Ocular Immunology and Inflammation

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ioii20

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To cite this article: Ghassan Elourimi, Michael Soussan, Matthieu Groh, Antoine Martin, Francoise Héran, Olivier Galatoire, Robin Dhote, Eric Vicaut & Sébastien Abad (2021): F-18 Fluorodeoxyglucose PET/CT as a Diagnostic Tool in Orbital Inflammatory Disorders, Ocular Immunology and Inflammation, DOI: 10.1080/09273948.2021.1957943

To link to this article: https://doi.org/10.1080/09273948.2021.1957943

Published online: 28 Jul 2021.

OCULAR IMMUNOLOGY AND INFLAMMATION
https://doi.org/10.1080/09273948.2021.1957943

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RESEARCH ARTICLE

F-18 Fluorodeoxyglucose PET/CT as a Diagnostic Tool in Orbital Inflammatory Disorders

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ABSTRACT

Purpose: To assess the usefulness of FDG-PET/CT as a potential diagnostic tool for detecting underlying systemic diseases (SD) in patients with orbital inflammatory disorders (OID).

Methods: All consecutive patients managed for new-onset OID between 2011 and 2018 in a tertiary referral center, who underwent FDG-PET/CT as part of the etiological diagnostic workup were evaluated. To quantify the incremental value of FDG-PET/CT over standard diagnostic workup, the Net Reclassification Index (NRI) and Integrated Discrimination Index (IDI) were used.

Results: Among the 22 patients enrolled, 11 (50%) had a positive FDG-PET/CT. After clinicobiological evaluation, FDG-PET/CT correctly reclassified 4(29%) of 14 patients with SD ($p = .04$) and 1(13%) of 8 with idiopathic orbital inflammation syndrome ($p = .32$). NRI and IDI were 0.41 ± 0.17 ($p = .03$) and 0.38 ± 0.08 ($p < .001$), respectively. FDG-PET/CT successfully detected asymptomatic lesions in all (n = 4) patients with lymphoma.

Conclusion: FDG-PET/CT enabled accurate reclassification of more than one-quarter of patients with SD, especially extraorbital lymphomas.

ARTICLE HISTORY
Received 17 December 2020
Revised 13 July 2021
Accepted 14 July 2021

KEYWORDS
Adnexal orbital lymphoma; FDG-PET/CT; idiopathic orbital inflammatory syndrome; IgG4-related ophthalmic disease; inflammatory orbital pseudotumor

Orbital inflammatory diseases (OID) involve all anatomical structures of the orbit (*e.g.*, oculomotor muscles, orbital fat, sclera, and optic nerve) and its annexes (*e.g.*, lacrimal glands and eyelids).[1] OID may correspond to the ophthalmological presentation of systemic diseases (SD), including Graves' disease, sarcoidosis, granulomatosis with polyangiitis (GPA), crystal storing histiocytosis (CSH), adult onset asthma and periorbital xanthogranuloma (AAPOX), or IgG4-related disease (IgG4-RD).[2] In the absence of underlying local or systemic causes, the diagnosis of idiopathic orbital inflammation syndrome (IOIS, a nonspecific inflammatory disorder restricted to the eye) is considered. Since lymphoid malignancies of the ocular adnexa can mimic the clinical picture of IOIS, obtaining tissue biopsies is of paramount importance.[3] Yet, the latter can be difficult to obtain, depending on the anatomical site of involved tissues and the risk of damaging the optic nerve. In such situations, the diagnostic workup must be as exhaustive as possible in order to avoid delayed diagnosis of the underlying cause.[4,5]

In the last decade, FDG-PET/CT has become routine practice in the management of lymphoma,[6] and can be a useful diagnostic tool for sarcoidosis,[7] GPA,[8] IgG4-RD,[9] or AAPOX.[10] Because of its high sensitivity, FDG-PET/CT could be able to detect asymptomatic localizations of the above-mentioned SD. In the current study, we aimed to assess the potential utility of FDG-PET/CT as a diagnostic tool for detecting underlying SD in the course of OID.

