Unexplained fever in children—Benefits and challenges of FDG-PET/CT

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Abstract
Aim: To explore [fluorine-18]-fluoro-2-deoxy-d-glucose positron-emission-tomography/computed tomography (18FDG-PET/CT) in patients where standard investigations were non-diagnostic.
Methods: We reviewed medical records of previously healthy children who had 18FDG-PET/CT performed at Copenhagen University Hospital in 2015–2020 due to unexplained fever.
Results: Thirty-five of 819 paediatric 18FDG-PET/CT were performed due to unexplained fever. The final diagnoses were malignancy (11%), infections (23%), inflammatory diseases (43%) and miscellaneous (26%). 18FDG-PET/CT was diagnostic in six cases with Takayasu's arteritis, tuberculosis, Langerhans cell histiocytosis and Ewing sarcoma. Sixteen cases had focal 18FDG-uptake, but 18FDG-PET/CT could only differentiate malignancy, infection and inflammation in three cases. In six cases with inflammatory diseases and no focal signs, PET/CT was normal except increased non-specific 18FDG-uptake in bone marrow and spleen in five cases. One case was false positive (suspicion of appendicitis) and two false negative (leukaemia and inflammatory disease).
Conclusion: 18FDG-PET/CT was diagnostic, or contributed to the diagnosis, in several children with unexplained fever referred to a tertiary centre. Challenges comprised (i) only increased non-specific 18FDG-uptake in bone marrow and spleen in half of cases with inflammatory diseases, (ii) no differentiation between complicated infections, malignancy and inflammation in most cases with focal processes and (iii) a small risk of false positive and false negative results.

KEYWORDS
FUO, paediatric infectious diseases, persistent fever, PET-CT

Abbreviations: 18FDG-PET/CT, [fluorine-18]-fluoro-2-deoxy-d-glucose positron-emission-tomography/computed tomography; CT, computed tomography; FUO, fever of unknown origin; MRI, magnetic resonance imaging.
1 | INTRODUCTION

Children with unexplained fevers is a diagnostic challenge. Unexplained fever includes prolonged fever, defined as daily temperature of 38.0°C or above for 7–14 days or more, of unknown origin (FUO) or with suspected anatomical origin (but unknown aetiology), and recurrent fever, defined as new fever after 48 h of being afebrile. The diagnostic approach to such children has changed in recent decades due to, among others, a new era of microbiological analyses, easy access to computed tomography (CT) and magnetic resonance imaging (MRI) and fast genetic analyses for autoinflammatory diseases.

Regardless, the aetiology of unexplained fever remains unsolved in some children in whom the four most common disease categories are infections, malignancy, non-infectious inflammatory diseases and miscellaneous, the latter primarily involving fever resolving without a definitive diagnosis. In adults with FUO, [fluorine-18]-fluoro-2-deoxy-d-glucose positron-emission tomography/CT (18FDG-PET/CT), a method combining both anatomic and functional imaging, is increasingly used if standard investigations are non-diagnostic. The diagnostic yield of 18FDG-PET/CT in adults cannot be directly extrapolated to children, as the aetiology of unexplained fever vary between children and adults. In children, very limited evidence is available for the use of 18FDG-PET/CT in unexplained fever. We here report the results of 18FDG-PET/CT as diagnostic procedure in previously healthy children with unexplained fever during a 6-years period.

2 | METHODS

We retrospectively identified previously healthy children aged 0–18 years who had 18FDG-PET/CT performed at Copenhagen University Hospital, Rigshospitalet, in the period January 1, 2015 to December 31, 2020. Copenhagen University Hospital, Rigshospitalet, is a tertiary care referral centre for nine paediatric departments in the Capital Region of Denmark and Region Zealand (2.6 million inhabitants), the Faroe Islands and Greenland. Patients were included if they had unexplained fever despite in-depth conventional diagnostic work-up for persistent fever, including negative or equivocal results on conventional imaging. Patients were excluded if they received immunosuppressive therapy (e.g. children with cancer or juvenile idiopathic arthritis) or had chronic underlying diseases (e.g. congenital heart disease). Medical records were reviewed for the final diagnosis, clinical and laboratory data during hospital admission and recurrence of symptoms during the follow-up period. The follow-up period was from the time of 18FDG-PET/CT-scan to the last outpatient visit, or any hospital admission documented in the joint electronic medical record from any of the referring hospitals, until January 1, 2022.

