Diagnostic Value of Magnetic Resonance Imaging in Fibrodysplasia Ossificans Progressiva

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ABSTRACT
Using $^{18}$F Sodium Fluoride (NaF) Positron Emission Tomography (PET) it is not only possible to identify the ossifying potency of a flare-up, but also to identify an asymptomatic chronic stage of fibrodysplasia ossificans progressiva (FOP). The purpose of this study was to investigate the diagnostic role of a more widely available imaging modality, Magnetic Resonance Imaging (MRI), which is of special interest for studies in pediatric FOP patients. MRI and $^{18}$F NaF PET/CT images at time of inclusion and subsequent follow-up CT scans of 4 patients were analyzed retrospectively. Presence, location, and intensity of edema identified by MRI were compared with activity on $^{18}$F NaF PET. Occurrence or progression of heterotopic ossification (HO) was examined on the follow-up CT images. Thirteen different lesions in various muscle groups were identified: five lesions with only edema, five lesions with both edema and increased $^{18}$F NaF uptake, one lesion with only increased $^{18}$F NaF uptake, and two lesions with neither edema nor uptake of $^{18}$F NaF. Mild edema, found in three lesions, was present at asymptomatic sites, which did not show increased $^{18}$F NaF uptake or progression of HO on consecutive CT images. Moderate edema was found in three symptomatic lesions, with increased $^{18}$F NaF on PET and progression of HO on CT. Severe edema was identified in four lesions. Interestingly, two of these lesions did not develop HO during follow-up; one of these two even gave obvious symptoms of a flare-up. MRI can identify whether symptoms are the result of an acute flare-up by the presence of moderate to severe edema. The occurrence of severe edema on MRI was not always related to an ossifying lesion. The additional diagnostic value of MRI requires further investigation, but MRI does not seem to fully replace the diagnostic characteristics of $^{18}$F NaF PET/CT in FOP. © 2020 The Authors.

KEY WORDS: ANALYSIS/QUANTITATION OF BONE; CLINICAL TRIALS; DISEASES AND DISORDERS OF/RELATED TO BONE; FIBRODYSPLASIA OSSIFICANS PROGRESSIVA; RADIOLGY

Introduction

Fibrodysplasia ossificans progressiva (FOP) is an extremely rare disease leading to ankyloses caused by excessive heterotopic bone formation in connective tissue. This progressive autosomal dominant disorder is characterized by periodic flare-ups. A flare-up is thought to start with an inflammatory process in muscles, tendons, and ligaments. Flare-ups often, but not always, result in formation of heterotopic ossification (HO).

Nowadays, a flare-up is defined by its symptoms, the most prominent ones being swelling and pain. Because of the lack of (blood) markers, a flare-up is still a clinical diagnosis. $^{18}$F Sodium fluoride (NaF) Positron Emission Tomography (PET) / Computed Tomography (CT), however, it has become possible to identify which of these flare-ups will lead to HO. Recently, it was shown that $^{18}$F NaF PET/CT can also identify asymptomatic
chronic progression of existing HO based on relatively lower, but still increased $[^{18}F]$NaF uptake.\(^{(8)}\) Using this new marker of active and chronic FOP disease, it has become possible to investigate the diagnostic role of other, more widely available imaging modalities such as Magnetic Resonance Imaging (MRI). The absence of ionizing radiation makes this technique especially interesting for the pediatric FOP population.

MRI provides high soft tissue contrast and is able to detect edema, a potential marker of inflammatory stages in FOP.\(^{(9-12)}\) MRI is currently used in FOP to evaluate the presence of edema early in flare-ups.\(^{(10)}\) Whether the two stages of FOP, active flare-ups and asymptomatic chronic FOP disease, have similar inflammatory patterns and corresponding MRI signals is not yet known.

A few FOP case reports have described hyperintense foci on T2-weighted images during flare-ups,\(^{(9,11,13-15)}\) but whether these hyperintense foci on MRI led to formation of HO was not investigated. Nevertheless, in R206H Acvr1 knock-in mice, it was shown that sites of HO formation coincided with hyperintense T2 signals. Once HO was formed, the signal subsided. In this animal model, the MRI T2-signal was in accordance with the $[^{18}F]$NaF PET signal.\(^{(16)}\) For human FOP patients, however, it is not known whether edema on MRI can distinguish between ossifying and nonossifying flare-ups, as well as between active and asymptomatic chronic FOP disease, as in the case for $[^{18}F]$NaF PET/CT.\(^{(8)}\) Therefore, the aim of this study was to assess whether MRI can identify different stages of FOP. Although ossifying and nonossifying flare-ups are clinically indistinguishable,\(^{(5)}\) it is possible that the severity of edema on MRI may predict the fate of a flare-up. In addition, assuming that HO formation is always accompanied by edema, it should be possible to detect the chronic component of disease by MRI.

