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Does [18F]F-FDG-PET/MRI add metabolic information to magnetic resonance image in childhood-onset Takayasu's arteritis patients? A multicenter case series

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Abstract

Background: The observation that 2-deoxy-2[18F]fluoro-D-glucose-positron emission tomography/magnetic resonance imaging ([18F]F-FDG-PET/MRI) revealed high-grade arterial wall FDG uptake, without arterial wall thickening with contrast-enhancement, in a considerable number of c-TA patients in our previous study, encouraged us to compare patients with both PET and MR angiography (MRA) positives, with those with PET positive but MRA negative. Our aim was to evaluate the relevance of these two imaging modalities together.

Methods: A three-center cross-sectional study with 17 patients who fulfilled the EULAR/PRINTO/PReS criteria for c-TA and who underwent [18F]F-FDG-PET/MRI was previously performed. Herein we compared patients/vessels with positive PET (arterial wall ^{18}F-FDG uptake higher than liver) and positive MRA (arterial wall thickening with contrast-enhancement)—group 1, with those with positive PET but negative MRA—group 2.

Results: Median disease duration of 17 c-TA patients was 10.4 years. Nine patients were classified as group 1 and six as group 2. Median of metabolic inflammatory volume (MIV) of all arterial segments was significantly higher in group 1 (2346 vs. 1177 cm^3; p = 0.036). Fifty-four (19%) from 284 available arterial segments presented positive findings in vessel wall in one or both images. Positive findings were concordant between PET and MRA in only 13% arterial segments (group 1); most changes (28–59.6%) that were discordant between both images, were positive in PET and negative in MRA (group 2).

Conclusion: Our study demonstrated that [18F]F-FDG-PET/MRI added information about inflammation in vessel wall of c-TA patients. Prospective multicenter studies are needed in order to get solid data to guide immunosuppressive tapering and withdrawal.

Keywords: Takayasu arteritis, Vasculitis, PET, PET/MRI, Children, Adolescents

Background

Childhood-onset Takayasu's arteritis (c-TA) is a chronic and relapsing vasculitis that leads to the progression of arterial lesions adding morbidity to young patients in the long term [1].

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Although most c-TA patients present a progression of arterial lesions, reliable biomarkers for detecting activity are still lacking, and studies with this purpose showed non-replicable results [2–4]. Therefore, an accurate assessment of the arterial wall is imperative to detect signs of inflammation in order to guide immunosuppressive therapy. Although imaging techniques for vessel wall studies, such as magnetic resonance angiography (MRA), computed tomography angiography (CTA), and 2-deoxy-2[18F]fluoro-D-glucose-positron emission tomography ([18F]F-FDG-PET), have been improved in recent years, the best protocol or algorithm for these images has not been established yet [5–7]. Hybrid imaging systems that provide anatomic (CTA or MRA) and metabolic images (PET) at the same time may add incremental data about vascular inflammation [8, 9]. In childhood, the fusion of MRA with [18F]F-FDG-PET would be preferable, especially because of the absence of radiation involved in the MRI [10–12].

In a recent study, our group observed that the majority (88.2%) of the 17 c-TA patients who underwent [18F] F-FDG-PET/MRI had high-grade FDG-uptake, and roughly a half (58.8%) had thickening plus enhancement in vessel wall of large-size arteries [13]. It was observed that six patients had high-grade arterial FDG-uptake but without thickening and enhancement in the vessel wall. There was positive correlation between SUVmax and CRP levels but no correlation between SUVmax and vessel wall thickening or enhancement in MRA. We have not explored the differences between patients with both positive images and patients with positive PET but negative MRA neither the differences between vessels with both positive images and vessels with positive PET but negative MRA.

Therefore, the aim of the present study was to compare patients and vessels with both PET and MRA positives *versus* patients and vessels with positive PET and negative MRA, in order to evaluate the relevance of adding a metabolic imaging to MRA.

Materials and methods

Study population

Patients with c-TA were recruited from three reference centers in Pediatric Rheumatology in Sao Paulo, Brazil. The inclusion criteria were patients with c-TA diagnosed up to 18 years old who fulfilled the EULAR/PRINTO/PReS classification criteria for c-TA and current age between 6 and 21 years [14]. Exclusion criteria included the presence of other chronic pediatric conditions, acute infection during the last 30 days, current pregnancy, acute or chronic renal failure, and those patients that required anesthesia to perform [18F]F-FDG-PET/MRI imaging. Data were collected between October 2017 and April 2018 [13].