Patients and Methods

This was a retrospective cohort study conducted in the internal medicine department of Avicenne University Hospital (Bobigny, France) with expertise in the field of OID. This study was conducted in compliance with the Good Clinical Practice protocol and the Declaration of Helsinki principles and was approved by the local Institutional Review Board (CLEA), which waived the need for written informed consent.

Study Participants

Between January 2011 (*i.e.*, when PET was included in the systematic diagnostic workup of patients with OID in our institution) and May 2018, all consecutive patients investigated for new-onset OID were retrospectively evaluated.

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Data Collection

Clinical data were retrieved from medical charts using a standardized anonymous form and included age at diagnosis, gender, past medical history, ongoing immunosuppressive therapy, white blood cell count, biological markers of inflammation (*i.e.*, fibrinogen and C-Reactive Protein), and the etiological workup for autoimmune diseases (including serum angiotensin-converting enzyme (ACE), IgG4 levels and testing for antinuclear (ANA), thyroid, and antineutrophil cytoplasmic (ANCA) autoantibodies). Additionally, minor salivary gland biopsy was performed routinely either in case of sicca syndrome or elevated serum ACE levels.

Data from magnetic resonance imaging or computerized tomography of the orbit were also retrieved. For each patient, the following locations and their laterality were screened in order to specify the anatomic structures involved in the inflammatory process: lacrimal gland, extra-ocular muscles, orbital fat, globe or sclera, apex and optic, or infra-orbital nerve.

As of January 2011, routine care PET/CT imaging was included in our institution in the etiological workup of newly diagnosed OID. Hence, a PET/CT scanner (Gemini TF; Philips Medical Systems, Best, the Netherlands) was performed in patients with serum glucose level of less than 1.6 g/L at the time of injection. PET/CT imaging was performed 60 min after intravenous injection of 3 MBq/kg of FDG, while time per bed position was 105 s. CT images were obtained without injection of contrast media by using the following settings: 120 kV; 100 mA; collimation, 16 × 1.5 mm; pitch, 0.69; section thickness, 3 mm; increment, 1.5 mm. PET images were reconstructed by using a blob ordered subset–time of flight list-mode iterative algorithm with two iterations and 33 subsets, including attenuation and scatter corrections. A single-scatter simulation model was used for scatter correction. No postreconstruction smoothing filter was used. The image voxel size was 4 × 4 × 4 mm for PET and 1.17 × 1.17 × 1.5 mm for CT. SUVs were calculated from the reconstructed activity concentration values and were normalized to body weight. PET images were reviewed blindly by an expert in the field (MS). Images were considered as positive if they showed an extraorbital lesion (lymphadenopathy or other visceral lesions) with a maximum standardized uptake value above the blood pool background and not related to a physiological uptake.

When available at diagnosis, orbital biopsy specimens were also analyzed blindly by a pathologist with expertise in the field (AM). Except for cases with evidence of lymphoma, additional immunohistochemical staining was systematically performed using anti-IgG (rabbit polyclonal anti-IgG antibody, Ventana-Roche) and anti-IgG4 antibodies (rabbit monoclonal anti-human IgG4 antibody clone EP4420, GeneTex, Irvine, USA). The average number of IgG4-positive plasma cells within three fields with the highest number of IgG4+ plasma cells (magnification x40) was used to estimate the density of the IgG4-positive inflammatory infiltrate.[11]

Patient Classifications

All diagnoses were reassessed by investigators with expertise in the fields of both OID and SD (GE, RD, SA), taking into account the etiological workup and the entire follow-up. The final diagnosis was based on histological confirmation for lymphoma, AAPOX or CSH, and international criteria for Graves' disease,[12] autoimmune thyroiditis,[13] or GPA.[14,15] The diagnosis of IgG4-RD was based both on the 2012 comprehensive clinical diagnostic criteria for IgG4-RD[16] and the 2019 American College of Rheumatology/European League Against Rheumatism Classification Criteria for IgG4-RD.[17] As suggested by Stone et al., an orbital localization of IgG4-RD was referred to as IgG4-related ophthalmic disease (IgG4-ROD).[18] In the absence of features of SD, a nonspecific orbital inflammation supported the diagnosis of IOIS. When biopsies were potentially sight-threatening, in agreement with the recent international recommendations, the diagnosis of IOIS was retained in the case of negative etiological workup and a minimal follow-up duration of 6 months.[5]