**Methods**

Adult FOP patients, under the care of the FOP expertise center of the Amsterdam UMC, in whom both MRI and $[^{18}F]$NaF PET/CT scans were performed, were included. MRI and $[^{18}F]$NaF PET/CT scans had to be acquired within 14 days of each other to allow for reliable comparisons. In addition, a follow-up CT scan, obtained at least 6 months after the initial scans, had to be available to assess whether HO had formed. Any additional MRI and $[^{18}F]$NaF PET/CT images, available within the studied timeframe, were included in the analyses as well. Patients were asked to sign a consent form for analyzing and publishing their data anonymously. The study had been approved by the Medical Ethics Review Committee of Amsterdam UMC.

MRI was acquired on a 1.5-T system (Signa Excite HDxt; GE Healthcare, Milwaukee, WI, USA) and a 3-T system (Vantage Titan; Canon Medical Systems, Otawara, Japan). MRI scans were obtained either at an annual follow-up or for a suspected flare-up. Although different imaging protocols were used, T2 STIR (short-T1 inversion recovery) acquisitions were available for all MRI scans included. MRI parameters are presented in Table 1 of the supplemental material. The intensity of edema was graded on a semiquantitative scale: absent, mild, moderate, or severe.\(^{(17-19)}\) Two reviewers (BPT and EB) independently graded the degree of edema. BPT was not involved in clinical care of the FOP patients at the time of image acquisition. Both reviewers were blinded to clinical data. To limit bias, the review of $[^{18}F]$NaF PET and CT data was performed at least 2 months apart from the review of the MRIs. The reviewers were instructed to grade edema in accordance to Davis et al. a juvenile dermatomyositis scoring system for MRI.\(^{(17)}\) Discrepancies were resolved by consensus.

$[^{18}F]$NaF PET/CT scans were obtained using a Gemini TF-64 PET/CT scanner (Philips Medical Systems, Best, The Netherlands). Patients were scanned from the top of the skull to the toes. The $[^{18}F]$NaF dose was adjusted to weight (eg, 83 MBq $[^{18}F]$NaF for a 70- to 79-kg patient) and a scan time of 2 min per bed position was used. Uptake of $[^{18}F]$NaF was considered increased for chronic lesions when SUV\(_{peak}\) exceeded 8.4.\(^{(8)}\) The method used to analyze $[^{18}F]$NaF PET/CT has been previously described.\(^{(8)}\) For flare-ups, no SUV\(_{peak}\) cut-off was available, but in practice it is assumed to be 2 to 3 times higher than that for a chronic lesion.\(^{(8)}\) Whole-body CT images were acquired at 120 kV with a tube current varying between 30 and 60 mAs. CT volumes were obtained for each heterotopic lesion identified. Two reviewers (EB and BPT) independently analyzed $[^{18}F]$NaF PET/CT images. Again, discrepancies were resolved by consensus.

Follow-up low-dose whole-body CT scans were also acquired at 120 kV with a tube current varying between 30 and 60 mAs. The volumes of the various lesions were analyzed to assess whether these lesions progressed during the course of this study. The same two reviewers (EB and BPT) independently analyzed CT images. Discrepancies were resolved by consensus.

Clinical data were evaluated separately to assess clinical signs of the patients at the time of MRI, $[^{18}F]$NaF PET/CT, and follow-up CT scans. A flare-up was assessed and confirmed by the physician based on the presence of symptoms, eg, swelling, redness, and pain. When HO progressed in the absence of any clinical symptoms at that site in the last 6 months it was considered chronic.

Interobserver correlation was assessed using Cohen’s kappa. Spearman’s rho was used for correlation between edema grading and SUV\(_{peak}\) values. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (SPSS, Inc., Chicago, IL, USA).