2.1 | 18FDG-PET/CT imaging

Patients fasted for 4–6 h, rested for 30 min under a warm cushion before 3 MBq/kg 18FDG was injected intravenously and had a resting uptake-period of 60 min. Patients were scanned from head to toe with 3 min per bed position using a Biograph mCT 128 scanner. The CT component of the combined 18FDG-PET/CT was a non-contrast low-dose CT (max. 0.5 mSv) performed for the purposes of attenuation correction and anatomical correlation. Diagnostic CT with intravenous contrast was performed during the same procedure in case of non-physiological 18FDG-PET uptake or known focal disease prior to referral. PET and fused PET/CT images were displayed on Siemens syngo via workstations for analysis. The 18FDG-PET/CT scans were described by consultants in nuclear medicine specialised in paediatric PET and experienced radiologists.

The study was approved by the Danish Patient Safety Authority (3-3013-1774/1) and the Danish Data Protection Agency (RH-2017-09/05214). A waiver of requirement of informed consent was obtained.

3 | RESULTS

A total of 819 18FDG-PET/CT scans were performed during the study period. Of these, 35 (4%) were performed in previous healthy children with unexplained fever. The median age was 12 years (range 0–17). The duration of febrile illness prior to the 18FDG-PET/CT varied from 14 days to 2 years (median 6 weeks). Six patients had continuous fever, while 29 had recurrent fever with irregular intervals of the fever. No children had periodic fevers occurring at regular predictable intervals. Prior to 18FDG-PET/CT, all patients had serial clinical and laboratory evaluation, including extensive viral and bacterial investigations, and a median of 3 (range 1–5) imaging modalities performed, for example X-ray, ultrasound, CT and/or MRI of one or more organs. The final diagnosis of the 35 cases was infectious diseases (N = 8; 23%), malignancy (N = 4; 11%), inflammatory diseases (N = 15, 43%) and unknown with spontaneous fever resolution (‘miscellaneous’) (N = 8; 23%). Among all patients, 18 (51%) had no focal suspicion clinically and normal conventional imaging prior to 18FDG-PET/CT.
(Table 1), while 17 (49%) had focal suspicion clinically and/or by conventional imaging prior to $^{18}$FDG-PET/CT (Table 2).

Among the 18 patients with no focal suspicion clinically or by conventional imaging prior to $^{18}$FDG-PET/CT, the scan was diagnostic in three patients including one with Langerhans cell histiocytosis (case 1; Figure 1) and two with Takayasu’s arteritis (cases 2–3) (Table 1). In six patients with inflammatory diseases (cases 6–11), $^{18}$FDG-PET/CT did not reveal focal $^{18}$FDG-uptake but increased non-specific homogeneous $^{18}$FDG-uptake in the bone marrow and spleen in five cases (cases 6–10). In seven patients, $^{18}$FDG-PET/CT was normal and true negative (cases 12–18). The febrile illness in these patients resolved spontaneously without an established diagnosis. Six of these seven patients had normal C-reactive protein at repeated investigations, in contrast to only one of 11 of the remaining cases where a final diagnosis was subsequently established (Table 1). During the follow-up period of a median of 4 years (3–5 years), six of the seven cases with spontaneous fever resolution had affiliation to outpatient clinics for psychology according to the results of $^{18}$FDG-PET/CT. The scan was diagnostic in two patients with tuberculosis (cases 19–20) and one case with malignancy (Ewing sarcoma; case 21). In 13 (76%) patients (cases 22–34), $^{18}$FDG-PET/CT confirmed known localised lesions and excluding additional lesions, but did not differentiate between complicated infections, malignancy and inflammation. In cases 22–25, $^{18}$FDG-PET/CT guided the site of biopsy. In one patient (case 35), $^{18}$FDG-PET/CT was true negative and ruled out malignancy and infection. In the three cases with inflammatory diseases (cases 29–31), $^{18}$FDG-PET/CT confirmed known focal lesions and revealed increased non-specific $^{18}$FDG-uptake in the bone marrow and spleen. Figure 2 presents the cases according to the results of $^{18}$FDG-PET/CT.

