The ROYAL COLLEGE of OPHTHALMOLOGISTS

www.nature.com/eye

ARTICLE

Check for updates

Clinical, biological, and ophthalmological characteristics differentiating arteritic from non-arteritic anterior ischaemic optic neuropathy

Simon Parreau[1,2]✉, Alexandre Dentel[3], Rania Mhenni[4], Stéphanie Dumonteil[2], Alexis Régent[1], Guillaume Gondran[2], Dominique Monnet[4], Antoine P. Brézin[4], Kim-Heang Ly[2], Éric Liozon[2], Thomas Sené[5] and Benjamin Terrier[1]

BACKGROUND/AIMS: To identify characteristics that can distinguish AAION from NAAION in emergency practice.
METHODS: This is a multicentre retrospective case-control study. Ninety-four patients with AAION were compared to ninety-four consecutive patients with NAAION. We compared the clinical, biological, and ophthalmological characteristics at baseline of patients with AAION and those with NAAION.
RESULTS: Patients with AAION were older and more likely to have arterial hypertension. Cephalic symptoms and acute-phase reactants were more frequent in AAION. Profound vision loss and bilateral involvement were more frequent in AAION at baseline. Central retinal and cilioretinal artery occlusions was only observed in AAION, and delayed choroidal perfusion was more frequently observed in AAION than in NAAION. Using logistic regression, an age >70 years (OR = 3.4, IC95% = 0.8–16.1, $p = 0.105$), absence of splinter haemorrhage (OR = 4.9, IC95% = 1.4–20.5, $p = 0.019$), delayed choroidal perfusion (OR = 7.2, IC95% = 2.0–28.0, $p = 0.003$), CRP > 7 mg/L (OR = 43.6, IC95% = 11.6–229.1, $p < 0.001$) and platelets >400 × G/L (OR = 27.5, IC95% = 4.6–270.9, $p = 0.001$) were independently associated with a diagnosis of AAION. An easy-to-use score based on these variables accurately distinguished AAION from NAAION with a sensitivity of 93.3% and specificity of 92.4%.
CONCLUSION: In patients presenting with AION, a set of ophthalmological and laboratory criteria can efficiently discriminate patients with AAION and NAAION and can identify which patients would benefit from high-dose glucocorticoids. External validation of our results is required.

Eye (2023) 37:2095–2100; https://doi.org/10.1038/s41433-022-02295-w

INTRODUCTION

Anterior ischaemic optic neuropathy (AION) is one of the most common causes of blindness among the elderly. It is characterized by a sudden, but painless decrease in visual acuity due to ischaemia of the anterior part of the optic nerve head, which is mainly supplied by short posterior ciliary arteries. Ischaemia leads to optic disc swelling followed by optic disc atrophy about 6 weeks after the acute injury. Roughly 90% of AION cases are non-arteritic (NAAION), and the disease is multifactorial with various risk factors [1, 2]. The key risk factor is anatomical crowding of the optic disc. Arteritic AION (AAION) is most frequently related to giant cell arteritis (GCA), a large vessel vasculitis that can affect individuals >50 years of age [1]. GCA is characterized by cranial (i.e., headaches, scalp tenderness and jaw claudication) and/or constitutional symptoms (i.e., fever, anorexia, fatigue, and weight loss), and is typically associated with increased levels of acute-phase reactants. Histological analysis of temporal artery biopsy (TAB) can confirm the diagnosis of GCA, by showing inflammatory infiltrates with a predominance of mononuclear cells or granulomatous inflammation [3]. However, skip lesions may occur. Noninvasive imaging techniques, mainly ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET), temporal artery ultrasound and magnetic resonance imaging (MRI), help to confirm the diagnosis according to the EULAR recommendations [4].

Arteritic AION is a medical emergency because of the risk of imminent vision loss involving the 2nd eye, as even with prompt intervention the vision loss may be irreversible. Because it is related to inflammatory thrombosis of the short posterior ciliary arteries, the treatment is based on high-dose glucocorticoids (GCs), whereas there is no evidence-based treatment for vision loss NAAION, and management focuses on modification of possible risk factors, aiming to try and reduce risk of similar involvement of the 2nd eye [5]. Distinguishing AAION and NAAION is therefore critical in the early phase of visual manifestations to ensure appropriate treatment. However, distinguishing these two entities can be problematic, especially when cranial or systemic symptoms suggestive of GCA are inconsistent. Systemic manifestations have been reported to be absent in 21% of GCA cases associated with vision loss, which have been called

[1]Department of Internal Medicine, Paris Descartes University, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, Paris, France. [2]Department of Internal Medicine, Hôpital Dupuytren, Limoges, France. [3]Department of Ophthalmology, Fondation Adolphe-de-Rothschild hospital, Paris, France. [4]Université de Paris, Department of Ophthalmology, Hôpital Cochin, Paris, France. [5]Department of Internal Medicine, Fondation Adolphe-de-Rothschild hospital, Paris, France. ✉email: simon.parreau@hotmail.com

Received: 26 April 2022 Revised: 27 September 2022 Accepted: 13 October 2022
Published online: 22 October 2022

occult GCA [6]. To date, only few large-scale studies have directly compared AAION and NAAION [7–22].

