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IMAGING (L MECHTLER, SECTION EDITOR)

Multiple Sclerosis-Related Pain Syndromes: An Imaging Update

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Abstract Pain in multiple sclerosis (MS) is a common manifestation, made up of complex phenomenon involving intricate neurophysiological processing at central levels of the pain pathway. Our understanding of the clinical and neurophysiological mechanisms of central/neuropathic pain related to MS continues to improve with improved imaging techniques but remains a challenging area of research. The advancements in imaging techniques for lesion evaluation of the various neuroanatomic structures have improved our detection, diagnosis, and understanding of MS pain and help validate subjective symptoms. This article will discuss the updated criteria of MS neuropathic pain and critically review some of the latest research into imaging correlations of MS pain syndromes. And discuss how advanced MRI imaging techniques (such as functional magnetic resonance imaging [fMRI], 3D imaging, fluid attenuated inversion recovery [FLAIR*], and diffusion tensor imaging [DTI]) have detailed neuropathic pain with a focus on migraines and trigeminal neuralgias and will highlight some of the ongoing limitations, variabilities, and deficiencies.

Keywords Pain · Multiple sclerosis · MS · Migraine · Neuropathic pain · MRI · Trigeminal neuralgia

This article is part of the Topical Collection on *Imaging*

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Introduction

The International Association for the Study of Pain (IASP) defines pain as: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (http://www.iasp-pain.org/) [1]. Several brain areas may be involved in processing pain signals and emotional responses to pain. The brain regions involved in processing pain depend on the type of pain experienced. Generally, the ascending pain processes divide signals into two main pathways: localization (somatosensory cortex) and emotional/motivation centers (VPL thalamic nuclei, periaqueductal grey, and limbic forebrain). Moreover, attentional, anticipation, emotional, and expectation states also affect pain processing [1–4]. A key distinction between acute and chronic pain states is that the brain regions that are involved in interpreting chronic pain states appear to be activated differentially. Previously, an overview of imaging studies (including mainly functional MRI [fMRI] studies) found that six brain regions were consistently and significantly activated: the prefrontal cortex, the insular cortex, the anterior cingulate cortex, the primary somatosensory and secondary somatosensory cortices, and the thalamus [3–5].

Patients with central nervous system diseases such as multiple sclerosis (MS) may suffer from different types of pain throughout their lifetime, namely initially nociceptive, or somatic pain, then mainly neuropathic and/or mixed pain. Furthermore, a normal response to acute pain is generally protective and adaptive, but persistent MS pain is associated with neuroplastic changes that affect pain perception and potentially result in neuropathic pain. [6] IASP simply defines central neuropathic pain as pain caused by a lesion or disease of the central somatosensory nervous system.

MS is an unpredictable neurodegenerative autoimmune disease of the central nervous system (CNS) characterized

by demyelination and axonal loss. It is a heterogeneous CNS disease with a variety of sign and symptoms, and since its earliest descriptions, the potential link between MS and pain has been reported (as far back as the earliest descriptions by Charcot in 1872). In MS, the lesions of demyelination in the CNS can occur throughout the above mentioned pain centers, resulting in hyper-excitability with signal disruptions and misperceptions of pain. Pain is a frequently disabling symptom in MS patients, its prevalence and characteristics are not fully well established and can be variable due to disease heterogeneity. Associated clinical variables and neuro-radiological correlates of neuropathic pain syndromes have continued to remain challenging despite ongoing evolution and improvements in advanced imaging techniques.

Discussion of MS pain

Pain is becoming more common in MS than previously recognized. In large cohort studies, 65–85 % of MS patients reported pain during the course of their disease. They experienced mainly chronic variable pain; women experienced pain more than men; pain prevalence was higher with greater disability, depression, and anxiety; and more in the progressive MS forms [2–4, 7, 8].

Remarkably, pain was reported to be the presenting MS symptom in nearly 20 % (alone or in combination with other symptoms). Some researchers have reported that prevalence of central/neuropathic pain is around 30 % in MS patients [9, 10]. It has been elucidated that MS patients with neuropathic pain have more severe forms and greater disability, as assessed by the expanded disability severity score (EDSS), than those without pain [9, 11].

