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AIM AND SCOPE

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EDITORS FOR THIS ISSUE

Cerebellum and neurodegenerative diseases: Beyond conventional magnetic resonance imaging

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Abstract

The cerebellum plays a key role in movement control and in cognition and cerebellar involvement is described in several neurodegenerative diseases. While conventional magnetic resonance imaging (MRI) is widely used for brain and cerebellar morphologic evaluation, advanced MRI techniques allow the investigation of cerebellar microstructural and functional characteristics. Volumetry, voxel-based morphometry, diffusion MRI based fiber tractography, resting state and task related functional MRI, perfusion, and proton MR spectroscopy are among the most common techniques applied to the study of cerebellum. In the present review, after providing a brief description of each technique's advantages and limitations, we focus on their application to the study of cerebellar injury in major neurodegenerative diseases, such as multiple sclerosis, Parkinson's and Alzheimer's disease and hereditary ataxia. A brief introduction to the pathological substrate of cerebellar involvement is provided for each disease, followed by the review of MRI studies exploring structural and functional cerebellar abnormalities and by a discussion of the clinical relevance of MRI measures of cerebellar damage in terms of both clinical status and cognitive performance.

Core tip: The cerebellum is involved in movement control and cognition. Conventional and advanced magnetic resonance imaging (MRI) techniques are widely used for the morphologic evaluation and the microstructural and functional investigation of the cerebellum. In this review we show the state of the art of advanced MRI techniques in the investigation of cerebellum alterations, especially in patients affected by neurodegenerative diseases. In particular, we evaluated advantages, limitations and future perspective of these techniques in multiple sclerosis, Parkinson's disease and Parkinsonisms, Alzheimer's disease and hereditary ataxia, highlighting how the investigation of cerebellum may play a key role in the assessment of motor performance and clinical status of these diseases.

INTRODUCTION

The cerebellum plays a key role in normal brain function and its structural and functional involvement in several neurological diseases is associated with the impairment of both motor and non-motor functions such as cognition, mood and behavior. Imaging studies have been challenged in the past by the complex cerebellar anatomical structure and by its location in the posterior fossa. The advent of high-field magnets and the development of new algorithms for image acquisition and analysis have, at least in part, improved the study of cerebellar structure and functions. This review provides a brief description of cerebellar macro- and microscopic anatomy and functions and focuses on the imaging methods and segmentation tools for the analysis of the cerebellum with emphasis on each method's advantages and limitations. Further, the clinical implications of the cerebellar involvement in neurological diseases such as multiple sclerosis, hereditary ataxias, Parkinson's and Alzheimer's disease are discussed.

Anatomy and function

The cerebellum is a large folded structure consisting of two cerebellar hemispheres, united by a central part known as vermis located in the posterior cranial fossa, lying dorsal to the brainstem and inferior occipital lobes.

It is separated from the cerebrum by a dura mater layer known as tentorium cerebelli and it is surrounded postero-laterally and infero-medially by venous structures, respectively transverse and sigmoid sinuses. The cerebellar cortex is tightly folded and composed by three layers: Molecular layer, Purkinje cell layer and granular layer. Each ridge or gyrus of gray matter is called folium. Underneath these layer of gray matter there is a central mass of white matter, also called corpus midollare or arbor vitae (tree of life), in which are embedded the three deep gray matter cerebellar nuclei: Fastigial nucleus, interposed nucleus (composed by the emboliform and globose nuclei) and dentate nucleus. Three white matter peduncles (superior, middle and inferior) connect the cerebellum to the brainstem, respectively to the midbrain, pons and medulla oblungata. In addition to the above reported macro- and microscopic description, cerebellar structure can be further characterized from a morphologic, phylogenetic and functional perspective. The morphologic classification describes, without any functional basis, a division into three lobes: Anterior, posterior and flocculonodular lobe, while the phylogenetic classification divides the cerebellum into archicerebellum (the most ancient portion), paleocerebellum (developed after archicerebellum) and neocerebellum (the newest portion). The functional classification divides the cerebellum in three regions: Vestibulocerebellum, spinocerebellum and cerebrocerebellum based on the location of the afferent and efferent neurons[1,2]. The vestibulocerebellum corresponds to the flocculonodular lobe, with afferents neurons arising from vestibular nuclei (and some portion of visual cortex) and efferents neurons going to vestibular nuclei. It modulates gait balance and eye movements. The spinocerebellum is formed by the superior and inferior portion of the vermis (with the exception of the nodule) and by a bilateral paravermian portion, located on both sides of the vermis. The vermian part of the spinocerebellum has its afferent neurons arising from the spinal cord, vestibular, visual and acoustic nuclei and has its efferents neurons going through the fastigial nucleus. It modulates head and neck muscle movement as well as trunk and limb proximal portions. The paravermian part of the spinocerebellum has its afferents neurons arising from the spinal cord and trigeminal sensory nuclei, and its efferents neurons going through the interposed nucleus. It completes movement modulation performed by the vermian part, acting on limb distal portions. The cerebrocerebellum is composed by the two cerebellar hemispheres and receives afferent neurons from most of the neocortex (frontal, parietal, temporal, and occipital lobes) through the pons nuclei, sending its efferent neurons to thalamus and cerebral cortex through the dentate nucleus. Functional specificity is granted by the presence of multiple close-loop circuits between cerebral and cerebellar cortex, in which the same brain area that is the major target of output from the cerebro-cerebellar circuit it is also its major source of input[3,4]. In each loop, a specific cortical area projects through the pontine nuclei to a distinct region

of the cerebellar cortex. A specific portion of the dentate nucleus projects then to a specific cortical area through a distinct thalamic region, thus closing the cerebro-cerebellar loop[5,6]. According to studies conducted on primates, the dentate nucleus is topographically organized in a ventral portion, projecting to the prefrontal and posterior parietal cortex, and a dorsal portion, projecting to the motor cortex[7]. Both motor and non-motor domains of the dentate also project to the stria-tum (input stage of basal ganglia processing), raising the hypothesis that cerebellum could also modulate basal ganglia facilitation of voluntary movements[8]. The cerebrocerebellum is the largest part of the cerebellum and accounts for motor planning and motor learning. It is responsible for the transition from controlled to automatic movement: Once motor memories storage has been achieved in the cerebellar cortex, the execution of movements can be triggered by sparse high-level command from cerebral cortex[9]. The ability of the cerebellum to adjust performance according to context, automatically integrating interoception with perception and internal models, does not apply only to movements controls but also to cognitive function, as proved by the occurrence of the cerebellar cognitive-affective syndrome following acute cerebellar lesions of the posterior lobe[10]. In particular, lesions of the posterolateral hemispheres cause cognitive disturbances, while vermis lesions induce behavioral and affective alterations. Cerebrocerebellum is considered an essential modulator of cognitive abi-lities, such as language processing and visuospatial perception (respectively lateralized in the right and left cerebellar hemisphere), as well as high order functions as emotions, behaviors and personality. For example, thanks to its connection to the prefrontal cortex, the cerebellum is involved in the execution of abstract rules that govern response selection, regardless of whether they specifically relate to the selection of actions[11,12].

MRI of the posterior cranial fossa

The posterior cranial fossa (PCF) is located between the tentorium cerebelli and foramen magnum and houses the cerebellum and the brainstem. For its peculiar conformation, small dimensions and contained structures, an accurate study by means of computed tomography (CT) and MRI had always represented a great challenge[13-15]. However, several progresses have been made in this field to avoid the artifacts related to the X-ray beam hardening and the partial volume effects (which is non-linear) caused by the thickness and the irregularity of the skull-base bones. Specifically, the introduction of thin-section spiral multidetector CT, which allows the acquisition of isotropic voxel scans and the use of MRI scanners which allow the acquisition of multiplanar and multiparametric images have contributed to minimize PCF artifacts[16-23]. Most of PCF artifacts are related to blood flow pulsation, inflow/outflow of cerebro-spinal fluid (CSF) and to the brain-bone-air interfaces[24-30].

Artifacts related to vessels blood pulsation generate a signal that is displaced from its correct anatomical position causing a wrong/inappropriate image, also called "ghost" artifacts[31]. Transverse sinuses blood-flow related artifact, which often generate a false image projecting onto cerebellar parenchyma, may lead to an inaccurate or inappropriate interpretation of MR images. Artifacts related to the inflow and outflow of CSF inside PCF from the superior or inferior regions can be minimized by the use of fluid attenuated inversion recovery (FLAIR) images where the CSF signal is nulled out by setting a proper inversion pulse. Unfortunately, these artifacts can still be present if the inversion pulse is spatially selective, allowing a partial suppression[30,32]. As shown by Baksi *et al*[30] and Lavdas *et al*[33] this type of artifact may mimic or hide a brain parenchymal lesion due to the presence, along with the phase encoding direction, of a redundant CSF signal.

The brain-bone-air interfaces artifact represents one of the magnetic susceptibility artifacts that are often present on gradient-echo sequences[28], especially in regions like the skull base, petrous temporal bone, paranasal sinuses and orbits[34,35].

It should be noted that some MRI sequences are more prone to specific artifacts than others: *i.e.*, gradient-echo for susceptibility artifacts (since this sequence does not use a refocusing 180° pulse and signal dephases fast due to field inhomogeneity), inversion recovery (*e.g.*, short tau inversion recovery and FLAIR) for pulsatile artifacts, or 2D time-of-flight for slow-flow artefactual gaps in non-dominant transverse sinus[13,30,33,36]. Nonetheless, some of these artifacts are routinely exploited for diagnostic purposes: Susceptibility weighted images (and in general T2*w gradient-echo images) thanks to its capability of being susceptible to paramagnetic molecules, is able to recognize small amounts of blood degradation products better than other sequences and to distinguish between parenchymal calcifications and blood products[37].

Although the combined use of MRI and CT is recom-mended for the diagnosis of PCF pathologies, MR is preferred to CT in order to evaluate soft tissue structures and to determinate their spatial relationship. While MRI provides higher accuracy in detecting bone marrow changes, brain parenchyma, meningeal infiltration, peri-neural and perivascular spread caused by tumors[14,38,39], CT is more sensitive for the evaluation of bone structures, PFC tumoral and non-tumoral conditions[14,40].

High and ultra-high field MRI

The possibility to study the brain at high and ultra-high field strength has become quite common after the United States FDA approval of MR magnets up to 4 Tesla (T) for clinical use. Currently, the term ultra-high field is used for MR scanners with a magnetic field strength higher than 3T. The application of high and ultra-high static magnetic field strength can improve the visualization of brain anatomy and the study of changes in brain structure and function in several neuropsychiatric diseases. For example, the higher signal-to-noise ratio (SNR) of 3T scanners allows not only to perform faster imaging compared to 1.5T scanners (doubling the strength of the

magnetic field would theoretically lead to a reduction of acquisition time of a factor of four), but also to acquire images at higher spatial resolution, that turns be very useful in the evaluation of small structures such as the cerebellum and the brainstem. It has been shown that higher spatial resolution is helpful in studying the cerebellar cortex, whose thickness is lower than cerebral thickness (< 0.5 mm *vs* the 3-4 mm, respectively)[41,42].