In this case-control study, we compared the characteristics of patients with NAAION and AAION to identify diagnostic features that could be useful for discriminating the two entities in daily practice.

MATERIALS AND METHODS

Study design

We conducted a multicentre retrospective case-control study including consecutive patients diagnosed with AION between 2005 and 2021 at the Ophthalmology Departments of three French tertiary-care teaching hospitals (Cochin Hospital [Ile de France], Ophthalmological Adolphe de Rothschild Foundation Hospital [Ile de France], and Dupuytren Hospital [Nouvelle-Aquitaine]). Anterior ischaemic optic neuropathy was defined as a sudden decrease in visual acuity associated with a typical visual field defect and optic disc swelling, progressing to optic disc atrophy within 2 months. AAION was defined as AION associated with a diagnosis of GCA according to the American College of Rheumatology (ACR) classification [23]. The diagnosis of GCA was retained when the TAB showed an active arteritis with an inflammatory parietal infiltrate composed of lymphocytes, macrophages ± giant cells. A diagnosis of GCA was retained in biopsy-negative cases if at least three of the ACR criteria were fulfilled, or if only two criteria were fulfilled but FDG-PET scans showed greater circumferential FDG vascular uptake compared to liver uptake in at least one of the following eight vascular segments: thoracic, abdominal aorta, subclavian, axillary, carotid, iliac/femoral, and upper and lower limb arteries [24], temporal artery ultrasound revealed a halo sign [25], or high resolution MRI of the cranial arteries demonstrated mural inflammation [26]. If the erythrocyte sedimentation rate (ESR) was not available, C-reactive protein (CRP) was used as a surrogate diagnostic criterion with a positivity threshold of >20 mg/L as described in a recent study [27]. We also included patients with a diagnosis of NAAION during the same period and in the same centres, with a 1:1 ratio. Diagnosis of NAAION was based on the presence of fewer than three ACR criteria, a negative TAB and/or noninvasive imaging tests not suggestive of large-vessel vasculitis, and the absence of progression to GCA at least 1 year after AION onset.

Data collection

All clinical, laboratory, and radiological data at the time of diagnosis of AION were collected retrospectively using a standardized case report form. Cardiovascular (CV) risk factors were collected, as well as use of antiplatelet agents, anticoagulants and statins at the time of AION onset. The CHA_2DS_2-VASc score was calculated based on the clinical information available at the time of diagnosis [28]. The temporal artery was considered abnormal if any of the following features were present: weak or absent pulse, beaded and/or indurated artery, and local redness or tenderness. Constitutional syndrome was defined as a temperature of >38 °C for >1 week associated with asthenia and/or weight loss of >5%.

Ophthalmological data were collected by ophthalmologists. Amaurosis fugax was defined as temporary loss of vision in one or both eyes before diagnosis of AION. Visual acuity was measured at 3 m and expressed as a decimal before being converted into logMAR. Unquantifiable low acuity was defined in decreasing order as follows: counting fingers, hand motion, light perception, and no light perception. Intraocular pressure was measured using a Goldmann applanation tonometer on presentation. Delayed choroidal perfusion was demonstrated by fluorescein angiography and defined as a delay in choroidal perfusion (sectorial or global) of >20 s or a difference of 20 s in choroidal filling between the two eyes.

Statistical analysis

Continuous variables are expressed as medians and interquartile ranges, and categorical variables are expressed as frequencies with percentages. Variables were compared by the Pearson's chi-square, Fisher's exact, or Wilcoxon's test, as appropriate.

For missing data (~10%, evenly distributed), multiple imputation chained equation was used with four matrices [29]. To determine the profile of patients with GCA, logistic regression was carried out on baseline variables with p values <0.25. The Box-Tidwell transformation adds the neperian logarithm of the selected continuous variables to the logistic regression. These terms have a significant p value, indicating a non-linear relationship with the variable of interest. The graphs of the partial residuals show a hyperbolic type of relationship. To meet the assumptions of linearity of the model, these variables are discretized to obtain a simple score to be used in the current practice. The thresholds are obtained using a supervised method (decision tree). The initial multivariate model was simplified by the backward stepwise elimination method, and the final model included only variables significantly associated with AAION. Model calibration was assessed using the Pearson residual. Receiver operating characteristic (ROC) analysis was performed, where an area under the curve (AUC) of 1.0 reflects the highest possible reliability. All were two-sided and a p value < 0.05 was considered indicative of significance. Calculations were performed using R software (version 3.2.2; R foundation for Statistical Computing, Vienna, Austria).

