Section Editors: Clare Fraser, MD
Susan Mollan, MD

Use of Retinal Angiography and MRI in the Diagnosis of Giant Cell Arteritis With Early Ophthalmic Manifestations

Alexandre Dentel, MD, Gaelle Clavel, MD, Julien Savatovsky, MD, Catherine Vignal, MD, Thomas Senè, MD, Frédérique Charbonneau, MD, Kevin Zuber, MSc, Augustin Lecler, MD, Rabih Hage, MD

Background: Giant cell arteritis (GCA) is a vasculitis often revealed by visual signs. Diagnosis is challenging and urgent. Retinal angiography (RA) and MRI allow effective diagnosis. We compared those and proposed an imaging-based approach to diagnose GCA in ophthalmological practice.
Methods: We conducted a retrospective study based on the data collected from patients suspected to have GCA on ophthalmological findings. Fluorescein (FA) and indocyanine green (ICG) RAs and MRI were performed and compared with final diagnosis.
Results: Among the 41 patients included, 25 were diagnosed with GCA. Sensitivities and specificities of FA and ICG were not different. MRI showed a higher sensitivity and specificity. The approach consisting in performing RA followed by MRI provided a better accuracy.
Conclusion: Our study shows that RA can be supplemented by MRI in a specialized center to provide the most accurate diagnosis in GCA revealed by visual signs.

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Giant cell arteritis (GCA) is a vasculitis involving large-sized and medium-sized arteries (1). It is the most common systemic vasculitis in the elderly (2,3) with a mean age of 71 years at diagnosis (4). The sex ratio is approximately 7 women for 3 men (5). The cranial form of GCA (C-GCA) is the most common in ophthalmology clinics (6). By affecting arteries supplying the eyes and the cranial nerves, C-GCA can induce a variety of visual manifestations in up to 68% of cases (7–11). In patients with GCA with optic nerve ischemia, visual prognosis is poor, with a high prevalence of irreversible visual loss (12,13). Emergent diagnosis and treatment are therefore needed (14) because bilateralization concerns up to 54% of patients within the few days after the first eye involvement (15–17). Several diagnosis tools are available. Blood testing allows screening for signs of inflammation (increased C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR]) (5). Histopathological evidence with temporal artery biopsy (TAB) remains widely performed as a gold standard test in GCA and can reveal segmental and focal nonnecrotizing giant cell panarteritis (18). However, numerous studies showed lower diagnostic accuracies of TAB in GCA when compared with imaging (19–23). Several studies showed that contrast-enhanced vessel-wall MRI (CE-VW MRI) (referred below as "MRI") can analyze parietal inflammation in cephalic arteries, allowing effective diagnosis in GCA (24–28). Better resolution and diagnostic accuracy were demonstrated using 3 T units (29–33). Besides, a strong superiority of "reformated" 3D MRI over "classic" 2D MRI has been proven, reaching 100% specificity (34).

However, MRI, ultrasound, and even TAB need significant resources and trained operators to provide reliable results. They are not routinely available to every ophthalmologist suspecting GCA. Fluorescein (FA) or indocyanine green (ICG) retinal angiographies (RAs) are more widely available examinations in ophthalmological primary care centers or clinics. Most ophthalmologists are trained to identify typical angiographic findings in GCA, that is, choroidal circulatory filling delay related to posterior ciliary network ischemia (35–37).

The goal of this study was to assess the use of FA, ICG, and MRI for diagnosing GCA in patients with suspicious

Department of Ophthalmology (AD, CV, RH), Foundation Adolphe de Rothschild Hospital, Paris, France; Department of Internal Medicine (GC, TS), Foundation Adolphe de Rothschild Hospital, Paris, France; Department of Neuroradiology (JS, FC, AL), Foundation Adolphe de Rothschild Hospital, Paris, France; and Department of Clinical Research (KZ), Foundation Adolphe de Rothschild Hospital, Paris, France.