Neuropathic Pain Criteria

The emphasis of neuropathic pain was recently realized by the International Classification of Headache Disorders. As in 2013, they released their 3rd edition (ICHD-3) that updated its requirements by including all of the following in terms of central neuropathic pain attributed to MS:

- Facial and or head pain
- MS has been diagnosed with MRI demonstration of a dominating lesion in the brain stem or ascending projections of the trigeminal nuclei
- Pain has developed and temporal relation to demyelinating lesion or led to its discovery
- Not better accounted for by another ICHD-3 diagnosis

Neuropathic pain is notoriously variable in its severity and impact on MS patients, as the pain may be continuous or paroxysmal. It may coexist with dysesthesia but also hypoesthesia, anesthesia, hyperalgesia, and paresthesia (http://www.ihs-classification.org (ICHD-3)).

The taxonomy of MS pain can perhaps be classified as encompassing the following pain subtypes (all of which can potentially overlap): face pain (mainly trigeminal neuralgia), headache (mainly migraine), musculoskeletal/limb pain/spasticity pain (secondary to lesions in the spinothalamic pathways), and central/neuropathic pain (mainly thalamic/brainstem).

Imaging MS Pain

MS pain diagnosis remains challenging, particularly since it is a subjective complaint that may mimic clinical and radiographic appearances of a number of other syndromes and diseases, and there are few conventional tests available to objectively validate pain. To that end in early 2014, Seixas et al. published a fairly comprehensive systematic review of neuroimaging studies related to pain in MS (from inception till 2013 that were published in English). All the studies investigated neuropathic pain or headache and most reported associations between location of demyelinating lesions and pain, but authors concluded by calling for the need of ongoing high quality hypothesis-driven neuroimaging. Various case reports or series were classified in terms of pain syndrome, MRI localization, and basis of association (see Table 1) [12••].

These studies mainly showed that culprit demyelinating lesions are most commonly reported in the brainstem and less commonly in the spinal cord. The identification or neuroradiological correlates of neuropathic pain syndromes in headache or facial pain syndromes are disproportionately represented. Moreover, the investigators mainly used conventional MRI techniques and only two articles (from 2010 to 2013) were using 3 T MRI platforms. Diffusion tensor Imaging (DTI) on a 3 T MRI was used in only one of the reported studies and was deemed to be an unconventional technique used to study thalamic abnormalities (that correlated with extremity pain) [13].

Additional limitations were identified: Investigators had mainly focused on neuropathic pain and headaches and no studies focused on nociceptive/somatic pain or psychogenic pain, more specifically limited investigation of age, or evolution of lesions in relation to pain, or by use of either serial imaging, or use of gadolinium contrast.

Recently, additional imaging studies have been published (that will be discussed in further detail) that have advanced our understanding, these include newer conventional techniques for improved diagnosis (e.g., FLAIR*), better visualization of trigeminal neuralgia (TN), to using non-conventional techniques (diffusion tractography-DTI), and additional incorporation of contrast enhancement. Conversely, the imaging focus

Table 1 Location of candidate culprit multiple sclerosis lesions in the origin of pain as detected by magnetic resonance imaging in the case reports/series retrieved

