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EFNS GUIDELINES/CME ARTICLE

EFNS guidelines on the use of neuroimaging in the management of motor neuron diseases

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Background and purpose: These European Federation of Neurological Societies guidelines on neuroimaging of motor neuron diseases (MNDs) are designed to provide practical help for the neurologists to make appropriate use of neuroimaging techniques in patients with MNDs, which ranges from diagnostic and monitoring aspects to the *in vivo* study of the pathobiology of such conditions.

Methods: Literature searches were performed before expert members of the Task Force wrote proposal. Then, consensus was reached by circulating drafts of the manuscript to the Task Force members and by discussion of the classification of evidence and recommendations.

Results and conclusions: The use of conventional MRI in patients suspected of having a MND is yet restricted to exclude other causes of signs and symptoms of MN pathology [class IV, level good clinical practice point (GCPP)]. Although the detection of corticospinal tract hyperintensities on conventional MRI and a T2-hypointense rim in the pre-central gyrus can support a pre-existing suspicion of MND, the specific search of these abnormalities for the purpose of making a firm diagnosis of MND is not recommended (class IV, level GCPP). At present, advanced neuroimaging techniques, including diffusion tensor imaging and proton magnetic resonance spectroscopic imaging, do not have a role in the diagnosis or routine monitoring of MNDs yet (class IV, level GCPP). However, it is strongly advisable to incorporate measures derived from these techniques into new clinical trials as exploratory outcomes to gain additional insights into disease pathophysiology and into the value of these techniques in the (longitudinal) assessment of MNDs (class IV, level GCPP).

Background

The term 'motor neuron disease' (MND) comprises a group of disorders involving preferential damage to upper (UMN) and/or lower motor (LMN) neurons. The clinical spectrum of MNDs is wide in adulthood, ranging from simultaneous involvement of UMN and LMN (classic ALS, and 90% of all MND cases), a pure UMN syndrome [primary lateral sclerosis (PLS)] and an isolated LMN involvement [variably defined by the term progressive muscular atrophy (PMA)]. A diagnosis of MND predominantly relies on the interpretation of clinical symptoms and signs, with the use of paraclinical and laboratory tests to exclude other causes [1,2]. Indeed, the greatest contribution of neuroimaging to the diagnosis of MND so far has been its sensitivity to detect changes suggestive of alternative diagnoses [3].

Reliable objective biomarkers of both UMN and LMN involvement are critical for the early diagnosis

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and monitoring of disease progression in patients with MNDs. Proton magnetic resonance spectroscopic imaging (^{1}H-MRSI) and diffusion tensor imaging (DTI) hold particular promise for the UMN lesion in this regard [3]. Moreover, it is recognized that ALS is characterized by an extramotor cerebral pathology that, to a variable extent, overlaps with the clinico-pathological features of frontotemporal lobar degeneration (FTLD) [4]. The use of other neuroimaging techniques, such as positron emission tomography (PET) and functional MRI (fMRI), has provided a more complete picture of this extramotor involvement and permitted functional changes to be studied in MNDs.

These guidelines comprise an objective appraisal of the evidence in regard to the utility of neuroimaging techniques in adult patients with MNDs, which ranges from diagnostic and monitoring aspects to the *in vivo* study of the pathobiology of MNDs. Consensus recommendations are given and graded according to the European Federation of Neurological Societies (EFNS) guidance regulations [5]. Where there was lack of evidence but consensus was reached, we have stated our opinion as good clinical practice points (GCPP).

Aims of the EFNS Task Force

Following are the objectives of the 'Task Force on Neuroimaging of MND': (i) To provide guidelines for the application of conventional MRI for the diagnosis and monitoring of adult patients with MNDs in clinical practice; (ii) To clarify the current status and clinical role of advanced neuroimaging techniques in MNDs; and (iii) To investigate the role of neuroimaging for exploring differences in the patterns of brain involvement between sporadic and familial MND groups.