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Address correspondence to Alexandre Dentel, MD, Department of Ophthalmology, Foundation Adolphe de Rothschild Hospital, Paris, France; E-mail: adentel@for.paris.

diplopia or visual loss. We will (1) establish the sensibilities and specificities of these 3 examinations and (2) propose an imaging-based approach to diagnose GCA in ophthalmological practice.

METHODS

Patients

We conducted a retrospective single-centered study at the *Hôpital Fondation Ophtalmologique Adolphe de Rothschild* (Paris, France), based on data collected from the HORTIM cohort. From December 2014 to September 2017, the HORTIM cohort prospectively included patients who (1) were at least 50 years; (2) were clinically suspected of having GCA; and (3) underwent several imaging examinations including FA, ICG, and MRI. Patients were not included in the HORTIM cohort if (1) they were already given a diagnosis of GCA and (2) TAB or final diagnosis preceded imaging. We excluded HORTIM cohort's patients from this study if they (1) did not initially complained about visual loss or diplopia; (2) did not undergo FA, ICG, MRI, or TAB; and (3) had an ocular or systemic condition that could interfere with RAs lecture (see below).

On admission, each patient underwent (1) physical examination by an internal medicine specialist; (2) comprehensive ophthalmic examination including visual acuity measurement, eye motility examination; (3) nonmydriatic fundus photograph; and (4) measurement of ESR and CRP rates. Each patient was classified according to the visual impairment(s) they presented at baseline, deemed "afferent" if there was loss of vision caused by ischemia of the retina or the optic nerve, "efferent" if there was binocular diplopia related to cranial nerve palsy, and "mixed" when both loss of vision and diplopia were reported (Table 1). Clinical and paraclinical findings were reviewed by 2 neuro-ophthalmologists. Two follow-up clinical examinations were performed in the neuro-ophthalmology department (at 2 and 6 weeks after presentation).

Retinal Angiography

Each RA included at least 8 images between the early and late phases of the angiogram, both dyes collected at identical time intervals, captured on SPECTRALIS Optical Coherence Tomography (OCT) Angiography Module (Heidelberg Engineering). Their analysis was performed by experienced retinologists, blind to the final diagnosis.

RA was considered positive if it showed extensive or sectorial choroidal circulation filling delay in either eye at inclusion. A difference of artery filling by 20 seconds between the 2 eyes (or between 2 sectors of the same eye) was considered abnormal (Fig. 1). The presence of other causes of choroidal ischemia, such as uveal effusion syndrome, posterior scleritis/inflammation, ipsilateral high-grade stenosis of the internal carotid artery, severe hypertension, and shock (39), was excluded.

MRI

MRI was performed on a Philips Ingenia 3 T (Philips Medical Systems), with systematic intravenous injection of gadobutrol. The results were blindly analyzed by 2 neuroradiologists (AL and FC) because it has been described and recommended (24,38). Each MRI was scored on 3 levels: certain (Fig. 2), suspicious, or negative, following previously referenced keys. In this study, we considered MRI as positive if scored as certain and negative if not.

Temporal Artery Biopsy and Final Diagnosis

The final diagnosis of GCA was assessed by a multidisciplinary team of rheumatologists and internists who were not involved in patient's care, based on the 1990 American College of Rheumatology (ACR) criteria (including TAB)

TABLE 1. Different types of visual impairments reported in the HORTIM cohort at baseline

	Ophthalmic Diagnosis	Vascular Network Involved
Afferent system impairments related to 1 vascular network	AION	Ciliary arteries
	CLRAO	Ciliary arteries
	CRAO	Central retinal artery
	TVL	Ciliary or central retinal arteries
Isolated efferent system impairment	ONP, either transient or fixed	Ocular motor nerve arteries (ophtalmic artery system)
Afferent visual impairments related to multiple vascular networks	AION and previous TVL	Ciliary arteries with or without central retinal artery
	AION and CRAO	Ciliary and retinal central arteries
	AION and CLRAO	Ciliary arteries
Mixed visual impairments	ONP and AION	Ocular motor nerve arteries associated with ciliary or central retinal arteries
	ONP and CRAO	
	ONP and AION and CRAO	

AION, anterior ischemic optic neuropathy; CLRAO, cilioretinal artery occlusion; CRAO, central retinal artery occlusion; ONP, oculomotor nerve palsy; TVL, transient visual loss.

