Pediatric Whole-Body MR Imaging Status Quo and Practical Aspects in Daily Routine

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Introduction

Up until the start of the last decade, whole-body magnetic resonance imaging could not be performed in one single examination due to the technical constraints associated with the equipment e.g., field-of-view (FOV), number of coils, and number of high-frequency channels were all subject to limitations. In addition, it was extremely time-consuming to transfer both patients and coils to perform a multi-stage/whole-body MRI examination (WB-MRI). It was only when MR systems were enhanced by means of coil elements that offer flexible switching and multiple receiver channels, as well as automatic table movement (Tim – Total imaging matrix; introduced in 2003) that whole-body examinations with high spatial resolution became clinically feasible. Furthermore, the use of high-density coils is

1 Sequence protocol for staging solid pediatric tumors. 17-year-old male, clearcell sarcoma in the gluteal region (asterisk) and pulmonary metastasis (arrow). Left side: basic module (coronal TIRM whole-body, transversal TIRM head and neck, T2w TSE fat sat with PACE and ECG triggering thorax, T2w TSE fat sat with PACE). Upper right side: head module. Lower right side: local staging.
absolutely essential if parallel imaging techniques are to be used effectively, because they play a key role in allowing MRI to be performed within a clinically-efficient time frame, without compromising the resolution, etc. [1]. The use of this MR technology is now widespread and it serves as the basis for developing fully-integrated MR/PET systems (molecular MRI) that are suitable for clinical applications [2]. WB-MRI marks a paradigm shift in MR imaging, because examinations no longer have to be purely organ-focused and can be used to carry out illness-related evaluations instead. As far as children* are concerned, systematic diagnosis without using ionizing radiation is of paramount importance. At the same time, fewer multiple and sequentially performed partial-body examinations are required. The benefits of combining diagnostic information for treatment-related decisions into a single examination are clear. However, within the field of pediatric radiology in particular, it is essential to take into account that many examinations require sedation. A range of main indications have emerged for WB-MRI in pediatric centers: ■ Assessment of multifocality in the case of bone marrow processes ■ Rheumatic diseases, including fever syndromes ■ Diagnosis of the spread of solid tumors There are, however, several questions surrounding the use of WB-MRI, which relate to the following issues: ■ Examination protocols and strategies ■ Findings evaluation and reading ■ Indications and diagnostic accuracy This review aims to summarize the current state of this method in everyday clinical applications. It also covers practice-related aspects which are of significance when WB-MRI is used in a pediatric context. In this respect, we are able to draw on our own experience of having carried out over 600 whole-body examinations on children* and young patients, which also clearly demonstrates the clinical relevance of this method in everyday clinical routine.

**Technical requirements, examination protocols, and strategies**

The current systems support the planning and implementation of a whole-body examination in diverse ways; for example, table movement, coil selection, and calibration for parallel imaging are fully automatic. The whole-body images that are often required to demonstrate findings are also generated automatically by the scanner and variations in signal intensity, which are in part due to multiple-channel coils are optimally compensated. Patients are examined in a supine position with their arms resting by their sides. Consequently, the arms can also be included in the scan and assessed easily. In our experience, it takes approximately 3 minutes to put the coils in place for a WB-MRI, although the specific needs of the child must be taken into account. Experience to date shows that using a large number of surface coils only rarely causes claustrophobia, even among children. Nevertheless, our experience shows that the administration of a sedative/endotracheal anesthesia should be factored in when planning a whole-body MRI for a child up to the age of seven. This decision depends both on the examination time and, therefore, on the clinical question, as well as the local conditions for preparing a child appropriately for an MRI examination. Essentially, preparing a child for a whole-body scan is no different from what is required for a partial body scan. However, an effort should be made to keep the scan time as short as possible, particularly in the case of non-sedated patients. In general, this necessitates thorough protocol planning prior to the start of the examination, with modifications being implemented during the actual scan where necessary.