Statistics

To evaluate FDG-PET/CT's contribution for detecting underlying SD in patients with OID, we used as relevant comparator the standard diagnostic workup performed in all patients referred for OID at presentation in our institution. The latter standard workup included careful screening for extra-orbital manifestations suggestive of SD, the presence elevated inflammatory biomarkers (*i.e.*, either leucocytosis (N < 10 G/L), elevated serum C-reactive protein (N < 5 mg/L), and/or fibrinogen (N < 4 g/L) levels) and/or positive markers for autoimmune diseases. Hence, such standard diagnostic workup (model 1) was considered as positive when it detected either clinical signs suggestive of SD and/or elevation of above-mentioned biological parameters.

The main outcome measure was the percentage of patients correctly reclassified by FDG-PET/CT (model 2). To quantify the incremental value of FDG-PET/CT over the standard diagnostic workup, the Net Reclassification Index (NRI) and Integrated Discrimination Index (IDI) were used in addition to the area under the receiver operating characteristic (ROC) curve (AUC) whose analysis provides an overall judgment for decision-making.[19] The ΔAUC is produced by taking the difference in discrimination metrics between the models with (model 2) and without (model 1) FDG-PET/CT. We calculated the net reclassification index (NRI) according to Pencina et al.[20] and the integrated discrimination index (IDI), which integrates the NRI over all possible cutoffs and is equivalent to the difference in discrimination slopes in both models of diagnostic procedure. In its simplest form for binary outcomes (correct or not classification), NRI was calculated by examining events (SD) and nonevents (IOIS) separately.[19] The relative IDI is calculated as the ratio of IDI over the discrimination slope of the model without FDG-PET/CT.[19]

Patient characteristics are reported as the number and percentage for categorical variables and as the median (Q1-Q3) for continuous variables. All statistical analyses used the SAS software package version 9.4 (SAS Institute Inc, Cary, NC, USA). A two-sided *P*-value <0.05 was considered statistically significant.

Results

Patients

Twenty-two consecutive patients underwent FDG-PET/CT over the study period and were included in this study. Their characteristics are presented in Table 1. Patients were predominantly females (F/M: 14/8 (1.75)) and their median age at diagnosis was 51 (32–62) years. At referral, four of the latter patients were still receiving prednisone at the minimal dose of 5 mg daily. Patients mainly presented unilateral manifestations (n = 15, 68%). The main anatomical sites involved (as per MRI analysis) were lacrimal gland (n = 15, 68%), orbital fat (n = 10, 45%), extraocular muscles (n = 8, 36%), apex syndrome (n = 4, 18%), and sclera or optic nerve (n = 1, <1%). Of the 22 enrolled patients, 14 (63%) were finally diagnosed as having an underlying SD, while IOIS was diagnosed in the 8 (37%) remaining patients (Table 1). Of the latter, two patients (follow-up durations of 12 and 18 months, respectively) with retro-orbital involvements could not benefit from biopsies owing to the risk of optic nerve damage during the procedure (Table 1).

Table 1. Baseline characteristics of patients with orbital inflammatory disorders.