Search strategy

Data for this review have been identified by searches of Medline for relevant articles from January 1965 to July 2009. The search terms 'amyotrophic lateral sclerosis', 'primary lateral sclerosis', 'progressive muscular atrophy', 'motor neuron disease', 'frontotemporal dementia AND motor neuron disease', 'frontotemporal dementia AND amyotrophic lateral sclerosis', 'superoxide dismutase-1', 'corticospinal tract', 'magnetic resonance imaging', 'atrophy', 'voxel-based morphometry', 'proton magnetic resonance spectroscopy', 'proton magnetic resonance spectroscopy imaging', 'diffusion-weighted MRI', 'diffusion tensor MRI', 'diffusion tensor imaging', 'diffusion tensor imaging-based tractography', 'magnetization transfer MRI', 'positron emission tomography', 'functional MRI' and 'disability' have been used. Using this strategy, we identified 386 articles. We also searched the reference lists of reports identified by this search strategy and selected those we judged relevant. Original articles, meta-analyses, review articles as well as guideline recommendations were reviewed. Only articles published in English were considered.

Methods for reaching consensus

MF and FA searched for relevant articles and prepared an initial draft. Consensus was reached by circulating drafts of the manuscript to the Task Force members and by discussion of the classification of evidence and recommendations.

Signal changes on conventional MRI in patients with sporadic MNDs

The revised criteria of the World Federation of Neurology Research Group on MNDs [6] state that conventional MRI studies are not required in those cases that have a clinically definite disease with a bulbar-or pseudobulbar-onset. On the other hand, in patients with clinically probable or possible ALS, routine brain and/or spinal cord MRI can be useful in excluding several 'ALS mimic syndromes', including cerebral lesions (e.g., multiple sclerosis and cerebrovascular disease), skull base lesions, cervical spondylotic myelopathy, other myelopathy (e.g., foramen magnum lesions, intrinsic and extrinsic tumours and syringomyelia), conus lesions and thoraco-lumbar-sacral radiculopathy [7].

Corticospinal tract (CST) hyperintensities on T2-weighted, proton density (PD)-weighted, and fluid-attenuated inversion recovery (FLAIR) images are frequently found in MND patients [8–17]. CST hyperintensities, which are best followed on coronal scans, have been reported mostly bilateral and can be recognized in the caudal portion of the posterior limb of the internal capsule. They typically extend downward to the ventral portion of the brainstem, and less consistently upward through the corona radiata. Such lesions may occur more often in younger patients with greater disability [13]. It is not clear yet which may be the most sensitive MR sequence to detect CST hyperintensities in patients with MND. Three studies have found PD-weighted images as more reliable than T2-weighted images [9,18,19], whereas two other groups showed the opposite [16,20]. Finally, other studies reported that CST signal abnormalities in ALS are better detected with FLAIR imaging [11]. In patients with MND, increased T2-signal intensity has also been described in extramotor frontotemporal regions [21,22].

Increased CST signal intensity has also been described in healthy individuals [14] and, strikingly,

after hepatic transplantation [23]. Thus, CST hyperintensity is considered non-specific for MNDs overall. Furthermore, the reported frequency of conventional MRI abnormalities in patients with ALS is very heterogeneous, ranging from 15% to 76%. However, most of the studies used a dichotomic approach (present/absent) to interrogate the signal abnormality of the CST, and this may have contributed to the reduced sensitivity of conventional MRI. In contrast, Cheung *et al*. [9] evaluated the spatial extent of CST signal changes and reported the highest MRI sensitivity for detecting CST abnormality. In a recent study in patients with ALS and PLS, the combined application of T2-weighted, PD-weighted and FLAIR images reached a sensitivity of about 62% [19]. It is interesting to note that in patients with PLS, the sensitivity was higher (approximately 78%), whilst in 'possible' or 'probable-laboratory supported' patients with ALS (according to the revised El Escorial criteria [24]), the sensitivity of conventional MRI dropped significantly, being about 21% [19]. Finally, CST signal changes on FLAIR images increase with disease duration but do not correlate with clinical scores [11].