Table 1 provides an overview of the MRI protocols used at our institution. Even though no standardized examination protocol has yet been established for pediatric WB-MRI, STIR (Short Tau Inversion Recovery) sequence acquisition is now commonplace and has proven to offer the sensitivity for practically all medical issues [3–10]. Therefore, a coronal STIR sequence is normally used as search sequence at the beginning of the examination. What we refer to as the basic module (Fig. 1) is then supplemented by transverse STIR/T2-weighted imaging with fat saturation in the head/neck area and trunk of the body. At the same time, the use of a respiratory trigger in the abdomen as well as a respiratory and cardiac trigger in the thorax achieves excellent image quality, which enables assessment of the internal organs, including the lungs (Fig. 2). As an alternative or in addition, the BLADE technique can be used to further reduce both motion and flow artifacts [10]. Diffusion-weighted imaging (DWI) is not included in the table shown. As clinical experience involving this technology grows, the proposed examination protocols will undoubtedly undergo significant modifications. Further sequences are determined by indication and disease (for example, bone and bone-marrow vs. whole-body staging for solid tumors) and by the clinical context (initial examination vs. follow-up). To facilitate visualization of the spinal column processes, a sagittal plane is advantageous [7], combining STIR and T1-weighted native sequences helps to distinguish marrow infiltrates from reactive changes or red bone marrow [3, 7, 10]. Small osteoblastic metastases can also be detected more reliably using T1-weighted sequences [12]. Some working groups have proposed the additional administration of contrast agents for bone marrow pathologies within the context of WB-MRI [3, 13]. Particularly in the context of initial diagnosis of soft tissue tumors or tumor-like pathologies in children, it is our policy to run additional native sequences in both the cranial and abdominal areas (Table 1) based on the experience of other working groups [14], although this approach has not even been adopted in recent studies [6, 15]. In our view, T1-weighted fat-saturated sequences are also required.

* MR scanning has not been established as safe for imaging fetuses and infants under two years of age. The responsible physician must evaluate the benefit of the MRI examination in comparison to other imaging procedures.
after administering contrast agents (Table 1) if the WB-MRI is to provide a definitive diagnosis of tumors beyond the scope of medical studies and the available reference standard (e.g. Positron Emission Tomography, PET). Further indications for administering contrast agents are when neoplastic syndromes can be discounted and in the case of fever syndromes or rheumatic joint diseases when the synovia need to be analyzed. A distinction needs to be made between the proposed protocols referred to above and dedicated regional organ protocols similar to those used for partial body measurements. For example, in the case of solid tumors, these are based on guidelines or national and international study protocols produced by various specialist medical associations and practitioners. This means that it is either necessary to extend the scan time accordingly or to omit certain aspects from the WB-MRI protocol (e.g. no additional abdominal and cranial imaging in the case of osteogenic sarcoma). Whole-body angiography in pediatric applications is only rarely performed (e.g. in vascular malformations and aneurysms).

The aforementioned whole-body DWI could, in the future, make a significant contribution to differentiating tissue and the effects of treatment. If further steps can be taken to bolster diagnostic accuracy, this method may allow significant streamlining of the WB-MRI protocols described [16, 17].

**Findings**

In contrast to organ-focused scans, WB-MRI generates large numbers of images. In scenarios that also involve the acquisition of T1-weighted images before and after administering contrast agents and dedicated examinations of the central nervous system (CNS) or diffusion-weighted images of the body, approximately 1,000 images constitute the norm, even in the case of pediatric whole-body examinations. Using optimized software (which, for example, automatically displays a complete series for a particular region or organ system and all the sequences associated with a lesion) can considerably reduce the time required for image analysis. Particularly in view of the multiple follow-ups involved, software solutions are becoming increasingly important [19]. In addition to the number of images, which demands a high level of attention, up until now there has