Study	Pain syndrome or location	Localisation of the lesions possibly explaining the pain syndrome	Basis of association (A/S/C)
Spinal cord			
Tosi (1998)	Radicular	Cervical (C5–C6) dorsal root entry zone and posterior horn	A, S
Alstadhaug et al. 2008	Headache (type not defined)	Posterior part of the upper cervical spinal cord	A, S
Burkey (2010)	Upper limb pain	Posterior columns from C2 to C4	A
Hellwig (2006)	Painful dysaesthesia at thoracic level and/or below	Posterior upper thoracic spinal cor; cord lesions at the level of C1, C4/5, Th3 (Two cases)	A, C
de Santi (2009)	Occipital neuralgia	Right antero-lateral spinal cord at C2; C1, C2, C3 and D1-D2; C2-C3 lesion (three cases)	A, S, C
Marchettini (2006)	Back, leg, flank or abdominal pain	Spinal cord location of the lesions assumed; MRI was used to exclude other causes of pseudo-radicular or visceral pain (five cases)	n/a
Brain			
Andrade (2012)	Painful stereotyped involuntary posturing movements of the left upper limb	Pyramidal tract lesions (cerebral peduncle, internal capsule and corona Radiata)	A, S, C
Bentley (2002)	Painful third nerve palsy (including pupil)	Midbrain adjacent to right third nerve fascicle	A, S
Donat 2012	Cluster-like headache	Right dorsal pons	A
González-Quintanilla (2012)	Cluster-tic	Left and right trigeminal root inlet and main sensory nucleus in the brainstem	A, S
Tanei (2010)	Facial pain (non-TN)	Right dorsal pons and medulla oblongata	A
Haas (1993)	Headache (type not defined)	Periaqueductal grey	A, S, C
Liu (2008)	Probable TAC with allodynia and other symptoms	Right lateral tegmentum of the lower pons	A, S
Leandri (1999)	TAC	Root entry zone of the trigeminal nerve on the right	A
Gentile (2007)	Cluster headache/TAC with sensory symptoms	Left brachium pontis	A, S
Meaney (1995)	TN (unilateral or bilateral)	Root entry zone of both trigeminal nerves (one case out of seven cases described)	A
Nakashima (2001)	TN	Left trigeminal root entry zone (one case out of five cases described)	A
Fragoso (2007)	Migraine without aura	Brainstem (two cases)	A
Cordella (2009)	TN	Trigeminal root entry zone (five cases)	A
Pichiecchio (2007)	TN	Trigeminal root entry zone bilaterally and enhancement of trigeminal nerves	A/C
Vilisaar (2006)	SUNCT	Anterior pons, right cerebral peduncle and medulla (one case)	A

[Used with permission from Elsevier [12••]]

A anatomically plausible lesion, *S* serial imaging demonstrating emergence or plaque in line with clinical pain syndrome, *C* contrast enhancing plaque, *n/a* not applicable, *TN* trigeminal neuralgia, *TAC* trigeminal autonomic cephalalgia, *SUNCT* short-lasting unilateral neuralgiform headache with conjunctival injection and tearing, *MRI* magnetic resonance imaging

has remained on MS diagnostic differentiation and on imaging of migraines and TN and with the focus on lesion localization.

Imaging Differentiates MS Patients Who Present with Migraines

One recent exciting article reported that imaging can differentiate MS patients who present with migraines by the detection of the so called "central vessel sign" (CVS). In histopathological studies (at autopsy), most MS lesions are centered around veins, and a variety of imaging techniques using susceptibility-weighted imaging on ultrahigh-field 7-tesla research magnets have demonstrated this relationship in vivo [14]. Recently, a small ($n = 20$) case–control study, using a novel imaging technique, showed the identification of CVS using FLAIR* on a standard 3 T MRI can help differentiate MS from migraine. Solomon et al. showed by co-registering T2-weighted FLAIR (fluid attenuated inversion recovery—1 mm isotropic), and post-contrast T2*-weighted

multi-shot echo-planar imaging (0.55 mm isotropic voxels) data helps in identification of CVS, particularly in the subcortical and deep white matter. "All 20 participants had migraines and lesions in the subcortical and deep white matter. There was no between-group difference in the number of lesions per participant in this region. However, MS participants had a higher percentage of CVS in deep white matter lesions" [15] (see Fig. 1).

They identified a median percentage of CVS lesions in MS participants of 84 %, compared to 22 % in migraine patients, ($P = 0.008$). "Additional sub analysis by brain region showed, in the subcortical and deep white matter, the median percentage of lesions in MS participants with CVS was 88 % compared to 19 % in migraine ($P = 0.004$). This difference was not identified in juxtacortical, periventricular, or infratentorial regions" [15].

Therefore, the identification of CVS using FLAIR* imaging on widely available 3 T MRI platform showed promise for the differentiation of MS from migraine in practical clinical settings, where white matter lesions are seen. Although this study was limited by having a small cohort and requiring some post-processing, further evaluation of quantifiable CVS lesions in larger prospective cohort studies may perhaps lead to clinically practical methods to supplement current MS diagnostic criteria [15].