Patient involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination of this research.

Ethics

The study was conducted in compliance with good clinical practice guidelines and the Declaration of Helsinki and was approved by the local Institutional Review Board of Cochin-Port Royal Hospital, Paris, France (approval number: AAA-2021-08061). All patients were informed that their anonymized clinical data could be used for research purposes, and they give their written consent for such use/none opposed their use.

RESULTS

Characteristics of the patients

In total, 110 patients with AAION were initially screened. Twelve patients with missing data and four with an incorrect diagnosis of AAION were excluded. Thus, 94 patients with AAION (and 94 consecutive recent patients with NAAION; controls) were included in the final analysis (Supplementary Fig. 1). The demographics, CV risk factors, visual characteristics, and extra-ocular manifestations of the participants are summarized in Tables 1–3, respectively.

Among the 94 AAION cases, 72 underwent TAB, which showed evidence of temporal arteritis in 61 (85%) patients. Forty-nine patients had doppler ultrasound of the temporal arteries, which revealed a halo sign in 31 (63%). For the 33 AAION cases with negative TAB or TAB not performed, 20 patients had at least 3 ACR criteria. Among the 13 patients who did not meet at least three ACR criteria, 2 had a positive TAB, 4 had temporal artery ultrasound showing a halo sign, and 7 had a CRP level >20 mg/L with no other plausible cause. Seventy-seven (81.9%) AAION patients had a typical GCA. The seventeen (18.1%) remaining AAION patients had atypical features of GCA (Supplementary Fig. 2). Among atypical AAION patients, eight patients (8.5%) had a typical clinical presentation of GCA, without an increase in acute-phase reactants, but an abnormal TAB was seen in five patients and a bilateral positive halo sign was revealed by temporal artery ultrasound in four. Seven patients (7.4%) had an atypical presentation of GCA but increased acute-phase reactants and a positive TAB for GCA in all cases. Finally, two patients (2.1%) had neither clinical symptom of GCA nor increased acute-phase reactants, but did show evidence of vasculitis on TAB.

Factors associated with the diagnosis of AAION

Tables 1–3 show the results of univariate analyses of patients with AAION and NAAION. Patients with AAION were older (median age, 78 [75–84] *vs*. 72 [65–78] years, $P < 0.001$) and more likely to have hypertension (63.8 *vs*. 44.7%, $P = 0.013$), and had a higher mean CHA_2DS_2-VASc score (3.0 [3.0–4.0] *vs*. 2.5 [1.0–4.0], $P = 0.001$).

Amaurosis fugax (39.4 *vs*. 5.3%, $P < 0.001$), bilateral AION (24.5 *vs*. 6.4%, $P = 0.0012$) and a profound decrease in visual acuity (LogMAR > 1.0) (75.3 *vs*. 43.0%, $P = 0.001$) were significantly more frequent in AAION patients. Patients with AAION also had a lower rate of splinter haemorrhage (37.2 *vs*. 57.8%, $P = 0.012$), higher rate of central retinal artery occlusion (13.8 *vs*. 0.0%, $P = 0.001$) and delayed choroidal perfusion on fluorescence angiography

Table 1. Demographics and cardiovascular risk factors of the AAION and NAAION groups.

	n (%) or median [interquartile range]			
	Non-arteritic AION $n = 94$	**Arteritic AION $n = 94$**	**Total $n = 188$**	***p* value**
Demographics				
Age, years	72 [65, 78]	78 [75, 84]	76 [70,81]	<0.001
Age ≥70 years	58 (61.7%)	84 (89.4%)	142 (75.5%)	<0.001
Female	40 (42.6%)	52 (55.3%)	92 (48.9%)	0.110
CV risk factors				
Current smoking	13 (13.8%)	16 (17.0%)	29 (15.4%)	0.686
Dyslipidaemia	30 (31.9%)	32 (34.0%)	62 (33.0%)	0.877
Obesity	6 (6.4%)	5 (5.3%)	11 (5.9%)	1.000
Atrial fibrillation	2 (2.1%)	9 (9.6%)	11 (5.9%)	0.058
Congestive heart failure	7 (7.4%)	13 (13.8%)	20 (10.6%)	0.237
Hypertension	42 (44.7%)	60 (63.8%)	102 (54.3%)	0.013
Diabetes mellitus	16 (17.0%)	12 (12.8%)	28 (14.9%)	0.539
Stroke, TIA, or TE	5 (5.3%)	7 (7.4%)	12 (6.4%)	0.766
Vascular disease*	9 (9.6%)	17 (18.1%)	26 (13.8%)	0.139
CHA_2DS_2VASc score	2.5 [1.0, 4.0]	3.0 [3.0, 4.0]	3.0 [2.0, 4.0]	<0.001
Antiplatelet agent	28 (29.8%)	26 (27.7%)	54 (28.7%)	0.872
Anticoagulant	4 (4.3%)	9 (9.6%)	13 (6.9%)	0.250
Statin	22 (23.4%)	32 (34.0%)	54 (28.7%)	0.147