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**Table 1:**

1.5T WB-MRI protocols used at the University of Tübingen for pediatric patients

<table>
<thead>
<tr>
<th>Module</th>
<th>Region</th>
<th>Sequence</th>
<th>Slice thickness [mm] **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic module</td>
<td>WB</td>
<td>coronal STIR TSE</td>
<td>3.0 – 5.0</td>
</tr>
<tr>
<td></td>
<td>Head/Neck</td>
<td>transversal STIR TSE</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>Thorax</td>
<td>transversal T2 TSE fs*</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>Abdomen and Pelvis</td>
<td>transversal T2 TSE fs*</td>
<td>4.0</td>
</tr>
<tr>
<td>Extensions</td>
<td>WB</td>
<td>coronal T1w TSE</td>
<td>3.0–5.0</td>
</tr>
<tr>
<td></td>
<td>Brain</td>
<td>transversal FLAIR</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>Brain</td>
<td>transversal T1w-SE</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>Abdomen and Pelvis</td>
<td>transversal T1w 2D GRE</td>
<td>4.0</td>
</tr>
<tr>
<td>Extensions after CM application</td>
<td>WB</td>
<td>coronal T1w TSE fs</td>
<td>3.0–5.0</td>
</tr>
<tr>
<td></td>
<td>Brain</td>
<td>transversal / coronal T1w-SE</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>Neck, Thorax Abdomen and Pelvis</td>
<td>transversal T1w 2D GRE fs</td>
<td>4.0</td>
</tr>
</tbody>
</table>

*Triggering: Thorax (breath and ECG), Abdomen (breath).

**Adaption of resolution to size/age required.

Measurement times are given for 5 stations. When imaging infants and small children this can be reduced to 2 to 3 stations.

fs (fat saturation) technique is used depending on region-of-interest.
been a risk of clinical oversights in terms of findings which are not immediately obvious, particularly during screening examinations. Given that, in contrast to scintigraphic methods, both normal findings and pathological changes can display the same signal intensity in STIR sequences, small foci, e.g. in the vicinity of a hyperintense bowel, are easily overlooked. In principle, other sequences, such as T1 both before and after administering contrast agents, and particularly DWI are useful for effectively detecting pathological findings.

Diseases, indications, and related questions to be answered by WB-MRI

Since WB-MRI was introduced for pediatric applications, several studies have been published which compare the method against various reference standards (conventional imaging, functional imaging, clinical parameters) by focusing on small patient groups that are frequently heterogeneous and studying different techniques and medical issues [3–5, 7–11, 14, 16, 21–23]. Various problems have been identified concerning the widespread use of WB-MRI in pediatrics, particularly with regard to treatment planning and follow-up. These problems are linked to the issue of evidence-based medicine involving large populations. Nevertheless, clear indications can be derived from the available studies for a range of malignant and non-malignant diseases in children that eliminate the need for additional imaging completely, or at least help to reduce it. In this respect, bone scintigraphy is particularly worthy of mention. We shall now move on to a discussion of the key diseases, indications and medical issues that have been investigated to date using WB-MRI, along with details of possible diagnostic algorithms.

Unifocal vs. multifocal

For all diseases where using a unifocal, rather than a multifocal approach has consequences for the type of treatment, WB-MRI for pediatric applications has an extremely important role to play. A typical example of this would be Langerhans’ cell histiocytosis (LCH). Based on the guidelines of the AWMF (Arbeitsgemeinschaft der medizinischen Fachgesellschaften e.V. – association of the scientific medical societies in Germany) covering the fields of pediatric oncology and hematology (current version dated 01/2008), the primary form of image-based diagnosis would comprise the following: X-ray of thorax, radiographic skeletal survey and any supplementary skeletal scintigraphy that may be required, along with a CT of the thorax and a cranial MRI examination [20]. Multifocal analysis has major consequences both with regard to treatment and follow-ups (e.g. local treatment or even a wait and see strategy as opposed to systematic treatment with steroids and Vinblastine). A series of studies on a variety of diseases has revealed that WB-MRI is superior to X-ray-based methods or skeletal scintigraphy for the
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Purpose of assessing bone marrow infiltration [4, 7, 12, 21, 22]. The reduced sensitivity of scintigraphy is easily explained, particularly in the context of LCH (where this sensitivity problem has been documented in a small number of cases), as it is linked to the primary attack on the bone marrow and the rapid bone deterioration that sometimes occurs subsequently [9, 22]. The inferiority of X-ray examination is also evident [10, 22]. Another reason for using WB-MRI is that it is possible to detect extraskeletal manifestations, including attacks on the CNS [22].

