elastic laminae, and do not contain vasa vasorum (15,16). But recent literature has shown that intracranial vessel involvement is more frequent than previously thought, with the development of more advanced imaging techniques including 3T MRI. The most affected intracranial arteries are first internal carotid, followed by intradural vertebral arteries part (V4) and posterior cerebral arteries, and these patient have high incidence of CIE and poor prognosis (30–32). In a prospective study, Siemonsens *et al*., using 3T MRI with fat-saturated T1WI pre- and

post-contrast application optimized for assessment of intradural vessel wall enhancement, found that, among 20 GCA patients, 10 (50%) presented intradural internal carotid artery involvement, 9 presented vertebral arteries involvement, 5 of them bilateral. One patient presented an involvement of the middle cerebral artery. However, intradural vessels involvement did not correlate with intracranial steno-occlusive lesions, nor cerebral infarction, thus its prognostic value remained uncertain (33). Our study confirms the high prevalence of intracranial arteries involvement among GCA patients who presented CIE, with 7 (50%) of our 14 patients with GCA-related CIE presenting intracranial arteries involvement on brain MRA and/or CTA, but the clinical-radiological correlation was not constant. Moreover, we identified a significant association between intracranial arteries involvement on CTA and/or MRA and GCA-related CIE (50% vs 1.8%, $p<0.001$).

These findings and our results support the fact that GCA-related CIE can also occur in non-vertebrobasilar territory, and that high performance MRI can be useful in this context. Further research is needed to better define the prognostic value of vertebral and intracranial arteries involvement, and its predictive potential for the occurrence of CIE.

Functional imaging (PET/CT)

Axillary arteries are among the most often involved arteries in GCA. Kermani *et al.* found that the most frequently affected arteries on morphological imaging in GCA were subclavian (42%) and axillary (32%) in their prospective cohort of 187 patients (38). Blockmans *et al.* found that the most affected arteries on PET/CT at diagnosis were subclavian (74%), abdominal (54%) and thoracic (51%) aorta, and axillary (40%) in

their prospective cohort of 35 patients (34). In our study, we found an association between axillary arteries involvement on PET/CT and GCA-related CIE (55% vs 20%, p=0.016).

Few studies have evaluated the risk of ischemic complications according to PET/CT findings. In a prospective study by Mestre-Torres *et al.*, 30 GCA patients, of which 21 presenting ischemic complications at diagnosis (mainly ophthalmologic, only one patient had CIE) underwent PET/CT during the first 10 days of steroid therapy. Patients with ischemic manifestations showed vertebral artery hypermetabolism on PET/CT more frequently than patients without, although the difference did not reach statistical significance (OR 5, 95% CI 0.99-24.86, p=0.051). The involvement of all other territories on PET/CT was found protective against ischemic complications, including aorta (OR 0.05, 95% CI 0.008-0.36, p=0.001) and axillary arteries (OR 0.08, 95% CI 0.01-0.49, p=0.004) (35).

Comparison of these results with our findings is difficult as our primary endpoint consisted exclusively of CIE. Moreover, in our larger cohort, 171 patients underwent PET/CT with a median delay from steroid initiation of 1 day (-7-20). Further studies are needed to assess the usefulness of the PET/CT for evaluating the risk of ischemic events, especially CIE.

Cardiovascular events during follow-up and mortality

Among our patients with GCA-related CIE, 2 of them presented a non GCA-related CIE during follow-up, but this complication occurred later than in the control group. This might be explained by tighter follow-up and a better control of cardiovascular risk factors in these high-risk patients on corticosteroid therapy.

Patients with GCA-related CIE presented a shorter follow-up period in our cohort. This could be explained by a higher mortality in this group. Indeed, we observed a non-significant trend toward a higher mortality in patients with GCA-related CIE (29% vs 11%, p=0.075), which is consistent with the results of Pariente *et al*. who showed that the overall survival was significantly decreased in GCA patients with stroke (17).