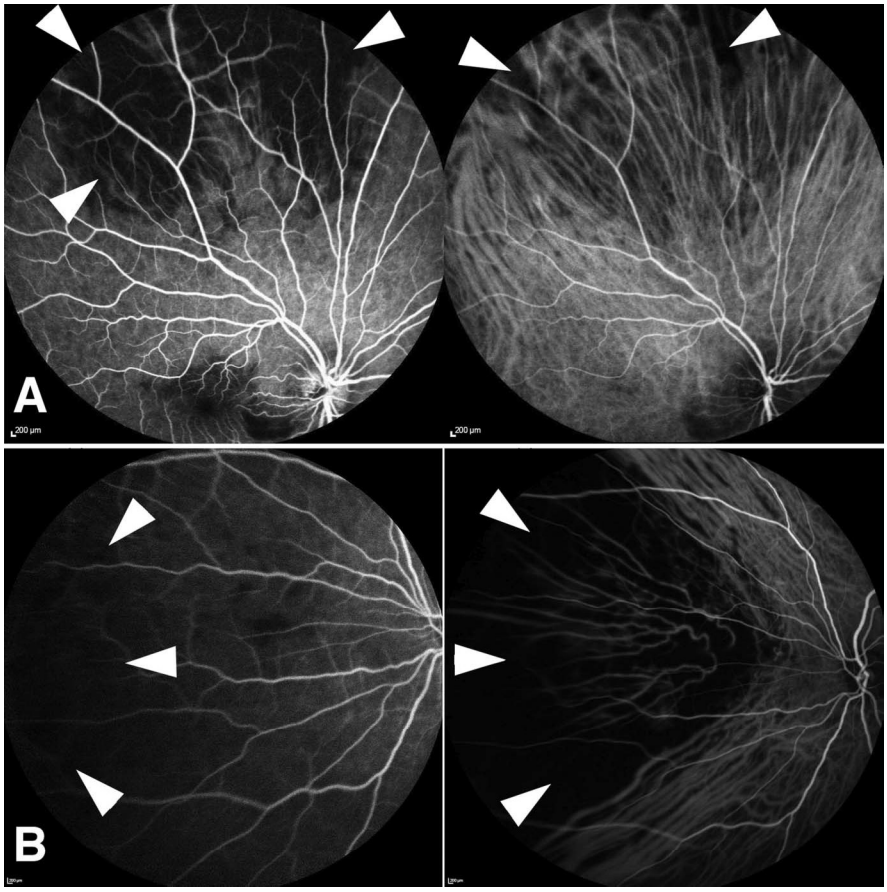

FIG. 1. Sample images of RA illustrating a choroidal filling delay. **A**. FA (left) and ICG (right) angiograms in a right eye, 30 seconds after the dyes were injected: 2 typical triangle-shaped choroidal delay in the upper temporal territory (corresponding to the short posterior superior ciliary arteries), seen as well with both dyes (*arrowheads*). This patient was diagnosed with GCA and suffered from a contralateral anterior ischemic optic neuropathy. **B**. FA (left) and ICG (right) angiograms in a left eye, 40 seconds after the dyes were injected: typical triangle-shaped choroidal delay in nasal territory (corresponding to the short posterior nasal ciliary arteries), better on the indocyanine green angiography (*arrowheads*). This patient was diagnosed with GCA and suffered only from diplopia related to a left fourth nerve oculomotor palsy (repeated comprehensive ophthalmological examinations including visual fields excluded any optical or retinal ischemia). FA, fluorescein angiography; GCA, giant cell arteritis; ICG, indocyanine green angiography; RA, retinal angiography.

(40). TAB was considered as positive or negative depending on the pathologist's report.