The local ethics committees from the three centers have approved the research protocol. All participants and their legal guardians, when appropriate, provided written informed assent and/or consent.

Clinical assessment

Activity and damage scores were applied as follows: Indian Takayasu Arteritis Clinical Activity Score (ITAS2010), Paediatric Vasculitis Activity Score (PVAS), Paediatric Vasculitis Damage Index (PVDI) and Takayasu Arteritis Damage Score (TADS) [15–18].

Laboratory assessment

Blood samples of all recruited patients were collected two half-lives after immunosuppressive medication temporary withdrawal. Erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) were assessed.

[18F]F-FDG-PET/MRI Protocol

Images were acquired using a hybrid PET/MRI scanner (GE healthcare SIGNA PET/MRI 3-Tesla, Milwaukee-MI, USA), allowing simultaneous acquisition of MR and PET images. The imaging protocol was performed in a single center, as previously described [13]. In summary, after 6 h fast, patients received an injection of ^{18}F-FDG. Then, patients rested for 60 min before the imaging acquisition. The combined acquisition of PET/MRI started with an estimated acquisition time of 2–4 min per bed position (BP). The following sequence was also performed in MRI analysis: T1-weighted (LAVA) volumetric sequences before and after 15 min of intravenous contrast injection, to assess vessel wall thickness and late enhancement. A dynamic angiography was performed, including the proximal third of cervical vessels and extending to the common iliac arteries, using a dedicated time-resolved technique (TRICKS), before and after contrast injection in the coronal plane. All patients received intravenous contrast gadoterate meglumine (Dotarem), followed by a 15–20 ml saline flush. This technique allows proper morphological evaluation of the vessels.

Interpretation of [18F]F-FDG-PET/MRI findings

Three experts imaging specialists, including two abdominal radiologists (HL and FMAC) and one nuclear radiologist (ML), all blinded to patients' clinical and laboratory data, reviewed the MRA and ^{18}F-FDG-PET images, respectively. Discrepancies were resolved by consensus.

Seventeen arterial segments were analyzed: right and left common carotid arteries, right and left vertebral arteries, innominate artery, right and left subclavian

arteries, ascending aorta, aortic arch, descending aorta, celiac trunk, superior mesenteric artery, abdominal aorta, right and left renal arteries, and right and left iliac arteries.

The parameters studied in each arterial segment were the following:

1. Thickness of the vessel wall (considered positive ≥ 3 mm) in MRA;
2. Grade of wall enhancement using the late post-contrast phase in MRA.
3. Semi-quantitative large-vessel ^{18}F-FDG uptake, graded using the maximum standardized uptake value (SUVmax). SUVmax of the patient was defined by the value of his/her arterial segment that presented the highest value of SUVmax;
4. Metabolic Inflammatory Volume (MIV) was assessed to quantify the total inflammatory load per patient, calculated by the sum of MIV of each arterial segment. This nomination was derived and adapted from Metabolic Tumor Volume (MTV), which measures the volume of FDG-avid disease and is used to quantify tumoral load in the oncologic studies [19];
5. Qualitative large-vessel ^{18}F-FDG uptake was determined by Visual Score (VS) as follows: I—low-grade uptake (higher than soft tissue but lower than liver); II—intermediate-grade uptake (similar to the liver); III—high-grade uptake (higher than liver);
6. A qualitative score of ^{18}F-FDG uptake across the arterial segments, namely PET Vascular Activity Score (PETVAS), was calculated by the sum of the visual scores of the arterial segments [6].

The patient was defined as having positive MRA for vascular disease activity when there was at least one arterial segment with both thickening and enhancement of the vessel wall. The patient was defined as having positive PET for vascular disease activity when there was at least one arterial segment with high-grade FDG uptake (VS = III). According to the positivity of vessel wall findings in PET and/or MRA, patients, as well as all arterial segments were classified into three different groups: presence of signs of vessel wall inflammation on PET and MRA (PET+MRA+: group 1), presence of signs of vessel wall inflammation on PET but not on MRA (PET+MRA−: group 2). and absence of vessel wall inflammation on PET and presence on MRA (PET−MRA+: group 3).

Arterial segments that had undergone surgical intervention were excluded from the analysis. The angiographic type was defined according to the Hata Classification [20].