In the research field, 7T MR scanners have proven to be of great use for the identification and the study of each cerebellar folia (which are approximatively 260)[43] and for the study of cerebellar cortical layers. Specifically, the granular and molecular cerebellar layers, whose thickness is approximatively 240 μm, are well recognized and morphologically studied at 7T which has the unique advantage to allow an in-plane voxel size of 120 μm not possible at low-field MR scanners[44]. It is important to bear in mind that higher magnetic fields bring the inherit heavy burden of several artifacts and limitations. For instance chemical shift imaging and susceptibility artifacts, are only some of the artifacts that will increase with high magnetic field. These phenomena, which may cause images misinterpretation, can also be exploited, leading for example to a better separation of metabolites in spectroscopy, a better performance in perfusion weighted imaging, or a better blood products detection. Further, when using high and ultra-high magnetic fields in humans, the specific absorption rate (SAR) should also be carefully evaluated, since it will be quadruplicate with the doubling of the field strength, limiting the use of some sequences and making some parameter modulation necessary in order not to exceed the SAR threshold limit given by International Electrotechnical Commission[45].

MRI techniques available for the study of cerebellum
Conventional morphologic techniques
The remarkable wide range of MR sequences available for the study of the PCF and the cerebellum comes with the difficulty of making the optimal selection based on the clinical or research question. In a standard clinical study the MRI protocol should include a turbo spin-echo (TSE) T1weighted (T1w) sequence to assess shape and dimension of the cerebellum and of the PCF, TSE-T2w and FLAIR-T2w sequences to detect potential white matter (WM) lesions. The choice of an isotropic voxel ($\leqslant$ 1 mm) should always be preferred when available or when a high-resolution multiplanar evaluation is needed. For example, it has been showed that, in comparison to TSE-T2/proton density sequences, isotropic 3D-FLAIR is more accurate in detecting not only white matter lesions but also cortical and infratentorial lesions in patients with multiple sclerosis (MS)[46]. 3D FLAIR has advantages even when acquired at ultra-high magnetic field, such as in the study of Kilsdonk *et al*[47] in which cortical gray matter (GM) lesions were better detected at 7T with 3D FLAIR than with GM-Specific 3D double inversion recovery (DIR) or with 2D-T2w and 3D-T1w. Finally, quantitative T1 and proton density (ρ) magnetic resonance imaging at 3T

provide a good visualization of deep cerebellar nuclei, like dentate nuclei at 1.5T[48]. Similarly, susceptibility weighted imaging (SWI) allows a better detection of the dentate nuclei at 1.5T while higher magnetic field allows visualization of the dentate wall corrugation, which is the iron-poorer dorsal portion of it[49].

Volumetric techniques
There is an ever-increasing interest in the evaluation of cerebellar volume as a potential correlate of motor and cognitive performance and as a biomarker of progression and/or treatment outcome in neurodegenerative disorders[50].

Several computerized methods with specific advantages and limitations are available to perform cerebellar segmentation, lobule parcellation and thus to assess global cerebellar volume, regional or lobular volumes and GM and WM volume. Although manual volume segmentation is considered the "gold standard", this option is extremely time-consuming and its reliability may vary with the experience of the raters[51]. Several semi-automatic computerized methods have been developed and validated in order to minimize operator-dependent limitation. We will focus on the methods that have been more extensively applied in clinical studies and will describe each method's advantages and limitations.

SUIT (spatially unbiased atlas template of the cerebellum and brainstem) is a Statistical Parametric mapping software (SPM) toolbox for MATLAB, based on a nonlinear coregistration of MRI images to a high-resolution cerebellum template obtained from images of healthy controls[52]. This method allows the parcellation of the cerebellum in at least 28 lobules, thus measuring GM volume for each lobule and the global GM volume as the sum of all lobule volumes (Figure 1). SUIT has been applied to the study of several diseases such as multiple sclerosis (MS), autism spectrum disorder, attention deficit hyperactivity disorder, developmental dyslexia and primary craniocervical dystonia, and it has been shown that it has higher sensibility to volume changes than conventional whole-brain voxel-based morphometry (VBM) methods[50,53,54]. The main advantage of SUIT is that it provides an optimal overlap of the cerebellar lobules, preserving anatomical details, and thanks to its cropping step avoids results bias from supratentorial structures[50,53,54]. However, Bogovic *et al*[51] reported that SUIT accuracy may decrease in patients with severe cerebellar atrophy especially with regard to lobule specific segmentation.

Cerebellar analysis toolkit (CATK) is based on a Bayesian framework of FMRIB's Integrated Registration and Segmentation Tool[55]. Using hand-delineated examples, active appearance models are created in order to perform cerebellar labeling and segmentation. CATK has shown a high reliability (Intraclass Correlation Coefficients, ICCs, of 0.96 for test-retest) a good manual segmentation agreement (ICC 0.87) and a better performance than other softwares, such as SUIT (v 2.7) and Freesurfer when compared to manual segmentation

Figure 1 SUIT atlas (top) and template (bottom) showing the central cerebellar slice in the sagittal, coronal and axial planes. The atlas does not explicitly identify white matter apart from the dentate nuclei (from Ref. [55]).

Figure 2 Comparative plots of total cerebellar volumes and combined vermal areas are shown against manually labeled examples, in 20 subjects with (A) CATK, (B) SUIT and (C) Freesurfer. Both test and retest are plotted, illustrating the repeatability of each method (from Ref. [55]).

(gold standard). However, the main limitation when compared to other softwares, is that CATK does not allow cerebellar hemisphere parcellation, although Price *et al*[55] in their paper stated a pending further improvement which would solve this issue and which would give higher image delineation (Figure 2).

ECCET is a semiautomatic toolkit based on a manually drawn region of interest ROI software. It is able to perform a fast semiautomatic segmentation after a manual outline drawing of few brainstem slices. It allows, when needed, manual editing in a 3D volume rendering mode (https://www.eccet.de/projects/neuro_en.html). This method has shown a good interobserver (ICC =

0.98, 95%CI = 0.74-0.99) and test-retest reliability (ICC = 0.99, 95%CI = 0.98-0.99) and the capability of avoiding some segmentation errors such as the inclusion of venous sinuses without the need of manual editing[56].

Unfortunately, to date, all the above-mentioned softwares provide pipelines for one time point evaluation (cross-sectional), but not for longitudinal analysis along time. This gap has been fulfilled by Freesurfer, which is a software that allows a reliable automatic whole brain segmentation, with up to 40 subcortical structures, labelling each voxel in a normalized space of the brain volume[57]. In addition to the cross-sectional analysis, Freesurfer comprises a longitudinal stream where each

Figure 3 Reconstruction of cerebellar white matter tracts using constrained spherical deconvolution. Sagittal rotated view (A), superior axial view (B), and coronal view (C) show each fiber bundle manually colored: Superior cerebellar peduncle (blue), middle cerebellar peduncle (red), and hemispheric cerebellar tracts (yellow). The tridimensional sagittal rotated view shows color-coded cerebellar hemispheric streamlines according to the principal eigenvector's direction (with permission of Springer, from Ref. [63]).

time-point is co-registered to a subject-specific template by creating an average segmentation along time points, resulting in volume and GM thickness estimation[57]. Although Freesurfer presents this important advantage, it does not allow sub-regional segmentation in cerebellar lobules[55]. Moreover, manual editing of segmentation outputs is needed in order to improve volume evaluation reliability[58]. Although the editing can be performed manually, resulting in a very time-consuming (up to 4h) and operator-dependent approach, Wang *et al*[58], in a recent paper, proposed an accurate and efficient new machine-learning based method in order to overcome this issue.

Diffusion weighted imaging and fiber tractography

Diffusion magnetic resonance imaging (dMRI) is a MRI technique able to detect water molecules diffusion inside brain tissue. While diffusion of water molecules in GM is isotropic, diffusion in WM is anisotropic, *i.e.*, it occurs in one main direction due to the presence of myelin barriers[59]. The evaluation of diffusion in a three dimensional space and along at least 6 directions, allows the creation of a diffusion tensor matrix, which provides the bases of tractographic reconstruction of brain neural circuitry[60]. Diffusion tensor imaging (DTI) and more advanced approaches (such as diffusion spectrum imaging or constrained spherical deconvolution) have been applied to determine cerebellar pathways and their connection with other supratentorial areas[61-63] (Figure 3). Although conventional DTI techniques are the most used technique to reconstruct cerebellar pathways by means of tractography, they are also well known for their limitations in the study of connectivity. DTI, indeed, is limited by the inability to discriminate different fiber populations with complex configurations at a voxel level (kissing fibers, bridging fibers, merging fibers, crossing fibers), thus leading to artefacts in fiber reconstructions and connectivity evaluations. Methods such as diffusion spectrum imaging and Q-ball imaging have been developed over the last few years to overcome these limitations; however, the more complex hardware set up and the longer acquisition times have limited so far their application in the clinical setting[64]. Other promising techniques, such as diffusion kurtosis imaging (DKI), neurite orientation dispersion and density imaging (NODDI) and constrained spherical deconvolution can be performed within clinically feasible acquisition times[65] (Figure 3). Moreover, all these techniques can be analyzed with both deterministic and probabilistic fiber reconstruction models. While deterministic models reconstruct streamlines (virtual fiber tracts) taking into account the principle eigenvector of fractional anisotropy (FA) in each voxel, probabilistic models generate a connectivity map from a larger numbers of possible pathways, obtaining the probability of each voxel to be connected to another[66]. Regardless of the used approach, tractographic output can be used not only to reconstruct the spatial configuration of fiber tracts but also to measure diffusion parameters (*i.e.*, FA or mean diffusivity) at voxel level. However, it has been proved that, not only parameters' quantification but also the accuracy of tractographic results may be affected by the poor quality of the acquired data that can lead to the detection of false connections or to miss detection of a real connections between structures[59]. Therefore, a better data quality, optimized in terms of SNR, spatial resolution, number of diffusion directions, and number and values of *b* values, with the choice of a proper tractography method, may improve the method performance avoiding

inaccuracy in structural connectivity analysis[67]. Since cerebellar pathways tracking is particularly difficult due to the presence of sharp turning angles along their crossing, the assessment of cerebro-cerebellar and intra-cerebellar connectivity could especially benefit from data quality improvement[61,63].

Resting state and task related fMRI

Functional MRI (fMRI) is based on the detection of the blood oxygen level-dependent (BOLD) changes that take place as a consequence of neuronal activity. An increase in neural activity leads to an increase in the arterial blood flow, in order to increase the activity itself. To this increase in the amount of oxygenated blood does not correspond a similar increase in oxygen extraction at the level of capillary bed, leading to a relative decrease of deoxyhemoglobin levels, that directly affects the MR signal.

fMRI experiments can be divided in task and rest-related. The first measure brain activity during a task performance, the second evaluate the interaction between different brain regions without the execution of any specific task, in a rest condition (resting-state fMRI - RS-FMRI).

With regard to task-based fMRI studies, two main experimental paradigms are commonly used[68]. The first one is the so-called block design experiment, in which stimuli are presented to the subject in blocks of variable length alternated to blocks of rest, in which the stimulus is removed. MRI signals are then compared between the two conditions, in order to extrapolate the areas that show more activation during the execution of the task. The second is the event-related experimental design, in which the stimuli and the resting blocks are not alternated in a set sequence, but the administration, as well as the duration of the stimulus, are randomized.

RS-fMRI experiments can be analyzed using two major approaches. The first one is the seed-based approach, in which a region of interest is selected and the corresponding time-activity curve is extracted. Then, voxels with similar activation are searched whole brain, and are assumed to be functionally correlated to the chosen seed[69]. The second method is the independent component analysis (ICA), a mathematical algorithm that allows to subdivide a multivariate and noisy signal in its subcomponents[70]. In this approach, no a priori seeds are chosen, but the operator is asked to identify the component of interest, and discard those obtained from noise or physiological signals. ICA analysis has allowed the identification of preferential connections between specific cerebral structures, that take the name of resting state networks[71]. Cerebellar lobules are not only hubs of several of these resting state networks (*i.e.,* lobule IX in the default mode network, crus I and II in the executive control network or lobule VI in the salience network)[72], but also an entire and separate cerebellar network is recognized among the major resting state networks[71].