### Table 1 Cases with persistent unexplained fever and normal conventional imaging

| No | Age (years) | Fever duration | CRP<sup>a</sup> | Prior to $^{18}$FDG-PET/CT | $^{18}$FDG-PET/CT result | Final diagnosis |
|----|-------------|----------------|-----------------|---------------------------|--------------------------|----------------|
| 1  | 0           | 5 weeks        | 109             | FUO                       | Malignancy               | Langerhans cell histiocytosis |
| 2  | 16          | 10 weeks       | 110             | Recurrent fever           | Giant vessel arteritis    | Takayasu's arteritis         |
| 3  | 9           | 5 weeks        | 186             | Recurrent fever           | Giant vessel arteritis    | Takayasu's arteritis         |
| 4  | 0           | 4 weeks        | 128             | Recurrent fever           | Appendicitis              | Unknown. Spontaneous fever resolution<sup>b</sup> |
| 5  | 6           | 4 weeks        | 88              | Recurrent fever           | No focal processes<sup>c</sup> | Leukaemia                    |
| 6  | 8           | 2 weeks        | 309             | FUO                       | No focal processes<sup>c</sup> | sJIA                        |
| 7  | 9           | 6 weeks        | 234             | Recurrent fever           | No focal processes<sup>c</sup> | sJIA                        |
| 8  | 2           | 5 weeks        | 113             | Recurrent fever           | No focal processes<sup>c</sup> | sJIA                        |
| 9  | 14          | 6 weeks        | 47              | FUO                       | No focal processes<sup>c</sup> | Kawasaki disease             |
| 10 | 12          | 8 months       | 213             | Recurrent fever           | No focal processes<sup>c</sup> | Autoinflammatory fever syndrome<sup>d</sup> |
| 11 | 3           | 18 months      | <10             | Recurrent fever           | Normal                    | Autoinflammatory fever syndrome<sup>d</sup> |
| 12 | 7           | 5 weeks        | <10             | Recurrent fever           | Normal                    | Unknown. Spontaneous fever resolution<sup>e</sup> |
| 13 | 15          | 24 months      | <10             | Recurrent fever           | Normal                    | Unknown. Spontaneous fever resolution<sup>e</sup> |
| 14 | 9           | 3 months       | <10             | Recurrent fever           | Normal                    | Unknown. Spontaneous fever resolution<sup>e</sup> |
| 15 | 13          | 4 months       | <10             | Recurrent fever           | Normal                    | Unknown. Spontaneous fever resolution<sup>e</sup> |
| 16 | 11          | 8 weeks        | <10             | Recurrent fever           | Normal                    | Unknown. Spontaneous fever resolution<sup>e</sup> |
| 17 | 11          | 5 months       | <10             | Recurrent fever           | Normal                    | Unknown. Spontaneous fever resolution<sup>e</sup> |
| 18 | 8           | 8 months       | <10             | Recurrent fever           | Normal                    | Unknown. Spontaneous fever resolution<sup>e</sup> |

Abbreviations: CRP, C-reactive protein; FUO, fever of unknown origin; sJIA, systemic juvenile idiopathic arthritis.

<sup>a</sup> Highest CRP during the fever episode (reference value below 10 mg/L).

<sup>b</sup> Exploratory laparoscopy excluded appendicitis.

<sup>c</sup> Increased non-specific $^{18}$FDG-uptake in bone marrow and spleen.

<sup>d</sup> Autoinflammatory disease caused by mutations in nucleotide oligomerisation domain 2 (NOD-2).

<sup>e</sup> Neonatal-onset multisystem inflammatory disease (CINCA variant).
This study showed that $^{18}$FDG-PET/CT was beneficial as a diagnostic tool in several previously healthy children with unexplained fever, where extensive conventional diagnostic investigations did not reveal the diagnosis. In the study, $^{18}$FDG-PET/CT was diagnostic, or raised suspicion of the correct diagnosis, in children with tuberculosis, Langerhans cell histiocytosis, Ewing sarcoma and Takayasu’s arteritis. Further, $^{18}$FDG-PET/CT contributed to the diagnosis in several cases by excluding additional lesions, mapping the extent of the disease, for example lymph nodes and/or guiding site of biopsy. Previous studies have also reported $^{18}$FDG-PET/CT to reveal the diagnosis, or be contributory, in febrile children with (1) infectious diseases, among others tuberculosis, osteomyelitis, spondylodiscitis and endocarditis, (2) malignancy, such as leukaemia, hepatosplenic T-cell lymphoma and Ewing sarcoma and (3) inflammatory diseases, including systemic juvenile idiopathic arthritis, Crohn’s disease, Takayasu arteritis, Kawasaki disease, polyarteritis nodosa and systemic lupus erythematosus. In our study, all cases with normal CRP and no focal signs had normal $^{18}$FDG-PET/CT. Thus, $^{18}$FDG-PET/CT may not be contributive in children with normal inflammatory parameters, as also indicated by a study by Pihl et al.

