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Review Article

GIANT CELL ARTERITIS AS AN OPHTHALMIC EMERGENCY

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Abstract

Giant cell arteritis (GCA) is a critical medical emergency due to its potential to cause visual loss, which can be avoided through prompt and intensive diagnosis and treatment of affected patients. GCA is a form of vasculitis characterized by inflammation that primarily affects the elderly population and may lead to visual impairment. The present review examines the advantages of timely detection and intervention, and deliberates on the treatment modalities that are at disposal for the management of the condition. This review aims at focusing on the benefits of early treatments and its available options.

Keywords: *Giant cell arteritis, "Anterior ischemic optic neuropathy", Diagnostic approach, "Central retinal artery", "Posterior ciliary artery occlusion*.

1. Introduction

GCA is a type of vasculitis characterized by granulomatous inflammation that primarily affects arteries of both large and medium sizes. The most commonly affected arteries include the aorta, extracranial branches of the carotid arteries and branches of the ophthalmic artery [1-5]. The complications associated with GCA are typically a result of ischemic injury, aneurysm formation and rupture and systemic inflammation [6]. GCA is a medical condition that requires prompt diagnosis and treatment. Failure to recognize and treat GCA in a timely manner may lead to ischemic complications resulting in permanent vision loss, which occurs in approximately 15 to 25% of cases [7]. The findings of a research investigation on the delayed diagnosis of GCA leading to irreversible vision loss indicate that a significant proportion of patients, specifically 35%, exhibited systemic symptoms for an average duration of 10.8 months prior to the onset of permanent vision loss. In contrast, 65% of patients experienced transient visual symptoms for a period of 8.5 days before receiving a diagnosis [1]. Contemporary studies have underscored the significance of prompt identification and intervention in enhancing both ocular and systemic outcomes among individuals afflicted with GCA [1,8,9].

2. Epidemiology

The prevalence of GCA exhibits a geographical variation, with a higher incidence observed in the northern hemisphere. Notably, the highest incidence of GCA has been documented in Scandinavia, with a rate of 21.6 per 100.000 individuals, whereas the incidence in Europe is reported to be 7.3 per 100,000 individuals [10]. This discrepancy in incidence rates suggests a possible role of environmental factors in the pathogenesis of GCA. Publications on epidemiology regarding the incidence in Olmsted County, USA, which have been extrapolated to represent the incidence in the entire USA, may have resulted in an overestimation. This is due to the fact that the county has a higher proportion of individuals with Scandinavian ancestry, as reported in previous studies [10,11]. Thus, it can be observed that the genetic susceptibility is strongly associated with the geographical distribution, as reported in previous studies [12,13]. The occurrence of GCA has been consistently linked to major histocompatibility complex molecules, specifically HLA-DR3, HLA-DR4, HLA-DR5, and HLA-DRB1, with a particular emphasis on the presence of HLA-DRB1*04 alleles. GCA primarily impacts individuals who are 50 years of age or older, with an increasing occurrence in the setting of a progressively aging populace and a zenith in the seventh decade of life [14]. Females exhibit a 2.5-fold higher susceptibility to developing the aforementioned ailment compared to males [15].

3. Pathophysiology

GCA is distinguished by the presence of granulomatous infiltration, which arises from the improper migration of T cells and the consequent release of inflammatory cytokines into the vascular adventitia. The disease's pathogenesis can be segmented into various stages, to put it in basic terms. Upon an unidentified stimulus, there is an activation of vascular dendritic cells, leading to the activation and polarization of CD4+T cells [16,17]. The cytokines that promote inflammation have the ability to alter the differentiation of T-cells, favoring the development of Th17 and Th1 cells, as evidenced by previous research [18]. The Th17 cells exhibit dependence on Interleukin (IL)-6 and generate IL-17, alongside other interleukins. This group of cells holds a dominant position during the initial stages of Giant Cell Arteritis (GCA) and undergoes fluctuations in accordance with the level of disease activity. It is of significance that this particular cluster exhibits a heightened level of responsiveness to conventional glucocorticoid therapy [19]. The induction of Th1 cells that release interferon (IFN)-y, which are linked to chronic disease and exhibit greater resistance to glucocorticoids, is observed in response to IL-12 and IL-18 [20].