Treatment

In our study, patients with GCA-related CIE tended to receive tocilizumab more often than the control group, with borderline significance (29% vs 12%, p=0.081). In 4 patients, GCA-related CIE motivated the prescription of tocilizumab (2 at a relapse, 2 immediately associated with corticosteroids at diagnosis). Interestingly, none of the patients who were prescribed tocilizumab experienced recurrent CIE after the introduction of the immunosuppressant, although one of them with severe multifocal strokes died within the 3 months after diagnosis from stroke complications. However, the design of our study does not allow us to draw conclusions about the potential protective effect of tocilizumab against CIE, and further research is needed to determine the usefulness of tocilizumab in GCA-related CIE.

Strengths and limitations

The major strengths of our study are a large cohort of 271 well-phenotyped GCA patients, the use of strict criteria to define a CIE to be GCA-related, and the availability of detailed clinical, laboratory and various imaging modalities characteristics. Our systematic review and meta-analysis of the literature allowed us to estimate the pooled prevalence of GCA-related CIE. Although our study has shed the light on new

associations between patients' imaging characteristics and GCA-related CIE, no multivariate analysis could be performed mainly because each patient did not undergo the complete set of these different imaging modalities. Further studies are needed to confirm risk factors of CIE in GCA.

CONCLUSION

CIE are among the most severe ischemic complications of GCA, with an uncertainty regarding their real prevalence, due to the difficulties to relate them to GCA. According to our meta-analysis of the literature, the pooled prevalence of GCA-related CIE is 4%. Because GCA-related CIE increase morbidity and mortality, identifying their risk factors is crucial to prevent their occurrence and improve patients' prognosis. Our study highlights new associations between various imaging modalities features and GCA-related CIE, such as vertebral artery thrombosis on Doppler US, vertebral artery involvement and intracranial artery involvement on CTA and/or MRA, and axillary artery involvement on PET/CT. Further research is needed to confirm these associations as risk factors. Finally, although the use tocilizumab was motivated by the occurrence of GCA-related CIE in 4 of our patients with successful results, further studies are needed to establish its use in the prevention of GCA-related CIE.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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ANNEXES

Table S1. GCA-related CIE characteristics

Case	Age (years)	Time from diagnosis/ relapse to GCA-related first CIE (days)	Constituted (C) or transient (T)	First CIE territory	Treatments initiated	Recurrent CIE territory	Treatment changes
1	77	-15	C	Vertebrobasilar: multiple bilateral cerebellar and pontine ischemic lesions	Corticosteroids 1 mg/kg/d without pulse	Vertebrobasilar: right paramedian pontine ischemic stroke, with bilateral PET hyperfixation of vertebral arteries, and circumferential contrasting of basilar stem and right vertebral artery on MRA, indicative of a GCA relapse 8 month after diagnosis	Initiation of TCZ and reascending corticosteroids at 1 mg/kg/d
2	81	0	C	Carotidian: right lenticulo-caudal stroke during a relapse at 19 months from diagnosis, while steroid tapering	Reascending corticosteroids at 1 mg/kg/d	0	
3	63	-2	T	Carotidian TIA: transient monocular visual loss of the right eye	Corticosteroids 1 mg/kg/d preceded by steroid pulse	0	
4	86	-51	C	Vertebrobasilar: bilateral multiple ischemic lesions in the vertebrobasilar territory	Corticosteroids 1 mg/kg/d	0	
5	68	0	T	Vertebrobasilar TIA: mouth deviation and dysarthria during a relapse at 14 months from diagnosis	Initiation of MTX and reascending corticosteroids at 1 mg/kg/d	0	
6	63	-6	C	Intracranial cerebral vasculitis: 2 hemorrhagic strokes in the right frontal and occipital lobes, disseminated punctiform cortical ischemic lesions,	TCZ immediately associated with corticosteroids 1 mg/kg/d preceded by steroid pulse	0	