**Results**

Four FOP patients were included: All four MRI and $[^{18}F]$NaF PET/CT images, and at least one follow-up CT scan, were

| Table 1. Demographic Characteristics of the Included Patients |
|-----------------------------|--------------------|--------------------|
| **Sex** | **Age\(^{a}\)** | **Flare-up\(^{b}\)** | **Medication\(^{c}\)** |
| 1 | ♀ | 19 | m. psoas, m. iliopsoas | Prednisolone, ibuprofen |
| 2 | ♀ | 23 | - | - |
| 3 | ♀ | 23 | Flare-up bilateral jaw | Prednisolone, ibuprofen |
| 4 | ♂ | 20 | Suspicion flare-up jaw | Naproxen |

\(^{a}\)Age at the time of the first MRI. \\
\(^{b}\)Flare-up during the course of the study. \\
\(^{c}\)Medication taken during the course of the study. This may have been temporarily or continuously.
Table 2. Identified Muscle (Groups) by Either Complaints, Edema on MRI, or Increased [18F]NaF Uptake on PET/CT

| Muscle (group)         | MRI edema | [18F]NaF PET (SUV<sub>peak</sub>) | Clinical signs | Progression HO volume |
|------------------------|-----------|-----------------------------------|----------------|-----------------------|
| Jaw dextra             | None      | 4.1                               | Present        | No                    |
| Jaw sinistra           | None      | 2.3                               | Present        | No                    |
| Paracostal area dextra | None      | 9.8                               | Absent         | Yes                   |
| M. psoas sinistra      | Mild      | 5.4                               | Absent         | No                    |
| M. glutei dextra       | Mild      | 1.4                               | Absent         | No                    |
| M. glutei sinistra     | Mild      | 2.2                               | Absent         | No                    |
| Jaw dextra             | Moderate  | 28.5                              | Present        | Yes                   |
| Jaw sinistra           | Moderate  | 26.4                              | Present        | Yes                   |
| M. psoas dextra        | Moderate  | 32.5                              | Present        | Yes                   |
| M. lliopsoas dextra    | Severe    | 3.9                               | Present        | No                    |
| Mm. adductors dextra   | Severe    | 48.7                              | Present        | Yes                   |
| M. quadriceps dextra   | Severe    | 41.9                              | Present        | Yes                   |
| M. glutaeus maximus    | Severe    | 2.1                               | Absent         | No                    |

In bold: SUV<sub>peak</sub> that exceed the threshold of 8.4, as found by Botman et al.<sup>(8)</sup> 
HO = Heterotopic ossification; M. = musculus.

Available In fact, for the assessment of these four patients, eight MRI scans, six [18F]NaF PET/CT scans, and four follow-up CT scans were available.

Using MRI, 10 different edematous lesions were found. Increased sodium fluoride uptake was found in only five and clinical signs of a flare-up were present in only six of the lesions identified by MRI (Table 2). Using [18F]NaF PET/CT, six lesions showed increased uptake of [18F]NaF. In five lesions, edema was present and for five of those six [18F]NaF-positive lesions patients complained of discomfort. Six sites were identified solely by discomfort that was recognized by the patient as a flare-up. In four of the six symptomatic sites, edema was demonstrated by MRI. Only three of these six symptomatic sites showed increased [18F]NaF uptake on PET. Combining the lesions and sites found with MRI, [18F]NaF PET/CT, and clinical signs, 13 distinctive sites were identified and analyzed further.

Of the 10 edematous lesions identified by MRI, edema was classified as mild in three, moderate in three, and severe in four lesions (Table 2). There was a good correlation in scoring of edema between the two independent reviewers (Cohen’s κ = 0.7; p < 0.05).

None of the three mildly edematous lesions showed progression of HO. There was no increased uptake of [18F]NaF, nor were there any clinical signs reported at these sites. In contrast to these mild lesions, all three with moderate edema were followed by HO progression. In addition, all showed increased [18F]NaF uptake and were accompanied by signs of a flare-up. Interestingly, two of the four sites with severe edema did not develop HO. Although one of these lesions was accompanied with common flare-up symptoms, such as swelling and pain (Fig. 1A-C, blue arrows), it did not show increased activity on [18F]NaF PET. Interestingly, the adjacent muscle showed moderate edema (Fig. 1A-C, white arrows), which did result in HO development. [18F]NaF uptake was increased only in the muscle group that showed HO development. Figure 1D-1F shows the course of the edema over 11 months, with great differences in edema intensity after one month. After 11 months, the edema had completely resolved.

The other lesion with severe edema was a clinically asymptomatic lesion. Again, the [18F]NaF PET scan did not show increased uptake of [18F]NaF in this area and the successive CT scan did not reveal any HO progression of that particular region.