4. Diagnostic Approach

The “American College of Rheumatology” (ACR) established diagnostic features for GCA in 1990. The ACR criteria, originally designed for research purposes, demonstrated a sensitivity of 93.5% and a specificity of 91.2% in diagnosing GCA when utilizing a diagnosis threshold of 3 points [21]. Since its inception, the ACR criteria have been utilized for the clinical diagnosis of suspected GCA patients, enabling prompt identification and management without the need for a “temporal artery biopsy” (TAB) [4]. The proposed scoring system comprises of seven distinct criteria, as outlined by the authors. **1)** The existence of ischemia in the” anterior extracranial circulation”, including conditions such as “arteritic anterior ischemic optic neuropathy” (A-AION), “ophthalmic artery occlusion”, “central retinal artery occlusion” (CRAO),” posterior ischemic optic neuropathy” (PION), “amaurosis fugax” or

"cilioretinal artery occlusion", may be regarded as indicative evidence. **2)** The emergence of neck pain or headache that was not previously present. **3)** The presence of atypical values in ESR, platelet count, or CRP levels. **4)** Jaw claudication is a medical condition characterized by pain and discomfort in the jaw muscles during chewing or speaking. **5)** During examination, an anomalous superficial temporal artery was observed, characterized by nodularity, local tenderness, absence of pulse, and beading. **6)** Constitutional symptoms, namely fatigue, weight loss, malaise are noticed. **7)** "Polymyalgia rheumatic" (PMR) is a medical condition. A score of one is assigned to each criterion, with the exception that an exemption of one point is applied in cases where an alternative chronic already present condition can account for the criterion in question. Based on the score of 1 point, the clinical suspicion for GCA in the patient is categorized as "very low". Therefore, it is recommended that an assessment for an alternative diagnosis be conducted. As per the authors' findings, a score of 2 denotes a moderate degree of clinical suspicion, which corresponds to a percentage of 33%. The recommendation put forth was to administer oral prednisone at a dosage of 1 mg/kg/day, followed by TAB. When the temporal artery biopsy (TAB) outcome is negative and there exists a clinical suspicion that is categorized as "moderate," it is recommended to investigate alternative diagnoses beyond GCA. On the contrary, it was recommended that patients exhibiting a clinical suspicion score exceeding 2 (56%) be administered with empirical steroids, such as intravenously administered methylprednisolone (1 g/day) or prednisone taken by mouth (1 mg/kg/day), and undergo a temporal artery biopsy, which is considered the gold standard. Irrespective of the degree of clinical suspicion, whether moderate or high, the scoring system considers a positive temporal artery biopsy (TAB) as indicative of a high post-test probability for GCA. In cases where the medically suspect persists despite an initial negative temporal artery biopsy (TAB), which is presumed to be a false positive, it is recommended to perform a contralateral TAB and to continue the administration of empiric steroids. The new algorithm determined that a positive TAB has an average sensitivity of 91.4%. When compared to the ACR criteria, the proposed diagnostic criteria show, It was shown that 21% of patients who tested negative for TAB were incorrectly labeled as false positives, leading to the start of steroid treatment [4]. Such an erroneous treatment approach should be avoided, given the potential adverse effects of prolonged corticosteroid administration. Additionally, a study has indicated that a considerable proportion of their biopsy-confirmed GCA patients, specifically 25.7%, not have met the requirements of the ACR [4]. This research demonstrates the ACR criteria's lack of specificity, which may cause undesirable results like inadequate treatment. While El-Dairi et al. [1,4] algorithm did improve the yield of a TAB in diagnosing GCA, Keep in mind that the quantity of symptoms is not as significant as clinical suspicion in making a diagnosis of GCA. One study found that 21.2% of the patient group with vision loss consisted of those who had been biopsied and diagnosed with GCA but who had no other systemic symptoms and solely complained of vision loss [1]. Systemic symptoms, if they occur are; regarded as a principal constituent for the diagnosis of GCA, timely detection may not be feasible, thereby jeopardizing the patient's visual acuity. The prevalence of headache among patients with GCA is high, as reported by various studies. However, Hayreh et al conducted a study that revealed a statistically insignificant difference (P-value: 0.084) between the occurrence of headache in patients with positive temporal artery biopsies (TABs) (55.7%) and those with negative TABs (45.5%) [1]. Whilst headache is frequently reported, it is not a highly distinctive symptom for GCA. When contemplating

the suitability of administering corticosteroid treatment at an early stage, it is imperative to consider the prognostic value of specific symptoms. As an example, it has been observed that the presence of jaw claudication is linked to a significantly higher likelihood of testing positive for temporal artery biopsy, with a reported nine-fold increase in risk [1].