$^{18}$FDG-PET/CT is a relatively expensive modality and not easily available at all hospitals. In line, our cohort consisted of patients referred to our tertiary hospital from nine paediatric departments, the Faroe Islands and Greenland. The scans were performed with low-dose CT of a maximum of 0.5 mSv and diagnostic CT with intravenous contrast only in cases of non-physiological $^{18}$FDG-uptake or known focal disease. This diagnostic strategy allows us to reduce radiation in many patients. The new generation ‘total body $^{18}$FDG-PET/CT’

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NYGAARD et al. will enable even lower radiation dose, for the PET-part below 1 mSv, and with the upcoming opportunities of combining this with artificial intelligence technologies, the radiation will be even lower. Among our cases, \[^{18}\text{FDG-}\text{PET/CT}\] confirmed all known localised lesions diagnosed by conventional imaging, for example CT and MRI. Thus, in tertiary centres, this may allow for new possibilities for the use of \[^{18}\text{FDG-}\text{PET/CT}\], for example earlier in the diagnostic workup to take advantage of the ‘all-in-one-head-to-toe’ scan and avoid multiple imaging modalities.

We found three important challenges for the paediatric clinician to be aware of when using \[^{18}\text{FDG-}\text{PET/CT}\] in the evaluation of previously healthy children with unexplained fever. First, in most children with inflammatory diseases, as systemic juvenile idiopathic arthritis and Kawasaki disease, \[^{18}\text{FDG-}\text{PET/CT}\] only showed increased non-specific homogeneous \[^{18}\text{FDG-uptake}\] in bone marrow and spleen, compatible with haemopoietic mobilisation, which is of limited diagnostic value. Further, \[^{18}\text{FDG-}\text{PET/CT}\] was normal in one child with a rare autoinflammatory disease. Thus, normal, \[^{18}\text{FDG-}\text{PET/CT}\]...
does not exclude inflammatory diseases. Children with inflammatory diseases constitute a larger proportion than infections, which may in part be due to fast microbiological diagnostics owing to a new era of fast and ‘broad-screening’ microbiological analyses, including PCR-based methods. Although inflammatory diseases may in some cases be diagnosed by $^{18}$FDG-PET/CT, several other studies have reported normal $^{18}$FDG-PET/CT in children with systemic juvenile idiopathic arthritis, Kawasaki disease, polyarteritis nodosa, systemic lupus erythematosus and familial Mediterranean fever, in line with our results. The inflammatory processes in, for example, Kawasaki disease are located to small blood vessels and/or tissue and, therefore, cannot be diagnosed by $^{18}$FDG-PET/CT, contrasting large vessel arteritis, as Takayasu’s arteritis, where $^{18}$FDG-PET/CT is diagnostic. This stresses the importance of continuous serial clinical evaluations and diagnostic workup, particular for inflammatory diseases, in case of normal $^{18}$FDG-PET/CT and, in particular, in case of increased non-specific FDG-uptake in bone marrow and spleen, if the child continues to have fever and/or other symptoms. Further, one child with only increased non-specific homogeneous $^{18}$FDG-uptake in the bone marrow had leukaemia. The fact that pathological $^{18}$FDG-uptake in the bone marrow may in some cases be impossible to distinguish from physiological $^{18}$FDG-uptake, or increased non-specific $^{18}$FDG-uptake seen in infectious or inflammatory diseases, has also been illustrated in other studies with cases of leukaemia, where patchy or diffusely increased splenic and bone marrow activity was regarded as reactive haematopoietic tissues. Concerning other false negative scans, our study did not include cases of infectious diseases, but such have been reported in meningitis, endocarditis, arthritis and urinary tract infection. This may be due to the fact that high physiological $^{18}$FDG-uptake in the brain, heart and joints, and the $^{18}$FDG excretion through the kidneys, which in some cases may hinder the detection of pathological $^{18}$FDG-uptake.

The second challenge was that complicated infection, malignancy and inflammation could not be differentiated in most of our cases with increased focal $^{18}$FDG-uptake. This is a well-known limitation also described with other imaging modalities, for example X-ray, ultrasound, CT and MRI. In line, $^{18}$FDG-PET/CT has in other studies suggested lymphoma in cases with generalised adenopathy caused by Epstein-Barr virus, varicella-zoster virus and chronic granuloma disease. This may be due to an overproduction of glycolytic transporters and enzymes in both cancer cells and inflammatory cells, such as granulocytes, monocytes and lymphocytes, resulting in accumulation of $^{18}$FDG in malignant tissues as well as in tissue with infectious and non-infectious inflammation. Thus, in cases where an infectious process is suspected clinically and/or by conventional imaging such as CT and/or MRI, but malignancy cannot be excluded, direct biopsy should be considered, although $^{18}$FDG-PET/CT in some cases may guide the optimal site of biopsy and map the extend of the disease.