One site was identified by increased uptake of [18F]NaF on PET, but did not reveal any edema. The patient denied having had complaints in that area for at least six months. The follow-up CT scan, however, revealed progression of HO in that particular lesion. Taking all edematous lesions into account, [18F]NaF SUV<sub>peak</sub> showed no significant correlation with edema intensity (Spearman’s ρ = 0.4; p = 0.222). In addition, the volume increase of new lesions or with HO progression was weakly related to the intensity of the edema as found by MRI (Spearman’s ρ = 0.6; p = 0.244).

Apart from lesions identified by MRI and [18F]NaF PET, two cases of disease activity: the [18F]NaF PET/CT. Results were evaluated using follow-up CT and clinical data. In this small series of patients, an active flare-up was always accompanied by moderate to severe edema on MRI. Interestingly, the presence and severity of edema did not always correlate with the ossifying potency of the involved muscle location. In addition, the chronic stage in FOP was not associated with edema on MRI. Finally, mild edema was seen at several sites, but this was not related to [18F]NaF PET/CT, HO, or to clinical complaints.

The finding that all flare-ups were accompanied by edema on MR-imaging is in line with five case reports.<sup>(9,11,13–15)</sup> In these

Discussion

The aim of this study was to determine the diagnostic value of MRI in FOP by comparing it with the recently validated marker of disease activity: the [18F]NaF PET/CT. Results were evaluated using follow-up CT and clinical data. In this small series of patients, an active flare-up was always accompanied by moderate to severe edema on MRI. Interestingly, the presence and severity of edema did not always correlate with the ossifying potency of the involved muscle location. In addition, the chronic stage in FOP was not associated with edema on MRI. Finally, mild edema was seen at several sites, but this was not related to [18F]NaF PET/CT, HO, or to clinical complaints.

The finding that all flare-ups were accompanied by edema on MR-imaging is in line with five case reports.<sup>(9,11,13–15)</sup> In these
case reports, often MRI was used to evaluate soft tissue swelling in, at that time, an undiagnosed child with FOP. As the course of these flare-ups was not followed, both implications and diagnostic value of MRI remained unclear. The present study shows a sensitivity of 83% of MRI as compared with \[^{18}\text{F}\]NaF PET. Therefore, MRI seems to have potential to rule out acute FOP activity. Chronic FOP activity, however, was not detectable by MRI. This was unexpected, as in a mouse model growth of HO was always associated with edema. This finding emphasizes the difference between the FOP phenotype in humans and the R206H Acvr1 knock-in mice.

The specificity to detect HO forming FOP activity using MRI was only 29%, as five edematous lesions did not show increased uptake on \[^{18}\text{F}\]NaF PET, nor did these lesions lead to HO progression. The implication of these edematous lesions is still unknown. It most likely is a manifestation of FOP itself, as MRI studies in healthy individuals did not or only sporadically showed edematous lesions. One might hypothesize that lesions with mild edema might reflect a very early stage of disease in which inflammation might still resolve spontaneously. In the current data set, only 6 months CT follow-up data were available. Whether these mild lesions develop into either the acute or the chronic stage beyond these 6 months remains unclear and will need further investigation.

MRI was compared with \[^{18}\text{F}\]NaF PET, a modality that was introduced recently as a method to quantify disease activity.

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**Fig. 1.** Consecutive MRI scans and \[^{18}\text{F}\]NaF PET scans of a patient with several flare-ups. Coronal MRI T2-weighted short-T1 inversion recovery (STIR) images are shown of a patient with multiple flare-ups. Starting in the loin (A + D), later also the groin (B) and upper leg (C + E). Time in months. A and D; T = 0. Clinically, a flare-up in the pelvic area with pain and swelling of the entire right loin. MRI (A) showed moderate and severe edema of the musculus psoas dextra (white arrows) and the musculus iliacus dextra (blue arrows), respectively. Also, the musculi adductors (red arrows) showed moderate edema, even though no clinical signs were noted. The MRI showed also an area of nonspecific mild edema (white circle). \[^{18}\text{F}\]NaF PET showed increased high uptake of tracer in the psoas muscle, mild uptake in the mm. adductors and no uptake in the iliopsoas muscle. B; T = 1. Edema at both the musculus psoas and musculus iliacus diminished, to mild and moderate edema, respectively. Edema intensity at the musculi adductors increased to severe, the patient now reported flare-up symptoms at the groin too. The mild edema seen in plane A resolved; no calcifications were noted. C and E; T = 11. Edema at the psoas muscle, and the iliacus and adductor muscles is completely resolved, but new edema formed in the quadriceps muscle (C). High \[^{18}\text{F}\]NaF uptake in the quadriceps (E); F; T = 21. Low-dose whole-body CT showed heterotopic ossification (HO) in the psoas muscle, HO at the site of the adductor muscles (red arrow), and in the quadriceps muscle. No HO formed in the iliopsoas (blue arrow).
Table 3. Proposed Stages of FOP Activity Based on MRI and \([^{18}\text{F}]\)NaF PET/CT Findings According to Eekhoff and Botman