Migraines

Neuropathic pain in MS patients can be concomitantly present with migraines. Migraines are not frequently known to be a symptom of MS, but the links between MS and migraines have been reported for nearly 50 years [16]. In a recent study, 32 % of the MS patients who presented both with migraine and neuropathic pain had more severe pain and lower health-related quality of life than MS patients with either migraine or neuropathic pain alone. The pain intensity in MS patients with migraine was also higher (6.0 ± 0.1) than that of neuropathic pain (4.9 ± 0.1) [10, 17•, 18, 19].

Several large case–control studies have reported that MS patients have higher frequency of migraine compared to healthy individuals (up to as high as threefold). Also recent

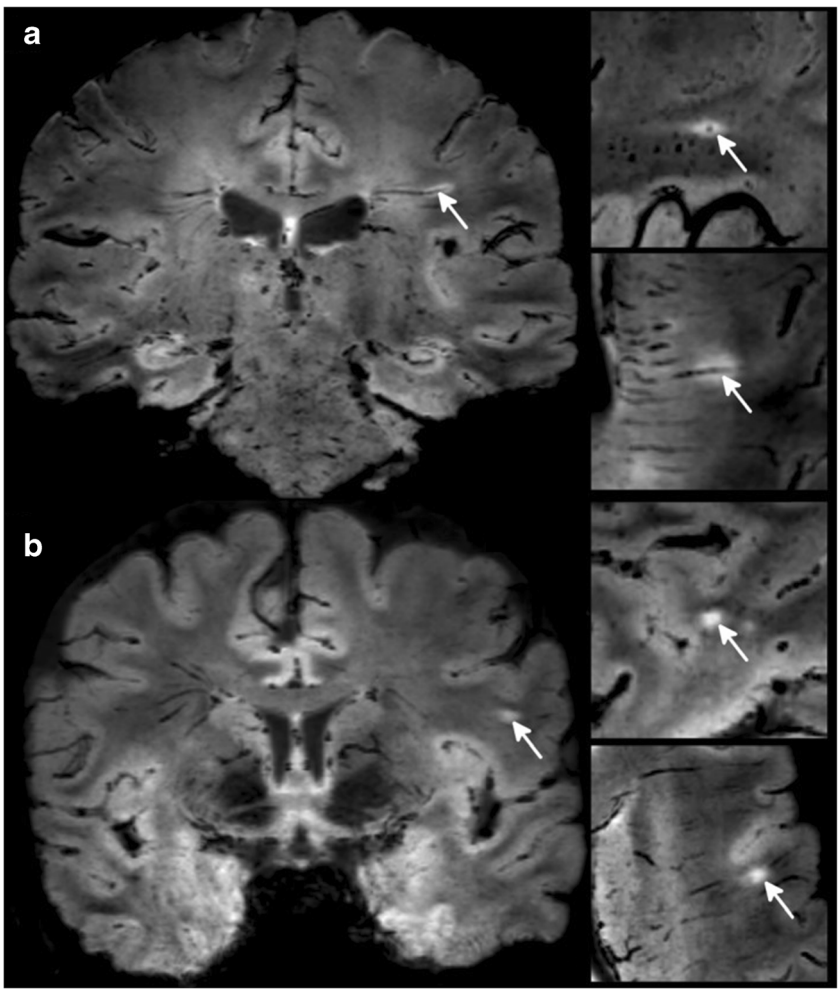

Fig. 1 Demonstrates a typical lesion with CV in the subcortical and deep white matter region in MS (**a**) and a typical lesion without CV in the subcortical and deep white matter region in migraine (**b**)

data shows that headache is about 50 % more frequent in MS patients than the general population [17•]. The most frequently reported primary headaches are migraine (without aura) and tension-type headache. Several described cases involved complicated migraine, ophthalmoplegic migraine-like headaches, and cluster-like headaches [17•, 20–22].