AION anterior ischaemic optic neuropathy, *TIA* transient ischaemic attack, *TE* thromboembolism.
*Prior myocardial infarction, peripheral arterial disease, or aortic plaque.

Table 2. Visual characteristics of the AAION and NAAION groups.

	Non-arteritic AION $n = 94$	**Arteritic AION $n = 94$**	**Total $n = 188$**	***p* value**
	n (%) or median [interquartile range]			
Amaurosis fugax	5 (5.3%)	37 (39.4%)	42 (22.3%)	<0.001
Initial bilateral AION	6 (6.4%)	23 (24.5%)	29 (15.4%)	0.001
LogMAR <0.3	33 (35.5%)	12 (13.5%)	45 (24.7%)	<0.001
LogMAR >1.0	40 (43.0%)	67 (75.3%)	107 (58.8%)	0.001
Count fingers	13 (13.8%)	18 (19.1%)	31 (16.5%)	0.432
Hand movement	9 (9.6%)	34 (36.2%)	43 (22.9%)	<0.001
Light perception	2 (2.1%)	6 (6.4%)	8 (4.3%)	0.278
No light perception	0 (0.0%)	2 (2.1%)	2 (1.1%)	0.497
Splinter haemorrhage	52 (57.8%)	29 (37.2%)	81 (48.2%)	0.012
Associated CRAO	0 (0.0%)	13 (13.8%)	13 (6.9%)	<0.001
Associated CLRAO	0 (0.0%)	4 (4.3%)	4 (2.1%)	0.121
Intraocular pressure, mmHg	15 [13,16]	14 [12,15]	14 [12,16]	0.004
Delayed choroidal perfusion	12/59 (20.3%)	54/66 (81.8%)	66/125 (52.8%)	<0.001

AION anterior ischaemic optic neuropathy, *CRAO* central retinal artery occlusion, *CLRAO* cilioretinal artery occlusion.

(81.8 [54/66] *vs*. 20.3% [12/59], $P < 0.001$). Finally, besides cranial, and constitutional symptoms, which were more frequent in AAION patients, as expected, the mean (sd) platelet count (443 [345–536] *vs*. 270 [198–300] G/L, $P < 0.001$) and monocytes (0.8 [0.5–1.0] *vs*. 0.5 [0.4–0.6] G/L, $P < 0.001$) were higher in the AAION compared to NAAION group.

Several variables were independently associated with AAION: an age over 70 years (+10 points), delayed choroidal perfusion (+17 points) on fluorescein angiography, absence of splinter haemorrhage (+13 points) on fundoscopy, blood platelet count >400 G/L (+28 points), and CRP > 7 mg/L (+32 points) (Table 4). A score > 48 points accurately identified patients with AAION, with a sensitivity of 93.3%, specificity of 92.4%, positive predictive value of 94.4%, and negative predictive value of 91.0% (Supplementary Fig. 3). Considering only AAION patients with a positive TAB, a score >48 points identified patients with AAION, with a sensitivity of 93.4%, specificity of 93.0%, positive predictive value of 91.8%, and negative predictive value of 94.3%.

DISCUSSION

We assessed the ability of baseline characteristics to distinguish AAION related to GCA and NAAION cases among subjects presenting with AION. We identified several variables associated with AAION and established a score to help for distinguishing AAION cases in ophthalmological emergency practice. The score

Table 3. Extra-ocular manifestations of the NAAION and AAION groups.