Analysis and Statistics

FA, ICG, and MRI were compared with each other using the McNemar test for sensitivity and specificity and a generalized estimating equation test for a positive predictive value and negative predictive value. Positive and negative rates of each examination were studied according to the final diagnosis and the types of visual impairment. Finally, 4 imaging-based diagnostic approaches were studied: FA followed by ICG, ICG followed by FA, FA followed by MRI, and ICG followed by MRI. Confidence intervals were set at 95% and were calculated using the Clopper–Pearson method because the normal approximation might not be suitable because of the small amount of data. Chi-square or Fisher exact tests were used to compare categorical variables. Comparison of numerical variables was performed using the t test or Mann–Whitney U test as appropriate. All analyses were performed using R version 4.0.2. A P value < 0.05 was considered statistically significant.

Ethics

This retrospective study adhered to the tenants of the Declaration of Helsinki and has been approved by a research ethics board (IRB00012801).

This study follows the Standards for Reporting of Diagnostic Accuracy Studies guidelines.

RESULTS

Forty-five patients were enrolled in the HORTIM cohort. Four patients were excluded, including 2 because of no visual impairment on admission, 1 because no MRI was available, and 1 because RA was not undergone. Among the

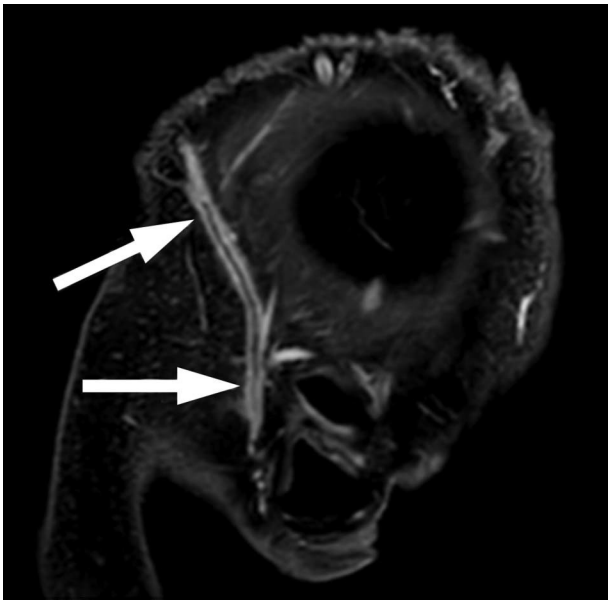

FIG. 2. Sample sagittal MRI section showing thickening and parietal contrast enhancement of the external carotid and the superficial temporal arteries (*arrows*).

41 patients included, 25 received a final diagnosis of GCA (Fig. 3). Patients' characteristics are presented in Table 2. GCA patients were significantly older, more likely to have higher CRP and ESR rates, or to complain about systemic GCA symptoms. All GCA patients had systemic symptoms. Two of them only reported asthenia. Multiple afferent visual impairments and mixed visual impairments were most common in GCA patients, and the visual acuity in the affected eye was lower (1 vs 0.2 logMAR). In the non-GCA group, only 1 patient had a possible multiple afferent impairment involving retinal and ciliary networks. All patients who presented with retinal ischemia and oculomotor nerve palsy at baseline were diagnosed with GCA.

RA was positive in 22 and 19 GCA cases (of 25) and negative in 11 and 13 non-GCA cases (of 16), respectively. The sensitivities of FA and ICG were 0.88 (0.69–0.97) and 0.76 (0.55–0.91), and the specificities were 0.69 (0.41–0.89) and 0.81 (0.54–0.96) for the diagnosis of GCA, respectively. CE-VW MRI was positive in 23 of 25 GCA patients, which is a sensitivity of 0.92 (0.74–0.99) and a specificity of 0.94 (0.70–1.00).

When compared statistically, there was no significant difference in sensitivity and specificity for the diagnosis of GCA between FA, ICG, and CE-VW MRI. Indeed, when comparing sensitivity of FA and ICG, the McNemar test did not show significant difference (P = 0.08). The same was found for specificity (P = 0.16). In addition, no significant difference was found between ICG and CE-VW MRI (P = 0.16 for sensitivity and P = 0.32 for specificity) and between FA and CE-VW MRI (P = 0.65 for sensitivity and P = 0.10 for specificity). However, absolute values showed the superiority of CE-VW MRI for sensitivity and specificity.

