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SYSTEMATIC REVIEW

Sixth cranial nerve palsy in giant cell arteritis: A systematic review

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ABSTRACT

Objectives: This study aimed to review and describe isolated sixth cranial nerve or abducens nerve palsy that may present with subtle ophthalmoplegia in patients with giant cell arteritis (GCA).

Materials and methods: In this systematic review following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Extension for Scoping Reviews, MEDLINE and EMBASE were searched for all peer-reviewed articles using the keywords "cranial nerve six," "abducens nerve," and "giant cell arteritis" from their inception to December 22, 2022.

Results: Twenty-five articles, including seven observational studies and 18 cases, were included. While the incidence and prevalence of sixth nerve palsy in GCA were variable, up to 48% of diplopia in GCA were attributed to the sixth cranial nerve palsy, according to the observational studies included. While 88.2% had a resolution of symptoms with 40-50 mg/day of prednisone-equivalent corticosteroids, it took a median of 24.5 days until the resolution of symptoms from the initiation of treatment.

Conclusion: This review summarizes the current understanding of the characteristics of sixth nerve palsy in GCA. While most patients may have reversible clinical courses, a few can suffer from persistent ophthalmoplegia, which is a potentially missed yet crucial clinical finding in GCA. Increased awareness of the sixth nerve palsy in GCA is crucial.

Keywords: Abducens nerve, giant cell arteritis, six nerve palsy, systematic review.

Giant cell arteritis (GCA) is a systemic inflammatory vasculitis typically affecting the aorta and its main branches, commonly encountered in adults over 50 years old.[1] GCA presents with constitutional symptoms and symptoms related to the affected artery, such as jaw claudication or headache. One of the most feared ophthalmologic complications in GCA is vision loss due to arterial inflammation of the posterior ciliary arteries.[2-4]

Although rare, GCA also causes oculomotor abnormality presenting as diplopia, with a previous report of about 3-8% among GCA and about 8-20% among GCA with ophthalmic symptoms.[3,5] GCA could affect oculomotor nerves, including the third, fourth, and sixth cranial nerves. Generally, the sixth cranial nerve palsy was reported to be the most common nerve paralysis among ocular motor nerves in isolation.[6-8] However, some sixth cranial nerve palsy cases in GCA were likely underdiagnosed given the lack of understanding about illness scripts and initial presentations, rendering a challenge for correct diagnosis.

At this point, it is unclear if the sixth cranial nerve palsy in GCA patients could be a temporary, reversible, or irreversible finding. Given the potential need for prompt diagnosis and treatment to address the overlooked symptom, clinical pictures of the sixth cranial nerve palsy in GCA need to be well-defined. In this study, a systematic review of existing literature related to the sixth cranial nerve palsy in GCA was performed to clarify detailed clinical presentations and characteristics.

MATERIALS AND METHODS

This systematic scoping review was conducted in accordance with the Preferred Reporting

Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping reviews.[9,10] MEDLINE and EMBASE were searched for all peer-reviewed articles from inception to December 22, 2022. No filters for study design and language were used. A manual screening for additional pertinent articles was done using the reference lists of all articles that met the eligibility criteria. The search strategy involved relevant keywords, including "cranial nerve six," "abducens nerve," and "giant cell arteritis." The search was conducted by two authors independently. See Appendix 1 for detailed search terms. The criteria for the inclusion of articles were as follows: *(i)* peer-reviewed articles describing cases of GCA with cranial six nerve palsy; *(ii)* randomized controlled trials, case-control studies, cohort studies (prospective or retrospective), cross-sectional studies, case series, case reports, and conference abstracts; *(iii)* adult patients. The exclusion criteria were qualitative studies, review articles, and commentaries.

Study selection

Articles selected for full-text assessment were assessed independently by two authors using EndNote 20 reference management software (Clarivate, Philadelphia, PA, United States). Articles considered eligible were then evaluated in full length with the inclusion and exclusion criteria.