Orbital inflammatory disorders (n: 22)	
Epidemiologic characteristics	
Sex ratio (F/H)	1.75(14/8)
Age at diagnosis, years	51(32–62)
Orbital sites	
Lacrimal gland	15(68)
Extraocular muscles	5(22)
Orbital fat infiltration	8(36)
Optic nerve	1(<1)
Unilateral involvement	15(68)
Extraorbital manifestations	
Clinical signs	5(22)
- Fever	2
- Asthma	1
- Chronic sinusitis	2
Biological signs	3(13.5)
- CRP > 5 mg/l and fibrinogen >4 g/l	2
- PNN > 10 000/mm3	1
Clinical and /or biological signs	6(27)
Clinical and biological signs	2(9)
Clinical signs only	3(13.5)
Biological signs only	1(4.5)
Treatments	
Corticosteroids (5 mg/d)	4(18)
Disulone	1(4.5)
None	17(77)
Underlying diseases	
Systemic diseases	14(63)
- GPA: LG, nose, trachea, pulmonary nodules, MPO-ANCA	1(4.5)
Lymphomas	4(18)
• MALT: orbit, isolated inguinal lymphadenopathy	1
• DLBL: orbit, axillary lymph nodes	1
• AITL: LG, fever, purpura, diffuse lymph nodes	1
• LL (AL IgG-type amyloidosis): orbit, chest	1
-AAPOX syndrome: lids, LG, late onset asthma	3(13.5)
-Crystal storing histiocytosis (MGUS IgAk): lids, orbit, lymph nodes, liver	1(4.5)
-IgG4-RD*	5(22.5)
• Probable IgG4-ROD (serum IgG4 ≤ 1.35 g/l): LG ±orbit	4
• Definite (serum IgG4 ≥ 1.35 g/l): orbit, parotid gland, pulmonary nodules, pancreas	1
IOIS	8(36)
-With histologic evidence: LG, orbit ± bone extension	6
-Presumed: orbital apex and retro-orbital involvements	2

*According to Umehara's criteria.[16]
Data are presented as n(%) or median(Q1-Q3) unless otherwise specified.
GPA: granulomatosis with polyangiitis, AAPOX syndrome: adult asthma and periocular xanthogranulomatosis syndrome, MALT: mucosa-associated lymphoid tissue, DLBL: diffuse large B cell lymphoma, AITL: angioimmunoblastic T-cell lymphoma, LL: lymphoplasmacytic lymphoma, MGUS: monoclonal gammopathy of uncertain significance, IOIS: idiopathic orbital inflammatory syndrome, LG: lacrimal gland.

Diagnostic Performances of the Standard Workup

The standard workup was positive in 8 (36%) of the 22 enrolled patients, yet one of them was finally diagnosed as IOIS. Among the 14 (64%) patients with negative workup, 7 additional patients with low-grade lymphoma (n = 2), CSH (n = 1), or probable IgG4-ROD (n = 4) were not correctly classified, leading to an overall 8 (36%) cases of misclassification when the diagnostic workup was restricted to the standard workup.

Diagnostic Performances of FDG-18-PET/CT

All 11 (50%) patients with positive FDG-PET/CT fulfilled criteria for SD (real positives: 100%) (Table 2). Among the latter, four (36%) patients were free from systemic manifestations and subsequently correctly reclassified by the positive FDG-PET/CT, including two patients with low-grade B cell lymphoma diagnosed owing to FDG-PET/CT-guided histological examination of extra-orbital sites (Table 2). In the first case, mucosa-associated lymphoid tissue (MALT) was diagnosed based on inguinal lymph node biopsy and subsequently confirmed on a larger biopsy of the orbit (Figure 1). In the remaining case, a hypermetabolic chest mass revealed amyloid light-chain amyloidosis and led to the diagnosis of orbital lymphoplasmacytic lymphoma upon second look. Overall, all extra-orbital low or high-grade lymphomas were detected by FDG-PET/CT (Table 2). Additionally, FDG-PET/CT also correctly reclassified two asymptomatic patients as rather having CSH (revealing monoclonal IgA kappa of uncertain significance) and probable IgG4-ROD (a single patient each). Conversely, a single patient (who had mistakenly been scored positive by the standard workup owing to fever) was correctly reclassified as IOIS owing to negative PET-FDG/CT scoring.