	n (%) or median [interquartile range]			
	Non-arteritic AION $n = 94$	Arteritic AION $n = 94$	Total $n = 188$	*p* value
Headache	8 (8.5%)	71 (75.5%)	79 (42.0%)	<0.001
Abnormal temporal artery	0 (0.0%)	32 (34.0%)	32 (17.0%)	<0.001
Jaw claudication	1 (1.1%)	58 (61.7%)	59 (31.4%)	<0.001
Scalp tenderness	2 (2.1%)	50 (53.2%)	52 (27.7%)	<0.001
Dry cough	1 (1.1%)	10 (10.6%)	11 (5.9%)	0.001
Fever	0 (0.0%)	9 (9.6%)	9 (4.8%)	0.003
Constitutional symptoms	4 (4.3%)	51 (54.3%)	55 (29.3%)	<0.001
Distal arthritis	1 (1.1%)	10 (10.6%)	11 (5.9%)	0.001
Polymyalgia symptoms	1 (1.1%)	14 (14.9%)	15 (8.0%)	<0.001
CRP (mg/L)	1 [1, 4]	70 [31, 108]	16 [1, 73]	<0.001
ESR, mm/h	13 [8, 22]	86 [57, 101]	48 [15,92]	<0.001
Leucocytes, G/L	7.9 [6.1, 10.9]	10.2 [8.4, 11.8]	9.6 [7.6, 11.7]	0.004
Haemoglobin, g/dL	13.4 [12.6, 14.4]	11.8 [10.9-12.9]	12.3 [11.0-13.5]	<0.001
Platelets, G/L	270 [198, 300]	443 [345, 536]	357 [274, 462]	<0.001
Fibrinogen, g/dL	3.5 [2.7, 3.8]	6.4 [5.2, 7.6]	5.7 [4.1-7.2]	<0.001
Lymphocytes, G/L	1.5 [1.1, 2.0]	1.6 [1.3, 2.0]	1.6 [1.2, 2.0]	0.503
Monocytes, G/L	0.5 [0.4, 0.6]	0.8 [0.5, 1.0]	0.7 [0.5, 0.9]	<0.001

AION anterior ischaemic optic neuropathy, *CRP* C-reactive protein.

Table 4. Factors associated with AAION.

	β	OR	IC95%	*p* value
Absence of splinter haemorrhage	1.6	4.9	1.4−20.5	0.019
Delayed choroidal perfusion	2.0	7.2	2.0−28.0	0.003
Age > 70 years	1.2	3.4	0.8−16.1	0.105
CRP > 7 mg/L	3.8	43.6	11.6−229.1	<0.001
Platelets > 400 G/L	3.3	27.5	4.6-270.9	0.001

included older age, delayed choroidal perfusion, absence of splinter haemorrhage, CRP level, and platelet count.

Accurate identification of patients with suspected AAION is critical because untreated GCA carries a high risk of bilateral involvement, and such event is preventable by high-dose GCs. Conversely, high-dose GCs could be detrimental in elderly people with NAAION. We aimed to identify AAION at onset in emergency department patients who could benefit from rapid initiation of high-dose intravenous methylprednisolone, and the present study is one of the largest studies to address this question [10]. Prior studies were either small or used only one imaging test [7–22] (Table 5). In addition, Ing et al. also developed multivariate predictive models for the diagnosis of GCA based on routine clinical and biological variables [30–33]. However, these models did not compare GCA with AAION and NAAION as in our study.

Patients with AAION were older and had a higher mean CHA^2DS^2VASc score, the latter being partly explained by frequent coexisting arterial hypertension. The CHA^2DS^2VASc score is predictive of CV disease in patients with and without atrial fibrillation. Czihal et al. showed that the risk of permanent vision loss in GCA was positively associated with a high CHADS2 score [34]. However, no previous study has directly compared these scores between AAION and NAAION.

Some ophthalmological variables were strongly associated with AAION, including the lack of splinter haemorrhage and the presence of delayed choroidal perfusion. More severe initial visual impairment observed in AAION in comparison to NAAION, as identified in univariate analysis, has long been known [35]. Also, it is not surprising that amaurosis fugax was seen in AAION more than in NAAION. We provide here strong evidence that delayed choroidal perfusion during fluorescein angiography is an important feature suggestive of AAION, as indicated by previous small studies [15, 16, 36]. However, delayed choroidal perfusion is not pathognomonic of AAION, because it is also observed in about 20% of patients with NAAION [37]. The cupping sign, *i.e.* acquired excavation of the optic nerve head, which also suggests AAION, appears at a late stage and is therefore of limited relevance to the emergency setting [22]. Other ocular examinations that assist the differential diagnosis of AION include Goldmann visual field testing, colour Doppler imaging of the ophthalmic artery [20], and MRI of the head of the optic nerve [21]. However, such procedures can be difficult to perform in the setting of emergency management.