In patients with ALS, the pre-central cortex can present a low signal intensity (hypointense rim) on T2-weighted images [9,12,13,15,16,25]. This so-called ribbon-like hypointensity is sharply contrasted by the hyperintense signal of cerebrospinal fluid in the adjacent sulci.

T2-weighted [15,26] or T1-weighted [16] hyperintensities of the anterolateral columns of the cervical cord have been observed in patients with ALS, with higher specificity than signal changes of brain MR scans [15,26]. T1-hyperintensity of the anterolateral cervical cord has been associated with younger patients and rapid disease progression [16].

Recommendations

1. All patients suspected of having a MND, where a plausible alternative unifying neuroanatomical explanation exists, should undergo an MRI of either or both the brain and whole cord depending on the clinical presentation (class IV, level GCPP) [2].
2. The detection of CST hyperintensities on T2-weighted, PD-weighted, FLAIR imaging and a T2-hypointense rim in the pre-central gyrus can support a pre-existing suspicion of ALS (class IV, level GCPP). However, considering the low sensitivity and specificity of such abnormalities and the weak correlation with clinical findings, the specific search of these abnormalities for the purpose of making a firm diagnosis of ALS is not recommended (class IV, level GCPP).

Advanced neuroimaging techniques in patients with sporadic MNDs

Atrophy

In patients with ALS compared to controls, reduced brain parenchymal fraction (BPF) has been reported in two studies [27,28]. It is remarkable that atrophy could be appreciated only in the analysis of BPF, defined as the proportion of brain parenchymal volume normalized to total intracranial volume, whereas neither the calculation of normalized brain volume [28] nor the absolute volume measurements in non-normalized 3D MR images [29,30] revealed significant group differences. This highlights the fact that global atrophy is relatively mild in ALS and regional differences may be more important. Lower whole brain volume has been recently demonstrated in a group of patients with PLS relative to controls [31].

With respect to the regional distribution of brain atrophy, the pattern and extent of volume loss vary amongst studies. Differences in image pre-processing and statistical analysis, as well as in the clinical characteristics of the cohorts of patients studied, may contribute to explain this variability. This is particularly relevant in relation to the cognitive status of the patients. Indeed, a significant proportion of patients with ALS (perhaps up to 50%) have cognitive or behavioural dysfunction because of co-existing FTLD [4]. Furthermore, a small subset of these patients meet criteria for frontotemporal dementia (ALS-FTD). Some studies have included patients with an ALS-FTD syndrome, whilst others restrict their sample to non-demented patients with and without cognitive impairment. Cross-sectional MRI studies did not reach firm conclusions regarding the presence of motor/pre-motor cortical atrophy in ALS, as this was found by some authors [22,27,32–37] but denied by others [28,29,38,39]. Although some MRI studies in patients with PLS failed to show consistent pre-central atrophy by visual assessment [40,41], central atrophy has been noted in PLS [20], and moreover in the same study, striking parietal region atrophy was noted in nearly half the cases of ALS [20]. A recent investigation using an automated analysis program demonstrated significant atrophy of the pre-central cortex in patients with PLS, which was associated with disease severity [31]. In patients with ALS with no cognitive impairment, voxel-based morphometry (VBM) studies found consistently a regional grey matter (GM) loss which extends beyond the motor cortex to the frontotemporal and parietal regions [27–29,32–36]. In non-demented patients with ALS, a trend was also observed with reduced amygdala size in patient group compared with controls [30].

A significant correlation between disease severity and GM atrophy was found only in one study [33].

In patients with ALS, white matter (WM) tissue loss along the CST has been observed in two studies so far [27,29]. Ellis *et al*. [29] demonstrated WM tissue loss extending bilaterally from the pre-central gyrus into the internal capsule and brainstem in patients with bulbar-onset, only. Extramotor WM atrophy, which included the anterior (pre-frontal) corpus callosum, cerebellum, and frontotemporal and occipital regions [27,39], was also found; however, this was not confirmed by other authors [33,34,36]. Corpus callosum atrophy has been recently reported in patients with PLS [31].