Data extraction and definition

A standardized data collection form that followed the PRISMA and Cochrane Collaboration guidelines for systematic reviews was used to obtain the following information from each study: title, name of authors, year of publication, country of origin, study characteristics, target outcome, aims, study and comparative groups, key findings, and limitations. Data from existing case reports and case series were also analyzed to identify the clinical characteristics of the included cases.

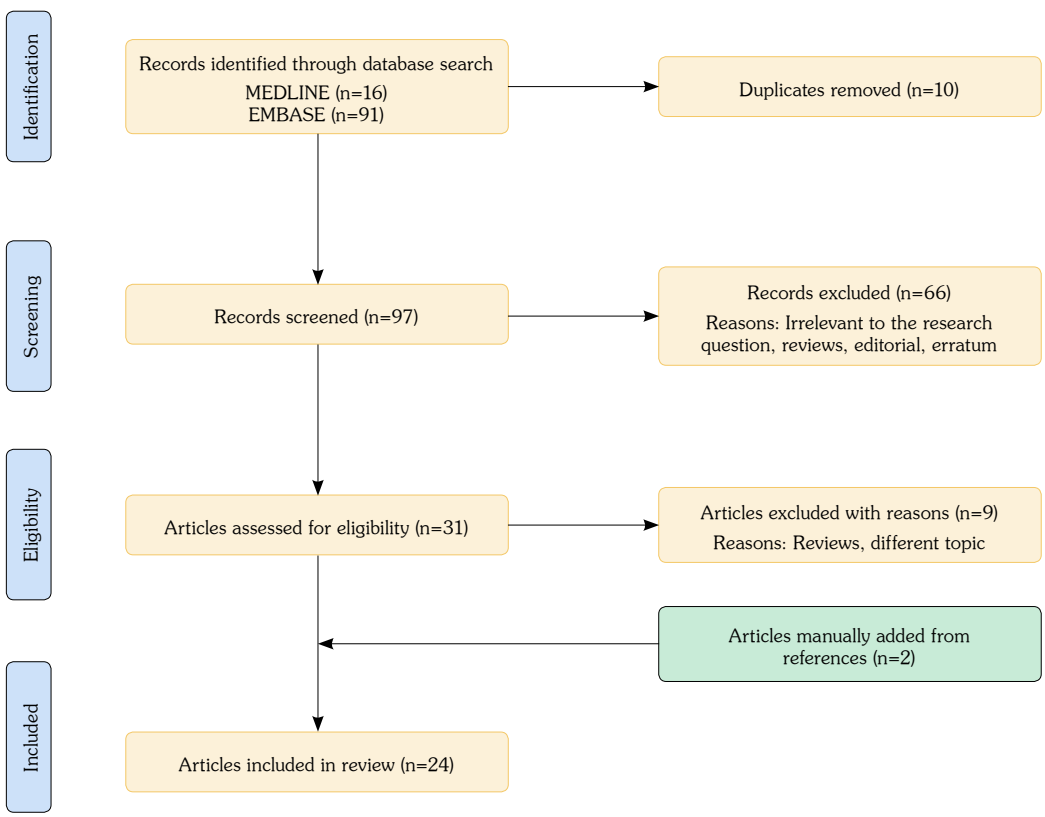

Figure 1. PRISMA flowchart of the search strategy.

Table 1. Main characteristics of the included observational studies in the scoping reviews