Although some have proposed that demyelinated plaques affect signaling pathway as the probable cause of migraine, the exact mechanism in MS remains unclear. However, certain associations have been reported: migraine frequency is increased in patients with relapsing forms of MS, whereas tension-type headache is more frequent in patients with chronic progressive MS [10, 23].

Previously, lesion localization remained the main focus where MRI-detectable structural abnormalities in MS patients with migraines were reported to be more significantly involving the substantia nigra and periaqueductal gray matter, than those without migraines [24, 25].

Recently, association with contrast enhancing (CE) lesions was reported and yield support to the hypothesis of inflammation. Initially described in a case study, a patient with history of migraines experienced worsening of migraine symptoms as the initial manifestation of MS, and MRI showed concomitant asymptomatic gadolinium CE lesions [21]. Recently, Graziano et al. published a large case-controlled study ($n = 509$ MS patients) using 3 T MRI where they further pursued this hypothesis and noted that more MS patients with migraine presented with CE lesions than compared to those without (35.4 vs. 23.7 %, $p = 0.013$). More relapsing forms of MS patients with migraine presented with CE lesions compared to those without (41.8 vs. 28.2 %, $p = 0.035$). No other MRI lesion and volume outcome differences were noted in subjects with and without migraine within MS disease subtypes [23].

This study had several limitations: timing of the MRI with contrast in relation to migraine onset; migraine subtype (with or without aura) and done prior to ICHD-3 guidelines (see above); and the association of increased CE lesion activity in relapsing MS patients with migraine could not prove causation (as contrast agent was not administered to the healthy individuals, and CE lesions are not typically seen in migraine patients).

The authors reiterate the importance of evaluating migraine inflammation by including contrast imaging and emphasize that enhancing lesions in migraine may be an initial trigger in some of the MS patients. “It is also possible that these findings are not mutually exclusive, and that both the lesion location and the inflammatory process contribute to pain and migraine onset. Moreover, the migraine MS patients were younger and had more likely relapsing MS. This indicates that neuropathic pain and migraine pain may be mediated by different mechanisms and that optimal treatment for management of the migraine pain warrants greater attention” [23].

Trigeminal Neuralgia

Both facial pain including trigeminal neuralgia (TN) and non-painful facial sensory disturbances are common in MS patients. If the presentation of face pain is determined to be TN in a patient under the age of 50, MS etiology is reported to be the most common etiology. However, the prevalence data has been overall variable in MS pain. While some studies have reported prevalence of MS central trigeminal involvement is reported to be between 12 and 38 %, with overall prevalence as high as 50 %; others have reported that TN occurs in about 5 % of MS patients, which still translates to about 20 times the prevalence in the general population [26, 27]. The ophthalmic branch of the trigeminal nerve seems to be commonly affected. This was highlighted in a recent case study where a patient presents with “stabbing eye pain”. Instead of the typical thought process, where the eye pain in MS mainly correlates with the diagnosis of acute optic neuritis, (when pain is related to eye movement correlated with inflammation (from nervi nervorum)), the workup ultimately resulted in the final diagnosis of TN (ophthalmic branch).

Overall, in MS patients, the description is a facial neuropathic pain syndrome is similar to classic TN with episodic features and similarly evoked pain (due to various stimulus). While classic TN is caused by neurovascular compression of the fifth cranial nerve (CN V), MS-related demyelination correlates with MRI abnormalities related to the trigeminal nucleus, nerve, and brainstem.

Previously, both peripheral and central mechanisms in TN related to MS had been described and perhaps supported a dual mechanism in some MS patients. Generally, studies of neurovascular decompression in MS patient have resulted in relatively poor outcomes [12••]. These provide further support that many patients with MS-related TN have pain that is centrally mediated, thus refocusing efforts on lesion localization via improved imaging techniques [25, 27].