Studies that have investigated the cognitive status of the patients have revealed that patients with ALS-FTD when compared to controls show a pattern of GM atrophy that involves motor/pre-motor cortices bilaterally, several pre-frontal regions, superior temporal gyri, both temporal poles and left thalamus [34]. Most of the frontal regions were significantly more atrophied in the ALS-FTD group than in the ALS group [34]. Compared with cognitively normal patients, patients with ALS with even sub-threshold variants of cognitive or behavioural impairment (not meeting criteria for dementia) demonstrated reduced GM in frontal, parietal and limbic lobes [42]. In cognitively impaired patients with ALS, the performance on measures requiring action knowledge correlated with cortical atrophy in pre-motor and pre-frontal cortex, whilst that on measures requiring object knowledge was associated with pre-frontal cortex atrophy [35]. Only one study reported greater WM tissue loss in frontotemporal regions in cognitively impaired (non-demented) patients with ALS compared with those with no evidence of cognitive impairment. Such tissue loss was associated with cognitive deficits on verbal fluency, although less extensive WM changes were also revealed in cognitively intact patients with ALS [39].

A few longitudinal studies have attempted to assess quantitatively the dynamics of brain atrophy in patients with ALS [43,44]. The first study showed that 16 patients with ALS with no evidence of cognitive impairment experienced progression of GM atrophy in the left pre-motor cortex and right basal ganglia over a period shorter than 1 year [43]. Patients with rapidly progressing ALS showed greater GM atrophy in motor and extramotor frontal regions compared to non-rapidly progressing cases [43]. In a second study, significant longitudinal cortical atrophy in motor and pre-motor areas after about 5 months was found in four patients with ALS-FTD compared with controls [44].

Compared with controls, patients with ALS demonstrated a decreased cervical cord cross-sectional area [45]. However, this finding was not confirmed by a second study [46]. A longitudinal study showed a significant development of cord atrophy over a 9-month follow-up [47].

^{1}H-MRSI

Nearly all ^{1}H-MRSI studies in ALS have demonstrated that either *N*-acetylaspartate (NAA) concentrations [48–50] or NAA/creatine (Cr) [50–54], NAA/choline (Cho) [51,55] and NAA/Cr + Cho [54] ratios are reduced in the motor cortex of these patients. The reduction in the NAA/Cr ratio in the motor cortex was found to vary from 5% to 32% [50,52–54,56,57]. NAA/Cho is reduced more than NAA/Cr in the motor cortex in those studies that measured both [51,55,56,58–61]. NAA/Cr and NAA/Cho ratios are reduced along the length of the intracranial CST from the motor cortex to the cerebral peduncle; however, this reduction is most significant rostrally in the pre-central gyrus and corona radiata [59]. Nevertheless, ^{1}H-MRSI changes in the brainstem have also been reported in patients with ALS, with the greatest decrease of the NA (NAA + *N*-acetylaspartylglutamate)/Cr ratio in the pons and upper medulla of patients with prominent UMN or bulbar signs [62]. The findings of reduced NAA concentrations or NAA ratios were confirmed by cross-sectional studies performed at 3.0 T [58,61,63].

Proton magnetic resonance spectroscopic imaging studies reported significant correlations between motor cortex NAA concentrations (or its earlier defined ratios) and disease severity (revised ALS Functional Rating Scale score [50,61,64]), the Norris limb scale [65], UMN signs [66] and maximum finger tapping rate [54]. Ellis *et al*. showed that bulbar-onset patients have a lower NAA/Cho + Cr ratio in the motor cortex compared with limb-onset patients. In a multiparametric study, T2 hypointensity of the motor cortex and bulbar-onset were associated independently with the degree of NAA loss [49]. In a prospective ^{1}H-MRSI study of patients with probable or definite ALS, a multivariate analysis showed reduced survival for individuals with lower NAA/Cho, older age, and shorter symptom duration [63]. Patients with NAA/Cho < 2.11 had a survival of 19.4 vs. 31.9 months of the others [63].