Statistical Analyses

Analyses of the diagnostic performances using ROC curves showed a significant advantage using the FDG-PET/CT-driven model (model 2) over the standard workup (model 1) (difference in AUC = +0.22; p = .025). When FDG-PET/CT was added to the standard diagnostic workup, the NRI was 0.41 ± 0.17 (p = .03). Despite thorough clinical and biological evaluation, FDG-PET/CT correctly reclassified 29% of patients with SD (p = .04) and 13% with IOIS (p = .32). The IDI test used to evaluate the improvement of FDG-PET/CT for SD detection was 0.38 ± 0.08 (p < .001). After FDG-PET/CT, probability changes for SD and IOIS were measured at 0.14 and −0.24, respectively, with a relative gain of 3.04 (Table 3).

Table 2. FDG-PET/CT results in patients with orbital inflammatory disorders according to systemic manifestations* detected by the standard diagnostic workup.

	Positive PET/CT					Negative PET/CT			
	Standard diagnostic workup					Standard diagnostic workup			
	Positive (n = 7)	Negative (n = 4)	Total (n = 11)	Sites	SUV	Positive (n = 1)	Negative (n = 10)	Total (n = 11)	Final total (n = 22)
Systemic diseases, n(%)	7(100)	4(100)	11(100)			0	3(30)	3(27)	14(64)
- GPA	1(14)	0	1(9)	SNM	3.1	0	0	0	1(4.5)
- Lymphomas	2(40)	**2(50)**	4(36)			0	0	0	4(18)
MALT	0	1	1	ADP^{i}	5.1	0	0	0	1
DLBL	1	0	1	ADP^{a}	4.7	0	0	0	1
AITL	1	0	1	ADP^{m}	12	0	0	0	1
LL (Amyloidosis)	0	1	1	$Mass^{m}$	2.3	0	0	0	1
- AAPOX syndrome	3(60)	0	3(27)			0	0	0	3(13.5)
	1	0	1	ADP^{a}	5	0	0	0	1
	1	0	1	ADP^{hm}	4.7	0	0	0	1
	1	0	1	ADP_{c}	7.1	0	0	0	1
- Crystal Storing Histiocytosis	0	**1(25)**	1(9)	ADP^{a}	3.5	0	0	0	1(4.5)
- IgG4-RD*	1(14.5)	**1(25)**	2(18)			0	3(30)	3(27)	5(22)
Probable (IgG4 ≤ 1.35 g/l)	0	1	1	ADP^{h}	3.7	0	0	0	1
Definite (IgG4 ≥ 1.35 g/l)	1	0	1	Sinus	6.4	0	3	3	4
IOIS, n(%)	0	0	0			**1(100)**	7(70)	8(73)	8(36)

FDG-PET/CT results in patients with orbital inflammatory disorders are shown according to systemic manifestations detected by the standard diagnostic workup. Systemic manifestations denotes clinical and/or biological signs.

Patients who were correctly reclassified by PET-18-FDG scanning are shown in **bold**.

GPA: granulomatosis with polyangiitis; AAPOX syndrome: adult asthma and peri-ocular xanthogranulomatosis syndrome; MALT: mucosa-associated lymphoid tissue; DLBL: diffuse large B cell lymphoma; AITL: angioimmunoblastic T-cell lymphoma; LL: lymphoplasmacytic lymphoma; IOIS: idiopathic orbital inflammatory syndrome; ADP: lymphadenopathy i (inguinal), a (axillary), m (mediastinal), c (cervical), h (hilar); SNM: sino-nasal mucosae.