More specifically, studies using conventional MRI imaging techniques have demonstrated demyelination in the trigeminal root entry zone (REZ) and intrapontine tracts (that could extend in either direction to the trans-cisternal part of the nerve) and to the trigeminal nuclei (both ascending and descending). The changes were reported to be at times bilateral and symmetrical, all visible using conventional diagnostic MRI. Additionally, Mills et al. expanded conventional techniques further by using high-resolution 3 T MRI of trigeminal lesions in a cohort of 47 MS patients: using 3D sequences of T2 TSE (turbo spin echo), T2 FLAIR and T1 IR (inversion recovery) acquired in the coronal plane (contiguous 1 mm slices with in-plane resolution of up to 0.5 mm by 0.5 mm). The results showed that 11 patients (23 %) had high signal in the trigeminal REZ (including the trans-cisternal nerve or pontine nucleus (see Fig. 2). Some of the lesions were noted to be bilateral and involved both the ascending and descending nuclei. The

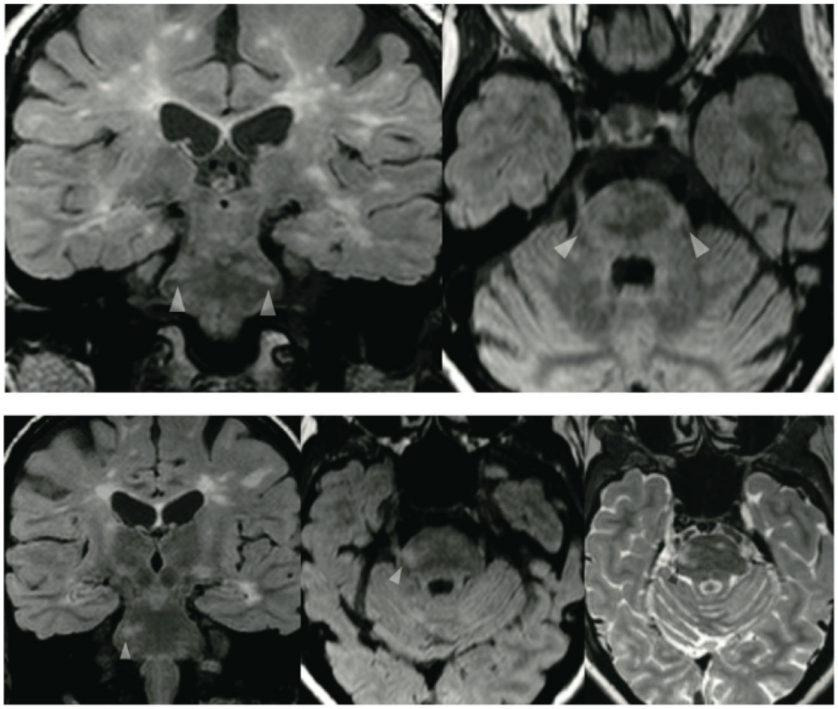

Fig. 2 *Top*: Coronal T_2 FLAIR (*left*) and axial reconstruction (*right*) showing bilateral hyperintense lesions in the trigeminal root entry zones and tracts (*arrowheads*), with increased signal in the transcisternal parts of the nerves. *Bottom* Coronal T_2 FLAIR (*left*), axial reconstruction (*middle*) and the corresponding axial T_2 TSE axial reconstruction (*right*) showing a hyperintense lesion in the trigeminal root entry zone (*arrowheads*), with high signal seen in the transcisternal part of the trigeminal nerve. Used with permission from the British Journal of Radiology: R J Mills, C A Young, and E T Smith; Central trigeminal involvement in multiple sclerosis using high-resolution MRI at 3 T, The British Journal of Radiology, 2010 83:990, 493–498. (Copyright 2010, British Institute of Radiology)

study concluded that high-resolution MRI at 3 T yielded a high prevalence of detectable trigeminal abnormality in the MS sample studied (see Fig. 3).

Moreover, the prevalence of trigeminal lesions in MS patients detected using high-resolution 3D MRI at 3 T was greater than the prevalence detected in other studies using standard two-dimensional, thicker-slice imaging at lower field strengths. Limitations include post-processing techniques, which could be applied only to the volume acquisition, "but did allow for excellent demonstration of the morphology of trigeminal lesions. However, even though, there was better delineation of the lesions on MRI, it did not to reflect either painful or non-painful facial sensory symptoms" [27].