In patients with ALS, decreased NAA/Cr ratios have been observed in pre-motor regions, primary sensory cortex and extramotor frontal regions, with relative sparing of the parietal lobe [53,65]. Decreased frontal NAA/Cr ratio correlated with cognitive dysfunction [65]. Strong *et al*. [67] showed that patients with ALS with bulbar-onset and greater cognitive impairment compared to those with limb-onset had a decrease in the NAA/Cr ratio in the cingulate gyrus.

Myo-inositol (mI), a spectroscopic marker for glial activity, was found to be increased in the motor cortex of patients with ALS [51,68]. Increased mI levels were associated with motor cortex hypointensity on T2-weighted images [68]. The NAA/mI ratio may provide better sensitivity and specificity for detecting disease than the other metabolites ratios as was shown by a cross-sectional study of patients with ALS using a magnetic field strength of 3.0 T [63]. In this study, decreased NAA/Cr and increased Ins/Cr had high sensitivity but low specificity, and decreased NAA/Cho had low sensitivity but high specificity; whilst the NAA/Ins ratio had moderate sensitivity (71%), the highest specificity (93%), and the best sensitivity and specificity profile amongst the four metabolite ratios [63].

Two studies in patients with PMA found normal NAA levels in the motor cortex [40,48]. However, more recently, a modest reduction in NAA/Cr ratio was found in nine PMA patients relative to controls [50], and abnormal ^{1}H-MRSI was found in 63% of 27 patients with PMA [66]. Reasons for this variability may include different sample size and methodology (i.e., single-voxel versus multi-voxel ^{1}H-MRSI) amongst studies. In two studies including patients with PLS, mean NAA/Cr values were significantly different relative to control subjects [40,50]: when the optimal cut-off was set (2.5), NAA/Cr values were found to be abnormal in 67% of patients.

Proton magnetic resonance spectroscopic imaging studies with an adequate follow-up are scarce. Moreover, study designs consisted of a relatively short follow-up period of no more than 15 months, with assessment at variable observation points. Together with the variety of image analysis used, this makes comparisons between studies very difficult. One longitudinal study investigated ^{1}H-MRSI changes in nine patients with ALS: in the most affected motor cortex, NAA/Cr and NAA/Cho + Cr ratios decreased significantly after 1 month, whilst no significant changes were found in the least symptomatic of the two sides of the motor cortex after 3 months [60]. Other follow-up studies showed similar results [55,69,70]. In one study, changes of metabolite ratios were significantly correlated with progression of disease severity [55]. However, one prospective study, using multivoxel ^{1}H-MRSI in 30 patients with ALS, did not confirm these findings [50]. Rule *et al.* [70] found a significant decrease in NAA levels outside the motor cortex after 9 months. These findings were not confirmed by another study where no longitudinal NAA, Cre and Cho concentration changes were detected in extramotor regions [60]. There is minimal experience of treatment effects on ^{1}H-MRSI measures in ALS. Kalra *et al.* [57,71] reported an increase in NAA/Cr ratio in the motor cortex of patients with ALS after only a short course of treatment with riluzole. No effect on ^{1}H-MRSI metrics was seen with treatment with gabapentin [72] or brain-derived neurotrophic factor [73].

Diffusion tensor imaging

Region of interest (ROI)-based DTI studies reported consistently decreased fractional anisotropy (FA) values along the CST in patients with ALS [74–81]. FA shows a downward linear trend from the cerebral peduncles to the pyramids [76]. Patients with bulbar-onset may have the most marked FA decrease [75]. Decreased FA was found to be related to disease severity [61,74,75,79], as well as to clinical [75,77] and electrophysiological [78] measures of UMN degeneration in patients with ALS. However, these findings were not confirmed by other studies [50,76,80]. Increased mean diffusivity (MD) along the CST, which was associated with disease duration [74,75], was reported by some studies [75–77], but not by others [79].

Using DTI-based tractography, lower mean FA was demonstrated in the CST of patients with ALS with rapid disease progression compared to controls [82]. A strong correlation was found between disease progression rate and left CST structural connectivity measures [82]. DTI-based tractography has also been shown to be helpful in guiding the placement of ROIs on the CST [83,84] and the corticobulbar tract [83] in these patients.