				and a small meningeal hemorrhage in the right frontal region			
7	93	-4	C	Vertebrobasilar: multiple bilateral ischemic lesions in the vertebrobasilar territory	Corticosteroids 1 mg/kg/d preceded by steroid pulse	0	
8	89	-24	C	Vertebrobasilar: Right anterolateral bulbar stroke and right middle cerebellar stroke during a relapse, 11 years after discontinuation of corticosteroids	Resumption of corticosteroids 1 mg/kg/d preceded by steroid pulse	0	
9	63	0	C	Vertebrobasilar: multifocal strokes in the territory of the posteroinferior cerebellar arteries and bilateral posterior cerebral arteries	Corticosteroids 1 mg/kg/d preceded by steroid pulse	0	
10	66	5	T	Multiple carotidian TIAs: bilateral tilting transient monocular blindness on day 2 of corticosteroid therapy, with bilateral inflammatory carotid stenosis	Corticosteroids 1 mg/kg/d preceded by steroid pulse	0	
11	77	-24	C	Vertebrobasilar: ischemic lesions in the territory of the left posterior cerebral artery: left parieto-occipital and thalamic lesions	Corticosteroids 1 mg/kg/d without pulse	0	
12	74	1	C	Carotidian: multifocal strokes in the right sylvian territory on day 2 of corticosteroid therapy, with bilateral severe involvement of both carotid, vertebral and intra-cranial cerebral arteries on brain MRA and CTA	Corticosteroids 1 mg/kg/d preceded by steroid pulse	Carotidian: recurrence of stroke within the first month after diagnosis in the right anterior cerebral artery territory, then multifocal strokes in left carotidian territory	Initiation of TCZ. Rapid death of the patient during follow-up
13	60	-27	C	Carotidian: Superficial right sylvian stroke with occlusion of the right suprabulbar internal carotid artery and stenosis of the left intracavernous internal carotid artery	TCZ immediately associated with corticosteroids 1 mg/kg/d preceded by steroid pulse	0	
14	82	-13	T	3 vertebrobasilar TIAs: linked to GCA because of P2 stenosis of the left posterior cerebral artery on MRA	Corticosteroids 1 mg/kg/d without pulse	0	

GCA: giant cell arteritis, CIE: cerebrovascular ischemic event, C: constituted, T: transient, TIA: Transient ischemic attack, MTX: methotrexate, TCZ: tocilizumab, MRA: magnetic resonance angiography, CTA: computed tomography angiography

Description of GCA-related CIE

14 patients (5.2%) presented a GCA-related CIE at diagnosis or relapse (10 constituted and 4 transient), with a median delay between the GCA-related CIE and diagnosis or relapse of GCA of 5 days (-22-0).

Regarding the territory of these 14 CIE, among the 10 constituted CIE, 6 occurred in the vertebrobasilar territory (4 of them bilateral), 3 in the carotidian territory, and the remaining one associated multifocal ischemic and hemorrhagic strokes related to intra-cranial vasculitis. Among the 4 transient ischemic attacks (TIA), 2 involved the vertebrobasilar territory and the 2 others the carotidian territory.

Regarding the delay between these 14 CIE and GCA diagnosis or relapse, 9 of them occurred at or before corticosteroid start, 2 occurred one day after the start of corticosteroid therapy (one case was a carotidian TIA, the other case was a carotidian constituted ischemic stroke), and 3 occurred during a relapse: one case was a vertebrobasilar constituted CIE occurring 11 years after the end of previous steroid therapy, one case was a carotidian constituted CIE occurring at 19 months from diagnosis while steroid tapering, and the remaining one was a vertebrobasilar TIA occurring at 14 months from diagnosis while steroid tapering.