Author, year, country	Study type	Aim	Outcome	Population	Comparative groups	Key findings	Limitations
Chazal et al.[14] 2022, France	Observational	To better characterize diplopia in newly diagnosed GCA patients	Characteristics and prognosis of binocular diplopia	GCA (n=111)	None	80/111 (72%) had visual signs, including 30/111 (27%) with binocular diplopia Diplopia was attributed to cranial nerve palsy in 21/24 (88%, especially third (50%) and sixth cranial nerve (48%) palsies	Mainly focused on diplopia rather than six nerve palsy No outcome data about six nerve palsy Conference abstract
Coronel Tarancón et al.[12] 2018, Spain	Observational	To check the frequency of stroke as presentation symptom of GCA and other findings related with it	Clinical and laboratory findings	GCA (n=123)	None	37/123 (30%) suffered from ischemic vents of internal carotid artery, 12/123 (10%) presented with neurological symptoms different from AION. Out of 12 patients with non-ocular ischemic symptoms of central nervous system, 2/12 (17%) of sixth nerve paresis	Data was mainly focused on stroke symptoms Conference abstract
Issa et al.[5] 2022, Canada	Observational	To compare characteristics of patients with and without systemic GCA with ocular manifestations	Clinical and laboratory findings, and ocular manifestations	Temporal artery biopsy positive GCA without systemic symptoms (n=6)	Temporal artery biopsy positive GCA with systemic symptoms (n=36)	In GCA without systemic symptoms, 5/6 (83%) presented with AION, 1/6 (17%) with isolated cranial nerve six palsy In GCA with systemic symptoms, 17/36 (47%) presented with AION, 1/36 (3%) with iso lated cranial nerve six palsy	Lacking detailed clinical data for six nerve palsy
Laskou et al.[13] 2018, USA	Observational	To obtain information regarding the burden of vision loss in GCA	Clinical findings and ocular manifestations	GCA (n=388)	None	Visual symptoms were present in 135/388 (35%) 8 had oculomotor nerve palsies (1 bilateral 3rd, 1 bilateral 6th, and 6 unilateral 3rd or 6th nerve palsy)	Lacking detailed clinical data for six nerve palsy
Nayak et al.[11] 2016	Observational	To evaluate epidemiologic characteristics of giant cell arteritis	Clinical findings	GCA (n=5337)	None	The most common noted cranial nerve palsy was of the sixth nerve (0.5%)	Date was extracted national database Lacking detailed clinical data for six nerve palsy

Table 1. Continued

Author, year, country	Study type	Aim	Outcome	Population	Comparative groups	Key findings	Limitations
Haering et al.[3] 2014, Switzerland	Observational	To compare patients with and without diplopia in CGA	Clinical and laboratory findings	GCA with diplopia (n=9)	GCA without diplopia (n=28)	Prospectively analyzed Abduction deficit was confirmed 5/9 patients by ophthalmologic evaluation. 1/9 patient history was consistent with abduction deficit Visual impairment and loss were diagnosed 4/9 (44%) in patients with diplopia, and in 7/28 (25%) in diplopia	Single center study

AION: Anterior ischemic optic neuropathy; GCA: Fiant cell arteritis.

Statistical analysis

Results are shown as median with interquartile ranges (IQR) of the data if applicable. All analyses were performed using JMP 15.1 (SAS Institute, Cary, North Carolina, United States).

RESULTS

Search results and study selection

Figure 1 demonstrates a PRISMA flow diagram summarizing the identification, screening, eligibility, and inclusion and exclusion processes of the studies involved. The initial MEDLINE and EMBASE databases review yielded 16 and 91 articles, respectively. Ten duplicate studies were removed. Ninety-seven articles were screened based on their relevance and article type. Sixty-six articles that were either review articles, editorials, or studies that focused on matters irrelevant to the research question were excluded from the study. Thirty-one articles were then evaluated for full-text review for study inclusion per our eligibility criteria. Review articles or papers describing different topics were excluded. Two articles were added to the reference list search. As a result, 24 articles, including six observational studies and 18 cases from case reports and series, were included in the review. See Appendix 2 for the list of the included case reports and series.

Description of included studies

Table 1 describes the main characteristics of the seven observational studies from the scoping review. Except for studies by Haering et al.[3] and Issa et al.,[5] they were investigational studies without comparative groups.[11-14]

Chazal et al.[14] performed an observational study including 111 GCA patients to characterize diplopia and ocular symptoms in the population. Interestingly, among those who had diplopia, 48% were attributed to the sixth cranial nerve palsy. The results were limited as it was a conference abstract. Similarly, Coronel Tarancón et al.[12] focused on the neurological symptoms of 123 GCA patients but noted that only two out of 123 had sixth cranial nerve palsy. Issa et al.,[5] Laskou et al.,[13] Nayak et al.,[11] and Haering et al.[3] also reported a low incidence of the sixth cranial nerve palsy in GCA. Haering et al.[3] included