With this knowledge, it is easy to understand how future improvement is warranted to increase the of

functional changes with respect of the cerebellar lobular anatomy. In particular, the possibility of increasing spatial resolution in fMRI experiments is a future challenge for investigating cerebellar functional connectivity due to the characteristic lobular anatomy. The increase in spatial resolution could further help in elucidating the exact functional lobular topography of the cerebellum, with regards to specific motor and cognitive functions[73].

Proton magnetic resonance spectroscopy

Proton magnetic resonance spectroscopy (^{1}H-MRS) is an analytical method that allows the investigation of brain metabolites. Every metabolite at sufficient concentration level generates a specific peak in function of its resonance frequency[74]. Since metabolic abnormalities occur earlier than structural MRI alterations, ^{1}H-MRS can provide a valid tool for early diagnosis and for monitoring of neurological diseases[75].

The most commonly studied brain metabolites are the N-acetylaspartate, a marker of neuroaxonal integrity, choline containing compounds, a marker of membrane turnovers, creatine/phosphocreatine, a marker of energy metabolism, and myo-inositol, a marker of astroglial activation. From a quantification point of view, metabolites' levels are expressed as absolute quantifications or as ratios where the denominator is the creatine level which is assumed to be stable in normal as well as in many pathologic states[76].

Although the infratentorial structures are often involved in neurodegenerative processes, strong B0 inhomogeneities due to nearby skull bone, scalp lipids and tissue/air interfaces constitute a technical challenge for the ^{1}H-MRS acquisition. In addition, the small size of cerebellum increases the risk of partial volume effects[77], which can be accounted for by combining spectroscopic data with structural MRI segmentation[78]. Nevertheless, ^{1}H-MRS of the infratentorial fossa is feasible[79] and could provide an early biomarker of neuronal damage in cerebellar diseases, with even increased specificity when used in combination with other techniques[80].

Perfusion MRI

Perfusion weighted imaging (PWI) allows the measurement of blood perfusion in brain tissue and it is categorized as: "minimally invasive" if requiring gadolinium injection (*i.e.,* dynamic susceptibility contrast MRI or DSC-MRI and dynamic contrast enhanced MRI or DCE-MRI) or "non-invasive" if no contrast agent is needed (*i.e.,* arterial spin labelling or ASL-MRI)[81]. Data from either technique above is subsequently processed and normalized to estimate the well-known perfusion values: cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), Ktrans and *etc.,* which are all representable on parametric color maps.

Cerebellar tissue is subject to a great blood supply, and measurement of local variations of blood request/availability is clinically relevant in the assessment of neurodegenerative diseases. Specifically, cerebral blood flow (CBF) alterations (*i.e.,* general or local CBF

reduction) appear to precede structural abnormalities (for example: atrophy). Moreover, the cerebellum has been used as a reference region for intensity norm-alization of "relative" Cerebral Blood Volume (rCBV), based on the assumption that its CBV is not affected in neurocognitive disorders[82]. Although hard to eradicate, this assumption is nowadays obsolete, as alternative reference regions have recently been proposed and validated[83].

With respect to the study of the cerebellum and the PCF, DSC-MRI provides higher spatial resolution, high sensitivity in transit time and whole-brain coverage in shorter scan times, and it is preferred in all situations where a fast assessment is required. DCE-MRI has the advantage of reducing artifacts especially for the measurement of CBV and Ktrans. ASL-MRI is often preferred in the study of neurodegenerative diseases for its complete lack of invasiveness, vessel selective capability[84] and the best accuracy in absolute tissue perfusion quantification[81]. Particular care in placing the "labeling plane" is essential to avoid artifacts in the lower cerebellar sections[85]. Another limit of ASL-MRI is WM assessment, which is particularly challenging due to the low blood transit and the consequent low SNR[86].

Unfortunately, despite the theoretical indications of each method, in the routine clinical settings, is the availability and practicality of the techniques that forces the choice, rather than its potential performance. This could explain the more frequent use of DSC and DCE imaging, faster, easy to perform and widely installed on most clinical scanners, compared to the use of ASL.

MRI AND CLINICAL APPLICATIONS ON NEURODEGENERATIVE DISEASES

Multiple sclerosis
Multiple Sclerosis (MS) is an inflammatory/demyelinating disease of the central nervous system (CNS) chara-cterized by heterogeneous symptoms and signs that can present a relapsing remitting (RR) or a progressive course. In 1877 Jean Martin Charcot first described the disease as a triad of symptoms consisting of nystagmus, dysartria and ataxia[87], thus underlining the dominant role of cerebellar deficits. Not only is the cerebellum frequently involved by the disease pathological processes but the presence of MRI visible infratentorial lesions provides high specificity to the diagnostic criteria for MS[88]. Indeed, 31% of patients with a clinically isolated syndrome (CIS) present with at least one infratentorial lesion and about 20.5% with a cerebellar lesion. The detection of a cerebellar lesion at onset is associated with an increased risk of conversion to MS[89]. In patients with a clinically defined MS, cerebellar lesions have been described in up to 49% of cases and patients with a progressive form have an increased number of PCF lesions when compared to patients with a RR type[90]. Disease pathology involves not only the cerebellar WM but also the GM; in fact, cortical cerebellar lesions are

observed in patients with MS, even at the early stages of the disease, and correlate with the cerebellar functional score of the expanded disability status scale (EDSS)[91]. Longitudinal studies have shown cerebellar GM volume loss and an increased number of cortical lesions in both CIS, RR and progressive patients[92,93].

Volumetry changes
Along with cerebral atrophy, also cerebellar volume loss occurs in patients with MS, at all the disease stages. Edwards and coworkers found reduced global cerebellar volumes in patients with a secondary progressive (SP) form when compared to RR patients, and in both groups when compared to healthy controls[94]. However, in a more recent study, when compared to healthy controls only MS patients with a SP form, but not RR or patients with benign MS, showed lower cerebellar volumes[50]. When cerebellar WM and GM are considered separately, study results are discordant. Ramasamy *et al*[95] found a reduced cerebellar WM but not GM volume in CIS and MS patients when compared to healthy controls. However, Anderson and coworkers detected a reduced cerebellar GM volume in RR and SP MS patients versus controls and only a trend of significance, when comparing WM volumes, between SP MS and controls[96]. In the latter study, cerebellar GM and WM volumes were related with performance at the nine-hole peg test, highlighting the clinical relevance of measures of cerebellar volumes. A greater loss of GM in patients with a progressive course and its correlation with measures of clinical outcome are findings mirroring the process at the whole brain level.

Structural connectivity changes
DTI has been widely used for the study of cerebellar WM, in particular to evaluate the damage of the cerebellar peduncles and its clinical impact. Anderson *et al*[97] found reduced FA and increased radial diffusivity values in the middle cerebellar peduncle in patients with primary progressive (PP) MS; DTI metrics correlated with clinical impairment both of the upper and lower limbs. A study on a cohort of patients at different stages of the disease revealed greater mean, axial and radial diffusivity and reduced FA in MS patients, when compared to healthy controls, at the level of the middle and superior cerebellar peduncles; moreover, when compared to cerebellar peduncles T2 lesion load or atrophy, diffusivity measures better distinguished between patients with a worse EDSS score[98]. Disability in RR patients also correlated with the FA values of the cerebellar normal appearing WM[99].

Functional MR changes
MS is characterized by a reorganization of the functional connectivity. Functional MR studies with motor tasks revealed an increased activation in several cortical areas within the sensorimotor network, including the cerebellum, in patients when compared to healthy controls[100,101] (Figure 4). The altered functional cerebellar connectivity could represent a compensatory mechanism to WM

Figure 4 Motor training-dependent functional magnetic resonance imaging signal changes in healthy volunteers and in MS patients. Maps of training-related functional magnetic resonance imaging signal changes are reported in healthy volunteers (indicated as controls) and in patients ($Z > 2.3$, $P < 0.05$, cluster corrected). Comparison between patients and controls show a higher signal reduction in the patients in regions corresponding to the secondary visual areas (V2 and V4) and in the cerebellum (lobule V-VI) (from Ref. [100]). V5: Visual cortex; R5: Right hemisphere; fMRI: Functional magnetic resonance imaging.

damage; accordingly, in RR MS patients a damage in the dentatorubrothalamic tract, assessed by means of DTI, was related to an increased functional connectivity between right sensorimotor cortex and cerebellum[101]. The cerebellum activation is also increased in patients with greater perceived fatigue where fatigue is conceived as a correlate of an increased resource demand for motor activities[102].

Cerebellum and cognitive impairment
Besides the classical motor clinical features associated with cerebellar dysfunction, lately more attention has been focused on the role of cerebellum in cognitive impairment. MS patients with cerebellar signs perform worse at the symbol digit modalities test (SDMT) and the paced auditory serial addition test (PASAT); moreover, the PASAT execution is predicted by cerebellar lesion volume[103]. In particular the posterior cerebellum has been implicated in cognitive processing; in MS patients, a reduced posterior volume predicted a worse cognitive performance[50]. Information processing speed impairment has been associated with GM atrophy of the posterior lobules, especially at the level of the vermis VI[104]. As with

motor tasks, a functional reorganization could also occur in response to the impairment of cognitive processes. Recently, a greater functional connectivity of the dentate nucleus with frontal and parietal cortical areas was detected in MS patients versus controls[105,106] and the increased connectivity was related to a better cognitive performance. Moreover, an increased connectivity between anterior cingulate cortex and cerebellum was also associated with a better performance at PASAT in CIS, RR and SP patients versus controls and authors suggested an adaptive mechanism[107].

Dentate nuclei hyperintensity
The hyperintense signal on T1-weighted images at the level of dentate nucleus has been detected in almost 50% of patients with a secondary progressive phase of the disease, in contrast to what found in the RR or PP form[108]. Although this change in signal could be related to the reduction in the number and axosomatic synapses in the dentate nucleus as documented by pathological studies[109], an association between the nuclei hyper-intensity in T1-weighted images and Gadolinium retention has recently received greater attention[110].

Figure 5 Graphic representations of Fractional Anisotropy mean decrement along X (red), Y (green), and Z (blue) direction samplings of Parkinson's disease patients compared to healthy subjects. Colors follow principal eigenvector's directions (with permission of Springer, from Ref. [63]). PD: Parkinson's disease.

PARKINSON'S DISEASE AND OTHER MOVEMENT DISORDERS

Parkinson's disease
Parkinson's disease (PD) is a neurodegenerative disorder pathologically characterized by the loss of dopaminergic neurons of the pars compacta of the substantia nigra; clinical features include motor, in particular rest tremor, bradykinesia and rigidity, and non-motor symptoms. The role of cerebellum in the physiopathology of this frequent neurodegenerative disorder has received increasing interest. Studies on monkeys discovered direct anatomical connections between cerebellum and basal ganglia, in particular with the subthalamic nuclei and the striatum[8,111]. Such findings have been confirmed with a DTI study in humans[112]. Interestingly, patients receiving deep brain stimulation had a clinical benefit when the electrode was positioned nearby one of these basal ganglia-cerebellum connections, in particular the dentato-thalamic tract.