MRI studies that employed a voxel-based approach to investigate differences in FA between patients with ALS and controls, reported that patients with ALS show a decrease of FA values not only in the CST but also in regions outside the 'classic' motor network [32,85–88]. FA decrease was found in the corpus callosum [32,85–88], in the pre-motor WM [85,87,88], in the pre-frontal WM [85,87,88] and in the temporal WM [87,88]. One study did not confirm extramotor FA changes in ALS [77]. A few studies have investigated the regional patterns of MD changes in ALS patients and found increased MD in the corpus callosum and in several frontal and temporal WM regions compared to controls [32,88].

Patients with PMA have been shown to have subclinical UMN involvement in a neuropathological study [89]. In one DTI study [79], patients with PMA had FA values in the posterior limb of the internal capsule that were similar to those of patients with UMN signs. A voxel-based DTI study of patients with ALS and PMA [86] showed decreased FA values along the CST in both groups relative to controls [86]; all patients with PMA later developed ALS, suggesting that DTI may be a marker for early and clinically silent UMN involvement [86]. In contrast, another study found no FA changes in

the CST of patients with PMA [74]. However, this latter study used more stringent criteria for the diagnosis of PMA, i.e., the presence of a pure LMN syndrome and areflexia for at least 2 years after diagnosis [74], which was not the case for the other studies [79,86]. The only voxel-based DTI study investigating differences in FA between patients with PLS and patients with ALS [85] showed that patients with PLS had lower FA than patients with ALS in the body of the corpus callosum and in the WM adjacent to the right primary motor cortex, whilst patients with ALS had reduced FA compared with patients with PLS in the WM adjacent to the superior frontal gyrus [85]. Significant correlations were found between disease progression rate and (i) FA in WM adjacent to the primary motor cortex in PLS, and (ii) FA along the CST and in the body of the corpus callosum in ALS [85].

Longitudinal DTI studies of patients with ALS gave conflicting results [43,50,87,90], as only one study of seven patients with ALS reported a significant progression of brain damage, which was moderately correlated with the concomitant worsening of disability [87], whilst others did not [47,50,90].

More recently, DTI has been successfully used to grade the extent of cervical cord damage associated with ALS [45]. Compared with controls, patients with ALS had significantly lower FA of the cervical cord, whilst MD did not differ between the two groups [45]. A strong correlation was found between cord FA and disease severity [45]. After a mean follow-up of 9 months [47], these patients showed a significant decrease of cord FA and a significant increase in cord MD [47]. In the same patient group, brain CST DTI metrics remained stable over time and did not correlate with cord damage [47].

Magnetization transfer (MT) MRI

In one preliminary study using T1-weighted MT contrast-enhanced images, hyperintensity along the CST was found in 80% of patients with ALS [91]. Two of the three reports on quantitative MT MRI in ALS showed a reduction in the MT ratio in the CST from 2.6% [92] to 20% [93] compared to controls. The other study did not find any difference between patients and controls [19]. It is not yet clear that this technique offers any significant advantages over DTI.

Functional imaging

In MND patients with UMN signs, activation PET studies using ^{18}F-fluoro-2-deoxyglucose demonstrated reduced regional cerebral metabolic rates (rCMRGlc) throughout the cerebral hemispheres [94,95], which was marked in the sensorimotor cortex and putamen [95]. The degree of glucose hypometabolism has been correlated with disease duration [94]. In contrast, patients with PMA appeared to have normal or near-normal rCMRGlc relative to controls [94]. At rest, a marked reduction in regional cerebral blood flow (rCBF) as measured by PET tracer $H_2{}^{15}O$ was found in the primary sensorimotor cortex and the adjacent pre-motor, parietal and insular cortices from patients with ALS [96,97]. During a motor activation task, rCBF was significantly reduced in the medial pre-frontal cortex, anterior cingulate gyrus and parahippocampal gyrus in these patients relative to controls [96,97]. rCBF changes were not seen in patients with PMA [98].