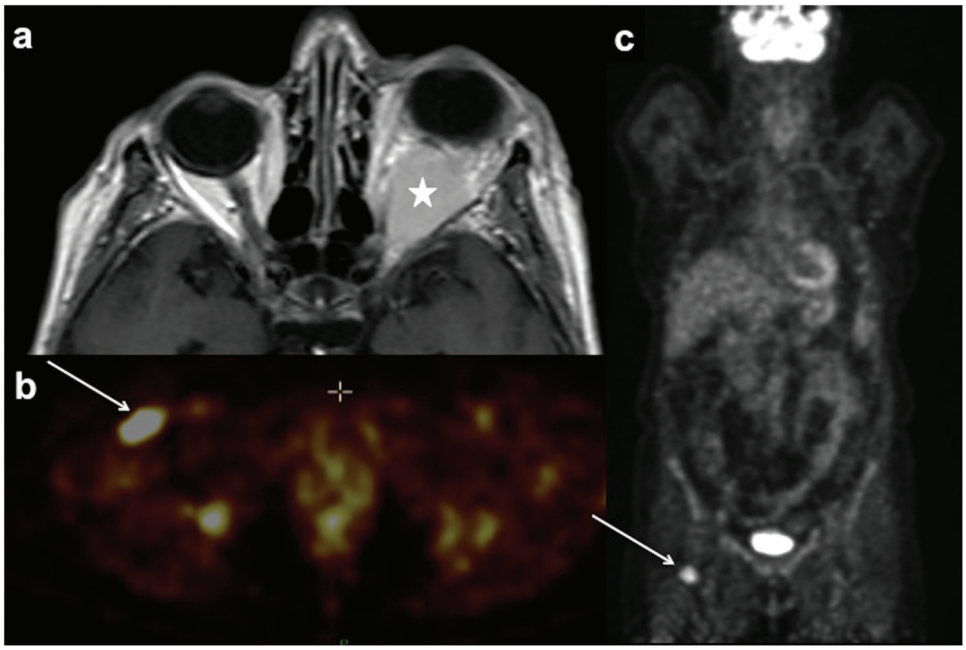

Figure 1. Usefulness of FDG-PET/CT in a patient with refractory inflammatory orbital disorder. A woman was admitted to hospital because of a corticosteroid resistant mass of the left orbit (a). Two years earlier, orbital biopsy had shown nonspecific inflammation. A mucosa-associated lymphoid tissue was finally evidenced owing to PET-FDG/CT-guided (SUV max: 5.1) right inguinal lymph node biopsy (b, c, arrows). A control biopsy of the mass was subsequently performed and confirmed the presence of the same low-grade lymphoma in the orbital tissue (a, star).

Discussion

Despite growing evidence supporting the use of FDG-PET/CT for the diagnosis of SD (including underlying causes for OID), no study has yet assessed the potential utility of FDG-PET/CT in the routine diagnostic workup of patients with OID. Here, these findings arising from a large cohort with homogeneous management of patients suggest that FDG-PET/CT could be a salient diagnostic tool in the etiological workup of patients with OID, able to correctly reclassify a significant proportion of patients with OID whose systemic manifestations would otherwise have remained unrecognized with the standard etiological workup. Hence, we suggest performing FDG-PET/CT as a second-line assay in case of negative first-line investigations (Figure 2).

To evaluate FDG-PET/CT's ability to distinguish SD from IOIS in patients with OID, we used NRI and IDI, two

Table 3. Diagnostic performance measurement of FDG-PET/CT in patients with orbital inflammatory disorders.

	Patients correctly reclassified by PET		NRI	Mean probability for disease			IDI	
	%	P value	(95% CI)	Model 1	Model 2	Probability change for disease with PET	(95% CI)	Relative IDI
SD	29	0.04	0.41	0.66	0.80	0.14	0.38	3.04
IOIS	13	0.31	(0.08; 0.74)*	0.54	0.3	−0.24	(0.22; 0.54)**	

NRI: net reclassification improvement,
IDI: integrated discrimination improvement,
Model 1: standard diagnostic workup,
Model 2: FDG-PET/CT + standard diagnostic workup,
SD: systemic disease,
IOIS: idiopathic orbital inflammatory syndrome,
*p: 0.03,
**$p < .001$.

performance indexes which have gained growing interest among researchers. Indeed, both are considered as simple, reliable, and intuitive manners of quantifying improvement offered by new diagnostic markers.[20] Despite the lack of comparative studies in the field of OID, NRI (which cumulates net proportions of SD and IOIS after their reclassification and can vary from −2 to 2) and IDI (which cumulates the probability changes for both SD and IOIS within the same range) values (0.41 and 0.38, $p < .05$, respectively) suggested clear reclassification improvement owing to FDG-PET/CT. In addition to a significant increase in the area under the ROC curve, these positive NRI and IDI values supported the fact that FDG-PET/CT is useful when investigating OID.