Volumetry changes
Cerebellar atrophy has been documented in patients with PD. MRI morphometric studies have shown cerebellar volume loss at the level of the left cerebellum when compared to controls[113], and at the level of the right quadrangular lobe and declive in patients with tremor compared to those without, thus suggesting a possible role of cerebellum in the genesis of rest tremor[114]. A more recent study confirmed cerebellar GM atrophy, which correlated with a reduced connectivity between cerebellum and sensorimotor, dorsal attention and default networks and an increased connectivity with the frontoparietal network[115]. Altogether these results confirm the role of cerebellum in the physiopathology of motor symptoms in PD. Atrophy occurs since cerebellum is involved in the neurodegenerative pathological process of the disease, with the accumulation of α-sinuclein and neuronal loss.

Structural connectivity changes
DTI studies have detected decreased FA in the cerebellar hemispheres of patients with PD when compared to healthy controls (Figure 5)[63,116]. Although no differences in DTI parameters in superior and middle cerebellar peduncles have been detected between patients with PD and healthy subjects[63], DTI metrics of the superior cerebellar peduncles could be helpful in differentiating PD and other parkinsonism, such as progressive supranuclear palsy (PSP)[117].

Functional MR changes
Cerebellar hyperactivation has been showed and confirmed in several studies on patients with PD, both with akynesia-rigidity subtype and with tremor subtype. Whether the contribution of cerebellum is mostly an adaptive mechanism or a primary pathologic change of the disease is still a matter of debate. In a resting-state fMRI study, Wu *et al*[118] observed an increased activation

in the cerebellum in PD patients versus healthy controls; moreover, the altered pattern of activation was normalized after levodopa administration. A substitutive hyperactivity of the cerebello-thalamo-cortical circuit has been proposed as a mechanism to compensate the hypoactivation of the striato-thalamo-cortical circuit in hypokinetic patients; however, for PD tremor subtype, a dysfunction in the cerebello-thalamo-cortical circuit has been advanced as a physiopathologic mechanism for rest tremor[118,119].

Multiple systemic atrophy

Multiple systemic atrophy (MSA) is a movement disorder, with a poor prognosis, which has two clinical phenotypes: one with a prominent akinetic-rigid parkinsonism (parkinsonian variant, MSA-P) and the other with a progressive ataxia (cerebellar variant, MSA-C). It has been suggested that imaging of cerebellum could be useful in the differential diagnosis of MSA. Atrophy of the middle cerebellar peduncles is frequent in patients with MSA and reduced volume of basal ganglia, middle and inferior cerebellar peduncles and pons have been found in the parkinsonian subtype of MSA, when compared with controls and PD patients[120]. Moreover, both MSA-P and MSA-C patients were found to have higher MD values in cerebellar hemispheres when compared to PD and PSP patients[121]. Brainstem and middle cerebellar peduncles atrophy have also been found to be very specific for the cerebellar subtype of MSA when compared to idiopathic late-onset cerebellar ataxia[122].

Dystonia

Dystonia is a disorder characterized by sustained and abnormal spontaneous muscle contractions. It can be classified according to the etiology (inherited or acquired) or the topographic distribution. Cerebellar dysfunction has been implicated in the physiopathology of dystonia. Morphological cerebellar abnormalities have been reported in 14% of patients with cervical or segmental dystonia[123]. Focal cerebellar lesions have been associated with dystonia and cerebellar atrophy has been described in patients with writer's cramp[124]. Besides morphological studies, several functional studies have shown an increased activation in cerebellum in patients with writer's cramp[125] and in patients with blepharospasm[126].

Hereditary ataxias

Ataxias are an heterogeneous group of conditions characterized by slowly progressive incoordination of gait, often associated with a reduction of coordination of hands, speech, and oculomotor signs[127]. Ataxias can be subdivided, basing on the etiology behind the development of the condition, in three major groups: acquired ataxias, nonhereditary degenerative ataxias and hereditary ataxias (HA), which can be further divided in dominant and recessive[127]. Spinocerebellar ataxia type 3 (SCA3) is the most frequent type of dominant ataxia, followed by SCA2 and SCA6, while Friedreich Ataxia (FRDA) and ataxia-telangiectasia (AT) are respectively the first and the second most common type of recessive ataxias, with FRDA that is, independently from the inheritance, the most frequent ataxia in terms of incidence[128].

Volumetry changes

Atrophy of the cerebellar cortex is not a distinguish feature of all the HA. Different patterns of atrophy can be identified, depending on the degree of cerebellar atrophy and the involvement of midbrain structures. In particular, SCA3 and SCA2 are characterized by the presence of cortical, cerebellar and pons atrophy[129]. On the other hand, SCA6 shows a pattern of pure cortical cerebellar atrophy, with a relative sparing of midbrain structures[130]. With regard to recessive ataxias, FRDA is characterized by a prominent spinal cord atrophy[131] compared to cerebellar cortical structures[132], with atrophy that, when significant, affects mainly the lateral cerebellar hemispheres[133]. Finally, AT is characterized by superior cerebellar hemispheres atrophy, in particular of the vermis, which appears hypoplastic in its inferior portion[134-137].

Structural connectivity changes

Unlike volumetric measures, almost all the major HA show similar microstructural changes affecting infratentorial WM tracts. Indeed, SCA3 patients showed a significant FA reduction in different cerebellar areas, including both anterior and posterior cerebellar lobes, nodule, culmen, dentate, fastigial, lingual, and all three cerebellar peduncles, as well as in pons and midbrain[138]. These abnormalities were correlated with clinical variables, such as scale for the assessment and rating of ataxia (SARA) scores or disease duration[138,139]. In SCA2, significant microstructural changes were present in cerebellar WM, brainstem and cerebellar peduncle[140,141], with changes in the mode of anisotropy that were lower in SCA2 patients compared to healthy controls in a longitudinal evaluation[141]. Unlike in SCA3, no correlation with clinical variables emerged for these infratentorial clusters of microstructural changes in SCA2. In FRDA, microstructural changes were found to affect predominantly cerebellar peduncles[142-145], as well as cerebellar hemispheres and vermis[144] and to be associated with clinical disability[142-144]. Finally, in AT patients a reduction of mean diffusivity was reported within cerebellar peduncle regions[146] (Figure 6).

Functional MR changes

Similar to structural connectivity, functional connectivity changes are present in almost all HA. However, these modifications are not limited to a somehow expected reduction of FC in HA patients compared to healthy controls, but also increase in FC are reported in some HA, probably due to compensatory phenomena, reflecting the known heterogeneity of this group of conditions. Indeed, a significant increase of activation of the ventral part of the dentate nuclei, but not of the cerebellar cortex, was found during an hand-movement task fMRI experiment in SCA3 patients compared to healthy controls, suggesting a

Figure 6 Somatosensory motor tracts in a representative control and ataxia telangiectasia (A-T) subject (age 23). Control tracts are displayed in the first and second rows comprising the left sagittal (first row) tracts, left and right coronal (second row) corticospinal (CST) and somatosensory tracts, and left coronal (second row) cortico-ponto-cerebellar (CPC) and cerebellar-thalamo-cortical (CTC) tracts. Patient tracts are displayed in the third and fourth rows comprising the left sagittal (third row) tracts, left and right coronal (fourth row) CST and somatosensory tracts, and left coronal (fourth row) CPC and CTC tracts. Tract colors are based on the direction of water diffusion (Blue: Ascending–descending diffusion; Red: Left–right diffusion; Green: Anterior–posterior diffusion). Compared to motor pathways in age matched controls, A-T CST and somatosensory pathways display a morphological thinning of tracts at the level of the thalamus in the coronal view. In addition, A–T CPC and CTC pathways display morphological thinning of tracts in the cerebellum at the position of the medial cerebellar peduncles (from Ref. [147]).

compensatory phenomenon of the *cerebrocerebellum* to a prominent damage of the *spinocerebellum*[147]. Moreover, a recent fMRI study, involving a bilateral audiopaced thumb movements paradigm, showed a diminished movement synchronization in SCA3 patients[148] that would suggest the presence of functional reorganization of the motor network and a potential role of fMRI as a tool to monitor the disease[148]. In SCA2, a seed-based fMRI analysis showed a decreased putaminal connection with the pons, together with a decreased connectivity between the rostral sensorimotor area and both cerebellum and pons[149]. Furthermore, a decrease of the functional connectivity of the cerebellar components of the default mode, executive and right fronto-parietal networks was described in SCA2, unrelated to the cortical gray matter volume loss[150], with some authors that showed a significant correlation between both motor and neuropsychological scores and the abnormal cerebellar functional connectivity strength[151]. In SCA6 patients, a significantly higher activation at the level of the lobules V and VI, as well as in the dentate

nuclei, was detected compared to controls when performing a hand-movement task fMRI experiment[147]. Likewise, in FRDA patients the same motor task showed a higher activation mainly prominent at the level of lobules V and VI and dentate nuclei, compared to healthy control[147]. Furthermore, a working memory task fMRI experiment showed that FRDA patients had a decrease functional connectivity between cerebellum and prefrontal areas, with a correlation between disease severity and cerebellar dysfunction[152].

Alzheimer's disease
Alzheimer's disease (AD) is the most common cause of dementia and it is preceded by a predementia phase, called mild cognitive impairment (MCI), characterized by a deficit in one or more cognitive domains. The role of cerebellum involvement in AD is controversial. While a volumetric MRI study in patients with AD, MCI and healthy controls found a volume loss at the level of the posterior cerebellar lobes in AD patients compared to healthy

Figure 7 Significant cerebellar GM and WM loss in Alzheimer's disease. A: Significant cerebellar GM loss in Alzheimer's disease (green) and dementia with Lewy bodies (red) relative to healthy older subjects; B: Significant cerebellar WM loss in AD relative to healthy older subjects; C and D: Whole brain maps depicting significant regions of GM (C) and WM (D) loss between groups. Results superimposed on a MRI T1 brain template image (L = left, R = right). AD: Alzheimer's disease; DLB: Dementia with Lewy bodies (from Ref. [154]). GM: Gray matter; WM: White matter.

controls, no significant differences were showed between patients with MCI and healthy controls[153]. Another study detected a regional GM atrophy in cerebellar lobule VI in patients with AD[154] (Figure 7). These findings were not confirmed[155] in a more recent study, suggesting that the decrease of cerebellar volume could be influenced by the patients' age. This is supported by the findings of cerebellar atrophy in patients with a late-onset, but not early-onset AD[156] and by the presence of cerebellar atrophy in cognitively preserved old subjects[157].

CONCLUSION

The cerebellum plays a key role in the control of motor and cognitive functions due to the multiple connections to the forebrain, the thalamus, and the spinal cord. However, the cerebellar complex anatomical structure and its

location in the posterior fossa represent a challenge for *in vivo* structural and cerebellar neuroimaging. The recent advancement in MRI hardware and software and the development of more accurate and robust algorithms for image analysis have improved the structural and functional assessment of the cerebellum. This is of paramount importance due to the frequent and early involvement of the cerebellum in several neurodegenerative diseases. Therefore, MRI measures of cerebellar structure and function could serve as early and sensitive marker of disease progression and help monitor response to current or experimental treatments.