The third challenge was the small risk of false positive results as in our case where $^{18}$FDG-uptake in the appendix resembled appendicitis and mislead to appendectomy. $^{18}$FDG-uptake not related to the underlying disease has also been stated in other studies, among others physiological $^{18}$FDG-uptake in the intestine resembling inflammatory bowel disorder and $^{18}$FDG-uptake in the thyroid gland and the ovaries not related to the underlying disease. Further, increased non-specific $^{18}$FDG-PET uptake in the bone marrow due to infection or inflammation has also been interpreted as leukaemia. It is, therefore, important to correlate $^{18}$FDG-PET/CT results to the clinical examination, as central with other imaging modalities.

There are several limitations in our study. First, the inclusion at our tertiary referral centre most likely have biased patients towards severity, compared to non-referral centres. Second, this is a retrospective case-series without predefined inclusion criteria, which makes the results exploratory only. Since other studies to date investigating the use of $^{18}$FDG-PET/CT in febrile children have also been retrospective case reports and case-series, the overall evidence of applying $^{18}$FDG-PET/CT in unexplained fever in the paediatric population is still insufficient. Importantly, clearer indications for $^{18}$FDG-PET/CT are needed, as our results indicated limited value of $^{18}$FDG-PET/CT in patients with normal inflammatory parameters.

5 | CONCLUSION

This study showed that $^{18}$FDG-PET/CT may be used as a piece in the diagnostic puzzle of previously healthy children with unexplained fever. $^{18}$FDG-PET/CT was diagnostic in cases with Takayasu’s arteritis, tuberculosis, Langerhans cell histiocytosis and Ewing sarcoma. Further, $^{18}$FDG-PET/CT was contributory in several cases by mapping the extent of the disease, excluding lesions and/or guiding the site of biopsy. Challenges included (i) that $^{18}$FDG-PET/CT only showed increased non-specific $^{18}$FDG-uptake in bone marrow and spleen in half of children with inflammatory diseases, (ii) that $^{18}$FDG-PET/CT could not differentiate complicated infections, malignancy and inflammation in many cases with focal processes, (iii) a small risk of false positive results. These challenges are important to be aware of if integrating this imaging modality in the diagnostic worupk of selected children with unexplained fever.

FUNDING INFORMATION

The study was funded by Innovation Fund Denmark (0176-00020B).

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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REFERENCES

1. Marshall GS. Prolonged and recurrent fevers in children. J Infect. 2014;68(Suppl 1):S83-S93. doi:10.1016/j.jinf.2013.09.017
2. Statler VA, Marshall GS. Characteristics of patients referred to a pediatric infectious diseases clinic with unexplained fever. J Pediatric Infect Dis Soc. 2016;5(3):249-256. doi:10.1093/jpids/piv008

3. Antoon JW, Peritz DC, Parsons MR, Skinner AC, Lohr JA. Etiology and resource use of fever of unknown origin in hospitalized children. Hosp Pediatr. 2018;8(3):135-140. doi:10.1542/hped.2017-0098

4. Chien YL, Huang FL, Huang CM, Chen PY. Clinical approach to fever of unknown origin in children. J Microbiol Immunol Infect. 2017;50(6):893-898. doi:10.1016/j.jmii.2015.08.007

5. Wright WF, Auwaerter PG, Dibble EH, Rowe SP, Mackowiak PA. Fever of unknown origin: a systematic review of the literature. Acad Emerg Med. 2005;12(5):412-420. doi:10.1197/jam.201914-2801-z

6. Fusco FM, Pisapia R, Nardiello S, et al. Fever of unknown origin and unexplained fever during immune suppression. Eur J Nucl Med Mol Imaging. 2014;41(10):1916-1923. doi:10.1007/s00259-014-2801-z

7. Li Q, Tian R, Sun X. More evidence is warranted to establish the role of 18F-FDG-PET/CT in children with fever of unknown origin or unexplained signs of inflammation. Eur J Nucl Med Mol Imaging. 2010;37(1):136-145. doi:10.1007/s00259-009-1185-y

8. Attard L, Tadolini M, De Rose DU, et al. Overview of fever of unknown origin in adult and paediatric patients. Clin Exp Rheumatol. 2018;36(Suppl 110):10-24.