In clinical terms and in terms of imaging, there can sometimes be an overlap between LCH and chronic recurrent multifocal osteomyelitis (CRMO). CRMO is characterized by non-bacterial inflammation with very heterogeneous processes. However, it is the typically multifocal nature of CRMO with occasional symmetric metaphyseal lesions which distinguishes CRMO and other conditions from bacterial osteomyelitis (Fig. 6). Investigations carried out at our clinic revealed that, in the case of CRMO, there was no significant correlation between the extent of skeletal lesions detected by WB-MRI and clinical parameters. However, they produced clear evidence that X-ray examinations (18%) are less sensitive than MRI in the case of this disease [13]. In our view, WB-MRI is the method of choice for CRMO, because it detects not only symptomatic but also inapparent manifestations, for example in a high-sensitivity examination of the spinal column.

Status in the case of rheumatic diseases

WB-MRI performed on adults allows to detect significantly more asymptomatic regions with arthritis or enthesitis than clinical examinations or tests [23]. The latter sometimes have a significant impact on treatment (for example, when using TNF-alpha inhibitors) and thus on the outcome [23, 24]. According to one study, 73% of patients examined with psoriatic arthritis underwent changes to their treatment [23]. Extraskeletal findings also play a significant role in cases of rheu-

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4 10-year-old girl with neuroblastoma, stage IV. Follow-up of a medullar metastases is shown (arrow). Comparison between DWI and MIBG Scintigraphy is provided. Left: pre-therapy; right: after therapy. Corresponding to therapy response an increase of the ADC can be seen.

5 Screening in case of battered child, 3-year-old boy. WB-MRI shows fractures of the right Tibia and right pelvis. No intracranial injury is seen. X-ray performed after WB-MRI shows obvious repair and scleroses of the fracture.
mantic and autoinflammatory diseases as well as vasculitides, such as (dermato) myositis, scleroderma/morphea and sarcoidosis [25]. In such cases, we believe that a clear indication for using WB-MRI is either when there are conflicting clinical and laboratory findings, or if multifocality is not detectable clinically or by using sonography (for example, on the cervical vertebrae), which then necessitates changes to treatment (Fig. 8).

**WB-MRI in the case of fever syndromes, unclear inflammation constellations and search for the focus of infection**

Both immunocompetent and non-immunocompetent patients fall into this heterogeneous indication group. A vague increase in individual or multiple inflammation markers is common to all patients. Reasons for this may include: a systemic disease, an undetected focus or a hitherto unknown/recurrent malignant occurrence. Up until now, thorax X-rays, abdominal sonography and sometimes sonography of pleura, joints, and lymph nodes have been recommended as the definitive imaging methods [26]. Reports concerning the use of WB-MRI in pediatric applications are scarce, yet it has been described as groundbreaking specifically where there is skeletal involvement. With regard to the newly-available MR/PET technology, reference is made to the results obtained from what we believe to be the largest study focusing on PET/ICT, which involved 32 patients with FUO (fever of unknown origin)/increased inflammatory parameters. In this context, the PET/CT technology resulted in a definitive diagnosis for 2 out of 3 children [28]. In light of this data, WB-MRI still represents a highly personalized diagnostic decision, but it should (given the relevant clinic and impact on treatment) clearly be taken into account when making diagnostic considerations.