5. Clinical Manifestations

5.1. *Systemic manifestations*

GCA is known to elicit both systemic and ocular manifestations. The occurrence of systemic manifestations is frequently observed prior to the onset of ocular manifestations in patients with GCA [4, 5]. Among these systemic symptoms, new-onset headache is the most prevalent. Roughly 50% of GCA patients experience systemic symptoms, myalgias, headaches, sensitive frontal arteries, jaw claudication, tender scalp, and constitutional complaints like anorexia, migraines, and weight loss are all possible [1,5]. Tenderness of the scalp is a common symptom of GCA, however it has been shown to be unreliable in the clinical identification of the disorder. Patients with reported scalp discomfort were found to have a positive TAB in 18% of cases when using this as the diagnostic criterion for GCA, while patients with identical symptoms but a negative TAB made up the remaining 10% [1]. Additionally, the presence of arm claudication may indicate "subclavian vessel" participation [3]. This is due to the narrowing of the subclavian and axillary arteries caused by inflammation, which leads to ischemia and subsequent arm pain during physical activity [5]. Jaw claudication is a result of ischemia affecting the masseter muscle, which is innervated by the maxillary artery. Consequently, the occurrence of exertional ischemia arises during the act of chewing or utilizing the jaw [4,5,22]. Jaw claudication is a prevalent symptom, occurring in approximately 50% of cases, and is considered to be a moderately sensitive finding. Additionally, it is highly specific and is most commonly associated with a positive TAB [4,8]. Research conducted by Hayreh et al. [1]. indicates that the presence of jaw claudication increases the likelihood of a positive TAB by ninefold.

5.2. *Ophthalmic manifestations*

The ocular complication of GCA resulting in visual loss in one or both eyes was initially documented by Horton and Magath [23] in 1937, and later by Jennings in 1938 [24]. Since then, a substantial body of literature has been amassed on this topic. The irreversible complication of GCA that is most feared is visual loss, which has been firmly established, rendering GCA an ophthalmic emergency. GCA exhibits a distinctive preference for the "posterior ciliary arteries" (PCAs) among the various orbital arteries. These arteries are responsible for providing blood supply to the choroid, "optic nerve head", and "cilioretinal artery". The ocular lesions observed in GCA are predominantly ischemic in origin, resulting from thrombosis caused by granulomatous inflammation of one or more posterior ciliary arteries (PCAs), and infrequently of the ophthalmic artery. The occlusion of the PCAs has been established through "fluorescein fundus angiographic" studies [25-27] and numerous histopathological investigations [28]. The incidence of ocular involvement has been reported to exhibit significant variability, ranging from 20% to 70%. According to reports, the likelihood of enduring visual impairment due to GCA rises with age, although it is comparatively lower in patients who exhibit constitutional symptoms at presentation [29]. GCA has the potential to impede vision by inducing ischemia in one of the two visual pathways, afferent or efferent [30]. The previous results in a

reduction in visual acuity, while the latter leads to diplopia. The acute optical symptoms of GCA are considered to be emergencies due to the potential for progressive and irreversible harm. "Arteritic anterior ischemic optic neuropathy" (AAION) is a prevalent cause of blindness associated with GCA. This condition is often severe and irreversible [31]. Granulomatous inflammation is a hallmark of GCA, and it causes the extradural arteries that supply the internal elastic lamina to become narrowed or blocked [32]. The ophthalmic artery and its branches, including the posterior cerebral arteries (PCAs) and the central retinal artery (CRA), are commonly affected by GCA-induced vasculitis in the orbit. The PCAs are responsible for perfusing the choroid, the outermost third of the retina and the optic nerve head are nourished by a vascular layer. The central retinal artery is responsible for sup-plying blood to the retinal ganglion cells and the axons that make up the optic nerve, which together constitute the inner two-thirds of the retina. The "ophthalmic artery" is accountable for providing blood to the "vasa nervorum" of the "ocular motor nerves" and the "extraocular muscles". The occurrence of ophthalmoparesis and diplopia [33]. Giant cell arteritis has the potential to impact both extracranial and intracranial blood vessels, leading to homonymous visual field loss. This refers to the loss of vision on the same side of each eye, which can be attributed to occipital cortex stroke.

5.3. *The categorization of ischemic lesions in the ophthalmic region associated GCA.*

These may be classified according to various anatomical parts of the eye involved. **Optic nerve**: "Amaurosis fugax", "A-AION, A-PION". **Retina**: "CRAO", "cilioretinal arteryocclusion", "cotton-wool spots". **Choroid**: "Choroidal ischemic lesions". **Anterior segment**: "Anterior segment ischemia", "pupillary abnormalities". **Extraocular muscle**: "Extraocular muscle ischemia and motility disorders". "Ocular ischemic syndrome". Orbital: "Orbital inflamematory syndrome". "Cerebral ischemic lesions": That produces visual loss.