Table 2. Baseline demographics, laboratory findings, and chief features of the included cases

	n	%	Median	IQR
Age (year)			75.0	70.5-79.3
Sex				
Male	10/18	55.6		
Female	8/18	44.4		
Symptoms				
Headache	12/18	72.2		
Diplopia	14/16	87.5		
Vision change or loss	6/18	33.3		
Fever	4/18	22.2		
Jaw claudication	8/18	44.4		
Abducens nerve laterality				
Unilateral	12/18	66.7		
Bilateral	6/18	33.3		
Duration of CN6 palsy before admission (days)	16/18	88.9	5.5	1.0-19.3
Duration until onset of CN6 palsy after onset of initial symptoms (days)	16/18	88.9	16.0	8.8-77.0
Concurrent PMR	0/18	0		
Concurrent diabetes	2/18	11.1		
Known autoimmune disease	0/16	0		
Biopsy-proven diagnosis	17/18	94.4		
Treatment				
Pulse-dose corticosteroid	4/15	26.7		
Prednisone-equivalent 60-80 mg/day	4/15	26.7		
Prednisone-equivalent 40-50 mg/day	5/15	33.3		
Dose unspecified corticosteroid	2/15	13.3		
Resolution of CN6 palsy after treatment	15/17	88.2		
Duration from initiation of treatment until resolution of CN6 palsy (days)	14/18	77.8	24.5	6.00-56.0
Laboratory findings*				
Erythrocyte sedimentation rate (mm/h)	14/18	77.8	59.5	43.8-84.5
C-reactive protein (mg/L)	11/18	61.1	19.0	12.0-58.0

IQR: Interquartile range; CN: Cranial nerve; PMR: Polymyalgia rheumatica; * Prevalence here is defined as the number of cases reported the variab le divided by the number of the total cases.

those with GCA with or without diplopia. While they only included nine patients with diplopia, 55.6% with GCA and diplopia had abduction deficit by ophthalmologic evaluation, which was more common than vision loss (44.4%).

Table 2 presents the baseline demographics, diagnostic findings, and chief clinical features from the individual cases (n=18).[4,15-31] The median age of the included cases was 75.0 (interquartile range [IQR], 70.5-79.3) years. Male patients constituted 55.6% of the sample. Headache and diplopia were the most common symptoms, followed by jaw claudication, vision loss, and fever. Of the patients, 33.3% had bilateral sixth cranial nerve palsies. While the duration of the sixth cranial nerve palsy before admission and after the onset of initial symptoms was variable, initial symptoms preceded the sixth cranial nerve palsy for a median of 16.0 (IQR, 8.8-77.0) days. A biopsy-proven diagnosis was present in 88.9%. Most patients received more than 40-50 mg/day of prednisone-equivalent corticosteroids, and 88.2% had a resolution of sixth cranial nerve palsy. Interestingly, it took a median of 24.5 (IQR, 6.0-56.0) days until the resolution of symptoms from the initiation of treatment.

DISCUSSION

In the present study, we thoroughly reviewed the literature and evidence regarding the sixth

cranial nerve palsy in GCA. This is the first study to clarify detailed clinical presentations and time course of the critical and potentially reversible symptoms. In particular, the result that patients usually require more than three weeks until resolution of symptoms from initiation of treatment may give internists, neurologists, and rheumatologists an idea of discharge planning and how to educate patients regarding conditions and follow-up.

Currently, evidence regarding the incidence and prevalence of sixth nerve palsy has been variable. However, given the results of the reviews, it may be more common than expected in those with diplopia, which mandates clinicians' close attention to ophthalmologic exams on subtle changes and ophthalmoplegia in addition to screening for vision loss. At the same time, differential diagnosis of the sixth nerve palsy is broad, including ischemic stroke, intracranial tumors, and demyelinating diseases, such as multiple sclerosis.[1,3,32-39] Extensive workup to exclude the above is crucial, as the sixth cranial nerve palsy due to GCA is a diagnosis of exclusion. Additionally, raising awareness of GCA as a differential diagnosis in patients with the sixth cranial nerve palsy symptoms among clinicians is crucial.