| Stages | MRI edema | \([^{18}\text{F}]\)NaF PET/CT activity | FOP disease stage |
|--------|-----------|-------------------------------------|------------------|
| 0      | −         | −                                   | No FOP activity  |
| 1      | +         | −                                   | Inflammatory stage |
| 2      | −         | +                                   | Chronic stage    |
| 3      | +         | +                                   | Acute stage      |

\([^{18}\text{F}]\)NaF PET detects metabolic changes within tissues, as the \([^{18}\text{F}]\)NaF-ion binds to newly formed hydroxyapatite. MRI, on the other hand, detects inflammation through the presence of edema. In the present study, the intensity of edema did not appear to correlate with the uptake of \([^{18}\text{F}]\)NaF PET, nor with HO formation or progression. One should take into account that prednisolone was used during flare-ups to suppress inflammation, which may have interfered with the results.

Although \([^{18}\text{F}]\)NaF PET is an established technique to evaluate ossifying disease activity in FOP, MRI (if validated in FOP) would be especially useful in pediatric patients, as it does not involve exposure to radiation. In addition, MRI is more widely available than PET. Finally, MRI might be informative in the very early detection of a flare-up as inflammation is the first stage of FOP lesion formation, as found in one lesion in the current data set.

The results of the present study indicate that both MRI and \([^{18}\text{F}]\)NaF are able to identify the acute stage in FOP, flare-ups, but that MRI is not suitable for identifying the chronic stage, progression of HO in the absence of any clinical signs. There is, however, a third stage, characterized by mild edema (Table 3), which requires further investigation as it is not fully understood. This stage might be a reversible stage that either develops into the acute or chronic stage (moderate to severe edema and \([^{18}\text{F}]\)NaF PET-positive) or resolves without HO growth.

Another finding of the present study was the long duration of edema present at flare-up sites. Edema was observed for five months after onset of a flare-up. In previously reported cases, MRI was performed only within two to five weeks after the onset of a flare-up. Therefore, it seems that the inflammation that coincides with a flare-up might be present for a longer period. The significance and explanation of this long duration of edema needs to be further investigated.

The MRI rating used in this study (mild, moderate, or severe) is based on previous studies. The degree of muscle inflammation was based on the overall impression of the muscle (eg, swelling) caused by the inflammation. Both in the present and in previous studies the agreement between two readers was moderate to good.

The present study is limited by its retrospective design, resulting in different protocols used for MRI. The resolution of images differs only slightly between imaging protocols, it is therefore likely that this has had no influence on our judgment of the edema. In addition, in one patient a field strength of 1.5 Tesla and 3 Tesla were both used. In STIR sequences, however, differences in field strength are not expected to affect the appearance of edema. A further limitation was the availability of longitudinal \([^{18}\text{F}]\)NaF PET/CT and MRI scans of only four patients. This is because of the extreme rarity of the disease, the poor mobility of patients, and the unpredictability of flare-ups. One could also argue whether newly formed cartilage could be misdiagnosed for edema, but this is unlikely because compared with edema, cartilage has lower signal intensity, is more compact, and shows structural distortion of muscle morphology.

In conclusion, this study is the first to compare longitudinal imaging data between MRI and \([^{18}\text{F}]\)NaF PET/CT to establish the diagnostic value of MRI in FOP. MRI is particularly helpful in identifying muscle edema in FOP patients, indicating a concomitant inflammatory process. Moderate and severe edema resulted in the formation of HO in six out of seven lesions. However, only half of the edematous lesions on MRI eventually developed into HO. Moreover, MRI could not detect chronic FOP disease. The significance of mild edematous lesions on MRI that were not related to HO or \([^{18}\text{F}]\)NaF PET/CT needs further exploration.

Disclosures

All authors state that they have no conflicts of interest.

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