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Lymph node imaging in initial staging of prostate cancer: An overview and update

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Abstract

Accurate nodal staging at the time of diagnosis of prostate cancer is crucial in determining a treatment plan for the patient. Pelvic lymph node dissection is the most reliable method, but is less than perfect and has increased morbidity. Cross sectional imaging with computed tomography (CT) and magnetic resonance imaging (MRI) are non-invasive tools that rely on morphologic characteristics such as shape and size of the lymph nodes. However, lymph nodes harboring metastatic disease may be normal sized and non-metastatic lymph nodes may be enlarged due to reactive hyperplasia. The optimal strategy for preoperative staging remains a topic of ongoing research. Advanced imaging techniques to assess lymph nodes in the setting of prostate cancer utilizing novel MRI contrast agents as well as positron emission tomography (PET) tracers have been developed and continue to be studied. Magnetic resonance lymphography utilizing ultra-small super paramagnetic iron oxide has shown promising results in detection of metastatic lymph nodes. Combining MRL with diffusion-weighted imaging may also improve accuracy. Considerable efforts are being made to develop effective PET radiotracers that are performed using hybrid-imaging systems that combine PET with CT or MRI. PET tracers that will be reviewed in this article include [18F]fluoro-D-glucose, sodium [18F]fluoride, [18F]choline, [11C]choline, prostate specific membrane antigen binding ligands, [11C]acetate, [18F]fluciclovine, gastrin releasing peptide receptor ligands, and androgen binding receptors. This article will review these advanced imaging modalities and ability to detect prostate cancer metastasis to lymph nodes. While more research is

needed, these novel techniques to image lymph nodes in the setting of prostate cancer show a promising future in improving initial lymph node staging.

Key words: Prostate cancer; Staging; Magnetic resonance imaging; Ultra-small super paramagnetic iron oxide; Molecular imaging; Positron emission tomography; Lymph nodes

Core tip: Accurate nodal staging at time of prostate cancer diagnosis is crucial in determining a treatment plan for the patient. This review article highlights the newest imaging techniques that have been and are being developed for imaging of lymph nodes in the initial staging of prostate cancer. Magnetic resonance lymphography utilizing ultra-small super paramagnetic iron oxide has shown to detect metastatic disease in normal sized lymph nodes. Considerable efforts are being made in molecular imaging to develop effective positron emission tomography radiotracers that may be combined with computed tomography or magnetic resonance to detect prostate metastasis as well as potential therapeutic applications.

INTRODUCTION

Prostate cancer is the most common cancer in American men and is associated with a significant likelihood of cure when patients have organ-confined disease through the use of local definitive therapy such as radical prostatectomy or radiation therapy[1]. However, once prostate cancer spreads beyond the gland to the lymphatic tissues, the opportunity for cure with a local therapy is lost in most cases and significantly diminished in others[1]. Due to the adverse prognostic implications associated with lymph node metastasis, detection of clinically occult lymph node metastasis is of extreme importance[2]. Risk assessment tools are used to predict patients who are at risk for higher pathologic stage and use inputs such as PSA, biopsy Gleason sum, percent positive biopsies, and magnetic resonance imaging (MRI) findings[3-5]. The prostate health index (PHI) test utilizes three forms of PSA (total PSA, free PSA and p2PSA) and the 4K panel (total PSA, free PSA, single chain intact PSA, and human kallikrein 2) have been shown to more accurately predict higher-grade prostate cancer[6,7]. Patients who are deemed low risk, defined as a predicted < 5% (or in some more conservative guidelines ⩽ 2%) for lymph node metastasis usually undergo definitive treatment with curative intent without any further radiological imaging or lymph node dissection[1]. Patients determined to be at higher risk for systemic disease need to undergo nodal staging. The most reliable method is pelvic lymph node dissection; however, this is invasive and may be associated with increased morbidity and risk of complications[1]. Furthermore, pelvic lymph node dissection is less than perfect as several studies have reported positive lymph nodes outside the routine dissection template[8-11]. Even extended pelvic lymph node dissections have been shown to miss up to 13% of metastatic lymph nodes[12].

Cross sectional imaging is a non-invasive tool utilized for nodal staging and largely relies on morphologic characteristics such as size and shape. A meta-analysis found a pooled sensitivity of 42% and specificity of 82% for computed tomography (CT) imaging and similar 39% sensitivity and 82% specificity for MR imaging for detection of metastatic lymph nodes[1]. Utilizing CT and MRI, determination of metastatic lymph nodes is determined largely by size. A threshold of 1.0 cm in short axis of oval nodes and 0.8 cm for round nodes are generally used as indicators of likely metastatic disease[13]. However, more than half of lymph nodes involved with metastatic prostate cancer may be less than 1 cm[14]. Moreover, non-metastatic nodes may be enlarged due to reactive hyperplasia. Given the lack of sensitivity of both CT and MRI based on size criteria alone, new techniques of MR lymphography (MRL) have been developed as well as molecular imaging techniques. Herein, we will discuss these modalities for improved prostate cancer lymph node staging.

LYMPH NODE IMAGING WITH MRI

MRL

High resolution MRI utilizing ultra-small super paramagnetic iron oxide (USPIO) has been utilized to improve sensitivity for detection of metastatic lymph nodes[15,16]. Lymphotropic superparamagnetic nanoparticles are avidly taken up by lymph nodes where they are internalized by macrophages[17]. Malignant nodes have a relatively paucity of macrophages compared to benign lymph nodes. The intracellular iron-containing particles cause benign lymph nodes to lose signal (appear dark) on T2* images (Figure 1) while lymph nodes affected by metastatic disease do not take up the USPIO as effectively due to the decreased macrophages and hence appear bright[18]. This evaluation of macrophage function does not rely on nodal size to detect metastasis[19]. Moreover, it does not depend on the functional activity of cancer in the lymph nodes as it labels normal macrophages in the lymph nodes[20]. Given the high spatial resolution of MRI, more lymph nodes at smaller sizes can be detected and accurately characterized as benign or malignant with macrophage replacement by metastatic cancer cells[20].

USPIO particles have been used extensively as a lymphotropic contrast agent for detection of metastatic prostate cancer in numerous clinical trials[16,21-26]. In an initial study that utilized USPIO (ferumoxtran-10), nodes
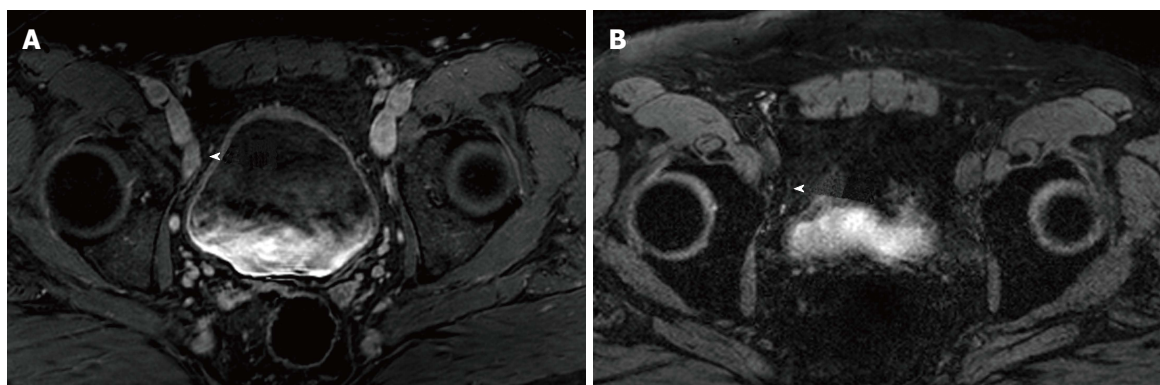
Figure 1 Selected imaged from a ferumoxytol enhanced magnetic resonance imaging in a 59-year-old man who underwent transrectal ultrasonography prostate biopsy for elevated PSA (10.8 ng/mL) which showed Gleason 3 + 4 disease of 4 cores. A: Initial prostate multiparametric T1 weighted post gadolinium magnetic resonance imaging (MRI) showed a 1.8 cm × 0.9 cm right external iliac chain lymph node that was suspicious base on size criteria (arrowhead); B: 24 h post injection of ferumoxytol (7.5 Fe/kg dose), T2* weighted MRI showed decreased signal intensity within the node (arrowhead), consistent with uptake of ferumoxytol. This was considered a benign lymph node based on these results. The patient underwent computed tomography guided biopsy for confirmation and the node was negative for malignancy.

were considered malignant when one of the following three criteria are present: (1) A decrease in signal intensity of less than 30 percent on T2-weighted fast spin-echo or gradient-echo sequences after the administration of USPIO; (2) a heterogeneous signal (giving the entire node a mottled appearance), discrete focal defects (isolated islands of high signal intensity), or both on gradient echo imaging; and (3) nodes with a central area of hyperintensity (excluding a fatty hilum) but a peripheral decrease in signal intensity[15]. This initial study utilizing ferumoxtran-10 demonstrated a sensitivity for detection of malignant lymph nodes with short axis diameter of 5-10 mm was increased with use of USPIO compared to MRI alone (96.4% *vs* 28.5%, respectively)[15]. Other studies have confirmed the ability of MR ferumoxtran-10-enhanced lymphography to detect metastatic disease in non-pathologically enlarged lymph nodes (< 7 mm) with high sensitivity and specificity[20,23,24,27-30].

Meijer *et al*[31] showed a better prognosis in a subset of patients with MRL positive lymph nodes that were < 8 mm and better outcomes in patients in whom all MRL positive lymph nodes were resected. This highlights a window of opportunity for cure in these patients as those with MRL-detected positive nodes that were entirely removed had a five-year distant metastatic disease free survival of 80% compared to 35% in the patients who did not have all MRL-detected positive nodes removed[31].

Additionally, the potential for MRL to detect metastatic lymph nodes outside of the routine dissection margin has potential for great clinical value including surgical and radiation therapy planning. In series of 269 men with moderate to high risk for nodal metastasis, 41% were found to have lymph node metastasis outside of the routine dissection area that were identified with MR ferumoxtran-10-enhanced lymphography[24]. MRL has been utilized to guide radiation therapy as another study showed that 53% of prostate cancer patients had

MRL positive lymph nodes outside of the target volume for pelvic radiation[32]. Salvage radiation therapy is associated with some toxicity[33], and improved selection of patients and detection of nodal targets can decrease morbidity and improve cure rates[25]. However, despite these promising results, ferumoxtran-10 failed to achieve Food and Drug Administration (FDA) approval and production was halted[34].

Ferumoxytol is a newly released USPIO agent that has been more recently utilized in detection of malignant lymph nodes[35]. Ferumoxytol is a compound closely related to ferumoxtran-10 that is FDA approved as iron replacement therapy in patients with chronic kidney failure with the recommended clinical dose of 1020 mg (two doses of 510 mg administered intravenously 3-8 d apart)[35,36]. In phase Ⅰ and Ⅱ clinical trials, ferumoxytol was associated with low adverse event rate which the most common events including nausea, dizziness, and diarrhea[37], although more serious reactions such as hypotension and anaphylaxis have been reported[38,39]. This has led to the FDA releasing a safety communication recommending modifications to give ferumoxytol as a dilute infusion[40].