**Screening for systemic diseases**

WB-MRI has already been used for asymptomatic patients to ensure both a better definition of diseases and improved assessment of the scale of systemic conditions [29]. However, the clinical benefit is still open to debate and practical aspects such as screening intervals remain unresolved. Nevertheless, data relating to pediatric patients is available for specific diseases
or syndromes and certain patterns of
disease progression. Neurofibromatosis-1
(NF-1) is one example of the progression
of malignant tumors. In young patients
with NF-1 who had already developed
a malignant peripheral nerve sheath
tumor, the tumor burden associated
with neurofibroma appeared signifi-
cantly larger on the WB-MRI scan than
for those patients where there was
no detectable malignant tumor [30].
However, this distinction could not be
detected in clinical examinations and
so patients with a high tumor burden
require close follow-up care. Differenti-
ating between fibromas and malignant
nerve tumors by means of morphology
is only possible to a limited degree
and in this context, the sensitivity of
conventional MRI is generally lower than
that of FDG PET/CT [31, 32].
WB-MRI allows effective screening for
the detection of asymptomatic osteone-
crosis. For patients who have received
high-dose chemotherapy in combination
with steroids, MRI detects considerably
more instances of avascular necrosis.
In particular, the ability to demonstrate
the extent of the condition and where
it is localized is crucial when making
treatment-related decisions [3] (Fig. 8).
Hereditary vascular malformations are
also a suitable indication for determining
how relevant a particular treatment is
(Fig. 7). In addition to showing the spread
of the disease, the technology makes it
possible to differentiate between hemangiomas and also between lymphatic and venous malformations.

**Child abuse**

In cases of child abuse cranial MRI is the most sensitive method for assessing hemorrhages, ischemic and axonal damage [33]. However, MRI is often used following a cranial CT scan in cases of acute impaired consciousness. Therefore, in our view it would be sensible to perform a whole-body scan afterwards as part of the same examination (Fig. 5). Indeed, a report comprising 4 cases has revealed that MRI offers a higher level of sensitivity than X-ray imaging when used for musculoskeletal injuries [34]. Nevertheless, X-ray scans are necessary e.g. to evaluate the age of fractures where multiple trauma has been sustained [33].

**Staging and spread of malignant tumors**

Unfortunately, the number of published studies and the number of pediatric patients included within these are limited. Furthermore, the entities and medical issues evaluated are often heterogeneous [4–9, 15, 30, 35]. Despite this, it is still possible to assert that WB-MRI generally produces a higher level of diagnostic accuracy for various organ systems compared to other whole-body imaging techniques, such as scintigraphy, CT, and PET/CT. The question as to when and for which entities WB-MRI should be used exclusively in the context of primary staging, or when it fulfils a supplementary role, cannot be fully answered on the strength of present studies. In our view, and in accordance with the available literature, an indication for using WB-MRI is when the diagnostic algorithm suggests skeletal scintigraphy: osseous Ewing’s sarcoma, osteosarcoma as well as suspected soft tissue sarcoma. Using an adapted methodology, e.g. as proposed in Table 1, soft tissue findings can be accurately diagnosed [6]. A supplementary CT of the thorax, as prescribed by the relevant guidelines, remains an essential part of the clinical routine even when WB-MRI is used during initial staging, although MRI of the lungs is now capable of producing extremely meaningful and reliable diagnostic information [36].

As far as the application of WB-MRI is concerned, neuroblastoma (among other conditions) occupies a special position among malignant tumors. Firstly, whole-body imaging is not generally indicated when the disease is clearly in the early stages or for early-stage nephroblastoma and hepatoblastoma; secondly, receptor scintigraphy involving metaiodobenzylguanidine (MIBG) has always been carried out up until now, although this only provides information about tumor spread if the findings are positive. In our view, and in the opinion of other authors [37], WB-MRI for neuroblastomas should be the preferred choice in two scenarios, in particular: 1) when there are extensive local primary findings in the context of a preoperative assessment of the regional (e.g. thoracoabdominal or spinal) spread and 2) when metastasis is suspected following a negative MIBG scintigram and/or a positive bone marrow biopsy (Fig. 4). The introduction of a new staging system by the International Neuroblastoma Risk Group (INRG) means that the assessment of multicompartiment extension using MRI has a major role to play. Furthermore, WB-MRI appears to offer a higher level of sensitivity than MIBG scintigraphy when used for bone and bone marrow findings. As far as lymphoma staging is concerned, it has been clear for a long time that MRI is capable of identifying more affected regions than conventional imaging (CT, scintigraphy) [5] (Fig. 3). A recent study demonstrates an almost identical level of sensitivity for nodal manifestations (99%) and only a marginally lower level of sensitivity for extranodal manifestations (91%) compared with FDG PET/CT [15]. However, in the case of nodal manifestations and assuming a threshold value of 1 cm, a purely morphological assessment results in the stage being under- or overestimated in individual cases. This limitation could be overcome by applying diffusion-weighted imaging [38, 39]. A study involving 40 patients has illustrated the superiority of FGD PET over MRI for both early and late treatment responses [40]. It is not yet clear whether MR methods such as DWI are capable of taking over this role, although initial results suggest that diffusion-weighted MRI is comparable with PET. Specifically in connection with the MR/PET technology that is now available, this opens up new horizons in terms of diagnosis and treatment monitoring.