Statistical analysis

Data analyses were performed using SPSS software, version 24.0, and GraphPad Prism for Windows, version 5.0. Numerical variables were presented as median and interquartile range (IQR). Categorical variables were presented as absolute numbers and percentages. Comparative analyses were performed between patients and vessels with PET+MRA+ and PET+MRA−, using Fisher's exact and Mann–Whitney tests for categorical and continuous variables, respectively. Values of $p < 0.05$ were considered statistically significant.

Results

A total of 17 c-TA patients, 11 (65%) female, from a total of 36 patients attending at the three Centers, were recruited to the study. Five patients were excluded due to the necessity for anaesthesia to perform imaging study (2 patients), associated chronic diseases (Crohn's disease—1 patient; ulcerative rectocolitis—1 patient) and renal insufficiency (1 patient). Sixteen patients were on clinical remission based on clinical scores (15 under therapy). The median disease duration, current age, and time to diagnosis were 10.4 (7.0–11.6) years, 18.7 (15.7–20.7) years, and 11.0 (4.0–30.0) months, respectively. Eight patients were undergoing imunossupressive therapy, eight were on combined therapy with biologic agents, and five were on glucocorticoids (one patient was off medication) (Table 1). Detailed demographic, clinical, laboratory, and therapeutic data of the patients are shown in our previous study [13].

Fifteen (88.2%) patients had high-grade ^{18}F-FDG uptake in vessel wall detected by PET (14 of them were on clinical remission based on clinical scores), and 10 (58.8%) had thickening plus gadolinium-enhancement in vessel wall detected by MRA. Nine patients were

Table 1 General characteristics of 17 c-TA patients

Features	Patients (17)
Current age, years	18.7 (15.7–20.7)
Median disease duration, years	10.4 (7.0–11.6)
Diagnosis delay, months	11.0 (4.0–30.0)
Clinical remission disease, n (%)	16 (94)
Elevated APR, n (%)	6 (35.3)
Positive PET, n (%)	15 (88.2)
Positive MRA, n (%)	10 (58.8)
Imunossupressive therapy, n (%)	8 (50)
Combined therapy with biologic agents, n (%)	8 (50)
Off medication	1 (5.9)

Numerical values are presented in mean (± SD) or median (IQR) according to normality tests, *APR* acute phase reactants, *PET* positron emission tomography, *MRA* magnetic resonance angiography

classified as group 1 (PET+MRA+) and six as group 2 (PET+MRA−). One patient had PET negative and MRA positive, and one had no vessel wall changes in both PET and MRA imaging.

Comparative analysis between patients from both groups showed median of MIV value significantly higher in group 1 compared to group 2 (2346 cm^3 [1438–3304] vs. 1177 cm^3 [869–1880]; p = 0.036) with no differences in other parameters (Table 2).

A total of 289 arterial segments (17 arterial segments × 17 patients) were assessed, of which five were excluded due to previous surgical intervention. Fifty-four (19%) of 284 available arterial segments presented vessel wall changes in one or both imaging modalities. Vessel wall changes were concordant between PET and MRA (group 1) in only seven (13%) of 54 arterial segments; most (28–59.6%) of the vessel-wall changes that were discordant between both images, were positive in PET and negative in MRA (group 2) (Table 3). Some arterial segments revelead changes in MRA but no changes in PET, such as descending aorta and abdominal aorta, (5 versus 1 and 4 versus 0, respectively).

Ascending aorta was the most frequently affected vessel and therefore, the only that enabled statistical analyses between group 1 and 2. The value of ^{18}F-FDG uptake into the vessel wall of ascending aorta measured by SUVmax and MIV was significantly higher in patients from group 1 compared to patients from group 2 (SUVmax = 3.8 [3.1–4.5] vs. 2.6 [2.4–3.3]; p = 0.044; MIV = 1560 cm^3 [857.5–2840] vs. 176.5 cm^3 [92.5–303.5]; p = 0.004).

Discussion

Current imaging modalities are not sensitive enough to pick up slight inflammatory changes in the vessel wall of c-TA patients, especially in those that are under immunosuppression, making the follow-up a challenge. Herein, positive PET but negative MRA was observed in six patients, and a considerable number of arterial segments (87%) had positive findings in vessel wall in just one of the two imaging modalities, most of them with positivity in PET. Additionally, we observed a higher arterial FDG uptake when there were changes in both images compared to when changes only in PET were present. From a clinical standpoint, these findings collectively suggest that [18F]F-FDG-PET/MRI may improve the assessment of vascular inflammation in c-TA patients.