Ocular adnexal lymphoma (OAL) accounts for approximately 1% of all non-Hodgkin lymphoma (NHL)[21] and, in a large series of OAL, only 20% of patients suffered from systemic manifestations at the time of diagnosis of OAL.[22] Diagnosing OAL can be challenging, with low-grade OAL and IOIS both sharing similar features. Moreover, tissue biopsies can sometimes miss out the few tumor cells inside the orbit.[3] The ability of FDG-PET/CT to detect malignant systemic lymphomas is no longer debated.[6] Yet, owing to the scarcity of the disease, FDG-PET/CT's potential utility for the diagnosis of OAL remains unclear.[23,24] Moreover, some authors stated that MALT lymphoma - a low-grade B-cell lymphoma accounting for up to 80% of AOL[21] - had relatively low FDG uptake, with possible subsequent false-negative findings on FDG-PET/CT.[25] Here, FDG-PET/CT (i) unsurprisingly showed high FDG uptakes in all patients with aggressive lymphoma (angioimmunoblastic T-cell lymphoma and diffuse large B-cell lymphoma, a single patient each); (ii) detected all cases of OAL in patients with IOD and systemic manifestations; (iii) correctly reclassified patients as either IOIS

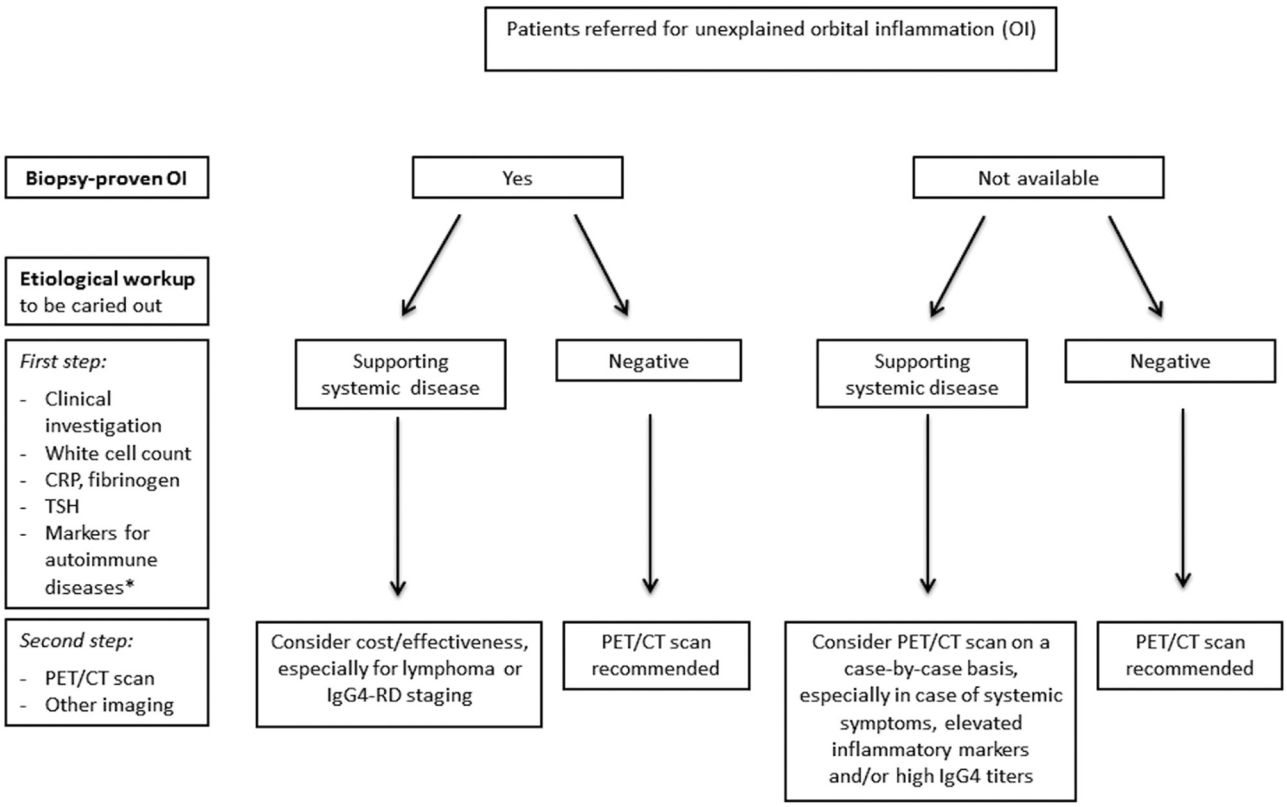

Figure 2. Proposal for a FDG-PET/CT-based etiological workup in inflammatory orbital disorders. *Markers for autoimmune diseases include serum angiotensin-converting enzyme, IgG4 levels, and testing for antinuclear, thyroid, and antineutrophil cytoplasmic autoantibodies. Additionally, minor salivary gland biopsy is considered either in case of sicca syndrome or elevated serum ACE levels.

or OAL with systemic expression. Strikingly, both patients with low-grade lymphomas (lymphoplasmacytic lymphoma and MALT) were asymptomatic, contrasting with positive FDG-PET/CT findings. Hence, FDG-PET/CT contributed remarkably well to the diagnosis a life-threatening condition that was initially misdiagnosed by the first biopsy of an orbital mass. These findings are in line with those reported in a case series including 12 cases of low-grade OAL, where FDG-uptake levels correlated with lymphoma staging but not with pathological findings (*i.e.*, lymphoma subtypes).[26] Likewise, in that study, all patients with low-grade orbital lymphoma and systemic manifestations exhibited FDG-avid lesions on pretreatment PET/CT.[26] Overall, these findings suggest that FDG-PET/CT seems to be useful for the diagnostic workup of OAL.