The results of the different examinations according to the type of visual impairment are presented in Tables 3 and 4. RA and CE-VW MRI were positive in every GCA patient presenting multiple afferent visual impairments (n = 5). The 3 examinations were also negative in every non-GCA patient presenting with isolated diplopia (n = 4). By contrast, in the multiple afferent visual impairments group, 1 non-GCA patient showed choroidal delay on RA. In GCA patients complaining about isolated diplopia at baseline, 1 presented choroidal ischemia on RA. Finally, only 1 cilioretinal artery occlusion was found in addition to choroidal delay on FA, in a GCA patient.

The different diagnostic approaches are presented in Table 5. RA's specificity and sensitivity were not

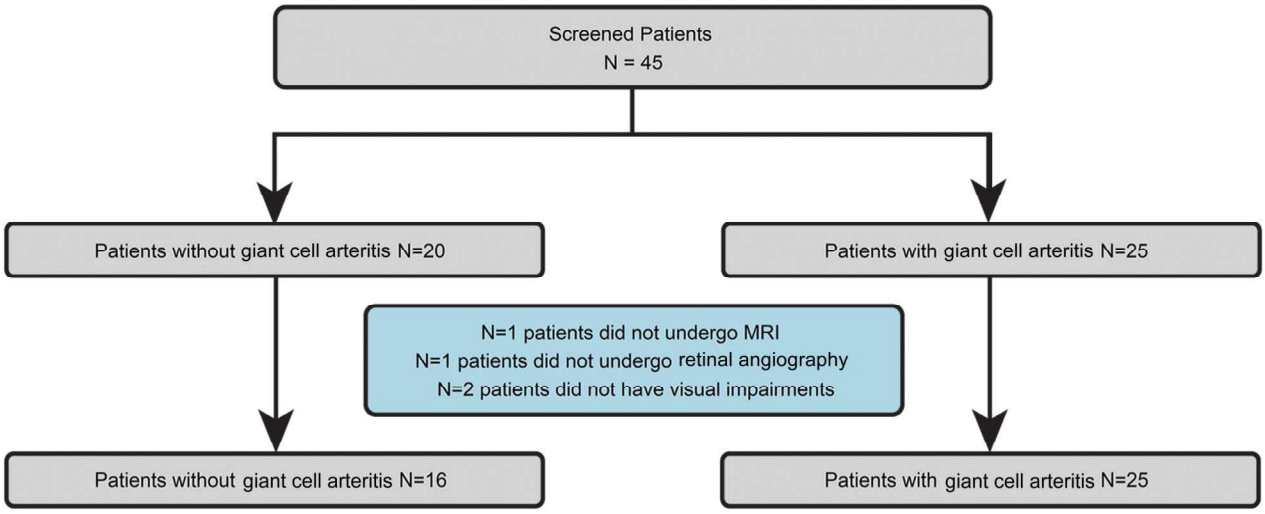

FIG. 3. Flowchart.