Patients with ALS have decreased glucose uptake in the frontal lobe, and some have additional abnormalities in the temporal, parietal and right thalamic regions [94,95]. One study linked the glucose hypometabolism of the frontal lobes to ALS-associated neuropsychological deficits [99]. Non-demented patients with ALS with decreased verbal fluency scores also have reduced rCBF of the pre-frontal cortex, pre-motor cortex, bilateral insular cortex and thalamus compared to those patients who were cognitively intact using a verbal fluency activation paradigm [100,101].

Using ligand-based PET, a reduction in cortical ^{11}C-flumazenil binding has been detected in the motor/pre-motor [102–104] and extramotor [102] cortical regions of patients with ALS. Poorer performance on verbal fluency correlated with decreased ^{11}C-flumazenil binding in frontotemporal regions, whilst poorer performance on a confrontation naming test correlated with decreased binding in the left middle frontal gyrus and cuneus [105]. One PET study with ^{11}C-WAY 100635, which binds selectively to the 5-hydroxytryptamine (5-HT)1A receptor on cortical pyramidal neurons, revealed marked binding reductions in the precentral and cingulate gyri and frontotemporal regions of patients with ALS [106]. Such reduced 5-HT1A receptor binding was also seen in similar areas in patients with FTD [107]. Microglial activation may have a role in ALS pathogenesis [108] and has been detected using PET *in vivo* in patients with ALS [109]: significantly increased ^{11}C(R)-PK11195 binding was found in the motor cortex, pons, pre-frontal cortex and thalamus, with a significant correlation between binding in the motor cortex and clinical UMN signs [109]. Increased uptake rate of ^{11}C(L)-deprenyl, which allows to localize astrocytosis *in vivo*, was demonstrated in patients with ALS in the pons and global WM [110].

Functional MRI studies have superseded activation PET in the investigation of patterns of cortical recruitment in MNDs [111] and have the advantage of wider accessibility, non-invasive study, and lack of

ionizing radiation. During motor tasks, fMRI has consistently demonstrated an increased activation of the contralateral sensorimotor cortex, supplementary motor area, basal ganglia, and cerebellum [112–115]. Increased sensorimotor activation was also reported in the hemisphere ipsilateral to the movement [114]. Furthermore, patients with ALS showed motor-associated reduced activation in the pre-frontal cortex [115]. One study demonstrated movement-associated decreased cortical responses of the contralateral sensorimotor cortex, pre-motor area, supplementary motor area, posterior parietal cortex and relatively increased responses of the putamen in patients with ALS relative to controls [116]. The difficulty to control task performance in patients with ALS may be responsible for the variability of motor fMRI studies. More recently, during a motor imagery task, patients with ALS showed a reduced activation of the left inferior parietal lobule, anterior cingulate gyrus and pre-frontal cortex [117]. In ALS, the analysis of the resting state fMRI demonstrated not only sensorimotor network changes in the pre-motor cortex but also a reduced activation of the default mode network [118].

In patients with ALS relative to controls, a letter fluency fMRI task revealed significantly impaired activation in frontal, parietal and temporal lobes [119]. A confrontation naming fMRI task also revealed impaired activation of a pre-frontal region (including Broca's area) and areas of the temporal, parietal and occipital lobes [119]. This pattern of dysfunction corresponded to the presence of cognitive deficits on both letter fluency and confrontation naming [119].