Besides lymphoma, FDG-PET/CT was also useful to detect subclinical CSH-related lymph nodes in another patient.[27] In addition, FDG-PET/CT demonstrated utility in staging autoimmune diseases, with extraorbital lesions being evidenced in two patients with ANCA-associated vasculitis and definite IgG4-RD. In light of these findings, FGD-PET/CT could be an interesting tool for the detection of underlying inflammatory lesions, able to provide an accurate disease staging at diagnosis. Yet, FDG-PET/CT was unsuccessful in diagnosing probable IgG4-ROD in 3 cases. The latter finding is not without surprise, since probable IgG4-ROD is a disease presumably restricted to the orbit. Contrary to definite IgG4-ROD, IgG4-ROD is considered as a probable diagnosis when serum IgG4 levels were normal despite pathological IgG4 staining of the orbit.[16] Conversely, since none of the patients with a final diagnosis of IOIS had extra-orbital FDG uptake, the specificity of FDG-PET/CT for the detection of SD was excellent, reaching 100%.

This study has some limitations. First, it was conducted in a tertiary referral academic center (where FDG-TEP/CT is widely performed) for the management IOD, which might have led to a selection bias. Next, the current study was not designed in order to evaluate the accuracy of FDG-PET/CT as a diagnostic tool for lymphoma with orbital-restricted presentation, and its diagnostic yield in this specific setting remains to be determined. Last, the cost-effectiveness of such FDG-PET/CT-guided diagnostic strategy was not addressed, and further studies using a whole-body CT-scan (a cheaper comparator than FDG-PET/CT) would also be of interest.

Notwithstanding these limitations, this study – the first to investigate the potential utility of FDG-PET/CT during the etiological workup of IOD – provides evidence suggesting that nuclear imaging could be helpful for diagnosing underlying (and yet undetected) SD, *e.g.*, potentially life threatening lymphoma. Further large-scale multicentric, comparative studies are needed to confirm this preliminary report.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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