TABLE 2. Patients' characteristics

Patients' Characteristics	Number of Patients (%) n = 41 (100%)		*P* value
Final diagnosis of GCA (ACR 1990)	Yes n = 25 (61,0)	No n = 16 (39,0)	
Gender			
Female	16 (64,0)	7 (43,8)	0.20
Male	9 (36,0)	9 (56,2)	
Mean age (extreme values)	79.4 (59–94)	71.4 (60–89)	0.006
Baseline blood tests			
Mean CRP (extreme values)	70.0 (9–179)*	12.5 (1–36)	<0.001
Mean ESR (extreme values)	67.1 (15–114)†	42.6 (3–100)‡	0.04
Presence of at least 1 symptom below	23 (92,0)	8 (50.0)	0.007
Presence of at least 2 symptoms below	18 (72,0)	1 (6.3)	<0.001
Recent headaches	18 (72,0)	7 (43,8)	
Jaw claudication	16 (64.0)	0 (0.0)	
Scalp tenderness	12 (48,0)	2 (12,5)	
Fever	0 (0.0)	0 (0.0)	
Shoulders or hips pain	2 (8,0)	0 (0.0)	
General symptoms below	15 (60,0)	6 (37,5)	0.16
Recent loss of body weight >10%	2 (8,0)	0 (0.0)	
Anorexia	1 (4,0)	1 (6,25)	
Asthenia	15 (60,0)	6 (37,5)	
Visual impairment with normal fundus§	0 (0.0)	1 (0.6)	1
Initial visual acuity of the impaired eye in logMAR (extreme values)	1 (0–2.6) [0.15–2.3]	0.2 (0–2.3) [0–0.6]	0.026
Simple afferent visual impairment	13 (52,0)	9 (56,3)	0,80
Isolated TVL	2 (8,0)	2 (12,5)	
Isolated AION	10 (40,0)	7 (43,8)	
Isolated CRAO	1 (4,0)	0 (0.0)	
Combined afferent visual impairment	5 (20,0)	2 (12,5)	0.68
TVL + AION	2 (8,0)	2 (12,5)	
CLRAO + AION	1 (4,0)	0 (0.0)	
CRAO + AION	2 (8,0)	0 (0.0)	
Isolated efferent impairment (diplopia)	2 (8,0)	4 (25,0)	0.19
Mixed visual impairment	4 (16,0)	0 (0.0)	0.14
Diplopia + AION	1 (4,0)	0 (0.0)	
Diplopia + CRAO	1 (4,0)	0 (0.0)	
Diplopia + AION + CRAO	2 (8,0)	0 (0.0)	
Positive FA	22 (88,0)	5 (31,3)	<0.001
CLRAO + choroidal filling delay	1 (4,0)	0 (0.0)	
Positive ICG	19 (76,0)	3 (18,8)	<0.001
Positive CE-VW MRI (certain)	23 (92,0)	1 (6,25)	<0.001
Negative CE-VW MRI	2 (8,0)	15 (93,8)	<0.001
Scored suspicious	2 (8,0)	1 (6,25)	
Scored negative	0 (0.0)	14 (87,5)	

*One value not available.
†Five values not available.
‡Three values not available.
§Related to a cataract.
AION, anterior ischemic optic neuropathy; ACR, American College of Rheumatology; CE-VW MRI, contrast-enhanced vessel-wall MRI; CLRAO, cilioretinal artery occlusion; CRP, C-reactive protein; CRAO, central retinal artery occlusion; ESR, erythrocyte sedimentation rate; FA, fluorescein angiography; GCA, giant cell arteritis; ICG, indocyanine green angiography; TVL, transient visual loss.

significantly different, regardless of the number of dyes used and of the sequence (FA then ICG or ICG then FA). The approaches consisting in performing initially RA followed by MRI provide a sensitivity of 100% (P = 0.014, when compared with using only ICG) when ICG is negative and a specificity of 100% (P = 0.025, when compared with using only FA) when FA is positive.

CONCLUSIONS

We found diagnostic accuracies of RA and MRI to be statistically similar in the diagnosis of cranial GCA revealed by visual signs. However, this result might be related to a lack of power, for we found a trend in favor of MRI, with a sensitivity reaching 92% and a specificity of

TABLE 3. Visual impairment in GCA patients in comparison with positivity of FA, ICG, and CE-VW MRI

Visual impairment	FA + (%)	ICG + (%)	CE-VW MRI + (%)
Isolated AION	9 (90,0)	8 (80,0)	10 (100,0)
Isolated TVL	2 (100,0)	0 (0.0)	2 (100,0)
Isolated CRAO	1 (100,0)	1 (100,0)	0 (0.0)
Isolated diplopia	1 (50,0)*	1 (50,0)*	2 (100,0)
Multiple afferent	5 (100,0)	5 (100,0)	5 (100,0)
Mixed	3 (75,0)	2 (50,0)	4 (100,0)

*Same patient.

AION, anterior ischemic optic neuropathy; CE-VW MRI, contrast-enhanced vessel-wall MRI; CRAO, central retinal artery occlusion; FA, fluorescein angiography; ICG, indocyanine green angiography; TVL, transient visual loss.