Due to its large size, ferumoxytol remains in a relatively steady concentration within the intravascular space for several hours (circulating half-life is 14-15 h) and then is gradually cleared by macrophages from the blood pool over several days[41]. Following macrophage breakdown, the iron oxide particles are taken up by the reticuloendothelial system[41]. In a recent phase I dose escalation trial, it was shown that the signal intensity of normal lymph nodes drop in a dose dependent manner with the optimal dose determined to be 7.5 mg Fe/kg[35]. A pilot study quantitatively compared the ability of ferumoxytol and ferumoxtran-10 to suppress signal intensity in normal lymph nodes (in patients with high risk prostate cancer) and showed that signal suppression was weaker for ferumoxytol MRL than for ferumoxtran-10 MRL[42]. This study was limited in that
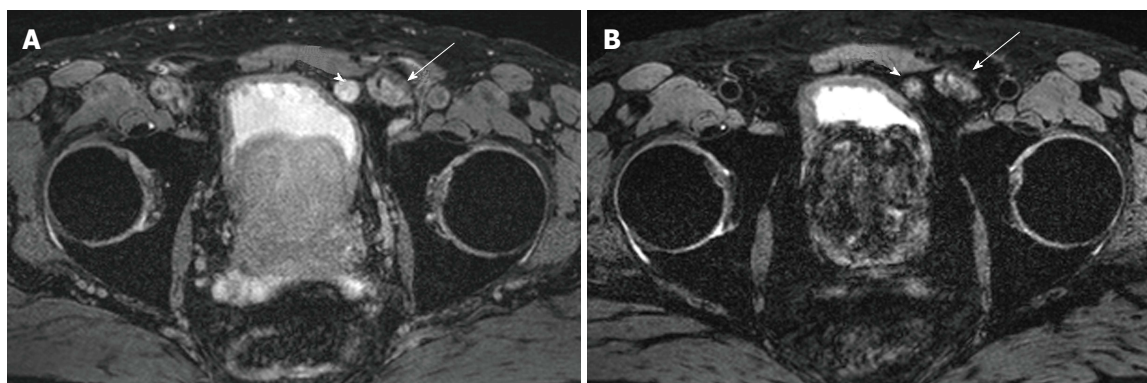
Figure 2 Selected images from a ferumoxytol enhanced magnetic resonance imaging in a 65 years old man status post magnetic resonance imaging/ultrasound fusion guided prostate biopsy revealing 3 + 3 prostate cancer and PSA 16.6 ng/mL. A: Baseline T2* weighted magnetic resonance imaging (MRI) showed a rounded lymph node anterior to the bladder (arrowhead) that measured 1.5 cm and was hyperintense. Lobular mass like lesion (arrow) lateral to the suspicious lymph node corresponds to hernia mesh; B: 24 h post injection of ferumoxytol (7.5 Fe/kg dose) enhanced MRI shows persistent heterogeneous hyperintensity within the node (arrowhead). The lack of ferumoxytol uptake within the node was suspicious for malignant involvement. Pathology revealed castleman's disease (false positive). Arrow again indicates hernia mesh.

only 4 patients received ferumoxytol and the dose was 6.0 mg Fe/kg, but further research is needed to validate the accuracy of ferumoxytol MRL[42]. Ferumoxytol MRL has also been preliminarily evaluated in non-human primates for use as an intraprostatic injection to directly map lymph nodes draining the prostate gland, with a potential of guiding lymphatic drainage patterns for specific gland segments[43].

MRL may have false positive results in the setting of reactive nodal hyperplasia or granulomatous diseases in which there are decreased number of macrophages in otherwise benign lymph nodes that may lead to mischaracterization of lymph nodes as malignant suspicion on imaging[44] (Figure 2).

Diffusion-weighted imaging

In diffusion-weighted imaging (DWI), the Brownian motion of water molecules within a voxel of tissue is imaged and can be quantitatively expressed using the apparent diffusion coefficient (ADC) value. DWI can be performed quickly without the need of a contrast medium. Malignant tissue tends to have increased cellularity with enlarged nuclei and an abundance of macromolecular proteins, resulting in restricted diffusion[45]. Typical malignant lesions appear hyperintense on images acquired at high b-values (800-1000 s/mm^2) and hypointense on the corresponding ADC maps.

Malignant lymph nodes have been shown to have a lower ADC value when compared to benign lymph nodes[46,47], but show less promising results in normal sized lymph nodes with a wide range of ADC values[45,48]. In a study of 29 patients with prostate cancer and a total of 118 lymph nodes evaluated by DWI-MRI, a cut off value of 1.3×10^{-3} mm^2/s yielded a sensitivity of 86% and specificity of 85%[46]. ADC values can be elevated in necrotic nodes due to the free diffusion of water, which can lead to misclassification[49]. While some authors have reporting the combination of nodal size and the relative ADC value nodes is more useful in

detecting pelvic lymph node metastasis[50], others have found less promising results[45]. Nevertheless, there can be an overlap of ADC values in benign and malignant lymph nodes[51].

In a more recent prospective study utilizing a 3T MRI system and a non-quantitative approach to evaluation DWI and ADC maps, revealed 94% specificity and 41% sensitivity for anatomical region based analysis (mean positive lymph node size was 1.2 cm)[52]. In a prospective evaluation of detection of normal sized metastatic lymph nodes in initial staging of prostate and bladder carcinoma, there was increased detection utilizing DWI when compared to conventional cross-section imaging techniques with detection of metastasis in 64%-79% of patients[51]. Evaluating additional morphologic features at MR imaging such as round shape, irregular border, low T2 signal may improve specificity than relying only on diffusion weighted imaging[51]. Further advances in DWI-MRI technique will require standardization of the technique, image acquisition and sequence parameters of different scanner platforms[53].

Combining DWI-MRI with other techniques such as USPIO or choline show perhaps the most promising results[30,54]. In a study evaluating 2,993 normal sized lymph nodes in patients with prostate or bladder cancer, combining DWI-MRI with USPIO improved sensitivity and specificity (65%-75% and 93%-96%; compared to 55%-65% and 71%-91%, respectively) and decreased imaging interpretation time compared to USPIO alone[30].

PET TRACERS FOR INITIAL NODAL STAGING OF PROSTATE CANCER

PET

Considerable efforts are currently being made to develop effective radiotracers to image prostate cancer in both the setting of primary staging as well as biochemical recurrence. Although not the focus of this paper, there is substantial evidence supporting the use of PET tracers for

PET tracers	Mechanism of action
[18F]FDG	Glucose metabolism
Sodium [18F]fluoride	Chemisorption to bone matrix
[18F]choline, [11C]choline	Cell membrane metabolism
[18F]DCFBC, [68Ga]HBED-CC	PSMA binding
[11C]acetate	Fatty acid metabolism
[18F]fluciclovine	Amino acid transport
[68Ga]DOTA-bombesin	GRPR receptor binding
[18F]FDHT	Androgen receptor binding

PET: Positron emission tomography; [18F]FDG: (18F)fluoro-D-glucose; [18F]DCFBC: (18F)fluorobenzyl-L-cysteine; GRPR: Gastrin-releasing peptide receptor.

biochemical recurrence, and two PET tracers [(11C)choline and (18F)fluciclovine] have been approved by the FDA for the detection and staging of biochemical recurrence. However, there has been less investigation regarding the use of PET in the initial nodal staging of prostate cancer. A wide range of PET tracers have been developed and investigated for prostate cancer imaging, and this section summarizes PET tracers that have demonstrated utility for detecting lymph node metastases from prostate cancer. These tracers and their key properties are summarized in Table 1.

Positron emission tomography (PET) is currently performed using hybrid imaging systems that combine PET with CT or MRI for attenuation correction and anatomic localization of the PET findings. In PET imaging, a positron emitting radiotracer is administered to the patient, which then emits 511 keV gamma rays through annihilation of the positron with an electron in the tissue which can be localized through coincidence detection[55]. Compared to conventional planar scintigraphy and single photon computed tomography (SPECT), PET provides higher spatial and temporal resolution. One of the limitations of PET is resolution, with decreased sensitivity of the detection and characterization of PET tracer uptake in lesions less than 8 mm. However, the use of hybrid imaging PET/CT or PET/MRI allows the combination of anatomical imaging from the CT or MRI with molecular information from PET.

PET tracers for prostate cancer imaging have been labeled with several different radionuclides that vary in terms of their physical half-life ($t_{1/2}$) and their chemistries. PET radionuclides include are carbon-11 ($t_{1/2}$ = 20 min), fluorine-18 ($t_{1/2}$ = 110 min), and gallium-68 ($t_{1/2}$ = 68 min). Carbon-11 and fluorine-18 are produced using cyclotrons while gallium-68 is produced using a generator system. Fluorine-18 is widely available, and its long half-life facilitates production of large batches of PET tracers and distribution to sites that do not have onsite production capabilities.

The most commonly used radiotracer for clinical oncologic imaging is 2-deoxy-2-(18F)fluoro-D-glucose (FDG), but this tracer is of limited utility for the initial staging of prostate cancer due to the low metabolic activity in the early phase of the disease which results in poor sensitivity[56]. Another disadvantage of FDG is urinary excretion, potentially decreasing sensitivity for pelvic lymph nodes[57]. For the evaluation of bony metastases, sodium(18F) fluoride (NaF) has been used for skeletal scintigraphy which takes advantage of higher spatial resolution when compared with conventional planar (99mTc)methyldiphosphinate (MDP). Several studies have demonstrated that cross-sectional skeletal scintigraphy with fluoride-PET/CT or MDP-SPECT/CT have superior sensitivity and specificity for detection of osseous metastases when compared to conventional planar bone scans (96% and 98%, respectively)[58]. The uptake of (18F)fluoride is based on bone turnover with increased binding to newly deposited mineralize bone matrix that occurs in bone metastases, particularly osteoblastic metastases. While (18F)fluoride-PET/CT may be useful in preoperative skeletal staging in prostate cancer, this tracer is not useful for the detection of lymph node metastases.

Choline is a naturally-occurring small molecule that is incorporated into tumor cells after phosphorylation by choline kinase, which is up regulated in prostate cancer[59]. (11C)choline uptake in metastatic lymph nodes occurs in the presence of viable malignant tissue, and (11C)choline has been approved by the FDA for use in the detection and localization of suspected biochemically recurrent prostate cancer. This PET tracer has been used for prostate cancer with a pooled sensitivity of 49.2% and specificity of 95% for detection lymph node metastasis[60]. Results are better for larger nodes, but sensitivity is limited in lymph nodes smaller than 7 mm[20]. Several studies combining (11C)choline PET/CT and diffusion weighted MRI showed that sensitivity remained too low to be clinically useful for initial staging[54,61].

Fluorinated analogues of choline have been developed to take advantage of the longer half-life of fluorine-18 [*e.g.*, (18F)fluorocholine and 2-(18F)fluoroethyl choline]. However, these fluorinated choline analogues have similar limited capability in detecting lymph node metastasis (sensitivity 40% and specificity 96%)[62,63]. Combining 18F-choline PET and MRI may help improve the results of choline PET imaging, but further research is needed[64,65]. The value of choline for the detection of recurrent prostate cancer in patients with low PSA levels (< 2.5 ng/mL) is limited[66,67]. Additionally, 18F-labeled analogues of choline are eliminated *via* the kidney and urinary tract activity, which is undesirable for pelvic imaging.

Acetate is a naturally occurring metabolic substrate that can enter the fatty acid metabolic pathway which is overexpressed in prostate cancer cells[68]. Most research has been done with (11C)acetate and has shown sensitivity of 68% and specificity of 78% in one study of intermediate and high risk prostate cancer[69], but has the disadvantage of requiring an on onsite cyclotron to due to the short half-life of 20 min.

Prostate specific membrane antigen (PSMA) is a protein expressed by the prostate and overexpressed in prostate cancer[70]. The initial molecular imaging

agent targeting PSMA that gained widespread use was (^{111}In)indium capromab pendetide, a radiolabeled monoclonal antibody that targets the intracellular portion of PSMA and is imaged utilizing SPECT/CT. While initial results showed improvement over conventional techniques, there was limited sensitivity and specificity[71,72]. However with the additional of MRI, sensitivity and specificity were increased[73]. The main disadvantage of (^{111}In)indium capromab pendetide is that it targets an intracellular protein making imaging only a possibility upon apoptosis or necrosis and not in viable tissue[55,70,74]. Additionally, the slow kinetics of (^{111}In)indium capromab pendetide requires imaging 5-7 d after injection. More recently, a great deal of research has been focused on small molecule ligands that bind to the extracellular portion of PSMA[75,76].