Recommendations

1. At present, advanced neuroimaging techniques do not have a role in the diagnosis or routine monitoring of MNDs (class IV, level GCPP).
2. Quantitative measurements of brain atrophy in clinical practice continue to be considered at a preliminary stage of development (class IV, level GCPP), as they need to be standardized in terms of acquisition and post-processing and validated further in the context of longitudinal and normative studies.
3. Measurement of cervical cord area is a promising tool to monitor MND evolution (class IV, level GCPP). However, at present, such an approach showed differences at a group level only in a single study and does not permit inferences at an individual level.
4. Brain and cord atrophy should be included as secondary end-points in disease-modifying agent trials of MNDs, to further elucidate the mechanisms responsible for disability in these conditions.
5. Monitoring NAA levels in the primary motor cortex and CST may be useful in the evaluation of MND progression and response to treatment (class IV, level GCPP).
6. Diffusion tensor imaging holds promise in the assessment of UMN damage before clinical symptoms of CST involvement become apparent (class IV, level GCPP).
7. The contribution of DTI and ^{1}H-MRSI in multicenter studies requires further evaluation. It is strongly advisable to incorporate measures derived from these techniques into new clinical trials as exploratory outcomes to gain additional insights into disease pathophysiology and into the value of these techniques in the assessment of MNDs.
8. Functional MRI can be useful in the assessment of cognitive network abnormalities in patients with MND (class IV, level GCPP), and should be considered first-line over activation PET studies for this purpose at present.
9. Ligand-based PET still has potential to generate new as well as test existing hypotheses relating to receptor changes within MND pathogenesis, but it will require the development of novel, robust ligands through investment in radiochemistry.

Neuroimaging in patients with familial MND

Mitsumoto *et al.* [50] showed reduced FA values in the CST at the level of the internal capsule in six patients with familial ALS relative to controls. Decreased FA values have been reported in the posterior limb of the internal capsule in eight asymptomatic members of a large Chinese family with autosomal dominant familial ALS with a known superoxide dismutase 1 (SOD1) mutation relative to controls [120].

Neuroimaging studies provide evidence for different patterns of cortical neuronal vulnerability in patients homozygous for the D90A (homD90A) mutation of the SOD1 gene versus sporadic ALS, which may explain the slower rate of disease progression in most familial cases. A VBM study showed that GM atrophy in the homD90A group was more pronounced within the frontal lobes, whilst the sporadic ALS group showed areas of atrophy mainly confined to motor and pre-motor cortices bilaterally [121]. Six patients with homD90A SOD1 ALS showed less extensive WM changes (i.e., decreased FA values) in motor and extramotor pathways compared to patients with sporadic ALS, despite similar disease severity [122]. In homD90A SOD1 ALS patients, FA values correlated with clinical measures of severity and UMN involvement [122]. Using ^{11}C-flumazenil PET, a

less extensive, more frontal pattern of reduced binding was observed amongst patients with homD90A SOD1 compared with patients with sporadic ALS and similar disability [103,104]. Finally, 11 homD90A SOD1 patients demonstrated significantly less reduction in the cortical binding of ^{11}C-WAY100635 than a group of patients with sporadic ALS of similar disability [123].

The presence of a thin corpus callosum or the 'ears of the lynx' abnormality in the forceps minor of the corpus callosum (i.e., the frontal horn region bore a remarkable resemblance to the ears of a lynx, with the areas of abnormal signal reminiscent of the tufts of hair crowning the tips of the ears of this animal) has been linked to the presence of a mutation in the SPG11 gene on chromosome 15, which is associated with a spastic paraparesis condition which can enter in the differential diagnosis of MNDs [124].

Mutations of the Senataxin gene are associated with autosomal dominant juvenile ALS (ALS4) and autosomal recessive ataxia-ocular apraxia 2 (AOA2). In a two-generation family, whose affected individuals had a clinical phenotype combining typical features of AOA2 and ALS4, MRI revealed severe cerebellar atrophy [125].

Recommendations

1. Diffusion tensor imaging may be useful in the assessment of UMN damage in asymptomatic members of family with familial ALS (class IV, level GCPP).
2. The presence of a thin corpus callosum or the 'ears of the lynx' abnormality in the forceps minor of the corpus callosum should raise the suspicion of a hereditary spastic paraparesis in an otherwise appropriate clinical context (class IV, level GCPP).
3. Neuroimaging techniques need to be further applied in familial ALS with mutations of newly identified genes (e.g., angiogenin gene, TAR DNA-binding protein-43 gene, fused in sarcoma/translated in liposarcoma gene).

Conflicts of interest

Members of this Task Force have no conflicts of interest related to the recommendations given in this paper.

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For a full list of References, please see Reference Appendix pp. e17–e20.

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