We defined positive MRA when both thickening and contrast-enhancement in the vessel wall were present in order to increase the specificity of MRA positive findings. The association between these MRA findings with disease activity varied over the studies [21–23]. Some authors found high sensitivity and specificity between these two imaging findings together and clinical disease activity [21]; others did not [22, 23]. It is challenging to validate imaging parameters to define disease activity since there is no gold standard feasible to detect disease activity in TA. Furthermore, there is variability among imaging protocols and different thresholds for vascular inflammation, hampering a standardization of these metrics in detecting disease activity.

We observed that from 15 patients with positive PET, six (40%) had negative MRA. This result reveals that more than one-third of the patients had negative imaging based only on the MRA scans, and they would be interpreted as inactive disease by imaging when relying only on MRA findings. Padoan et al. demonstrated no correlation between FDG uptake and clinically active disease or presence of wall thickness in patients with TA and giant cell arteritis [24]. Although there is uncertainty about the further repercussion of the higher vascular FDG uptake,

Table 2 Clinical, laboratorial, treatment data and PET findings in c-TA patients—groups 1 and 2 (15 patients)

	Group 1: n = 9 (PET+MRA+)	Group 2: n = 6 (PET+MRA−)	*P* value
Disease duration, years	11.0 (7.1–12.1)	8.1 (3.8–13.5)	0.906
Diagnosis delay, months	11.0 (3.0–27.0)	20.5 (1.6–41.3)	0.595
ESR, mm in 1st hour	8.0 (4.5–15.5)	4.5 (2.8–13.8)	0.407
CRP, mg/L	2.7 (0.3–15.9)	3.1 (1.6–6.3)	0.859
Angiographic type V, N (%)	5 (55.6)	0	0.044
SUVmax	3.4 (3.1–4.3)	3.1 (2.5–3.9)	0.272
MIV, cm^3	2346 (1438–3304)	1177 (869–1880)	0.036*
PETVAS	21.0 (19.0–26.0)	21.5 (21.0–25.0)	0.546
Prednisone, N (%)	4 (44)	1 (16.7)	0.580
Biologics, N (%)	4 (44)	2 (33.3)	1.000

c-TA childhood-onset Takayasu's arteritis, *ESR* erythrocyte sedimentation rate, *CRP* C reactive protein, *PET* positron emission tomography, *MRA* magnetic resonance angiography, *PET+MRA+* presence of signs of vessel-wall inflammation on PET and MRA, *PET+MRA−* presence of signs of vessel-wall inflammation on PET but not on MRA, *SUVmax* maximum standardized uptake value, *MIV* metabolic inflammatory volume, *PETVAS* PET Vascular Activity Score, numerical values are presented in median (IQR)

*Significant difference ($p < 0.05$)

Table 3 Vessel wall changes of each arterial segment (N = 284) grouped according to different imaging findings

Arterial Segments	PET+ (VS = III)	MRA+ (T + E)	Group 1 PET+MRA+	Group 2 PET+MRA−	Group 3 PET− MRA+
RCC	2	1	0	2	1
LCC	1	3	0	1	3
Right vertebral	0	0	0	0	0
Left vertebral	0	0	0	0	0
Ascending aorta*	11	5	5	6	0
Aortic arch	3	4	1	2	3
Descending aorta	1	5	1	0	4
Innominate	1	1	0	1	1
Right subclavian	1	1	0	1	1
Left subclavian	0	2	0	0	2
Celiac trunk	1	0	0	1	0
Superior mesenteric	0	0	0	0	0
Abdominal aorta	0	4	0	0	4
Right renal	3	0	0	3	0
Left renal	4	0	0	4	0
Right iliac	5	0	0	5	0
Left iliac	2	0	0	2	0
Number of arterial segments	35	26	7	28	19

PET positron emission tomography, *MRA* magnetic resonance angiography, *c-TA* childhood-onset Takayasu's arteritis, *PET* positron emission tomography, *MRA* magnetic resonance angiography, *PET+MRA+* presence of signs of vessel-wall inflammation on PET and MRA, *PET+MRA−* presence of signs of vessel-wall inflammation on PET but not on MRA, *PET−MRA+* absence of signs of vessel-wall inflammation on PET and presence on MRA, *VS* visual score, *T + E* thickening + enhancement, *RCC* right common carotid, *LCC* left common carotid

* Significant difference ($P < 0.05$)

Vessel-wall changes in PET and MRA from vessels that have undergone surgical intervention (5 arterial segments) were not considered

there is an agreement that these patients have increased vascular glucose metabolism, and this finding *per si* aware us for waiting the withdrawal of the immunosuppressant. Additionally, though the specificity of these findings and the positive predictive value for the vascular activity and accrual damage must be still clarified, the sensitivity of PET seemed to be high, as demonstrated in previous studies [22, 24,,25]. However, high-degree FDG-uptake can not be directly related to c-TA disease activity.