Novel small molecule imaging PSMA ligands have been developed such as *N*-{*N*-[(*S*)-1,3-dicarboxypropyl] carbamoyl}-4-(^{18}F)fluorobenzyl-L-cysteine [(^{18}F)DCFBC], which binds irreversibly to the extracellular component of PSMA and has been shown to improve detection of metastatic prostate cancer[77,78]. The most commonly used PSMA ligand in Europe is ^{68}Ga-N,N'-bis [2-hydroxy-5-(carboxyethyl)benzyl] ethylenediamine-N,N'-diacetic acid (HBED-CC) (Figure 3). In a study utilizing ^{68}Ga-labeled PSMA ligand (HBED-CC), there was improved accuracy of lymph node staging over conventional imaging with 65.9% sensitivity and 98.9% specificity[79]. A retrospective study examining ^{68}Ga-PSMA PET/CT in initial staging of patients with high risk of lymph node metastasis found 33.3% sensitivity and 100% specificity (mean size of true positive nodes was 13.6 cm and of false positive node was 4.3 mm)[80].

Amino acid radiotracers can accumulate in prostate cancer cells through the upregulation of transmembrane amino acid transport in prostate cancer[81]. The most work with a synthetic amino acid PET radiotracer for prostate cancer has been with (^{18}F)fluciclovine for detection of recurrent disease, and this PET tracer was approved by the FDA for use in biochemically recurrent prostate cancer in 2016 (Figure 4). Preliminary studies have reported results for initial staging[81,82]. In a multicenter phase IIb clinical trial for staging of initial prostate cancer, diagnostic accuracy of (^{18}F)fluciclovine PET/CT was compared to conventional imaging with CT and bone scan[83]. Overall accuracies were similar (85.5% for (^{18}F)fluciclovine PET/CT and 87.3% for conventional imaging); however, (^{18}F)fluciclovine PET/CT was positive in 5-9 mm nodes and skeletal lesions that were not detected by conventional imaging.

An additional molecular target that is currently under investigation is the gastrin-releasing peptide receptor (GRPR) which is overexpressed in prostate but has lower levels in benign prostate tissue including benign prostatic hyperplasia[84]. Initial studies demonstrate GRPR overexpression in 63%-100% of primary prostate carcinomas and 50%-85% of nodal and osseous metastases[85]. A number of peptide based ligands for GRPR have been developed including the 14 amino acid peptide bombesin, as well as analogues of the 27-amino

acid gastrin releasing peptide (GRP)[86]. A single human trial utilizing a ^{68}Ga-labeled GRPR antagonist for pre-operative staging has been completed[87]. This trial enrolled 11 patients with primary prostate carcinoma and three patients with evidence of biochemical recurrence, demonstrating a sensitivity of 88% and specificity of 81% for detection of the primary lesion (within a sextant level) and found evidence of biochemical recurrence in lymph nodes and the prostate bed in two out of three patients[88].

Androgen sensitivity and receptor expression remain a mainstay in the diagnosis and treatment of prostate carcinoma. Importantly, androgen receptor expression plays a role in both initial treatment strategies and in the setting for treatment for biochemical recurrence/metastatic disease. Preliminary human imaging studies have been performed using the androgen receptor ligand 16β-(^{18}F)fluoro-5α-dihydrotestosterone (FDHT). The initial human study compared FDHT and FDG, which demonstrated FDHT uptake in 46/59 lesions in seven patients with progressive metastatic prostate cancer (compared to FDG uptake in 57/59)[89]. The role, if any, of (^{18}F)FDHT in the pre-operative evaluation of prostate cancer is not yet defined.

An interesting future in targeted molecular imaging of metastatic prostate carcinoma is the use of PSMA and bombesin agents for targeted therapy with alpha-emitters or beta-emitters (including ^{90}Y and ^{177}Lu). These agents are currently being utilized in clinical trials for patients with biochemical recurrence, but are not currently approved for use in the United States[90,91]. These compounds may play a future role in adjuvant therapy post prostatectomy as the previously described molecular targeted PET agents become established for initial staging.

An exciting development that may increase the impact of molecular imaging for prostate carcinoma is the recent FDA approval of hybrid PET/MRI scanners. These scanners can acquire PET and MRI data simultaneously and combine targeted molecular imaging with PET with the soft tissue contrast and anatomic detail provided by pelvic MRI. The MRI component of PET/MRI can significantly increase detection of lesions compared to the non-contrast CT typically performed with conventional PET/CT. Evaluation of the prostate bed can also be significantly improved utilizing PET/MRI *vs* PET/CT. Given the established role of MRI for prostate cancer staging and lesion detection, PET/MRI may become the preferred platform for prostate cancer imaging in certain clinical scenarios. However, more data are needed to define the role of PET/MRI in the initial staging of prostate cancer.

CONCLUSION

Conventional imaging (CT and MRI) cannot depict small metastases in normal sized and normal appearing lymph nodes. The optimal strategy for the preoperative staging of prostate cancer remains a topic of ongoing

Figure 3 Prostate specific membrane antigen. Selected images from a [68Ga]PSMA-11-PET/CT study performed prior to therapy in a man with biopsy-proven Gleason 9 prostate adenocarcinoma, a serum PSA of 11.6 ng/mL, and a clinical tumor stage of cT2b. The anterior maximum intensity projection (MIP) image (A) and the axial PET (B), fusion (C), and CT (D) images through the pelvis demonstrate focal activity in a left external iliac lymph node. This appearance is highly suspicious for a lymph node metastasis. Images courtesy of Tom Hope, MD, University of California San Francisco, Department of Radiology. PSMA: Prostate specific membrane antigen; PET/CT: Positron emission tomography/computed tomography.

Figure 4 Fluciclovine. Selected images from a (18F)fluciclovine-positron emission tomography/computed tomography study performed in a man who underwent prostatectomy for Gleason 8 prostate adenocarcinoma 11 years ago. He developed biochemical recurrence with a serum PSA of 0.8 ng/mL and a PSA doubling time of 14 mo at the time of the (18F)fluciclovine-PET/CT study. The anterior maximum intensity projection (MIP) image (A) and the axial PET (B), fusion (C), and CT (D) images near the level of the pelvic inlet demonstrate focal activity in a subcentimeter right common iliac lymph node. This appearance is highly suspicious for a lymph node metastasis. Images courtesy of Ephraim Parent MD, PhD, and David Schuster, MD, Emory University, Department of Radiology. PET/CT: Positron emission tomography/computed tomography.

research. Advanced imaging techniques to assess lymph nodes in the setting of prostate cancer utilizing novel MRI contrast agents as well as PET tracers have been developed and continue to be studied. MRL utilizing USPIO has shown high sensitivity and specificity in detection of normal sized lymph nodes containing metastatic disease and thus a positive finding may alter the treatment course for the patient. Ongoing research is occurring in molecular imaging and continues to show a promising future for detection of prostate metastasis as well as potential therapeutic applications.

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MR neurography in intraosseous median nerve entrapment

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Abstract

Intraosseous entrapment of the median nerve is an un-common complication of elbow dislocation and fractures. The condition is seen to occur in adolescent age group with a remote history of trauma. We report two rare cases of type 2 intraosseous median nerve entrapment. Though the diagnosis of median neuropathy is made with clinical tests and neurophysiological studies, however exact site of entrapment and presurgical mapping of nerve is done accurately with MR neurography. Imaging thus plays a pivotal role in management of this condition.

Key words: Intraosseous; MR neurography; Median nerve

Core tip: Intraosseous entrapment of median nerve at the level of elbow joint is rare but serious complication of closed reduction of posterior elbow dislocation. We report two cases of type 2 intraosseous medan nerve entrapment (wherein the median nerve gets entrapped in fractured medial epicondyle) and discuss the role of MR neurography. MR delineates the posterior course of median nerve with altered signal intensity, thickening and loss of fascicular pattern. In addition, secondary denervation changes in muscles supplied by median nerve is indirect evidence of nerve pathology. Management of such cases would differ depending on the time of diagnosis.

INTRODUCTION

Intraosseous entrapment of the median nerve at the level of elbow joint is a rare but serious complication of closed reduction of posterior elbow dislocation[1]. The diagnosis often gets delayed due to subtle symptoms which leads to grave damage to nerve. Imaging plays a major role preoperatively determining the site of entrapment. We report two cases of type 2 intraosseous median nerve entrapment and discuss their MR neurography findings.

CASE REPORT

Case 1

An 18-year-old male suffered fracture of medial epicondyle of left humerus along with elbow dislocation after he fell from rooftop about two years back. He was managed with closed reduction of elbow, followed by cast immobilization and physiotherapy. After removal of cast, he progressively started having symptoms of median neuropathy in the form of numbness and paresthesia along the median nerve distribution in forearm and hand with inability to form a fist and weak hand movements (Figure 1A). Gradually there was thinning of the forearm muscles. On clinical examination, there was atrophy of forearm muscles (of the anterior compartment) and of thenar muscles (Figure 1B). He had weakness of small hand muscles as well in the median nerve distribution. Clinical impression was median nerve palsy. Ulnar and radial nerve function was normal on clinical examination. Nerve conduction studies revealed median nerve neuropathy at the level of elbow.

High resolution USG was done, which revealed grossly thickened and hypoechoic median nerve in the region of distal arm with an abrupt cut off at the level of elbow (Figure 1C). The nerve fibers were seen coursing posteriorly and distal median nerve could not be traced. Limited MR neurography of the elbow was done for further confirmation of diagnosis.It revealed the median nerve to be swollen and having abnormal signal intensity (hyperintense on T2) in the distal arm (Figures 1D and 2). It was seen to have an altered course as the median nerve was seen to course posteriorly through the fractured medial epicondyle and subsequently was entrapped between the olecranon of ulna and olecranon fossa of humerus. Thereafter, the nerve was not visualized for some distance after which it reappeared with decreased calibre in its normal course in forearm with normal signal intensity. The muscles of the anterior compartment, supplied by median nerve, showed hyperintense signal on T1w and T2w sequence suggesting chronic denervation with fatty infiltration. These features were suggestive of type 2 median nerve entrapment.

Case 2

A 20-year-old patient suffered supracondylar fracture of humerus 1 year back. The patient was managed conservatively by immobilization. Patient noticed weakness of hand grip and hand movements and decreased sensations of lateral half of forearm and lateral half of hand after immobilization was removed.

On examination, there was atrophy of anterior compartment muscles of right forearm and thenar eminence of hand. There was weakness of lateral half of hand fingers. All tests for median nerve were also positive in this case. NCV confirmed median neuropathy with likely site to be at elbow.

MR neurography revealed markedly thickened median nerve and was T2 hyperintense in the region of arm proximal to fracture site and traversed through the fractured fragment of humerus and coursed posteriorly (Figure 3). The nerve was entrapped between the olecranon and olecranon fossa and was seen coursing anteriorly back to its normal course with normal intensity and mildly decreased thickness. There was secondary atrophy of flexor digitorum profundus (lateral belly), flexor digitorum superficialis, flexor pollicis longus, pronator teres and of thenar muscles with fatty change s/o chronic insult.