As expected, increased acute-phase reactants, which are a hallmark of GCA, were more frequent in AAION than NAAION patients. Although potentially misleading, an elevated CRP level may also be seen in patients with NAAION and multiple comorbid conditions. Platelet count was also independently associated with AAION in our study. Whether thrombocytosis is an independent risk factor for permanent visual loss in patients with new-onset GCA has been disputed [9, 10]. Consistent with our results, Costello et al. reported that patients with GCA-related AION had significantly higher platelet counts, ESR, and CRP levels compared to patients with NAAION. Furthermore, the combination of a high platelet count and CRP level increased the likelihood of GCA in the setting of AION [10].

Finally, about 10% of our patients with AAION did not display clinical symptoms suggestive of occult forms of GCA. Hayreh et al. reported that occult forms accounted for 21% of 85 visually complicated GCA cases confirmed by TAB [6], similar to the work of Chen et al. [38]. Only two patients in our series had occult GCA without an increased CRP level. Both patients had bilateral visual impairment, with a sudden decrease in vision and delayed choroidal perfusion suggestive of AAION, and were biopsy-proven GCA. Other signs suggestive of AAION included chalky

Table 5. Summary of studies comparing AAION and NAAION.

First author (ref)	Year	Design	Patients (n)		Significantly different variables between AAION compared to NAAION				
			NAAION	AAION	Clinical	Biological	Ophthalmo.	Imaging	Main results
Costello [10]	2004	Retrospective	287	121	–	+	–	–	↑ESR ↑ CRP ↑ Platelet count
Inanc [8]	2017	Retrospective	33	12	–	+	–	–	↑Neutrophil/lymphocyte
Koçak [7]	2020	Retrospective	41	16	–	+	–	–	↑Age ↑ESR ↑ Neutrophil/lymphocyte ↑Monocyte/high-density lipoprotein
Siatkowski [16]	1992	Retrospective	19	16	–	+	+	–	↑Age ↑ESR ↑ Cup/disc ↓Choroidal filling times ↑Disk pallor frequency
Monteiro [12]	2006	Prospective	24	13	–	–	+	–	↑Optic disc area
Danesh-Meyer [29]	2001	Retrospective	32	42	–	–	+	–	↑Cupping frequency
Danesh-Meyer [13]	2010	Retrospective	53	18	+	–	+	–	↑Age ↑Visual acuity ↑Cup/disc ↓MD ↓ NFL thickness
Jonas [11]	1988	Retrospective	33	7	–	–	+	–	↑Optic disc area
Huna-Baron [19]	2006	Retrospective	16	16	–	–	+	–	↓Intraocular pressure
Valmaggia [17]	1999	Prospective	17	5	–	–	+	–	↓Choroidal filling times
Jonas [18]	2008	Retrospective	10	6	–	–	+	–	↓CRA collapse pressure
Pellegrini [15]	2019	Retrospective	20	20	+	–	+	–	↑Age ↑Visual acuity ↓MD ↓ Peripapillary CVI
Ghanchi [20]	1996	Retrospective	4	7	–	–	–	+	↓Blood flow in the posterior ciliary arteries
Remond [21]	2017	Prospective	15	15	–	–	–	+	↑Central Bright Spot Sign frequency

Ophthalmo ophthalmological, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *MD* visual field mean deviation, *NFL* nerve fibre layer, *CRA* central retinal artery, *CVI* choroidal vascularity index

white papilloedema and occlusion of the central retinal or cilioretinal artery [36].

The strengths of this study are that it is a large case-control study comparing the clinical, biological and ophthalmological characteristics of AAION versus NAAION. It is one of the largest existing series in the literature. We propose an easy-to-use score with common parameters to help the clinician to quickly diagnose AAION. For the first time, a threshold level of age and CRP are highlighted. In addition, the absence of splinter haemorrhage in favour of AAION is reported for the first time.

Limitations of our study include its retrospective design, which may have introduced referral bias. Also, the inclusion of GCA not confirmed by abnormal TAB or large-vessel imaging may have resulted in sampling bias. Moreover, although this was a multicentre study, the final sample size was relatively small, which may have obscured potentially relevant variables. Several patients did not have a fluorescein angiogram. Detailed data on the cup/disc ratio, which assists discrimination between AAION and NAAION [11, 12], were lacking. Nevertheless, this is one of the first study that directly compares the features of patients with AAION and NAAION, enabling development of an algorithm to identify AAION cases at admission to the emergency room or ophthalmological department. Finally, we excluded major ACR criteria for GCA from the statistical analysis since they were directly involved in AAION and NAAION classification and allowed the development of our model that correctly classified clinically doubtful cases. However, some rare cases remain incorrectly diagnosed by our model.