94%. These findings are consistent with previously published data. Dejaco et al found sensitivities and specificities of 93% and 81% compared with TAB, respectively, based on studies with 2D MRI (23). Our study used a new process based on 3D MRI, used by Poillon et al who found better diagnostic accuracies of 3D vs 2D MRI, with sensitivities of 80% vs 70% and specificities of 100% vs 85% (34). In our study, MRI caught up every false negatives and false positives of RA, still allowing RA to confirm diagnosis in cases where MRI is considered as "suspicious" (concerned 2 patients in our study). Moreover, it is important to keep in mind that MRI presents several interpretation traps (temporal artery atherosclerosis for instance) that can lead to potential misinterpretation and false positives. Regardless of the type of dye used, RA reached good diagnostic accuracy in our cohort. In specific clinical circumstances, it performed as well as MRI. In all patients with multiple afferent visual impairments, including anterior ischemic optic neuropathy (AION) preceded by transient visual loss (TVL), RA had remarkable sensitivity. We noted that AF and ICG are misreading in same patients, which means there would be no added value to perform both type of RA. In addition, ICG tends to be more specific, whereas FA tends to be more sensitive. These findings should be considered regarding the adverse events fluorescein can induce, which can lead to death. ICG is far safer than fluorescein (41,42). We therefore recommend performing ICG rather than FA in the early management of GCA revealed by visual signs.

TABLE 4. Visual impairment in non-GCA patients in comparison with negativity of FA, ICG, and CE-VW MRI

Visual Impairment	FA (%)	ICG (%)	CE-VW MRI (%)
Isolated AION	4 (57,1)	5 (71,4)	6 (85,7)
Isolated TVL	1 (50,0)	2 (100,0)	2 (100,0)
Isolated CRAO	†	†	†
Isolated diplopia	4 (100,0)	4 (100,0)	4 (100,0)
Multiple afferent	1 (50,0)*	1 (50,0)*	2 (100,0)
Mixed	†	†	†

*Same patient.

†None of the patients filled these categories.

AION, anterior ischemic optic neuropathy; CE-VW MRI, contrast-enhanced vessel-wall MRI; CRAO, central retinal artery occlusion; FA, fluorescein angiography; ICG, indocyanine green angiography; TVL, transient visual loss.

However, RA presented too high false-negative and false-positive rates to be considered as a standalone diagnostic tool. We believe that patients with visual manifestations and suspected GCA should undergo at least 2 imaging tests. We explored different approaches based on patients' usual pathway through the health care system. Because very few centers are equipped with technical facilities that allow urgent MRI examinations, RA would be the examination obtained in the shortest delay. It seems that the best approach is to perform RA followed by MRI (Fig. 4).

Considering patients with all types of visual impairments, performing ICG followed by MRI provides a sensitivity of 100% if ICG is mistaken and a specificity of 100% if not. This strategy allowed us to reach the correct diagnosis in all our patients.

In this study, all the patients had TAB and 6 GCA patients had a mistaken TAB. The lack of sensitivity of TAB is well-known (5), and the European League Against Rheumatism society allowed the diagnosis of GCA without carrying TAB (22). Our strategy is consistent with this approach and ensures that the final assessment is much more accurate than TAB.

This study presents several limitations, including a lack of power related to the number of included patients as discussed above. Considering MRI as negative if scored "suspicious" may also have minimized the chance of finding significant difference with RA. The retrospective design of this study introduces bias in data. However, inclusion in the HORTIM cohort and procedures/examinations did occur in a prospective way, which may prevent retrospective bias. Although our algorithm is designed for use in primary care medicine, it was based on the findings of this study conducted in a tertiary center. However, only 5 patients (presenting isolated AIONs) of the 41 analyzed were referred by a physician. All the others primarily sought medical attention in our eye emergency department. Because this study was conducted in a tertiary center, MRI and RA were performed and interpreted by GCA experts. It should be kept in mind that vessel-wall MRI currently requires reading by experienced neuroradiologists who are familiar with interpretation pitfalls. RA must also be interpreted by ophthalmologists trained to identify choroidal delay. Finally, we chose to classify patients according to the type of visual impairment and to consider TVL as a constituent of a multiple afferent mechanism. This decision was based on the assumption that the pathophysiological mechanism of TVL cannot be precisely determined.