9. Jasper N, Dabritz J, Frosch M, Loeffler M, Weckesser M, Foell D. Diagnostic value of [(18)F]-FDG PET/CT in children with fever of unknown origin or unexplained signs of inflammation. Eur J Nucl Med Mol Imaging. 2014;41(10):1916-1923. doi:10.1007/s00259-014-2801-z

10. Blokhuis GJ, Bleeker-Rovers CP, Diender MG, Oyen WJG, Draaisma JMT, de Geus-Oei LF. Diagnostic value of 18F-FDG-PET/CT in children with fever of unknown origin and unexplained fever during immune suppression. Eur J Nucl Med Mol Imaging. 2014;41(10):1916-1923. doi:10.1007/s00259-014-2801-z

11. Nadig V, Herrmann K, Mattaghy FM, Schulz V. Hybrid total-body pet scanners-current status and future perspectives. Eur J Nucl Med Mol Imaging. 2022;49(2):445-459. doi:10.1007/s00259-021-05536-4

12. Reichkendler M, Andersen FL, Borgwardt L, et al. Long axial field of view with 5 min acquisition time enables PET/CT in toddler without sedation. J Nucl Med. 2022. doi:10.2967/jnumed.121.263626

13. Chang L, Cheng MF, Jou ST, et al. Search of unknown fever focus using PET in critically ill children with complicated underlying diseases. Pediatr Crit Care Med. 2016;17(2):e58-e65. doi:10.1097/PPC.0000000000000601

14. Ben Shimol J, Amital H, Lidar M, et al. The utility of PET/CT in large vessel vasculitis. Sci Rep. 2020;10(1):17709. doi:10.1038/s41598-020-73818-2

15. Pakos EE, Fotopoulos AD, Ioannidis JP. 18F-FDG PET for evaluation of bone marrow infiltration in staging of lymphoma: a meta-analysis. J Nucl Med. 2005;46(6):958-963.

16. Schaefer NG, Strobel K, Taverna C, Hany TF. Bone involvement in patients with lymphoma: the role of FDG-PET/CT. Eur J Nucl Med Mol Imaging. 2007;34(1):60-67. doi:10.1007/s00259-006-0238-8

17. Rao A, Shirodkar K, Govindarajan MJ, Devaru S. Role of 18F-FDG PET/CT in patients with pyrexia of unknown origin. Radiol Infect Dis. 2016;34(3):145-156. doi:10.1016/j.rid.2016.11.006

18. Semb D, Hjalgrim H, Egelund KE, et al. Unexplained fever of unknown origin in children. J Microbiol Immunol Infect. 2017;50(6):893-898. doi:10.1016/j.jmii.2015.08.007

19. Chamroonrat W. PET/computed tomography in the evaluation of fever of unknown origin and infectious/inflammatory disease in pediatric patients. PET Clin. 2020;15(3):361-369. doi:10.1016/j.petc.2020.03.002

20. Vali R, Alessio A, Balza R, et al. SNMMI procedure standard/EANM practice guideline on pediatric (18)F-FDG PET/CT for oncology 1.0. J Nucl Med. 2021;62(1):99-110. doi:10.2967/jnumed.120.254110

21. Garg G, DaSilva R, Balhakia A, Milstein DM. Utility of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography in a child with chronic granulomatous disease. Indian J Nucl Med. 2016;31(1):62-64. doi:10.4103/0972-3919.172366

22. Liu B, Lee NJ, Otero HJ, Servaes S, Zhuang H, Rosai-Dorfman disease mimics lymphoma on FDG PET/CT in a pediatric patient. Clin Nucl Med. 2014;39(2):206-208. doi:10.1097/RLU.0000000000000267

23. Thomas DL, Syrbu S, Graham MM. Epstein-Barr virus mimicking lymphoma on FDG-PET/CT. Clin Nucl Med. 2009;34(12):891-893. doi:10.1097/RLU.0b013e31815bed135

24. Sheehy N, Israel DA. Acute varicella infection mimics recurrent Hodgkin’s disease on F-18 FDG PET/CT. J Nucl Med Clin Nucl Med. 2007;32(10):820-821. doi:10.2967/jnumed.121.263626

How to cite this article: Nygaard U, Larsen LV, Vissing NH, von Linstow M-L, Myrup C & Berthelsen AK et al. Unexplained fever in children—Benefits and challenges of FDG-PET/CT. Acta Paediatr. 2022;111:2203–2209. https://doi.org/10.1111/apa.16503