Overall, distinguishing AAION and NAAION is a challenge in daily practice, but is crucial because the two conditions require a different approach in terms of work-up and treatment. We identified several clinical, ophthalmological, and laboratory features strongly associated with the arteritic form of AION. This model can help to discriminate of AAION and NAAION, thus ensuring prompt and appropriate treatments for both patient populations.

SUMMARY

What was known before

- Differentiation of arteritic and non-arteritic anterior ischaemic optic neuropathies can be challenging.

What this study adds

- A set of ophthalmological and laboratory criteria can efficiently discriminate patients with arteritic and non-arteritic anterior ischaemic optic neuropathies.

DATA AVAILABILITY

Authors confirm that the data supporting the findings of this study are available within the article.

REFERENCES

1. Hayreh SS Ischemic optic neuropathies. Springer, Heidelberg 2011.
2. Hayreh SS, Joos KM, Podhajsky PA, Long CR. Systemic diseases associated with nonarteritic anterior ischemic optic neuropathy. Am J Ophthalmol. 1994;118:766–80.
3. Weyand CM, Goronzy JJ. Clinical practice. Giant-cell arteritis and polymyalgia rheumatica. N Engl J Med. 2014;371:50–57.
4. Hellmich B, Agueda A, Monti S, Buttgereit F, de Boysson H, Brouwer E, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2020;79:19–30.