Recently, a study of larger cohort of MS patients $N = 128$ with TN using conventional MRI without 3D concluded that trigeminal REZ abnormality was present in only 11 (8.6 %) of the MS patients. This may suggest that there is ongoing variability in the imaging of TN and perhaps using 3D imaging will provide a higher imaging capture with clinical correlation of face pain symptoms [28].

Diffusion tractography (DTI) has been used as a non-conventional MRI technique for over a decade, but in MS patients, it had served a limited role (Thompson et al. 2003) and still considered a research tool and mainly used to evaluate the effects of large white matter MS plaques on MRI. With higher field 3 T MRI, DTI has been used to evaluate small brainstem lesions as well and used to evaluate TN symptoms. As demonstrated most recently, Chen et al. used 3 T MRI multi-tensor DTI to evaluate differences between healthy controls, TN patients, and MS patients with TN. Diffusion metrics mainly fractional anisotropy (FA) were used to delineate CN V across cisternal, REZ, pontine, and perilesional segments. The results showed distinctive differences in the trigeminal nerve microstructure: TN group showed higher FA in the cisternal segment (ipsilateral to the side of pain, and lower FA in the ipsilateral REZ segment), the MS-TN group showed lower FA in the ipsilateral perilesional segments, "suggesting differential microstructural changes in MS patients" [29]. Although these DTI sequences can be obtained quickly, the post processing needed to obtain these interpretations can be time consuming for both the reader and technician with variable reproducibility across software and MRI platforms; perhaps the main limitation is the fact that DTI is still considered a research tool and thus not widely available or practical.

Overall, these studies indicate that the prevalence data for TN remains variable across imaging studies. They have implications both for understanding the etiology of TN pain symptoms in MS and for interpreting the clinical relevance of lesions elsewhere for localization.