On the other hand, one patient had positive MRA with negative PET, and one-third of the vessels had positive MRA and negative PET. A plausible explanation for this result is that these changes in MRA represent arterial remodeling, secondary to interstitial fibrosis, rather than active inflammation, as extracellular contrast diffusion may occur during the later contrast phase [21]. Additionally, we speculate that since the c-TA patients have had a long-term follow up, the occurrence of fibrosis is an expected finding reflecting chronicity but not activity in vessel wall.

Importantly, our results reveal that evidence of ongoing inflammatory process is higher when vessel wall changes are present in both imaging modalities. Therefore, we believe that a hybrid imaging study would be more reliable for follow-up, mainly in patients on clinical remission. It is still uncertain if this would support the medical decision, allowing the withdrawal of medication in case of a negative hybrid imaging, until solid data have been published. Further prospective multicenter studies with a larger c-TA population will be necessary to evaluate the role of hybrid imaging study in predicting flare during the disease course, and especially during immunosuppressive tapering.

The finding that vessel wall changes in abdominal aorta were detected only by MRA caught our attention, since PET had detected most of the positive arterial findings (65%). We could hypothesize that it could be related to the fact that this arterial segment is usually one of the first involved in c-TA, and fibrotic process may have been developed throughout the follow-up, increasing positivity in MRA. However, the role of MRA in detecting vessel wall inflammation should not be under valued since it is a more widely available imaging, but technique accuracy for the vessel wall study has to be improved.

The use of a high quality imaging offered by 3 Tesla MRI is the main strength of this study since it differs from most of the previously published studies that used a 1.5 T MRA scanner [5]. Additionally, current studies

with different modalities of images in c-TA patients are scarce, and herein, we performed state-of-the-art imaging that fused a metabolic to anatomic assessment. However, the limitations are the cross-sectional design, the inclusion of patients with different times of disease follow-up, the variable therapeutic regimens, and the limited number of patients to allow better comparison among the groups.

Conclusion

More accurate imaging is crucial to improve the detection of vascular activity in c-TA patients and to guide therapy. [18F]F-FDG-PET/MRI is a new modality of imaging that adds metabolic information to magnetic resonance image improving the assessment of inflammation in vessel wall of c-TA patients. Prospective multicenter studies are needed in order to get solid data to guide immunosuppressive tapering and withdrawal.

Abbreviations

[18F]F-FDG-PET/MRI: 2-Deoxy-2[18F]fluoro-D-glucose-positron emission tomography/magnetic resonance imaging; MRA: Magnetic resonance angiography; MIV: Metabolic inflammatory volume; SUVmax: Maximum standardized uptake value; VS: Visual score; ITAS2010: Indian Takayasu Arteritis Clinical Activity Score; PVAS: Paediatric Vasculitis Activity Score; PVDI: Paediatric Vasculitis Damage Index; TADS: Takayasu Arteritis Damage Score.

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Author contributions

Conception and design: GC, AWDS, HLF, FMAC, CB, ML, CC, RMRP, NA, CAS, LMAC, CA, BG and MMT. Data colletion and processing: GC, RMRP, NA, CAS, LMAC, GA and MTT. Imaging analisys: HLF, FMAC, CB, ML and CC. Statistical analysis and interpretation: GC, AWDS and MTT. Literature review: GC and AWDS. Writing: GC. Critical review: AWDS, HLF, FMAC, CB, ML, CC, RMRP, NA, CAS, LMAC, CA, BG and MMT. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated during this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Universidade Federal de São Paulo (coordinating center) and by the other participating centers (CAAE: 47801715.5.1001.5505). All participants and their legal guardians, when appropriate, provided written informed consent. All procedures were performed in accordance with the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standads.

Consent for publication

Publication consent was acquired on the original consent form.

Competing interests

Gleice Clemente, Alexandre W D Souza, Hilton L Filho, Fernando M A Coelho, Carlos Buchpiguel, Marcos Lima, Camila Carneiro, Rosa M R Pereira, Nadia Aikawa, Clovis A Silva, Lucia M A Campos, Gabriel Alves, Camilla Astley, Bruno Gualano, Maria Teresa Terreri declare that they have no conflict of interest.

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