5. Atkins EJ, Bruce BB, Newman NJ, Biousse V. Treatment of nonarteritic anterior ischemic optic neuropathy. Surv Ophthalmol. 2010;55:47–63.
6. Hayreh SS, Podhajsky PA, Zimmerman B. Occult giant cell arteritis: ocular manifestations. Am J Ophthalmol. 1998;125:521–6.
7. Koçak N, Yeter V, Güngör I. Monocyte to high-density lipoprotein ratio in patients with arteritic and non-arteritic anterior ischaemic optic neuropathy. Neuroophthalmology. 2020;44:294–8.
8. Inanc M, Tekin K, Budakoglu O, Ilhan B, Aydemir O, Yilmazbas P. Could platelet indices and neutrophil to lymphocyte ratio be new biomarkers for differentiation of arteritic anterior ischemic neuropathy from non-arteritic type? Neuroophthalmology. 2018;42:287–94.
9. Liozon E, Herrmann F, Ly K, Robert PY, Loustaud V, Soria P, et al. Risk factors for permanent visual loss in giant cell (temporal) arteritis: a prospective study of 174 patients. Am J Med. 2001;111:211–7.
10. Costello F, Zimmerman MB, Podhajsky PA, Hayreh SS. Role of thrombocytosis in diagnosis of giant cell arteritis and differentiation of arteritic from non-arteritic anterior ischemic optic neuropathy. Eur J Ophthalmol. 2004;14:245–57.
11. Jonas JB, Gusek GC, Naumann GO. Anterior ischemic optic neuropathy: non-arteritic form in small and giant cell arteritis in normal sized optic discs. Int Ophthalmol. 1988;12:119–25.
12. Monteiro ML. Anterior ischemic optic neuropathy: a comparison of the optic disc area of patients with the arteritic and non-arteritic forms of the disease and that of normal controls. Arq Bras Oftalmol. 2006;69:805–10.
13. Danesh-Meyer HV, Boland MV, Savino PJ, Miller NR, Subramanian PS, Girkin CA, et al. Optic disc morphology in open-angle glaucoma compared with anterior ischemic optic neuropathies. Invest Ophthalmol Vis Sci. 2010;51:2003–10.
14. Balducci N, Morara M, Veronese C, Barboni P, Casadei NL, Savini G, et al. Optical coherence tomography angiography in acute arteritic and non-arteritic anterior ischemic optic neuropathy. Graefes Arch Clin Exp Ophthalmol. 2017;255:2255–61.
15. Pellegrini M, Giannaccare G, Bernabei F, Moscardelli F, Schiavi C, Campos EC. Choroidal vascular changes in arteritic and nonarteritic anterior ischemic optic neuropathy. Am J Ophthalmol. 2019;205:43–49.
16. Siatkowski RM, Gass JD, Glaser JS, Smith JL, Schatz NJ, Schiffman J. Fluorescein angiography in the diagnosis of giant cell arteritis. Am J Ophthalmol. 1993;115:57–63.
17. Valmaggia C, Speiser P, Bischoff P, Niederberger H. Indocyanine green *versus* fluorescein angiography in the differential diagnosis of arteritic and nonarteritic anterior ischemic optic neuropathy. Retina 1999;19:131–4.
18. Jonas JB, Harder B. Central retinal artery and vein collapse pressure in giant cell arteritis *versus* nonarteritic anterior ischaemic optic neuropathy. Eye (Lond). 2008;22:556–8.
19. Huna-Baron R, Mizrachi IB, Glovinsky Y. Intraocular pressure is low in eyes with giant cell arteritis. J Neuroophthalmol. 2006;26:273–5.
20. Ghanchi FD, Williamson TH, Lim CS, Butt Z, Baxter GM, McKillop G, et al. Colour Doppler imaging in giant cell (temporal) arteritis: serial examination and comparison with non-arteritic anterior ischaemic optic neuropathy. Eye (Lond). 1996;10:459–64.
21. Remond P, Attyé A, Lecler A, Lamalle L, Boudiaf N, Aptel F, et al. The central bright spot sign: a potential new mr imaging sign for the early diagnosis of anterior ischemic optic neuropathy due to giant cell arteritis. Am J Neuroradiol. 2017;38:1411–5.
22. Danesh-Meyer HV, Savino PJ, Sergott RC. The prevalence of cupping in end-stage arteritic and nonarteritic anterior ischemic optic neuropathy. Ophthalmology 2001;108:593–8.
23. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990;33:1122–228.
24. de Boysson H, Dumont A, Liozon E, Lambert M, Boutemy J, Maigné G, et al. Giant-cell arteritis: Concordance study between aortic CT angiography and FDG-PET/CT in detection of large-vessel involvement. Eur J Nucl Med Mol Imaging. 2017;44:2274–9.
25. Rinagel M, Chatelus E, Jousse-Joulin S, Sibilia J, Gottenberg JE, Chasset F, et al. Diagnostic performance of temporal artery ultrasound for the diagnosis of giant cell arteritis: a systematic review and meta-analysis of the literature. Autoimmun Rev. 2019;18:56–61.
26. Dejaco C, Ramiro S, Duftner C, Besson FL, Bley TA, Blockmans D, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis. 2018;77:636–43.
27. Chan FLY, Lester S, Whittle SL, Hill CL. The utility of ESR, CRP and platelets in the diagnosis of GCA. BMC Rheumatol 2019;3:14 https://doi.org/10.1186/s41927-019-0061-z
28. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. Chest 2010;137:263–72.
29. Van Buuren S, Groothuis-Oudshoorn K. MICE: Multivariate Imputation by Chained Equations in R. J Stat Softw. 2011;45:1–67.
30. Ing EB, Lahaie Luna G, Toren A, Ing R, Chen JJ, Arora N, et al. Multivariable prediction model for suspected giant cell arteritis: development and validation. Clin Ophthalmol. 2017;11:2031–42.
31. Ing E, Su W, Schonlau M, Torun N. Support Vector Machines and logistic regression to predict temporal artery biopsy outcomes. Can J Ophthalmol. 2019;54:116–8.
32. Ing EB, Ing R. The use of a nomogram to visually interpret a logistic regression prediction model for giant cell arteritis. Neuroophthalmology. 2018;42:284–6.
33. Ing EB, Miller NR, Nguyen A, Su W, Bursztyn LLCD, Poole M, et al. Neural network and logistic regression diagnostic prediction models for giant cell arteritis: development and validation. Clin Ophthalmol. 2019;13:421–30.
34. Czihal M, Tschaidse J, Bernau C, Lottspeich C, Köhler A, Dechant C, et al. Ocular ischaemic complications in giant cell arteritis: CHADS2-score predicts risk of permanent visual impairment. Clin Exp Rheumatol. 2019;37:61–64.
35. Hayreh SS. Anterior ischaemic optic neuropathy. differentiation of arteritic from non-arteritic type and its management. Eye. 1990;4:25–41.
36. Mack HG, O'Day J, Currie JN. Delayed choroidal perfusion in giant cell arteritis. J Clin Neuroophthalmol. 1991;11:221–7.
37. Bei L, Lee I, Lee MS, Van Stavern GP, McClelland CM. Acute vision loss and choroidal filling delay in the absence of giant-cell arteritis. Clin Ophthalmol. 2016;10:1573–8.
38. Chen JJ, Leavitt JA, Fang C, Crowson CS, Matteson EL, Warrington KJ. evaluating the incidence of arteritic ischemic optic neuropathy and other causes of vision loss from giant cell arteritis. Ophthalmology. 2016;123:1999–2003.

AUTHOR CONTRIBUTIONS

Conception and design of the work: SP, TS, BT Acquisition and interpretation of the data: SP, AD, RM, SD, AR, GG, DM, APB, KHL, EL, TS, BT. Drafting the manuscript: SP, BT. Revising the work critically: AD, RM, SD, AR, GG, DM, APB, KHL, EL, TS.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41433-022-02295-w.

Correspondence and requests for materials should be addressed to Simon Parreau.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.