5.4. *Treatment of GCA patients with ophthalmic manifestations*

The introduction of corticosteroids in the treatment of GCA resulted in an immediate and significant improvement in the patients' condition. Undoubtedly, glucocorticoids have proven to be efficacious in the treatment of GCA. However, it is evident that the extended duration of therapy often required or utilized is associated with frequent occurrence of medically significant and potentially life-threatening side effects [34]. This methodology is generally effective for the majority of patients, however, in cases where patients receiving these lower initial doses encounter visual impairment, the expertise of neuro-ophthalmologists is sought. In cases where giant cell arteritis (GCA) is highly suspected, timely administration of glucocorticoids is imperative, regardless of the preferred dosage regimen. It is important to acknowledge that there is presently inadequate evidence-based guidance regarding the most effective dosing regimen for glucocorticoid treatment when used alone. It is imperative to note that in the event of the administration of glucocorticoid therapy, a small subset of patients who exhibit indications of GCA and blindness may potentially be afflicted with an infection, such as bacterial endocarditis or fungal sinusitis. Therefore, it is necessary [34]. Maintaining a state of vigilance with respect to the potential risks associated with glucocorticoid therapy is of utmost importance, as it may result in catastrophic consequences. Irrespective of the dosing preferences among subspecialists, the prompt administration of glucocorticoids is crucial for patients who are undergoing acute visual loss or stroke, as there is a possibility of severe, progressive, and irreversible deficits. The primary aim of administering glucocorticoids in this particular context is to prevent new ischemic events, which may include visual imp-

airment in the opposite eye, rather than visual recovery in the affected eye. In cases where patients experience sudden vision loss in one eye and exhibit symptoms or indications of ischemia in the other eye, it is common practice to commence medication with a three-day regimen of "intravenous methylprednisolone". This is due to the medication's swift onset of action and is administered at a dosage of 500-1000 mg per day. Subsequently, the individual is transitioned to a regimen of oral prednisone at a high dosage range of 100-120 mg per day. In cases where patients do not exhibit visual impairment or only experience it in one eye, it is customary in our practice to commence treatment with oral glucocorticoids, typically at a dosage of 80-120 mg/day. Typically, our methodology entails administering this dosage for a duration of 3-4 days, contingent upon the clinical progression, followed by a gradual reduction to 30 mg/day towards the conclusion of the third or fourth week. The standard protocol for patient treatment involves administering decreasing dosages over a period of 12 to 18 months. In cases where the pre-treatment ESR or CRP levels were elevated, it is recommended to conduct sequential tests to assist in the tapering process when the dosage reaches a relatively low level, such as 15 mg/day or lower. The occurrence of blindness subsequent to an initial phase of efficacious therapy, succeeded by a gradual reduction to a dosage of 15 mg, is an infrequent phenomenon among patients. It is recommended that dosing be administered once daily to patients, as there is a potential risk of blindness associated with switching to alternate-day dosing of prednisone. Assuming the absence of symptoms indicative of adrenal insufficiency and a normal morning cortisol level, the taper can typically be decreased by 2.5-mg increments when the dosage is at 10-15 mg/day. The aforementioned principle is subject to an exemption in cases where patients are diagnosed with PMR, as they tend to exhibit symptoms despite a gradual decrease of 1 mg per day in prednisone dosage. In instances where the level of suspicion for Giant Cell Arteritis (GCA) is not high, the administration of glucocorticoids may not be necessary. However, it is advisable to conduct a temporal artery biopsy to confirm the absence of the condition and provide reassurance. The administration of glucocorticoid therapy within a week of conducting a temporal artery biopsy does not appear to have an impact on the biopsy results. Low-dose aspirin has been frequently utilized as a supplementary therapy in GCA due to its antithrombotic and anti-inflammatory characteristics, as well as its advantageous side effect profile [35]. It is noteworthy to mention that there is a lack of randomized controlled trials that have assessed the efficacy of aspirin in preventing ischemic complications [36]. This is an area that requires further investigation. The findings of various retrospective studies have been inconclusive and contradictory [37-39]. A recent study of significant importance has exhibited the advantageous effects of administering tocilizumab on a weekly or biweekly basis for the management of GCA [40].

6. Conclusions

The occurrence of ischemic eye injury caused by GCA is a severe condition that can lead to complete loss of vision in both eyes in a matter of hours. In cases where a patient over the age of 50 presents with visual symptoms and there is a suspicion of GCA, prompt intervention is imperative to prevent vision loss. Time is of the essence and any delay must be avoided. Immediate administration of high doses of corticosteroids is recommended to the patient, as confirmatory examinations, including histological or imaging, maintain their sensitivity during the initial days of treatment. The significance of early diagnosis and prompt treatment of the critical condition necessitates the imperative collaboration between Rheumatologists and Ophthalmologists.

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