TABLE 5. Diagnostic approaches and values according to the performed order of the different exams

Approaches	First Examination	After Second Examination	*P*
FA → ICG (vs FA only)	Negative FA	se 88% [69–97]	NA
		sp 69% [41–89]	NA
	Positive FA	se 76% [55–91]	0.83
		sp 81% [54–96]	0.16
ICG → FA (vs ICG only)	Negative ICG	se 88% [69–97]	0.08
		sp 69% [41–89]	0.16
	Positive ICG	se 76% [55–91]	NA
		sp 81% [54–96]	NA
FA → CE-VW MRI (vs FA only)	Negative FA	se 100% [86–100]	0.32
		sp 63% [35–85]	0.32
	Positive FA	se 80% [59–93]	0.16
		sp 100% [79–100]	**0.025**
ICG → CE-VW MRI (vs ICG only)	Negative ICG	**se 100%** [86–100]	**0.014**
		sp 75% [48–93]	0.32
	Positive ICG	se 68% [46–85]	0.16
		sp 100% [79–100]	0.08

Sensitivity (se) and specificity (sp) reached after the second examination were compared with the sensitivity and the specificity of the first examination to determine the added value of the second examination. Statistically significant results are shown in bold.

CE-VW MRI, contrast-enhanced vessel-wall MRI; FA, fluorescein angiography; ICG, indocyanine angiography.

Given the presence of simultaneous AION and central retinal artery occlusion (CRAO) in the GCA group, we can consider TVL as a pre-CRAO or pre-AION state, regardless of what patients finally presented. This choice may have had a limited impact on our results because the number of TVL followed by AION is comparable in the 2 groups.

To conclude, GCA revealed by visual signs is a challenging and urgent diagnosis. We believe that ICG is still an important front-line test, ideally supplemented by MRI, which are safe and highly effective examinations in GCA revealed by visual signs.

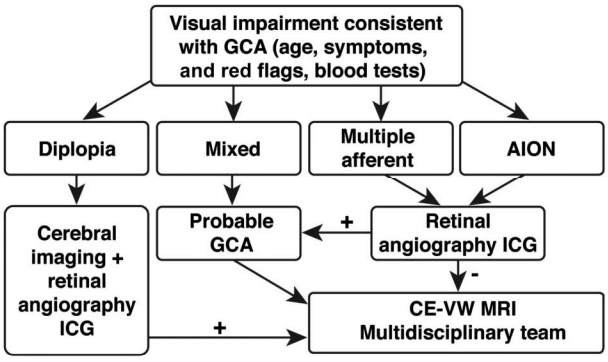

FIG. 4. Diagnostic algorithm based on retinal angiography (RA) as the first-line examination and contrast-enhanced vessel-wall MRI (CE-VW MRI) as the final examination in suspected giant cell arteritis (GCA) revealed by visual signs. AION, anterior ischemic optic neuropathy; CE-VW MRI, contrast-enhanced vessel-wall MRI; ICG, indocyanine green.

STATEMENT OF AUTHORSHIP

Category 1: a. Conception and design: A. Dentel, R. Hage, and T. Senè; b. Acquisition of data: G. Clavel, A. Lecler, F. Charbonneau, and J. Savatovsky; c. Analysis and interpretation of data: K. Zuber. Category 2: a. Drafting the manuscript: A. Dentel and R. Hage; b. Revising it for intellectual content: A. Dentel and R. Hage, T. Senè, G. Clavel, A. Lecler, F. Charbonneau, J. Savatovsky, and C. Vignal. Category 3: a. Final approval of the completed manuscript. A. Dentel, R. Hage, T. Senè, G. Clavel, A. Lecler, F. Charbonneau, J. Savatovsky, and C. Vignal.

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