During follow-up, only 2 (14.2%) of these 14 patients presented a second GCA-related CIE. One patient with a vertebrobasilar constituted CIE at diagnosis presented a second GCA-related constituted CIE in the vertebrobasilar territory while on corticosteroid tapering, concomitant to a relapse 8 month after diagnosis, which lead to adjunction of tocilizumab. One other patient with a carotidian constituted CIE at diagnosis presented 2 consecutive multifocal GCA-related strokes within the first month after diagnosis, while still on high dose steroids, leading to death despite

aggressive therapy with adjunction of tocilizumab. Interestingly, this patient presented bilateral severe involvement of both carotid, vertebral and intra-cranial cerebral arteries on the brain MRA and CTA performed at diagnosis.

For 5 of these 14 patients, GCA-related CIE motivated the prescription of an immunosuppressant, which was methotrexate for one of them at a relapse, and tocilizumab for the four others (2 at a relapse, 2 immediately associated with corticosteroids at diagnosis). Interestingly, none of the patients who were prescribed tocilizumab or methotrexate experienced recurrent CIE after the introduction of the immunosuppressant, although one of them with severe multifocal strokes died within the 3 months after diagnosis from stroke complications.

Notably, 7 (50%) of these 14 patients presented intra-cranial arteries involvement on brain MRA and/or CTA.

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Titre de la thèse : Complications ischémiques cérébrovasculaires au cours de l'artérite à cellules géantes : une étude française rétrospective de 271 patients, revue systématique de la littérature et méta-analyse.

Thèse - Médecine - Lille 2021

Cadre de classement : *Médecine Interne*

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Mots-clés : artérite à cellules géantes, événements ischémiques cérébrovasculaires, prévalence, facteurs de risque, imagerie, méta-analyse

Résumé : Contexte : Les événements ischémiques cérébrovasculaires (EIC) font partie des complications les plus graves de l'artérite à cellules géantes (ACG). L'hétérogénéité entre les différentes études quant à la définition des EIC liés à l'ACG engendre une incertitude quant à leur prévalence réelle. Les objectifs de notre étude étaient d'évaluer la prévalence des EIC liés à l'ACG et de caractériser ces patients dans une cohorte monocentrique française, puis de réaliser une revue systématique de la littérature et une méta-analyse sur la prévalence des EIC liés à l'ACG.
Méthodes : Dans cette étude rétrospective monocentrique, nous avons décrit les caractéristiques de patients atteints d'ACG recrutés du 1er janvier 2010 au 31 décembre 2020 au CHRU de Lille. Après avoir réalisé une revue systématique de la littérature, nous avons conduit une méta-analyse et déterminé la prévalence combinée d'EIC liés à l'ACG.
Résultats : 271 patients atteints d'ACG dont 89 hommes, d'âge moyen de 72 ± 9 ans, ont été inclus. Parmi eux, 14 (5,2%) présentaient un EIC lié à l'ACG. Les patients souffrant d'EIC liés à l'ACG présentaient plus fréquemment une thrombose de l'artère vertébrale à l'échographie doppler (17% vs 0,8%, p=0,012), une atteinte des artères vertébrales (50% vs 3,4%, p<0,001) et une atteinte des artères intracrâniennes (50% vs 1,8%, p<0,001) à l'angio-tomodensitométrie et/ou à l'angiographie par résonance magnétique, et une atteinte des artères axillaires sur la tomographie par émission de positrons (55% vs 20%, p=0,016). Douze études, dont la nôtre, ont été inclues dans la méta-analyse, représentant une population totale de 2870 patients. La prévalence combinée d'EIC liés à l'ACG était de 4% (IC 95% 3-6, I^2 = 70%).
Conclusion : La prévalence combinée d'EIC liés à l'ACG était de 4%. Nous avons identifié une association entre les EIC liés à l'ACG et l'atteinte des artères vertébrales, intracrâniennes et axillaires sur divers types d'imagerie.

<u>Composition du Jury</u> :

Président : Monsieur le Professeur Éric HACHULLA

Assesseurs : Monsieur le Professeur David LAUNAY,
Monsieur le Professeur Marc LAMBERT,
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