DISCUSSION

Intraosseous median nerve entrapment is relatively rare complication of elbow dislocation and fractures of lower end humeral, frequency of which varies from 1%-12.5%[2]. It was first described by Gurdjian and Smathers[3] in 1945. The condition is seen to occur in a relative younger age group (adolescents)with a slight male predominance[4].

Four types of intraosseous median nerve entrapment are described[5]. The first three types have been described by Hallet while type IV was described by al-Danielsson *et al*[6], Hallett *et al*[7], Steiger *et al*[8], Ozkoç *et al*[9], Noonan *et al*[10]. In type 1 intraosseous median nerve entrapment, the medial collateral ligament is torn and the median nerve slips posteriorly adhering to the posterior surface of humerus and gets entrapped between trochlea and olecranon process. In type 2, median nerve is entrapped in the fractured medial epicondyle. Type 3 is when nerve gets entrapped between the distal end of humerus and ulna in the ulno-humeral joint without any fracture. Type 4 is combination of type 1 and 2[11]. Both our cases were of type 2 variety; the median nerve was entrapped in the fractured medial epicondyle. Both the patients were young adolescent males having a remote history of trauma and were managednon-operatively.

Intraosseous entrapment of the median nerve should be suspected when there is failure of concentric reduction, presence of joint widening post reduction or the clinical symptoms persist or if there occurs cortical depression with surrounding sclerotic changes in the distal metaphysis of humerus(matev sign)[1,12,13].

Imaging played a pivotal role in preoperative diagnosis of this condition. Altered signal intensity and thickening of the median nerve with loss of fascicular
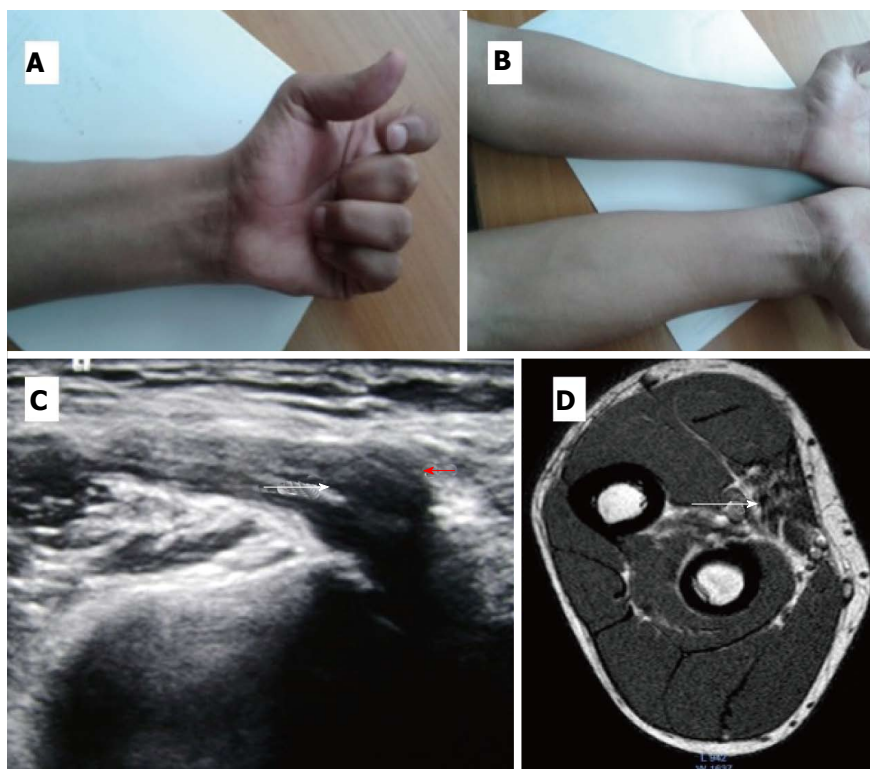
Figure 1 Images of first patient with intraosseous median nerve entrapment. A: Clinical Photograph showing inability to close fist completely with partial flexion of the index finger; B: Atrophy of anterior compartment muscles of left forearm; C: Sonogram shows thickened and hypoechoic median nerve (arrow), coursing posteriorly through the fractured bone; D: SE T1 W MR axial image shows atrophy of anterior compartment muscles of forearm with fatty infiltration s/o chronic denervation changes (arrow).
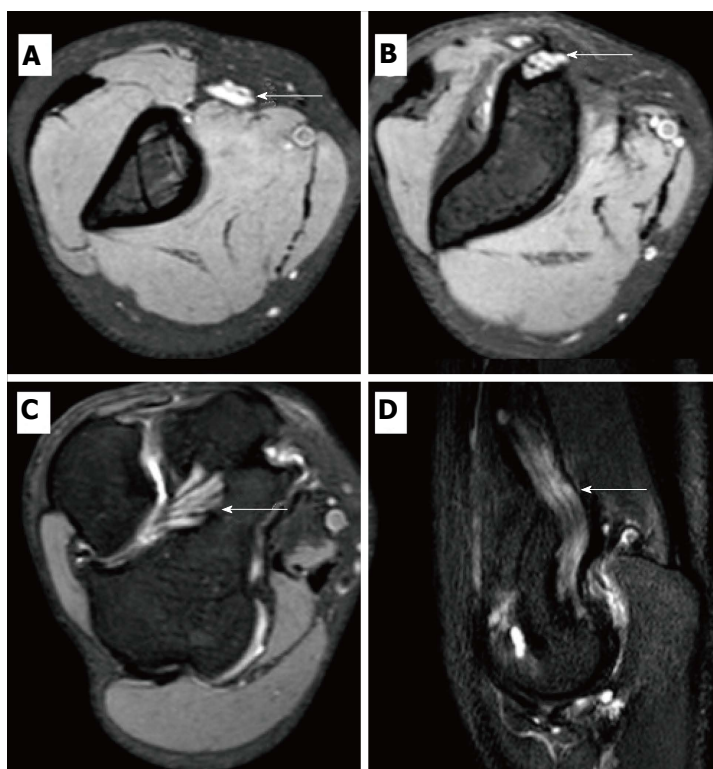

Figure 2 Images of second patient with intraosseous median nerve entrapment. A-C: 3D GRE T2W images showing markedly thickened and hyperintense entrapped median nerve (arrow), coursing posteriorly through the fractured medial epicondyle; D: STIR Coronal image showing markedly thickened and hyperintense median nerve (arrow).
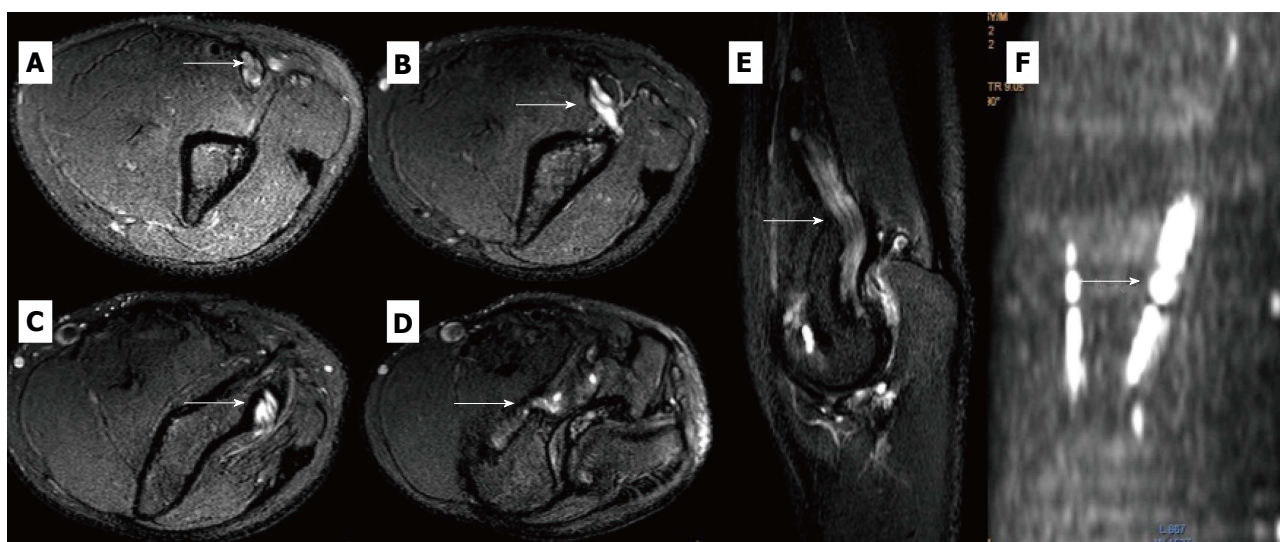
Figure 3 Images of third patient with intraosseous median nerve entrapment. A-D: SE T2W FS axial MR image shows markedly thickened and hyperintense nerve coursing through the fractured medial epicondyle; E: STIR coronal MR image shows entrapped median nerve coursing posteriorly; F: DWIBS coronal reformat highlights the abnormal median nerve.

pattern pointed towards the abnormality of the nerve. MRI clearly delineated the posterior course of the median nerve. In addition, secondary denervation changes in muscles supplied by median nerve were also seen.

Management of such cases would differ depending on the time of diagnosis. Usually the symptoms of median nerve entrapment are mild hence detection of this neuropathy is delayed. If detected early, relocation of the nerve from posterior to anterior compartment is done. If detected later then excision of the diseased segment with either nerve repair (end to end) or nerve grafting is done (with sural nerve graft). Early diagnosis and treatment ensures better prognosis. Both the cases we encountered were of chronic insult due to delayed diagnosis. The first case was lost to follow up and the second underwent nerve grafting.

MR neurography plays a vital role in the diagnosis of intraosseous entrapment of median nerve following medial epicondyle fracture by clearly demonstrating its altered course in the posterior compartment leading to its entrapment. In addition, presurgical mapping of the nerve can be accurately done with MRI and it also helps in deciding the correct management of the patient.

COMMENTS

Case characteristics
Numbness and paresthesia along the median nerve distribution in forearm and hand with inability to form a fist, and weak hand movements with gradual thinning of the forearm muscles.

Clinical diagnosis
Weakness and atrophy of muscles of median nerve distribution.

Differential diagnosis
Traumatic/entrapment/infectious/inflammatory neuropathy.

Laboratory diagnosis
Nerve conduction study will reveal reduced velocity across the median nerve.

Imaging diagnosis
MR delineates the posterior course of median nerve with altered signal intensity, thickening and loss of fascicular pattern.

Pathological diagnosis
Neuropathy at the fracture level.

Treatment
If detected early, relocation of the nerve from posterior to anterior compartment is done and if detected later then excision of the diseased segment with either nerve repair (end to end) or nerve grafting is done (with sural nerve graft).

Related reports
Four types of intraosseous median nerve entrapment are described. Intraosseous entrapment of the median nerve should be suspected when there is failure of concentric reduction, presence of joint widening post reduction or the clinical symptoms persist or if there occurs cortical depression with surrounding sclerotic changes in the distal metaphysis of humerus (matev sign). MRI clearly delineated the posterior course of the median nerve. In addition, secondary denervation changes in muscles supplied by median nerve were also seen.

Term explanation
Intraosseous entrapment of the median nerve is a rare complication of closed reduction of posterior elbow dislocation.

Experiences and lessons
MR neurography plays a vital role in the diagnosis of intraosseous entrapment of median nerve following medial epicondyle fracture by clearly demonstrating its altered course in the posterior compartment leading to its entrapment.

Peer-review
The case studies are described clearly and it is easy for the reader to follow.

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