As far as we are aware, no studies have been published regarding the use of WB-MRI for the restaging of malignant tumors in children. However, in our experience, significant inferences can be made using WB-MRI findings. Suspected recurrent tumors or metastasis involving symptoms such as pain, fever, and neurological abnormalities or other abnormalities detected in the lab can be swiftly ruled out or confirmed. Examination protocols can be adapted according to the suspected diagnosis, so that the full potential of MRI specificity can be utilized. Naturally, this also applies to renewed post-treatment monitoring, for which alternative regimes need to be validated (Fig. 1).

**Organ-focused diagnostic accuracy of WB-MRI**

Several studies on adults and children have demonstrated that, irrespective of the methodology selected, WB-MRI offers a significantly higher level of sensitivity than skeletal scintigraphy when used for malignant bone- and bone marrow lesions [4, 7, 12, 21, 22]. Compared to PET/CT, classifying the data is more difficult. In this respect, benchmark setting has an important role to play. Furthermore, it has been sufficiently well established that PET reveals considerable differences between specific tumor entities and the associated grading with regard to hypermetabolism, meaning that there are likely to be differences between the diagnostic accuracy of the two methods. In general, MRI is to be viewed as the imaging method of choice for assessing brain metastases, rather than using CT.
and FDG PET/CT [41]. It has also been demonstrated that, in the case of liver metastases also, WB-MRI offers a comparable or higher level of sensitivity than CT and PET/CT when used with adults [42]. As far as we are aware, no data has been published on the pediatric use of WB-MRI within this particular context. The ability to detect lung metastases depends not only on the technology used but also the size of the foci. In general, a threshold size of 3 to 5 mm at 1.5T can be assumed, with the likelihood of detection increasing with the size of the foci [43, 44]. In the case of those patients where lung metastases have consequences for treatment, the primary approach of our institute is to perform a CT scan after the WB-MRI. However, the use of CT for follow-ups is decreasing. Studies on adults have revealed that conventional WB-MRI offers lower levels of sensitivity and specificity when assessing lymphogenic metastasis of carcinoma than FDG PET/CT [42]. Nevertheless, in the field of pediatric oncology, it should be noted that lymph node metastasis may mean something quite different from what it signifies when dealing with carcinoma in adults. Consequently, lymph node involvement in neuroblastoma is not, per se, automatically associated with a worse prognosis [45] and, in the case of osteogenic sarcoma, lymph node metastases are, per se, to be regarded as rare [46]. In this context, we also wish to draw attention to staging based on lymph node sampling in the case of nephroblastoma [47].

References
20 www.awmf-online.de. (German language)
Summary

WB-MRI enables the effects of diseases on the organ systems of children and young people to be fully detected without exposure to radiation. At our clinic, WB-MRI not merely represents the ideal supplement to established methods. Rather, it forms an integral part of diagnosis because of the extensive diagnostic information that it provides and the way it reduces the need for further forms of imaging. It makes it possible to diagnose the spread of diseases in soft tissue/organs during an examination, thereby allowing risk stratification to take place before embarking on treatment. Hodgkin’s lymphoma constitutes an exception here, as the findings to date have revealed that PET (PET/ICT) is a superior form of technology for this disease, both during initial staging and treatment monitoring.