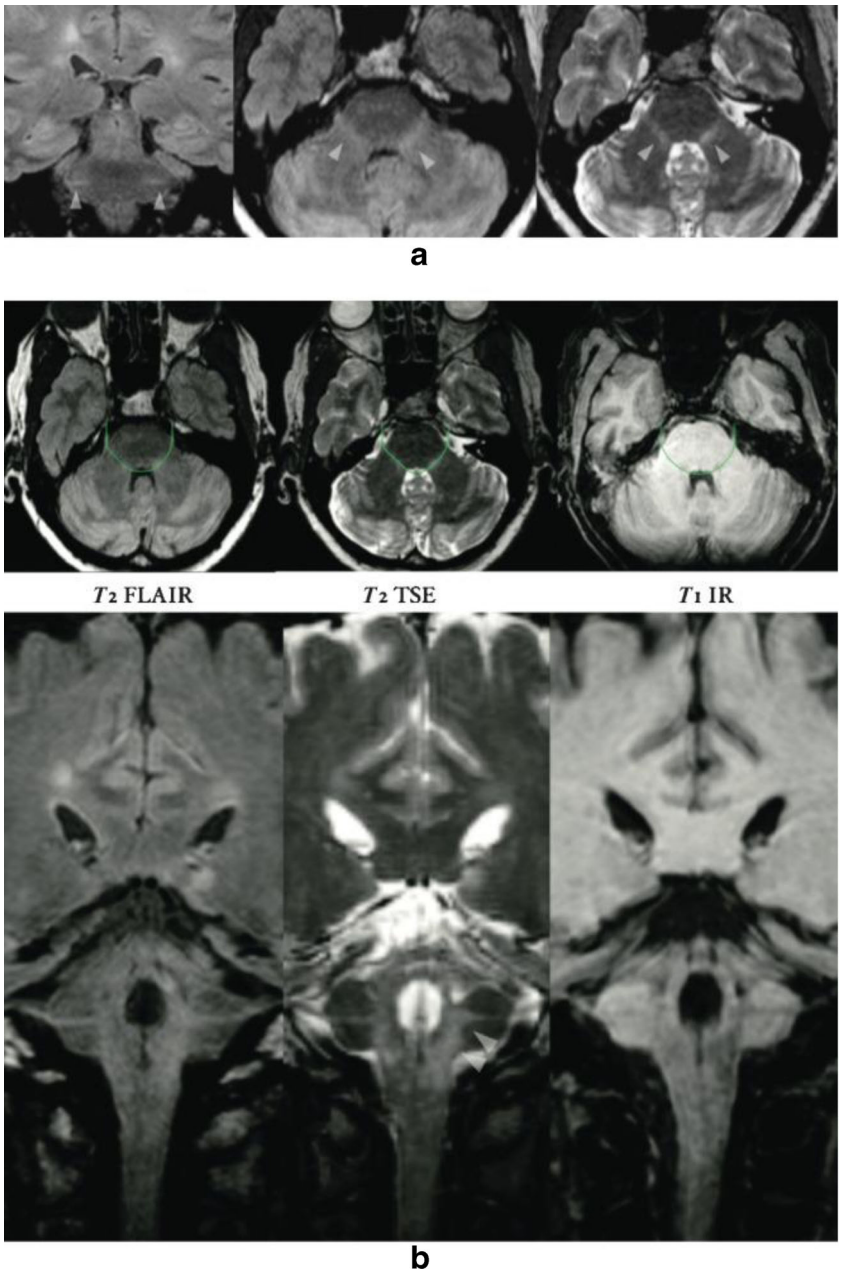

Fig. 3 **a** Coronal T_2 FLAIR (*left*), axial reconstruction (*middle*), and the corresponding axial T_2 TSE axial reconstruction (*right*) showing bilateral, well-demarcated, linear hyperintense lesions in the trigeminal root entry zones and tracts of otherwise lesion-free pontocerebellar structures. **b** Axial T_2 FLAIR reconstruction (*left*), corresponding axial T_2 TSE reconstruction (*middle*) and axial T_1 IR reconstruction (*right*) images from the same subjects as imaged in (**a**). The upper images show the curved plane (*green line*) in which the lower images were reconstructed. The lower images clearly show abnormal signal extending along the whole transcisternal and intrapontine course of both trigeminal nerves, which becomes confluent with lesions running rostrocaudally where the pontomedullary trigeminal nuclei would be found (*arrowheads*). Used with permission from the British Journal of Radiology: R J Mills, C A Young, and E T Smith; Central trigeminal involvement in multiple sclerosis using high-resolution MRI at 3 T, The British Journal of Radiology, 2010 83:990, 493–498. (Copyright 2010, British Institute of Radiology)

Conclusion

Conventional MRI imaging has served an imperative evolving role in the refinement of diagnostic criteria over the last several decades. Although the imaging evaluation of MS pain has remained challenging, this article demonstrates examples where it still serves an expanding dynamic role. Higher field strength conventional MRI magnets and advanced MRI techniques have improved our sensitivity and ultimately our understanding of pain in MS. Thus far, the imaging of MS pain has mainly focused on neuropathic pain with emphasis on migraines and trigeminal neuralgia, and these are still disproportionately represented in the current literature.

Overall, this article details how uses of newer improved conventional techniques (such as FLAIR* and 3D imaging), greater use of high field 3 T MRI (with contrast enhancement), and incorporating non-conventional techniques (e.g., DTI when available) can help complement MS pain interpretation. The expanded usage of conventional imaging combined with greater understanding of pathophysiology of MS pain and awareness of pain criteria can result in improved diagnosis and guide treatment plans where they may have a greater impact, and perhaps ultimately delay the evolution of neuropathic pain.

The imaging of face pain and migraine is still evolving and emphasizes the clinical importance of earlier MS diagnosis. This highlights the fact that inflammation requires aggressive

management, as it is associated with a higher risk of developing neuropathic pain.

Deficiencies in MS pain imaging persist, and additional quantifiable studies are needed. Perhaps longitudinal serial imaging of targeted neuropathic lesions on brain MRI can further advance the field of MS pain. Additional studies are also needed (beyond case reports and case series) and likely imperative in order to gain greater understanding of the emotional aspects of pain and to eventually be able to target specific mechanisms which are being further defined and refined.

Compliance with Ethical Standards

Conflict of Interest Amir Mazhari declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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