Regarding clinical characteristics, our results showed that patients with sixth nerve palsy in GCA were more likely to be male (55.4%). None of them had a concurrent diagnosis of polymyalgia rheumatica, and there was a very high biopsy-proven diagnosis rate of 94.4%. Additionally, one-third of the patients had bilateral sixth nerve palsy. This information might be useful for physicians who need to be more observant of sixth nerve palsy symptoms.

Regarding the response to the treatment, the present results were reassuring as close to 90% showed recovery of the sixth nerve palsy with treatment based on corticosteroids. However, it is essential to note that recovery took approximately three to four weeks, or even up to two months in some cases. While further accumulation of prospective data may be needed, patients with GCA solely with abducens nerve palsy without other signs of clinical flare could be transitioned to close outpatient follow-up with rheumatologists and ophthalmologists. Given that approximately 10% of the patients had persistent abducens nerve palsy, future studies are warranted to recognize who is at risk of prolonged or permanent sixth nerve palsy based on baseline demographics or clinical characteristics. In these cases, treatments such as pulse dose glucocorticoids or anti-interleukin-6 monoclonal antibodies could be an option pending further accumulation of evidence, although it remains uncertain if the sixth cranial nerve palsy in GCA is a prodromal symptom of vision loss, given its association with the cranial and pericranial ischemic. Further investigation to see the association with prospective studies is necessary.

There are several limitations to the study. First, authors could not be contacted to obtain data not mentioned in the literature. We specifically included not only peer-reviewed articles but also conference abstracts or preprints, leading to uncertainty in the evidence level discussed. However, the risk of reporting bias was reduced as a result. Second, there is a limited number of prospective studies, and the study included a small number of patients. Furthermore, for statistical case analysis, only data from well-documented existing case reports and case series were included to identify the clinical characteristics of the included cases with the level of detail required for the in-depth investigation. Nevertheless, to our knowledge, this is the first systematic review to investigate the detailed characteristics of sixth cranial nerve palsy in GCA. The data presented may be beneficial for physicians to use for determining diagnostic or treatment plans for such cases.

In conclusion, this review summarizes the current evidence and characteristics of the sixth nerve palsy in GCA. While most patients may have transient and reversible clinical courses, ophthalmoplegia is a potentially missed yet crucial clinical finding in those with GCA. Given many differential diagnoses for the sixth nerve palsy that potentially complicate the clinical scripts, increased awareness of the sixth nerve palsy in GCA and its differential diagnosis is crucial. Since a small portion of patients suffer from persistent or permanent abducens nerve palsy, future studies are warranted to identify factors associated with nonreversibility and the benefits of early and high-intensity

treatment, such as pulse dose glucocorticoids or anti-interleukin-6 monoclonal antibodies, in the population.

Ethics Committee Approval: Ethics Committee Approval: Since this is a systematic review, no ethics committee approval was required.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Searched the literature, assessed the quality of the studies, drafted, and revised the manuscript: H.S., Y.N.; Both supervised the process: Y.N., H.T.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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Appendix 1. Detailed search terms

Medline
("giant cell arteritis"[MeSH Terms] OR "giant cell arteritis"[All Fields] OR "temporal arteritis"[All Fields]) AND ("cranial nerve six"[All Fields] OR "cranial nerve 6"[All Fields] OR "sixth nerve"[All Fields] OR "abducens nerve"[All Fields])

EMBASE
('giant cell arteritis'/exp OR giant cell arteritis OR 'temporal arteritis'/exp OR temporal arteritis) AND ('cranial nerve six'/exp OR cranial nerve six OR 'sixth nerve'/exp OR sixth nerve OR 'abducens nerve'/exp OR abducens nerve)

Appendix 2. Included articles

1. Jay WM, Nazarian SM. Bilateral sixth nerve pareses with temporal arteritis and diabetes. J Clin Neuroophthalmol 1986;6:91-5.
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